Comprehensive Research Experience for Medical Students  
Summer Research Program 2021  
Supervisor/Project Information Form  

*Due February 24, 2021 by email to crems.programs@utoronto.ca*

**Supervisor Name:** Nathan Kolla, MD, PhD, FRCPC

**Project Title:** Investigating the Endocannabinoid System in Major Depressive Disorder: An [11C]CURB Positron Emission Tomography Brain Imaging Study

**Hospital/Research Institution:** Centre for Addiction and Mental Health

**Email:** nathan.kolla@camh.ca

**Field of Research (2 keywords):** brain imaging; major depressive disorder

**Department:** Psychiatry; Pharmacology and Toxicology

**School of Graduate Studies Appointment (IMS, LMP, IHPME etc)? Yes/No:**

If YES, please name: Yes – IMS (full appointment)
Major depressive disorder (MDD) is one of the leading causes of disability worldwide and one of the most prevalent psychiatric disorders, placing a large burden on society and healthcare costs. Clinically, MDD is characterized by symptoms such as depressed mood, anhedonia, feelings of guilt or worthlessness, disruptions in cognitive functioning, and self-harm or suicide. It is widely acknowledged that MDD is a heterogeneous condition, and approximately 50% of individuals with MDD do not respond to first-line treatments, which primarily target monoamines. This observation has turned the focus from the traditional monoamine hypothesis of depression to other neurochemical systems, such as the endocannabinoid system (ECS), which may not be targeted by first-line treatments, including selective serotonin reuptake inhibitors.

The ECS is composed of unique receptors, enzymes, and endogenous cannabinoids (e.g., endocannabinoids) that control a wide variety of physiological functions, including mood and cognition. Fatty acid amide hydrolase (FAAH) is a key enzyme that degrades anandamide (AEA), an endocannabinoid. AEA binds to cannabinoid receptors to stimulate neurotransmission and regulate mood. Thus, FAAH indirectly controls endocannabinoid neurotransmission and regulation of mood, affect, and cognition. A plethora of animal research has revealed that increased levels of FAAH in affect-modulate regions, such as the prefrontal cortex, hippocampus, and striatum, lead to depressed and anxious phenotypes. We, therefore, hypothesize that FAAH levels will be increased in these brain regions in patients with MDD.

Positron emission tomography is a brain imaging tool that is able to probe the living brain and offer insight into neurochemical underpinnings of different psychiatric disorders. At the Centre for Addiction and Mental Health, we have the only radiotracer in the world that is able to measure FAAH. For this experiment, we have been recruiting individuals with MDD and healthy controls who both undergo PET scanning to determine if levels of brain FAAH are different between groups. If brain FAAH levels are higher in MDD, this would provide incentive for testing FAAH inhibitors as potential new pharmacological treatments for MDD.

The prospective student will work alongside Dr. Kolla and the graduate student working on the project. The student will be interacting with depressed participants to better understand the phenomenology of MDD. The student will learn how to administer questionnaires and neuropsychological tests. The student will also learn the basics of brain imaging data processing techniques. The experience can be tailored for either a remote experience or an in-person experience or a combination of the two. Previous CREMS students have enjoyed working on brain imaging studies with me and they have been co-authors on the resulting papers.