UNDERGRADUATE SUMMER RESEARCH AWARD PROJECT DESCRIPTIONS
2019 - 2020
Project Title: Understanding psychiatric comorbidity in chronic immunoinflammatory diseases using genomics and epidemiology

Short Description of Research (250 words maximum):
Chronic immune-mediated inflammatory diseases (IMID), such as inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis, affect around 5% of Canadians. These conditions have a particularly high prevalence in Canada and are characterised by acute exacerbations and progressive disability. Management of these diseases involves immuno-modulatory and immunosuppressive drug therapies, although each disease may require unique drugs. The treatment goal for each disease is remission as these diseases are incurable. We aim to improve the understanding of the high burden of depression and anxiety in chronic IMID by investigating the biological susceptibility factors (polygenic risk scores) and clinical or demographic factors that contribute to psychiatric comorbidity in IMID. We expect to gain knowledge about how genetic variation mediates the risk of psychiatric comorbidities in IMID which may help to explain the higher prevalence of psychiatric disorders in IMID.

PI Name
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**Project Title:**
**Nanotechnology: The cutting-edge technology for Tumour targeting**

Short Description of Research (250 words maximum):
Nanotechnology is a cutting-edge branch of science that currently receives a lot of attention from researchers in the pharmaceutical and biomedical fields. Nanoparticles (engineered particles in the nanometer size range) have excellent potential for tumour targeting based on their unique physical and chemical properties. During this summer research project, the student will design a series of nanoparticles and characterize them. Nanoparticles will be decorated with specific legends to target fetus as evaluated by in vitro tumour cell models.

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**Project Title:**
**The activity and inhibition of DOT1L for the treatment of leukemia**

Short Description of Research (250 words maximum):
Mixed Lineage Leukemia is a childhood cancer that is difficult to treat and has a poor prognosis. It is caused by overexpression of the oncogene Homeobox protein A9 (HOXA9). The lysine methyltransferase (KMT) DOT1L methylates histone H3 at K79 (H3K79Me) in the HOXA9 promoter increasing its expression. Studies have shown that decreasing HOXA9 expression is sufficient to treat the disease. Inhibitors of DOT1L also reduce HOXA9 expression and are in clinical trials as a treatment for mixed lineage leukemia, however, initial results show that they have poor efficacy and dose limiting toxicities. DOT1L is active at multiple promoters, and we have shown that DOT1L inhibitors and drugs targeting epigenetic enzymes in general, alter the expression of many genes, likely leading to decreased efficacy and off-target effects. Therefore, to improve their efficacy and decrease adverse effects, DOT1L inhibitors should be targeted to the HOXA9 promoter. In this project the student will recombinantly express and purify DOT1L, and then measure its activity and inhibition in vitro using liquid chromatography tandem mass spectrometry (LC-MS/MS). Inhibitors in various phases of clinical trials will be tested in addition to broad spectrum methyltransferase inhibitors. The results will assist in the development of new inhibitors of DOT1L that are gene specific. Such inhibitors will be a new class of therapeutic for the treatment of Mixed Lineage Leukemia that will be more effective, while reducing required dose and toxicity compared to conventional DOT1L inhibitors.

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**Project Title:**
**New strategies to preserve insulin producing beta cells in diabetic patients**

Short Description of Research (250 words maximum):
Diabetes is the most common endocrine disorder worldwide. Two major types of diabetes are Type 1 (T1D; Juvenile onset) and type 2 (T2D; adult onset) diabetes. In both types of diabetes pancreatic islet beta cells fail to produce enough insulin leading to elevated blood glucose but the underlying mechanisms are different. Beta cell dysfunction and impaired insulin action in the peripheral tissues are two key events in T2D. Patients with T2D need glucose lowering drugs and eventually insulin treatment. In T1D patients, beta cells are destroyed by the body’s immune system leading to lifelong insulin therapy. Islet transplantation has provided a feasible approach for treatment of T1D but is currently limited by available donors and long-term survival of transplanted islets.

Formation of toxic protein aggregates, named islet amyloid, in patients with T2D and transplanted islets contributes to beta-cell death in both conditions. Studies in our group focus on exploring the mechanisms by which amyloid causes beta-cell death in order to develop new pharmacological strategies to protect islet beta cells from amyloid toxicity in T2D and prolong islet graft survival in patients with T1D. Students who join our research group will learn how to culture islets, prepare tissue sections, immunolabel live and fixed cells/tissues, and use imaging techniques. Students will also develop problem-solving, data analysis, and presentation skills by participating in our regular lab meetings.
**Brain pericyte calcium signaling and blood flow control**

Short Description of Research (250 words maximum):

Pericytes are cells found on brain capillaries. Exciting new evidence suggests that pericytes may regulate the blood-brain-barrier and dilate capillaries to increase blood flow where needed. Both of these roles are essential for brain health and pericytes may become dysfunctional or die during disease, such as stroke or Alzheimer’s disease. Our research focuses on calcium signalling in pericytes, which is likely important for regulating blood flow. We want to know: what causes calcium signals in pericytes? What happens as a result of these signals? These questions are fundamental for understanding pericyte physiology and their role in the brain. This work may also lead to future development of pericyte-specific drugs for therapeutic use. Students who join our energetic team will have the opportunity to work directly with mice, including mouse handling, training, and injections. Students will also learn two-photon microscopy, the latest, state-of-the-art microscopy technique in neuroscience. They will use this microscope to record movies of beautiful, never-before-seen calcium signals in pericytes in the brains of live mice in real-time. Students will also gain valuable computer skills by learning to analyze these calcium movies through programs such as MATLAB and R. Students will also develop communication and problem-solving skills by participating in regular lab meetings in a group setting.

**Synthesis of anticancer agents targeting topoisomerase I**

Short Description of Research (250 words maximum):

My group is in the process of preparing to file a patent for a series of anticancer agents with the assistance of a patent agent and the University of Manitoba Technology Transfer Office. I have been instructed not to disclose the general structure of the molecules to be patented; however, I can provide a brief overview of the project below. The summer student will synthesize new analogs relating to this patent application and assist in the study of the anticancer properties of the compounds using various biochemical assays. This is a medicinal chemistry project where the student will synthesize new molecules on a daily basis, and assist in the testing of their anticancer properties with the help of a doctoral student. Additionally, the student may also perform some in vitro cell based assays, following proper training. Overall, the student will spend the summer making new anticancer molecules relating to our provisional patent that will lead to the development of next generation topoisomerase I inhibitors (an approved class of anticancer agents).

**Antiepileptic drugs safety during pregnancy**

Short Description of Research (250 words maximum):

Epilepsy in pregnant women causes frequent seizures, increasing the risk of pregnancy-related complications. Antiepileptic drugs (AEDs) are prescribed to reduce the severity of epilepsy or help manage other conditions such as pain, psychiatric disorders, and migraine. Women taking AEDs – especially first-generation – have a greater risk of miscarriage and teratogenicity, because these agents can be transferred to the fetus via the placenta. The use of many first-generation AEDs (e.g. valproate) in pregnant women has been studied extensively. Several large-scale pregnancy registries were established to evaluate the safety of first- and newer-generation AEDs (e.g. topiramate and gabapentin). A major limitation of existing studies is the challenge in separating the effects of medications exposure from the effects of maternal illness itself. In addition, few studies to date have investigated the impact of AEDs exposure on long-term neurodevelopmental disorders and these have found conflicting results. Importantly, little is known about the comparative safety of antiepileptic treatment regimens, and previous studies comparing multiple AEDs are often small and underpowered. This project aims to examine the comparative safety of antiepileptic treatment regimens during pregnancy on short and long-term outcomes in newborns and children in Canada. A series of investigative studies will be conducted, including scoping and systematic reviews and cohort studies using administrative health data. This project aims to provide clinically relevant evidence that improves prescribing standards for pregnant women and facilitate evidence-based decision-making by health professionals and policy makers.