Dr. J. Alex Parker

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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.