Brain Canada

2014 Multi-Investigator Research Initiative (MIRI) Funded Researchers

Understanding stress to improve mental health

Recent estimates indicate that 1 in 5 Canadians are affected annually by mood, anxiety and other mental illnesses. These issues are exacerbated by stress. This is important because an acute episode of stress is the most common trigger for breakthrough presentations of many mental illnesses, and when stress-related disorders are accounted for, over 40% of the population is affected by a mental health disorder at some time in their life. This pressing problem, bordering on crisis, requires immediate attention. Here we outline a transformative approach, built around a unique team, to understanding the neural mechanisms of stress and its impact on behaviour. These studies have the potential to advance new treatments for mental illness.

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Team Members: Stephanie Borgland, Matthew Hill, Quentin Pittman, Keith Sharkey

The Frontier Trial - Field Randomization of NA-1 Treatment in Early Responders

Stroke is a life threatening emergency caused by blocked arteries that affects 45,000 Canadians a year. Each hour a stroke is left untreated means brain cells are dying. The only emergency treatment we have is a clot busting agent that can re-open blocked arteries if given within 3-4.5 hours of the onset of stroke symptoms. Unfortunately only 5-11% of all Canadian stroke victims receive this treatment. If we could administer a treatment that could slow down or halt the damaging effects of stroke early after calling 911 it may improve outcomes. NA-1 is a drug developed by Canadian scientists which can be given to most stroke victims. This drug has been shown in the laboratory, in animals and in a small number of patients undergoing brain surgery, that it has the ability to reduce damage of a stroke and improve brain function. We are hopeful that moving the drug into the hands of the paramedics will enable the drug effect to begin early and to provide the protection the brain needs to endure a stroke and minimize the brain damage.

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Adolescent Mental Health

Most mental disorders begin in adolescence; however, there are many gaps in our understanding of youth mental health. Clinical and policy gaps arise from our current inability to predict, from amongst all youth who experience mild behavioural disturbances, who will go on to develop an illness, what that illness will be, and what can be done to change its course and prevent its worsening to a serious mental illness (SMI). Our overarching goals are (i) to be able to identify youth at risk before they develop a SMI so that intervention can begin as soon as possible and (ii) to understand the triggers of SMI. We will assess a wide range of clinical and psychosocial factors in order to develop prediction models that will help determine how these risk factors interact in predicting negative outcomes for youth.

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Stimulating Endogenous Regeneration of Photoreceptors as a Potential Cure for Blindness

Sight is the most precious sense, and patients suffering vision loss endure a devastating experience. Blindness often results from the gradual death of photoreceptors, the retinal cells that perceive light. Many researchers are attempting to replace lost cells through transplantation of stem cell-derived photoreceptors. However, integration of injected photoreceptors into the retina is extremely inefficient and the cost to derive photoreceptors from each patient would be considerable. Rather than injecting cells into the eye, we will harness the regenerative potential of cells already present in the retina. In fish, these cells regenerate the entire retina after damage, but this capacity is hindered in mammals. We will devise ways to reengage this ancient regenerative power to achieve retinal repair.

Team Members: Donald Weaver, Michel Cayouette, Gautam Awatramani, Philippe Monnier

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Biomarkers for Crossing the Translational Divide in Acute Spinal Cord Injury

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Each year, over 1,500 Canadians sustain an acute spinal cord injury (SCI), and join close to 40,000 across our nation living with one of the most physically and psychologically devastating of injuries. Unfortunately, none of the promising treatments that have emerged from animal models of SCI have demonstrated convincing neurologic benefit in human clinical trials. The inability to translate clinically effective treatments from animal models of acute SCI is likely attributable, in part, to biological differences between the human and animal condition. In this initiative, we will perform a parallel interrogation of cerebrospinal fluid and serum from both human patients with acute SCI and from a large animal (pig) model of SCI. Not only will this fundamentally enhance our basic understanding of the pathophysiology of acute human SCI, but it will also establish biomarkers of SCI and common biological outcomes between the human and animal SCI condition that will provide important translational linkages between the two.

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Modulating memory circuits: focal DBS treatments to improve medial temporal lobe function

Alzheimer's disease tends to affect the hippocampus and its input/output relay structures earlier and more severely than other brain regions. In a recent clinical trial, direct stimulation of the fornix – one of two main pathways to the hippocampus – reversed some of the effects associated with hippocampal deterioration in Alzheimer's patients. The same structures are subject to pathological synchrony in temporal-lobe epilepsy. The mechanisms of stimulation that might support memory function and proper neural synchrony are unknown. Our multi-investigator team will test memory using the stimulation paradigm, and test different locations and ways of delivering stimulation to improve memory function and 'good' synchronization. We will also test for imaging-based correlates of this change, which can be used in clinical populations. With this line of investigation, we aim to identify protocols that alleviate memory decline in individuals with Alzheimer's disease and alleviate the seizure propagation in temporal-lobe epilepsy.

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Neurobiological correlates of TMS

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Noninvasive brain stimulation is gaining acceptance as an alternate therapy for an increasing number of disorders, including major depression, schizophrenia, stroke and Parkinson's disease. A form of noninvasive brain stimulation called transcranial magnetic stimulation (TMS) is less invasive and safer as compared to other brain stimulation therapies; however, lack of knowledge of its basic mode(s) of action impairs the development of better, more effective stimulation paradigms. This project aims to create a generalizable framework that informs the understanding of the basic cellular processes induced by TMS. Importantly, we will provide safety data to further refine the use of TMS as a therapeutic option. Logically, our data will be key to improving stimulation protocols and in turn increase the clinical benefits of noninvasive brain stimulation for numerous individuals with neurologic or mood disorders.

Team Members: Lara Boyd, Martin McKeown, Martin Parent, John O'Kusky, Alex MacKay, Fidel Vila-Rodriguez

Distinct neuro-immune interactions drive sex differences in chronic pain

One of the most important advances in our understanding of chronic pain over the last decade or so is the realization that neurons are not the only cells in the central nervous system participating in the processing of pain signals. Immune-like "glial" cells (especially microglia and astrocytes), thought previously to play mere structural supporting roles, are now known to be active players in pain processing, containing and releasing key molecules that themselves represent excellent novel targets for the development of analgesic drugs. As is typical in pain research and biomedical research in general, virtually every one of the studies demonstrating the important role of these "neuro-immune" interactions between glial cells and neurons in the spinal cord was performed on male rats or mice. Our Team has now convincingly demonstrated that spinal cord microglia are not required for the development of chronic pain in female mice as they are in males. The proposed studies are designed to examine, systematically, the role of glial molecules in pain in female rodents and non-human primates.

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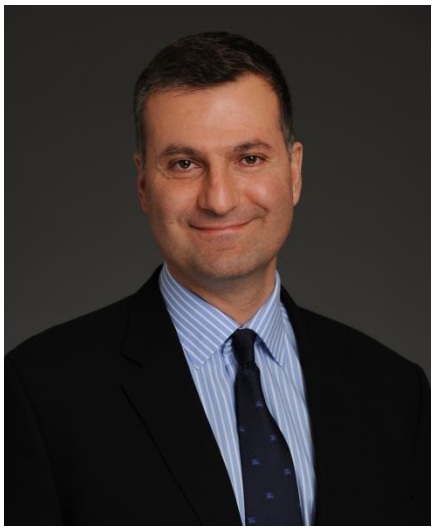
Canadian rTMS Treatment and Biomarker Network in Depression (CARTBIND) Trial



Zafiris Daskalakis
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Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for patients with depression who have not responded to antidepressant medications. rTMS involves stimulating the brain with a series of magnetic pulses delivered through a hand-held magnetic coil. Treatment duration is about 40 min and about 8-10 treatments per day can be administered. Recent studies have shown that a new type of rTMS - called intermittent theta-burst stimulation (iTBS) - can also be effective in treating depression. iTBS takes only 3 minutes to administer. For this proposal, we will conduct a clinical trial comparing standard rTMS to iTBS in 294 patients with medication resistant depression over a course of 20 treatment sessions. Understanding brain biology changes will help us to better predict which patients will or will not respond to rTMS treatment. Overall, this proposal will have 'real-world' impact by improving the efficiency of rTMS - one of the few established treatments in medication resistant depression - and by producing more personalized treatment approaches.

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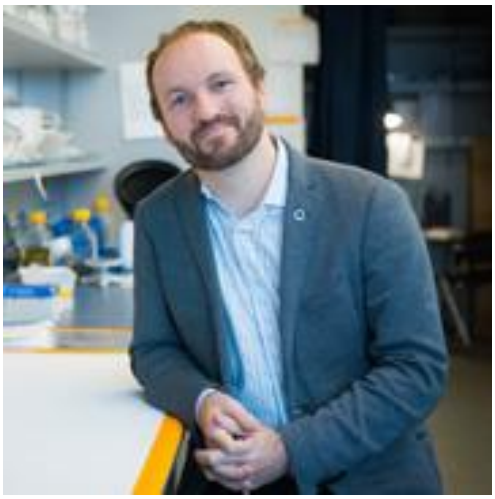
Locally produced brain insulin in memory and Alzheimer's disease: A multi-disciplinary approach to a key question

One percent of Alzheimer's disease is the early-onset type that runs in families. Extensive studies of these ultra-rare forms of Alzheimer's disease have revealed the genes that cause them. On the other hand, the most common forms of Alzheimer's disease are surprisingly understudied and poorly understood at the level required for therapeutic intervention. However, it is clear from population levels studies that there are important links between Alzheimer's disease and obesity, altered fat metabolism, diabetes and insulin. Interestingly, there have been many reports over the years that the brain actually produces a small amount of insulin. Here, we will test the hypothesis that insulin produced in the brain is a critical factor for the survival and function of brain cells in the context of both a genetic change that increases Alzheimer's risk and a diet that increases Alzheimer's risk. Our studies are likely to impact our understanding of Alzheimer's disease, potentially revealing a path to a cure.



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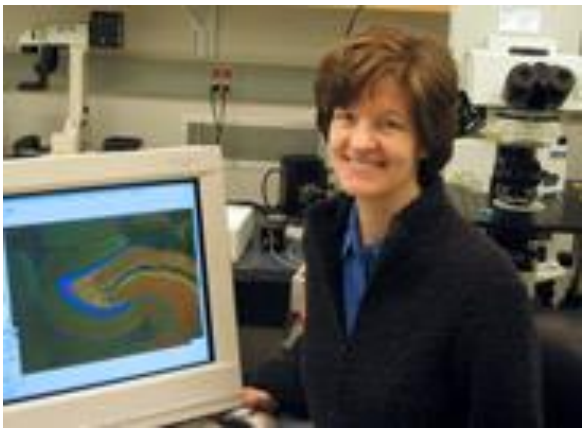
Targeting the Synaptic Pathway in Neurodevelopmental and Psychiatric Disorders



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Autism spectrum disorders are neurodevelopmental disorders characterized by deficits in social interaction, poor communication, and restricted, stereotyped patterns of behavior. Autism and schizophrenia affect over 1% of the population, and each has strong genetic associations with 60-90% heritability among twins. Recent research identified mutations in a shared genetic pathway in autism and schizophrenia, in genes that function to build synaptic connections between nerve cells, specifically in neurexin cell adhesion proteins and partners linked in a biochemical pathway. Here, we will study fundamental properties of the neurexin synaptic pathway in cell culture and animal models of autism. A major component of this research will be to test the efficacy of novel therapeutic agents for amelioration of behavioral and cellular phenotypes associated with the devastating consequences of these disorders. It is our belief that such in depth molecular studies based on the human genetics will ultimately lead to the most effective therapeutics for autism and schizophrenia.

Team Members: Michael Gordon, Timothy Murphy, Richard Brown

Targeting Amyloid Propagation in Alzheimer Disease: Structures, Immunology and Extracellular Vesicle Topology

A treatment or prevention of Alzheimer's disease is a top priority for medical science. Small aggregates of the protein amyloid-beta (A-beta), called oligomers, have been identified as being the primary cause of brain cell death in Alzheimer's disease. We have identified an amyloid-beta oligomer-specific targeting site, which exclusively detects amyloid-beta oligomers in the brains and spinal fluids of Alzheimer's disease patients. Since we only found amyloid-beta oligomers with our targeting site in the brains of Alzheimer's disease patients, it is possible that we have defined a targeting site specific to the amyloid-beta oligomers that cause disease. We will exploit this new knowledge and our unique tools to learn how toxic amyloid-beta oligomers spread from region-to-region in the brain causing disease. This knowledge is critical for the development of therapeutics to block the spread of neurodegeneration in the brain.

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Validation of Connexins and Pannexins as a target for Alzheimer's Disease

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Alzheimer's Disease (AD) is the most common cause of dementia, accounting for over two thirds of cases. There are currently no successful treatments, making the discovery of effective therapeutic interventions critical. The brain contains billions of neurons, and substantially more non-neuronal cells called glia; the major ones relevant to this proposal are astrocytes. While most therapeutic approaches target the neurons to prevent their death, this proposal focuses both on neurons and astrocytes to enhance their ability to protect neurons from death. We specifically propose to target a unique set of membrane channels, formed by connexins and pannexins, in astrocytes and neurons which modulate the extracellular environment in which the cells of the brain must function. The outcome of these studies will be the identification of unique new drugs which will not only directly target neurons but also enhance the astrocytes' abilities to protect neurons that are vulnerable to degeneration in AD.

Team Members: Weihong Song, Juan Saez, Christian Giaume, Luc Leybaert

Novel Retinal Biomarkers for Alzheimer's Disease

Detecting the beginning of Alzheimer's in an individual's brain in the early stages is difficult as the changes in behavior are subtle and hidden. Proper diagnosis is the key to successful treatment. Imaging can show that a brain is filled with a protein called amyloid, which accumulates beyond normal limits in Alzheimer's. However, brain imaging exams for amyloid are expensive, can be invasive, and not widely available. Some studies have suggested that amyloid also accumulates in the retina of individuals with Alzheimer's, but this has not been proven. We are proposing to develop a new retina imaging device using laser light that can show the presence of amyloid in the retina. Our work could lead to an inexpensive, non-invasive and widely deployable retina exam that could be used to screen individuals on a regular basis for the earliest signs of amyloid in the retina indicative of Alzheimer's.

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Preclincal development of a disease modifying small molecule therapy for Alzheimer disease

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No medications exist that can stop or even slow the progression for Alzheimer Disease (AD). The two pathological hallmarks of AD are protein aggregates deposited in the brain that are known as tangles and plaques. These aggregates form from inappropriately modified forms of the microtubule associated protein tau and peptide fragments, known as Aβ which are generated by cleavage of the amyloid precursor protein (APP). We have recently pioneered a new potential approach that has been shown to block disease progression in animal models of AD by blocking the toxicity of both of Aβ and tau. Our approach centers on a specialized sugar unit that is found attached to nuclear and cytoplasmic proteins, including both tau and APP. Our multidisciplinary team now aims to address the key remaining challenges that would clear the way for a promising new therapeutic target to advance to the clinic. These findings will enable the rapid advance of these optimized molecules into formal toxicology studies and downstream trials.

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