

## 2021-2022 Discovery Fund Accelerator Competition

**Awardee:** Dr. Fang Liu

**Title:** Testing the therapeutic effect of small molecule compounds in a mouse model for multiple sclerosis

**Abstract:** Multiple sclerosis (MS) is a demyelinating disease affecting young adults. It remains a significant therapeutic challenge and a major unmet medical need. Current medications can only mitigate symptoms but offer no cure, as they do not target the affected neurons or reduce long-term neurodegeneration. The need for drugs which act via a novel mechanism is further emphasised by the fact that most existing drugs are only effective for the treatment of the 55% of patients suffering from the relapsing-remitting form of MS (RRMS). There is very limited treatment available for the ~70% of RRMS patients who go on to have the primary and secondary progressive forms of MS. Recently, we have developed three novel small molecule lead candidates that have passed vigorous in vitro and in vivo preclinical screening. These lead candidates target and disrupt the interaction between GluR2 subunit of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and GAPDH (glyceraldehyde-3-phosphate dehydrogenase). They are able to dramatically reverse both the neurological and histological abnormalities in the most commonly used preclinical model for MS. The pharmacodynamics and pharmacokinetics properties are optimized for better half-life, better brain exposure, higher volume distribution and lower clearance. Therefore, this project has attracted lots of attention from industry partners. Most of the industry partners have required us to test our lead candidates in a second preclinical model before they will invest in this project. Thus, the specific aim of this proposal is to evaluate the effect of our novel small molecule compounds in the cuprizone demyelination mouse model.

**Awardee:** Principal Investigator – Dr. Etienne Sibille and Co-Investigator – Dr. Thomas Prévôt

**Title:** Determine Drug-like Parameters of Novel Compounds with Pro-Cognitive Efficacies

**Abstract:** Cognitive deficits (memory, attention, decision making) are prevalent in psychiatric and age-related brain disorders, contribute significantly to the burden of these diseases, worsen over time and are not treated by any pharmacological agents. These unmet clinical needs translate into chronic life-long conditions and in billions of dollars in health care costs and lost productivity. Cognitive deficits are due to lost connections between brain cells. We have identified a biological pathway that contributes to brain cell connections and that is affected in depression, aging and Alzheimer's disease. Our group has developed small drug-like molecules that are orally available, safe, easy to manufacture, and that selectively activate this pathway. Administration of our lead molecule restores brain cell connections and reverses cognitive deficits induced by chronic stress or aging in preclinical models. This proposal will characterize a series of novel molecules that we derived from the lead molecule. This effort will guarantee that the clinical development of this novel first-in-kind procognitive therapeutic does not rely on a single molecule, a current limitation to establishing external collaborations and partnerships. Specifically, we will determine the drug-like properties (e.g., selectivity, access to the brain, lack of toxicity) of ten newly-synthesized molecules that are chemically related to our lead molecule and that show significant procognitive efficacy in behavioural screens. These activities will increase the value of the academic asset and augment the probability of successful

bench-to-clinic translation for a first-in-kind treatment to help millions of people with various memory and other cognitive problems across the lifespan.

**Awardee:** Dr. Bruce G. Pollock – Principal Investigator Dr. Jose Nobrega, PhD – Co-Principal Investigator Dr. Tarek K. Rajji, MD – Co-Principal Investigator

**Title:** Validation of a new calcium fluorescence assay for quantification of agonist and antagonist Cholinergic activity

**Abstract:** On average, those over age 65 take five prescription medications in addition to over-the-counter drugs each of which has antimuscarinic effects. This cumulative anticholinergic burden has been associated with deleterious effects on cognition including delirium, particularly in those with underlying brain disorders. Anticholinergic effects on cognition have also been found to affect younger individuals suffering from schizophrenia. While these concerns have existed for many years, there is no widely available method for assessing total anticholinergic burden. An older assay depended on the dissection of rat cortices and required displacement of radioactive atropine. We have developed a new approach for quantifying anticholinergic activity in blood samples, which we believe will prove to be more reliable and commercially “packageable.” This approach based on cloned M1 receptor-driven mobilization of intracellular calcium stores provides a true functional index of both agonist and antagonist effects of medications. Moreover, by relying on fluorescence rather than radioactivity, the assay will be considerably more accessible for commercial laboratories. We propose to leverage our Brain Canada project in which we have already conducted comprehensive neuropsychological assessments in 311 older subjects with depression or complaints of mild cognitive impairment where serum samples have already been obtained to validate our assay in a clinically relevant population. Linear regression will be used to assess the relationships between the cholinergic measures and executive function controlling for age, gender, education and diagnosis. Validation of this novel assay will make it of considerable interest to diagnostic companies.

#### **Awardees**

Sean Kidd, Ph.D., PI Lena Quilty, Ph.D., Co-I David Castle, M.D., M.Sc., Co-I Tony George, M.D., Co-I Matthew Sloan, M.D., M.Sc., Co-I Peter Selby MBBS, Co-I Jessica D’Arcey, M.Sc., Co-I Amos Adler, M.Sc., Collaborator Wenjia Zhou, M.H.I., Collaborator

**Title:** App for Independence-O (A4i-O) – Expanding a Validated Platform for Complex Behavioral Health to Address Opioid Use Disorder

**Abstract:** Opioid Use Disorder (OUD) represents a serious and persistent challenge to healthcare systems, with increased overdose deaths during the COVID-19 pandemic. We are also in a context where there are rapid advances in the development of digital health interventions and supports for mental health and addiction problems. However, technologies in this area have several limitations, including (i) their lacking a theoretical framework and features that capture the psychological processes underlying OUD and comorbid mental health challenges (vs focusing only on OUD symptoms); (ii) having yet to provide validated models that assist with optimizing pharmacotherapy engagement and dosing, (iii) limited use of co-design approaches with the individuals affected, and (iv) having limited, rigorous research to back up claims of effectiveness of digital interventions. This Discovery Fund proposal takes a validated digital health platform for complex behavioral health conditions that currently targets the schizophrenia spectrum (App for Independence – A4i) and modifies the platform to address

OUD (A4iO). A4i-O will be co-designed with individuals recovering from OUD and their primary supports, addiction medicine and psychiatry practitioners, and digital health experts, moving from beta development and testing to a proof-of-concept clinical trial. This study will provide evidence-derived tools to (i) reduce OUD-associated risks, (ii) enhance community functioning, and (iii) enhance communication with care providers. This strategy, built upon a CAMH-Industry Partner collaboration, will produce a digital therapeutic that can help address a global healthcare priority.

**Awardee:** Andreea Oliviana Diaconescu – Principal Investigator Dr. Juveria Zaheer - Co-Investigator

**Title:** Suicidality Statistical Modelling for Prevention and Clinical Intervention Evaluation (SUSPINE): Technology for Treatment Evaluation and Suicide Prevention

**Abstract:** Suicide is the second leading cause of death among young adults. Current clinical practice relies mainly on self-report measures and lacks objective tests for assessing suicide risk, resulting in a trial-and-error process for early interventions. To overcome this impasse, we propose SUSPINE, a mobile application that integrates mathematical models with behavioural assessments of active escape bias to classify causes of emerging suicide risk in real time. SUSPINE can provide a more objective and accurate way to assess suicide risk and can offer important insights into the associated brain mechanisms, paving the way for more individualized clinical interventions. SUSPINE combines computerized cognitive tasks with state-of-the-art computational models to probe specific stress and control-related mechanisms that are implicated in suicidality. The tasks are optimized for capturing cognitive and neurobiological markers of suicidal ideation, while the models act as a metaphorical microscope allowing us to peer into the underlying mechanisms. In this proposal, we aim to establish the clinical validity of SUSPINE in a large-scale behavioural study (N=200), which will allow us to identify and map suicidality subtypes to risk and treatment trajectories. In its final form, SUSPINE can be readily applicable in clinical practice, requiring minimal time and equipment. This unique combination of mathematical modelling and behavioural assessment may offer a breakthrough in understanding the key neuronal mechanisms of suicidality, thus enabling more individualized interventions. It would be the first model based application of this kind for suicidality, establishing Canada as a world leader in precision psychiatry for suicide prevention.