Comprehensive Research Experience for Medical Students (CREMS)  
2022 Supervisor and Project Information Form

Please complete and return via email ONLY to crems.programs@utoronto.ca by February 18, 2022.

Supervisor Information

NOTE: CREMS will not support pre-determined pairings of students and supervisors. Supervisors must agree to open their projects to all students and interview all that are interested.

Name: Dr. Gelareh Zadeh  
Email: Gelareh.zadeh@uhn.ca

Department: Neurosurgery  
Hospital/Research Institution: University Health Network

SGS Department(s) (if applicable): IMS

ORCID ID (see https://orcid.org/ - If you do not have an ORCID ID we encourage you to sign up for one):  
https://orcid.org/0000-0002-6637-4502

Location of Work:  
PMCRT, 101 College St. Toronto, ON M5G 0A3

Field of Research (up to 4 keywords):  
Neuro-oncology, genetics, neurosurgery, epigenetics

Student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): Flexible
NOTE: If this project is selected, this information will be posted on CREMS website for interested student applicants to view research opportunities.

PROJECT TITLE:
Establishing the prognostic utility of plasma-based liquid biopsies in meningiomas using cell-free methylated DNA immunoprecipitation with deep sequencing

PROJECT DESCRIPTION:
Including background, aim(s), methodS and significance of the project. Maximum 300 words.

Introduction: Contemporary management of brain tumors is contingent upon invasively obtaining a tissue diagnosis through surgery. A “liquid biopsy” to sample the tumor genome from patient plasma can bypass risks of an operation while providing personalized prognostic information. This is of particular interest for brain tumors, as surgery to obtain tumor tissue for diagnosis carries a relatively higher risk of morbidity and even mortality compared to other parts of the body and is highly anxiety provoking for patients. Our group and others have previously demonstrated that the DNA methylation signatures of meningiomas, the most common primary brain tumor in adults, are not only diagnostic, but also uniquely prognostic. We therefore propose use of a novel technique: cell-free methylated DNA immunoprecipitation with deep sequencing (cfMeDIPseq) to non-invasively capture the methylome of meningioma patients within their plasma for both prognostication and prediction of treatment response to radiotherapy (RT).

Methodology: Plasma and tumour collection of patient samples was approved by the UHN Research Ethics Board (CAPCR 18-5820). Two hundred plasma samples from meningioma patients with matched tumor methylation data will be split evenly into meningiomas at high-risk and low-risk for recurrence based on clinical data and their tumour methylome, and into a discovery and validation cohort. Tumours within this cohort that received RT will also be similarly split in a RT-sensitive and RT-resistant group. We will perform cfMeDIP-seq on plasma samples and use differentially methylated regions comparing high- and low-risk meningiomas as well as RT-sensitive and RT-resistant meningiomas to train a machine-learning model to predict recurrence risk and response to RT using plasma signatures. Model performance will be evaluated 50-fold and validated in an independent testing cohort not utilized for training.

Anticipated Results: We anticipate the methylome of meningiomas, which predicts biological behavior in tumour tissue, will be recapitulated in plasma and can be leveraged for non-invasive prognosis. Conclusion: Success in this proposal will represent a paradigm shift in meningioma treatment by providing clinicians and patients with information that could dramatically alter management, followup, and surgical planning through a simple blood test.

Is this project remote-capable (in case of new restrictions) or have an alternative remote option?
☐ Yes, remote capable  ☒ No
☐ Yes, alternate remote option. Please specify (100 words max): Click or tap here to enter text.

If human subjects are involved, have the appropriate Research Ethics Board approvals been obtained?
☒ Yes  ☐ No  ☐ Not Applicable

If yes, please list the application submission date:

Do you expect this work will be published?
Research Environment and Student Roles and Responsibilities

Please be specific as possible. Please describe the research environment, including availability of required facilities/equipment/expertise, supervisor’s experience and mentorship plans. Please clearly outline the student role(s) and responsibilities related to the project, potential educational value, and indicate who will serve as the student’s direct report for daily oversight (PI, PHD student, technician, etc.). Maximum 300 words.

Dr. Zadeh’s research laboratory is on the 4th floor of the Princess Margaret Cancer Research Tower (PMCRT) which is affiliated with the University Health Network (UHN) in Toronto, Canada with active institutional certification for chemical and biological safety. There are 20 members, including but not limited to a junior research technician, animal technician, lab manager, PhD students, research associates, and scientific affiliates together with a team of bioinformaticians and computational scientists. Members of the laboratory are trained and qualified on wet lab safety protocols and procedures, biohazard safety, personal protective use, and safe operation of all lab equipment. The approximate 2500 square feet of laboratory space contains 10 rows of wet lab benches, each with 4 stations which are 1.5m in length. Half of these stations house lab equipment and the remaining stations are dedicated work benches for lab members. Additional rooms are dedicated to cell culture, microscope use, and -80°C freezer storage. Our team and facilities encompass a wide range of expertise in molecular techniques, equipment to conduct the requisite studies, tissue culture, and animal study resources together with expert bioinformatic and computational scientists with experience in the requisite data analysis. Students on this project will be expected to learn and eventually independently perform active wetlab experiments, perform clinical data extraction, learn and perform basic data analysis and bioinformatics, and become familiarized with basic genomic techniques in the lab such as DNA extraction, RNA extraction, DNA bisulfite conversion, cfMeDIP-seq, etc. and eventually prepare a scientific manuscript for publication. Daily oversight for the medical student will be the responsibility of an assigned PhD students/neurosurgery resident in the laboratory who will train, supervise, and mentor the student over the course of the summer and beyond. Progress will also be assessed by the PI in lab meetings twice per week.