2025 NAVIGATOR RESEARCH PROGRAM: RECIPIENT BIOS AND RESEARCH SUMMARIES

Dr. Blair R. Leavitt

University of British Columbia

Dr. Blair Leavitt is a full Professor in the Department of Medical Genetics & the Department of Medicine, Division of Neurology (Associate) at the University of British Columbia. Dr. Leavitt completed his medical degree at McGill, medical internship at Columbia-Presbyterian, and neurology residency at Cornell and Harvard. While in Boston, he completed a basic neuroscience research fellowship at Harvard Medical School and the Children's Hospital of Boston.

Blair is a consulting neurologist and Director of Research at the UBC Centre for Huntington's Disease. A scientist and physician, Dr. Leavitt's time (both clinical and research) is dedicated to developing new treatments for genetic brain disorders such as Huntington's disease. He also works on other neurodegenerative diseases, including amyotrophic lateral sclerosis and frontotemporal dementia. Dr. Leavitt is currently the Director of the CMMT Transgenic Animal Facility and a founding Editor-in-Chief of The Journal of Huntington's Disease. Dr. Leavitt previously received the HSC Navigator award in 2011, 2015, and 2021. His 2021 project titled "Design and evaluation of an epigenetic therapeutic strategy for Huntington's disease treatment" set the groundwork and mapped out the strategy used in his application this year.

Research Project Title: ***Targeted DNA methylation editing to ameliorate Huntington's disease phenotypes in human induced pluripotent stem cells***

Lay Summary: Huntington's disease (HD) is a brain disorder caused by a single, specific mutation in the DNA sequence of the huntingtin gene (HTT). This mutation produces an abnormal, toxic mutant huntingtin protein (mHTT) that causes a progressive loss of cells in the brain and leads to the development of HD symptoms. Many factors, including naturally occurring chemical modifications of DNA, impact levels of mHTT. In turn, mHTT levels affect the onset, progression, and severity of HD patient symptoms. One type of chemical DNA modification, called DNA methylation (DNAm), alters the activity of HTT in brain cells and may affect the loss of brain cells that occurs in HD. In this proposal, we will alter DNAm at HTT to selectively reduce the quantity of toxic mHTT protein produced from HTT, and we will evaluate how lowering toxic mHTT using this approach improves the health of cells carrying the HD mutation. These studies will use specialized human cells highly similar to the brain cells affected in HD, enabling accurate assessment of how altering HTT DNAm improves cellular HD symptoms. This work will increase our understanding of the impact of DNAm levels on toxic mHTT abundance and measure how altering DNAm levels at HTT improves cellular HD symptoms, and will evaluate the utility of altering DNAm as a novel approach for therapeutic mHTT lowering in HD.

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Dr. J. Alex Parker

Centre Hospitalier de l'Université de Montréal

(Co-investigator: Dr. Takehiko Sasaki, Tokyo Medical & Dental University)

J. Alex Parker, PhD, earned his doctorate at the University of British Columbia, Vancouver, and has a broad background in genetics, with specific training and expertise in neuroscience, science of aging, and hereditary diseases. As a postdoctoral fellow at INSERM (France), he constructed some of the first C. elegans models for polyglutamine toxicity and identified the sirtuins as therapeutic targets for neurodegenerative disorders.

Upon establishing his laboratory at the University of Montréal, Dr. Parker expanded his research to include amyotrophic lateral sclerosis. As principal investigator or co-investigator on several previous ALS Canada, Canadian Institutes for Health Research, and Muscular Dystrophy Association-funded grants, he developed a second-generation chemical genetic platform with C. elegans that reduces screening time from days to a number of hours. Dr. Parker's knowledge in the field of neurodegeneration and experiences in neuroscience is uniquely suited to make significant contributions to understand Huntington's disease. This will be Dr. Parker's first funding award from the Huntington Society of Canada.

Research Project Title: *Stimulation of Axonal Regeneration and Repair in Huntington's Disease*

Lay Summary: Huntington's disease (HD) is a neurodegenerative disorder marked by progressive motor dysfunction, cognitive decline, and early death. Despite advances in understanding its genetic basis, effective therapies are limited. Current efforts mainly focus on reducing mutant huntingtin (HTT) levels, but axonal degeneration, a key factor in neurodegeneration, remains inadequately addressed. Our project aims to validate SAC2/INPP5F as a novel therapeutic target for HD. SAC2, a lipid phosphatase involved in regulating endosomal dynamics and the PTEN/PI3K/mTOR pathway, shows promise in ALS research for maintaining axonal integrity. In ALS models, including C. elegans and zebrafish, SAC2 knockdown has been shown to provide protection against axonal degeneration and motor dysfunction. We have observed these protective effects in our ALS models. Additionally, other research teams have found that SAC2 knockout (KO) induces highly potent axonal regeneration phenotypes in human cellular axotomy models. Preliminary data from our research using htt-1 KO and PolyQ Huntington C. elegans models also indicate that SAC2 knockdown reduces axonal degeneration and enhances neuronal integrity. Our approach aims to stimulate axonal regeneration and repair mechanisms in models of HD, translating our promising ALS findings to HD and paving the way for new therapeutic strategies. By targeting SAC2, we aim to enhance existing gene therapies designed to reduce mutant HTT, offering a new strategy for preserving neuronal function in HD. This proposal seeks to validate SAC2 as a therapeutic target in HD and to develop small-molecule inhibitors and antisense oligonucleotides (ASOs) as potential therapeutic candidates.

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Dr. Lynn A. Raymond

University of British Columbia

(Co-investigator: Dr. Timothy H. Murphy, University of British Columbia)

Dr. Lynn Raymond is the Director of the Djavad Mowafaghian Centre for Brain Health. She is also a Professor in the Department of Psychiatry, the Louise A. Brown Chair in Neuroscience, and Clinic Director of the Centre for Huntington Disease. Dr. Raymond is an internationally renowned neuroscientist and neurologist, and her work bridges foundational science and clinical research.

She has more than 170 publications, and her work has been cited more than 11,000 times. She has devoted her career to better understanding the specific roles of altered neuronal circuits and amino acid neurotransmitter receptors in Huntington disease, with the aim of developing disease-modifying therapy. Her work is funded by the Canadian Institutes of Health Research, the John Evans Leadership Fund, and she has held funding from a variety of not-for-profit organizations, including the Cure Huntington's Disease Initiative and Huntington Society of Canada. Dr. Raymond has previously received the HSC Navigator award in 2012, and more recently in 2017 for work entitled "Impaired corticostriatal synaptic plasticity in HD: Investigating a role for aberrant endocannabinoid signaling."

Research Project Title: *Neurofeedback-Driven Restoration of Cortical Connectivity in HD*

Lay Summary: Huntington disease (HD) is traditionally viewed as a disorder of the deep brain (the striatum), but mounting evidence shows that even before clear symptoms appear, HD alters how different parts of the brain communicate, particularly in motor regions. In HD mouse models, neurons in cortical motor areas not only lose connection with other regions but also activate in a disorganized manner, impairing movement control. In our study, we will first confirm these circuit changes and investigate whether and how they correlate with performance in a fine motor control task (pulling a lever for water reward). Then we will test two ways to help them "rewire" the affected motor area: one teaches mice to boost the correct brain signals by giving them water rewards whenever they succeed (neurofeedback training), and the other uses direct stimulation to trigger those same cells on a fixed schedule (optogenetic stimulation). By comparing these approaches, we hope to restore coordinated activity in the affected motor region in the cortex and improve the animal's performance on the motor task. If successful, this could lead to simple, noninvasive brain-training programs for people with early-stage HD.

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Dr. Aurélie de Rus Jacquet & Dr. Francesca Cicchetti

Université Laval

Aurélie de Rus Jacquet, PhD, is a researcher in the Neurosciences program of the CHU de Québec-Université Laval Research Center, and an assistant professor in the Department of Psychiatry and Neurosciences in the Faculty of Medicine at Université Laval. She obtained her PhD in Medicinal Chemistry and Molecular Pharmacology from Purdue University (USA) in 2016, during which she undertook an ethnopharmacological approach rooted in the valorization of First Peoples' knowledge and discovered neuroprotective botanicals that attenuated Parkinson's disease-related pathology. She then joined the Howard Hughes Medical Institute to train in the use of induced pluripotent stem cells (iPSCs) in the laboratory of Dr. Randall Moon (2016–2017, Institute for Stem Cell and Regenerative Medicine, University of Washington, USA). Subsequently, she completed two postdoctoral trainings on the neurobiology of Parkinson's disease with Dr. Erin O'Shea (2017–2020, Howard Hughes Medical Institute, USA), and with Dr. Francesca Cicchetti (2020–2023, Université Laval, Canada). Her work has highlighted the role of glial cells, and astrocytes in particular, in the progression of neurodegenerative disorders such as Parkinson's and Huntington's disease.

While Dr. de Rus Jacquet is an early-career researcher, the co-PI, **Dr. Cicchetti**, is a well-established veteran of Huntington disease research whose research has been awarded the HSC Navigator three times: in 2006 and 2009 for her work on graft survival in HD, and most recently in 2019 for a project titled "Targeting the blood brain barrier to treat HD." She is now a professor at the Department of Psychiatry and Neurosciences, Faculty of Medicine of Université Laval. Dr. Cicchetti has published over 100 manuscripts in high-impact journals, and three of her recent publications have been awarded most influential papers in the field of Huntington's disease by the Huntington Study Group. She is an active member of several scientific committees and editorial boards. Her research program aims to understand the prion-like properties of abnormal proteins associated with neurodegenerative diseases and to develop therapeutic strategies that would target this aspect of the pathophysiology. More recent work focuses on elucidating the impact of Parkinson's and Huntington's disease-related proteins and toxins on the functionality of the blood-brain barrier.

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Dr. Aurélie de Rus Jacquet & Dr. Francesca Cicchetti

Université Laval

Research Project Title: ***Brain rejuvenation: an innovative approach to Huntington's disease therapy***

Lay Summary: Huntington's disease (HD) is a neurodegenerative disorder caused by a single defective gene known as huntingtin (HTT). This disease is characterized by uncontrolled movements, a decline of thinking ability, as well as psychiatric problems. The life span of affected individuals is usually 10 to 30 years after the appearance of symptoms. In this disease, an abnormal form of a protein referred to as mutant Huntingtin (mHtt) accumulates in brain cells, disrupting their normal function and eventually leading to their death. Recently, the Cicchetti group utilized a model system called "parabiosis" in which mice are surgically sutured to create the joint circulatory system and has provided exciting new evidence showing reduced pathology in the diseased (HD) mice that were surgically paired to normal mice. This study demonstrated the involvement of circulating factors from healthy blood in diluting/ameliorating disease pathology. Building on this new data, we designed a project that aims to identify the beneficial elements contained in healthy blood and to understand how they ameliorate brain health. To achieve this goal, we will isolate human plasma proteins capable of migrating from the blood into the brain because they will likely be the most neuroprotective factors. We will then evaluate if these proteins improve the survival and function of neurons and non-neuronal cells in a dish but also in a mouse model of HD. This project will help us identify circulating factors in healthy plasma that may prevent the death of brain cells and that therefore could be useful in treating various disease features. Additionally, outcomes of this study may encourage the transfusion of healthy human plasma as a potential therapeutic strategy to treat HD.

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