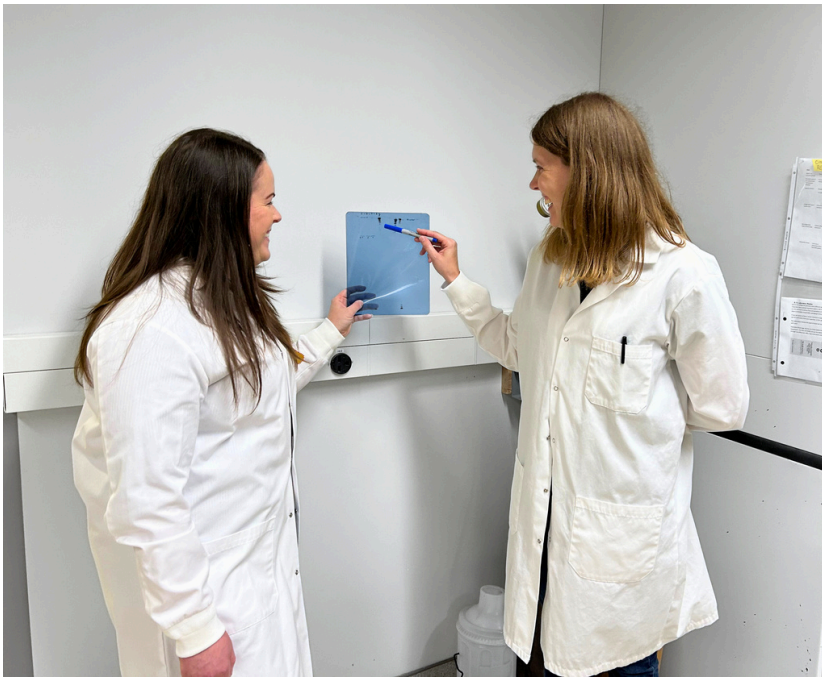
Huntington Society of Canada
HUNTINGTON
Société Huntington du Canada

HELIX

THE 2024 HSC RESEARCH REPORT
A NEW ERA IN HUNTINGTON DISEASE RESEARCH

Contents

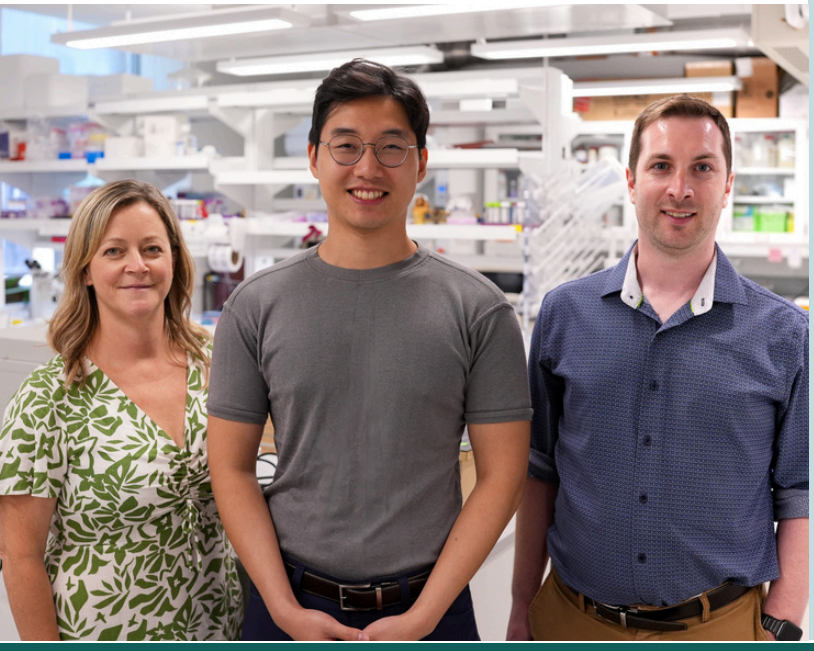


Community Note

A Year of Connection and Gratitude

This year, I had the privilege of attending several chapter events across the country, meeting and connecting with many of you. It was truly inspiring to witness the strength, resilience, and dedication that define the Huntington disease (HD) community. Every conversation I had and every story I heard reaffirmed how powerful your collective efforts are in supporting one another and pushing forward together.

I want to extend a heartfelt thank you to our incredible Chapter Presidents and the countless volunteers who dedicate their time and energy to organizing these events. Your leadership and commitment ensure that we have spaces to come together, share experiences, and offer support. It's a vital part of what keeps our community strong.



A special thank you also goes out to those of you who participate in HD research. Your willingness to contribute has a significant impact on our progress toward a significant treatment. By participating in clinical trials, sharing your experiences, or engaging in scientific studies, you help drive the research forward in ways that will continue to benefit the entire HD community for years to come.

To all the community members who come out to these events and fundraisers, thank you for your continued engagement and for helping to build a support system. Together, we can all make a real difference in the lives of those affected by Huntington disease, and I'm grateful for each of you. Let's continue to support one another and look ahead to what we can achieve as a community.

Alexander Maxan, PhD

Director of Research & Strategic Partnerships

Undergraduate Student Summer Fellowship

In 2023, we launched our inaugural Undergraduate Student Summer Fellowship that was met with encouraging interest and support. Thanks to Brain Canada for matching our funding this year, we were able to fund 7 fellowships that enabled young up-and-coming researchers to spend the summer working in HD research labs. Here are the 7 outstanding recipients for 2024:

Anthony Dang

University of Waterloo
Supervisor: Dale Martin

Project title: Computationally Driven Design and Biochemical Characterization of Improved APT1 Inhibitors as Therapeutics for the Treatment of Huntington Disease.

Ashleen Phandar

University of British Columbia
Supervisor: Michael Hayden

Project title: Characterization of HD Brain Tissues with Loss-of-Interruption (LOI) Modifier Variants.

Christiana Kennedy

Memorial University of Newfoundland
Supervisor: Matthew Parsons

Project title: Atypical NMDA receptors in HD.

Gabriel Gonzalez Vargas

University of Guelph
Supervisor: Melanie Alpaugh

Project title: Understanding the interactions between hypertension and Huntington disease.

Isabel Gibson

McMaster University
Supervisor: Ray Truant

Project title: Analysis of N6FFA levels in HD human cells and knockout lines by the use of immunofluorescence and expansion microscopy.

Jenni Nguyen

University of British Columbia
Supervisor: Mahmoud Pouladi

Project title: Investigating a putative modifier of HTT toxicity using cellular assays.

Mikaela Perron

University of Manitoba
Supervisor: Robert Beattie

Project title: Trace the origin of the somatic repeat instability-related cellular phenotype in HD.

Clinical Fellowship

As an organization, we want to ensure that each Canadian with HD receives appropriate medical expertise, treatment options, support services, and any other help needed. Supporting the training of the next generation of HD neurologists is an important part of our plan to ensure that these critical elements in the day-to-day management of HD are accessible and available. Our clinical fellowship program encourages more neurologists to have an HD practice in Canada.

The 2024 Neurology Fellowship recipient is Dr. Falen Fernandes.

Dr. Falen Fernandes
Neurology
University of Alberta

"Following the completion of my fellowship, I hope to give back to my community by working in those regions across our country where the need for Huntington Disease care is greatest."

- Dr. Falen Fernandes

We are excited to announce that in addition to a neurology fellow, we will also be supporting a neuropsychiatry fellow to play a part in expanding our options for multidisciplinary care across the country.

We are happy to introduce our 2025 Neuropsychiatry Fellowship recipient: Dr. Caroline Dance.

Dr. Caroline Dance
Neuropsychiatry
University of British Columbia

HSC Clinical Neurology Council

Dr. Mark Guttman

Neurologist

Toronto

Dr. Tiago Mestre

Neurologist & Associate Professor
Department of Medicine, Division of Neurology

University of Ottawa

Dr. Blair Leavitt

Neurologist & Professor
Department of Medical Genetics

University of British Columbia

Dr. Sylvain Chouinard

Neurologist & Clinical Assistant Professor

Université de Montréal

Dr. Oksana Suchowersky

Neurologist & Professor
Faculty of Medicine & Dentistry

University of Alberta

NAVIGATOR Research Program

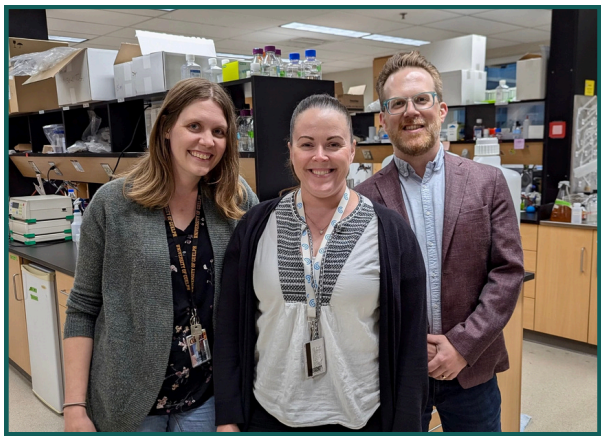
HSC's funding program is designed to support innovative, high-impact projects that advance the understanding of Huntington disease. The NAVIGATOR Program has been providing 2 years of funding to support HD researchers since 2003.

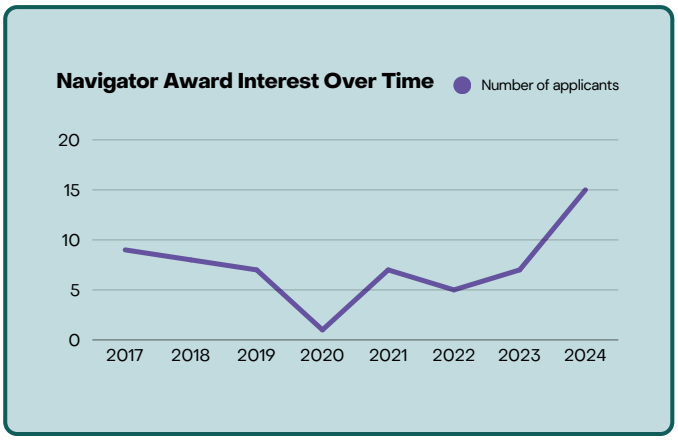
2023 Recipients

Chris Kay (University of British Columbia)
Michael Hayden (University of British Columbia)

Project Title: Determining the Role of Somatic Instability, RAN Translation, and RNA Toxicity as Mechanistic Drivers of CAG-CCG Modifier Variants in the HD Brain

Project Goal: Huntington disease (HD) is an inherited neurodegenerative disorder with onset typically in midlife. The cause of HD is an abnormally long stretch of repeated DNA in the huntingtin (HTT) gene. This abnormally long stretch of DNA, called the expanded CAG repeat, produces a toxic mutant protein. In brains of people with HD, the expanded repeat becomes especially long in neurons that are affected earliest in the disease. Dr. Hayden and Dr. Kay have recently shown that small variations in the DNA sequence of the CAG repeat and adjacent CCG repeat can change how early or how late someone develops HD, sometimes by more than a decade. They hypothesize that these CAG-CCG repeat variations may impact the rate of CAG repeat expansion or the resulting production of toxic mutant proteins in affected regions of the brain. This proposal aims to directly investigate the pathogenic effects of CAG-CCG variations in brain tissues from HD patients who have these variations and have early onset of disease. They will also investigate CAG repeat expansion and other hypothesized pathogenic mechanisms in neurons derived from HD patients to better understand how the CAG-CCG variations contribute to accelerated disease onset.

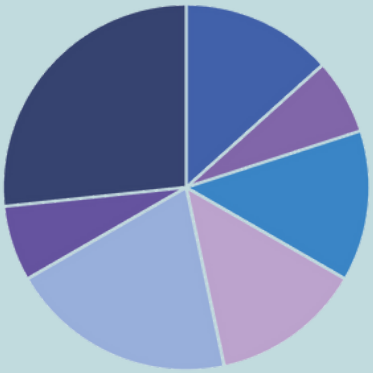




2024 Recipients: Shaun Sanders (University of Guelph), Dale Martin (University of Waterloo) and Melanie Alpaugh (University of Guelph)

Project title: DLK as a novel therapeutic target to treat Huntington Disease

Project Goal: This research project aims to explore a new potential treatment target for Huntington disease (HD) by focusing on a protein called DLK (Dual Leucine-zipper Kinase). DLK plays a key role in activating harmful signals in nerve cells when they are under stress or damaged. Previous studies have shown that blocking DLK can protect nerve cells and improve their connections in models of nerve injury. DLK has been linked to several other diseases that cause nerve damage, such as ALS, Alzheimer's, and Parkinson's, which has led to interest in developing drugs that inhibit DLK. However, its role in HD has not yet been studied. This project will examine whether blocking DLK can prevent nerve cell damage in HD by testing its effects in both mouse models and human nerve cells.



2024 Application Research Themes

- Neuroimaging (2)
- Cardiovascular (1)
- Epigenetic & Genetic Modifiers (2)
- Axonal Signaling & Therapeutic Strategies (2)
- Drug Development & Screening (3)
- Neuroinflammation & Brain Function (1)
- Protein Aggregation & Cellular Pathways (4)

Updates on Clinical Research

Current clinical strategies for HD include symptomatic therapies that aim to manage and alleviate the symptoms of the disease without altering its underlying progression. Disease-modifying trials such as huntingtin-lowering therapies target the root cause by reducing the production or activity of the mutant huntingtin protein, potentially slowing or halting disease progression. Both approaches are critical and several clinical trials this year tested the effectiveness of these strategies.

Symptomatic Treatment Trials

Sage Therapeutics announced topline results from its Phase 2 **SURVEYOR** Study, which demonstrated a statistically significant difference in cognitive function between healthy participants and those with HD using the HD-Cognitive Assessment Battery (HD-CAB) prior to treatment. The study highlighted the substantial cognitive impairment in HD, which often precedes motor symptoms, emphasizing the need for effective treatments. In the second phase, HD participants received dalzanemdor (SAGE-718) or placebo for 28 days. While the study wasn't powered to show significant cognitive differences, dalzanemdor was well-tolerated and exploratory analyses indicated potential positive effects on cognition and function. Sage plans to further analyze the data and release additional results from ongoing studies in late 2024. The only Canadian trial site is in Toronto.

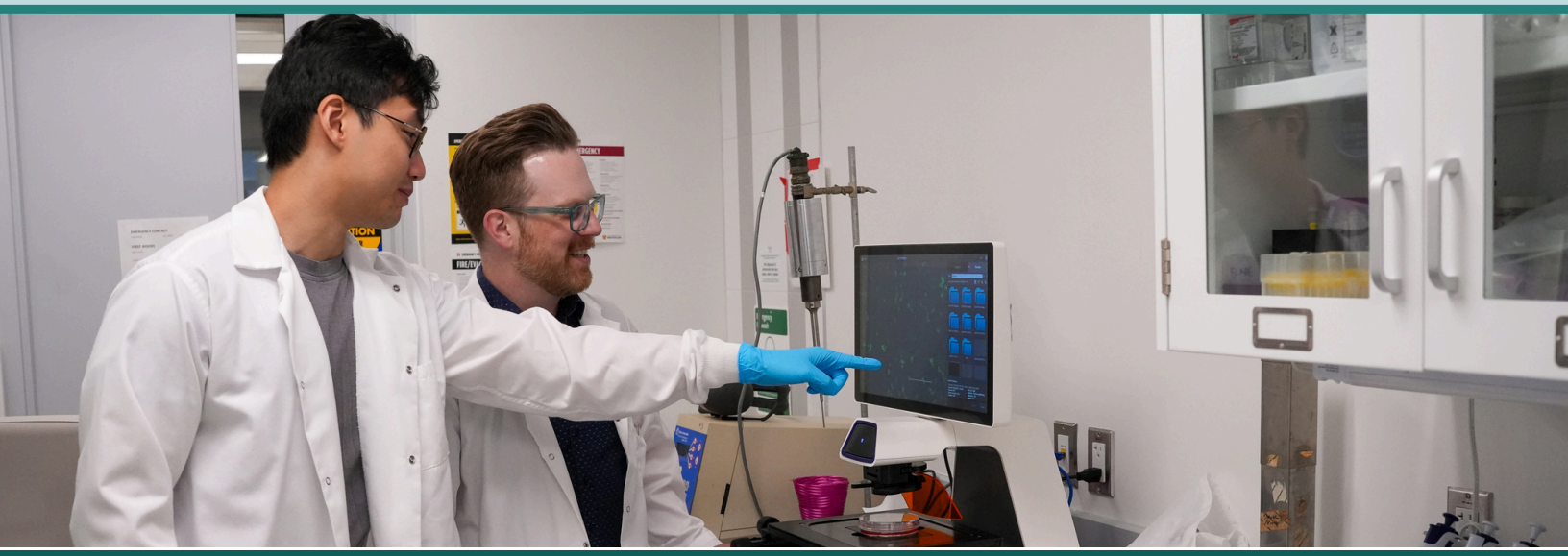
Prilenia Therapeutics announced the acceptance of its European Marketing Authorisation Application (MAA) for pridopidine, an oral sigma-1 receptor (S1R) agonist, as a potential treatment for adults with Huntington disease (HD). The European Medicines Agency's review of the application is expected to take 12-14 months. Previously, Prilenia ran the **PROOF-HD** Phase 3 trial, which started in 2020. Results of this trial were not encouraging as the trial failed to meet both the primary endpoint (improvement in day-to-day functioning) and secondary endpoint (overall assessment of HD severity) in the overall trial participation. This is the fourth trial of this drug that failed to meet primary endpoints. The drug was, however found to be safe and tolerable and Prilenia is currently exploring market approval options in Europe, while continuing conversations with North American regulatory agencies.

Disease-modifying Therapy Trials

Roche/Genentech is recruiting for the Phase 2 **Generation-HD2** trial to test **tominersen**, an antisense oligonucleotide (ASO), in people aged 25–50 with early HD symptoms. Following the Generation-HD1 study, enrollment is over 80% of the planned 300 participants and will test lower, less frequent dosing. Canadian sites include Edmonton and Montréal.

Wave Life Sciences reported results from its Phase 1b/2a **SELECT-HD** trial of **WVE-003**, an allele-selective ASO aiming to lower mutant huntingtin (mHTT) while preserving healthy wild-type huntingtin (wtHTT) in individuals with HD. Over 28 weeks, WVE-003 reduced mHTT levels in cerebrospinal fluid (CSF) by up to 46%, confirming a selective silencing mechanism. Canadian sites were in Edmonton, Ottawa, and Montréal. A larger study is being planned.

Vico Therapeutics shared positive interim data from its Phase 1/2a trial of **VO659**, an allele-preferential ASO targeting mHTT protein reduction in individuals with HD. Results showed a mean 28% mHTT reduction in cerebrospinal fluid by day 85, with effects seen as early as day 29. VO659 was safe and well-tolerated at 40 mg, with no significant changes in neurofilament light chain (Nfl, a key biomarker) levels. No Canadian trial sites are involved.



Disease-modifying Therapy Trials

uniQure's Phase I/II trial of **AMT-130**, a gene therapy for HD, has shown promising interim results in their **HD-GeneTRX-1** and **HD-GeneTRX-2** studies. AMT-130 is the first gene therapy for HD and is delivered via a one-time brain infusion. Data from 24 months revealed dose-dependent slowing of disease progression and reduced levels of Nfl (an inflammatory marker) in cerebrospinal fluid. Early results from the first few participants indicated about 50% lower huntingtin levels at 12 months after injection. They provided no updates on huntingtin-lowering or brain imaging. No Canadian trial sites are involved.

PTC Therapeutics conducted the Phase 2 **PIVOT-HD** trial to test an oral huntingtin-lowering therapy, **PTC-518**. Interim results show that PTC-518 reduced mHTT protein levels in both blood and CSF in individuals with Huntington disease. At 12 months, mHTT levels in the blood decreased by 22% and 43% at 5mg and 10mg doses, respectively, with similar dose-dependent reductions in CSF. The drug also showed favourable trends in slowing motor symptom progression, with less worsening compared to placebo. The only Canadian trial site is located in Ottawa.

Skyhawk Therapeutics updated on its Phase 1 trial of **SKY-0515**, an orally-administered small molecule targeting non-allele-specific HTT reduction. The trial in Australia initially tested SKY-0515 in non-HD participants with gradually increasing doses. Results show a dose-dependent HTT reduction, reaching around 72% at the highest 9mg dose. Next, Skyhawk will test HD gene carriers and aims to start a Phase 2 trial in early 2025. No Canadian sites are involved.

Working Towards Clinical Trials (not an exhaustive list)

Alnylam Pharmaceuticals is advancing a therapeutic pathway for Huntington disease based on RNA interference (RNAi) technology. Their lead candidate, ALN-HTT02, is designed to silence the mutant huntingtin gene by reducing its expression. This approach targets the root cause of Huntington disease by decreasing the production of the toxic huntingtin protein, which is implicated in disease progression. Pre-clinical models have shown promise in reducing huntingtin levels, and Alnylam is working towards bringing this therapy into clinical trials within the next few years.

Founded in 2019, **LoQus23 Therapeutics** has developed a suite of assays and a small molecule series of MutSα and MutSβ inhibitors with potential therapeutic applications for up to 30 triplet repeat disorders, including Huntington disease. By targeting somatic expansion, their approach aims to delay or stop the onset and progression of HD, supported by genetic studies and pre-clinical models. With Series A funding now secured, LoQus23 is advancing its lead program —an allosteric MutSβ inhibitor—through pre-clinical development, aiming for clinical trials by 2026.

HD-COPE

Together with the Huntington's Disease Society of America (HDSA), HSC co-organizes the Huntington's Disease Coalition for Patient Engagement (HD-COPE). This international group of volunteers from HD-affected families advises industry partners on the development of therapies for Huntington disease, ensuring that patient perspectives guide research and clinical advancements. Moving forward, we are eager to expand this group and welcome participation from community members who want their voices and experiences heard. If you are interested in contributing to the clinical development process, please reach out to us at research@huntingtonsociety.ca.

HSC Research Council

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HUNTINGTON SOCIETY OF CANADA

NATIONAL CONFERENCE 2025

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Huntington Society of Canada
HUNTINGTON
Société Huntington du Canada

Vision

A world free from Huntington disease

Mission

To improve the quality of life for those affected by Huntington disease

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