Huntington Society of Canada
HUNTINGTON
Société Huntington du Canada

HELIX

THE 2023 HSC RESEARCH REPORT

A New Era in Huntington Disease Research

Contents

Alexander Maxan, PhD

Director of Research & Strategic Partnerships

Community Note

Dear members of the Huntington disease community,

As we approach the end of another calendar year, I wanted to reflect on my first year with the Huntington Society of Canada (HSC) and introduce our new annual research report that I hope will illuminate some of the amazing advancements HSC and the Huntington disease (HD) research community have made over the past year. While we have made progress in our understanding of this disease and the development of potential treatments, we have also shown considerable growth as an organization in terms of our research offerings that we hope we can continue to expand for years to come.

As a community we have also endured some difficult news over the past few years, and it is important that we continue to lean on each other for support through the tough times as well. I hope you keep your heads held high, and your spirits resilient. Even though it may not always seem that way, every step we take is one in the right direction and we continue to learn from every research setback.

That is why I am asking each and every reader of this report to join us in a mission. Whether you are a researcher, clinician, or community member, there is a role for you to play in improving the lives of those affected by HD. I encourage you to get involved in any way that you can, whether it be through participating in studies, supporting research, raising awareness, or simply offering your time and support to those in need.

While the road ahead may be long and challenging, I am confident that by working together, we will ultimately be able to make a real difference in the lives and futures of those affected by Huntington disease. Thank you all for your support thus far. Please enjoy the first edition of HELIX: The HSC Research Report, as over the next few pages we highlight the research efforts made by Canadians, and others around the world in an effort to stand together against HD.

HSC Endowed Research Chair at Western University

With the goal to advance patient care outcomes and accelerate life-changing research in HD, Western University and HSC have partnered together to create what is called an endowed research chair that will pave the way for accelerated advances in HD research. The HSC Research Chair at the Schulich School of Medicine & Dentistry is a faculty position that will enable a world-class leader in neurodegenerative research to focus on finding new ways to prevent, identify and treat Huntington disease.

This position will also serve as a magnet for experienced and respected researchers, who are bringing with them a wealth of knowledge, expertise, and connections. By recruiting these individuals, we can expand our research capabilities, develop new research projects, and build our reputation as a research-funding leader in our field. In addition to these collaborations and researchers who will be working with the chair, we are also excited about the research assistants, postdoctoral fellows, PhD, master's and undergraduate students who will be thrilled to work alongside this prestigious chair and other researcher collaborators, helping to manage data, conduct literature reviews, and perform other essential research tasks. This role is expected to bring in several fresh faces who we will be able to target with our research funding initiatives while also profiling HD research efforts in Canada

Undergraduate Student Summer Fellowships

Rylee McDonald
I was a Bioengineering student at McGill University. My passion for biomedicine and design has flourished over the course of the degree. After learning about recent developments in the field of neuro-degenerative research in class, I became very interested in contributing to the field. In my research with Professor Adam Hendricks, we will work to uncover how mutations in the HTT huntingtin gene alter the constituents of the huntingtin transport complex and contribute to HD.

Etienne Sellar
Originally from Oakville, Ontario, I have recently earned my Honours BSc. degree majoring in Neuroscience at the University of Guelph. Thanks to the award this summer, I have the great pleasure of continuing to work under Dr. Alpaugh's supervision in the study of human blood brain barrier models. Specifically, we are looking at the proteins and types of cells involved in this barrier and how they change to form a less functional barrier in Huntington's disease models.

Developing the Next Generation of HD Researchers

We believe that by engaging the next generation of scientists we can make significant strides in understanding the disease and developing new treatments. This year, we launched an undergraduate research program. This program provides students with the opportunity to conduct hands-on research under the guidance of experienced faculty members. By doing so, students gain valuable experience in scientific inquiry, critical thinking, and problem-solving, while contributing to our understanding of Huntington disease. In 2023, HSC selected four researchers to receive this fellowship, jumpstarting their research endeavors through the study of HD pathology.

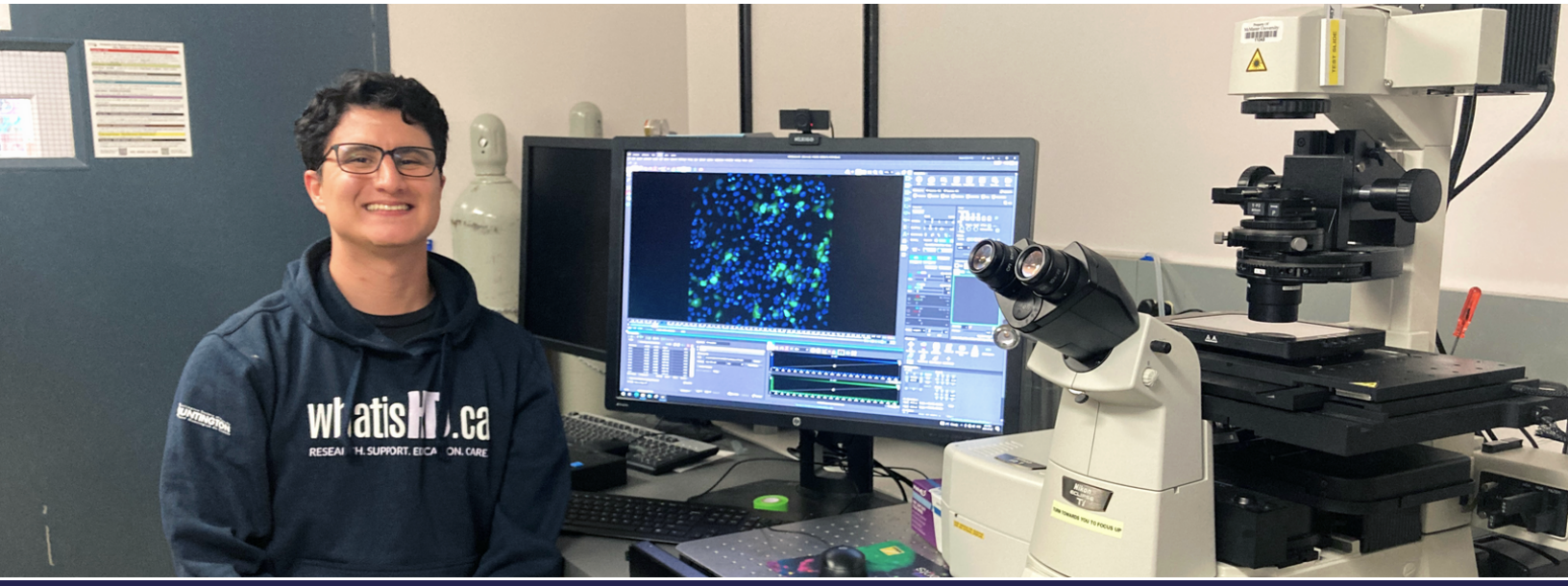
Undergraduate Student Summer Fellowships

Justin Alvarado

Hello HSC Community! I'm Justin Alvarado, a recent graduate of the Honours Biochemistry program at McMaster University. I completed my 4th-year thesis project in Dr. Truant's Lab, where I became enamoured with the drive and collaboration within our lab and the HD research community. I continue to work in Dr. Truant's Lab, where I will investigate the role of ATM kinase in HD and its therapeutic potential. I am extremely excited to get to work this summer and beyond grateful for the support from HSC.

Tess Leavitt

Hello everyone! My name is Tess Leavitt and I recently graduated from Queen's University with a Bachelor of Science in Kinesiology with honours. For the past two summers, I have worked as a student researcher at the Centre for Molecular Medicine and Therapeutics with a large focus on HD research, and I look forward to continuing this research this summer under the supervision of Dr. Michael Hayden at the University of British Columbia.



NAVIGATOR Research Program

The NAVIGATOR Program has been providing funding to support HD researchers since 2003.

2022 Recipient: Cheryl Arrowsmith, PhD
University of Toronto

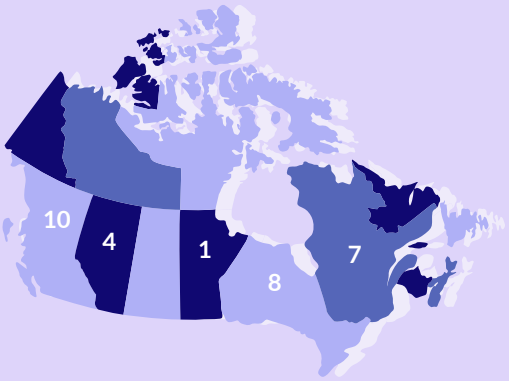
Project Title: HTT-RNA interaction dynamics as a target of therapeutic intervention

Project Goal: Evidence is accumulating for the role of the huntingtin protein in processes involving genetic material in our cells. Dr. Arrowsmith's lab has been able to show that huntingtin protein interacts with a certain type of genetic material, termed RNA, directly. They aim to identify the pathways by which huntingtin interacts with the specific RNAs and characterize them using a variety of biochemical and cellular methods. The lab has used cutting-edge microscopes to visualize huntingtin protein at high resolution, building on this work they want to now visualize how huntingtin protein interacts with specific RNAs. Their results will provide insight into how both normal and mutant huntingtin proteins interact with RNA in cells to regulate key processes involved in the health and HD-mediated death of neural cells. If the team can understand how these interactions occur, then they can develop strategies to avoid or rescue the effects of human huntingtin for potential treatment.

Our mission is to **improve the quality of life** for those affected by HD. One way we do this is by **investing in promising research like the NAVIGATOR Program.**

Where are NAVIGATOR Recipients Located?

A 20-Year Summary



NS: 1
NFLD: 1

NAVIGATOR Research Program

20
YEARS

32
AWARDS

15
INSTITUTIONS

19
RESEARCHERS

TOTAL AMOUNT AWARDED THROUGH NAVIGATOR FUND:

$4,393,205

2023 Recipients: Michael Hayden, MB, ChB, PhD, FRCP(C), FRSC & Chris Kay, PhD. 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.

HSC National Conference

Community uniting in education, support, research and care

This year's National Conference was held in beautiful Niagara Falls, Ontario. Keynote speeches featured Charles Sabine OBE, "How Far We Have Come and Where We Are Heading," Dr. Ray Truant's research presentation, " Huntington Disease Before Disease," HDBuzz Founders & Contributors Dr. Jeff Carroll, Prof. Ed Wild and Dr. Rachel Harding with "HD Buzz Global Research Update" and Nora Guthrie's "She Came Along To Me: The Marjorie and Woody Guthrie Story."

This year's national conference did well to provide various opportunities to learn more about ongoing research on HD. The conference featured an array of breakout sessions such as "Insights into the Huntington Disease Protein Molecule" with Dr. Rachel Harding, "From Bench to Bedside: How HD Basic Research Feeds the Clinical Trial Pipeline" with Kaitlyn Neuman & Dr. Tamara Maiuri and "Understanding Huntington disease: The Importance of Observational Studies and How to Participate" with Dr. Gabriel Amorelli. These three sessions provided an understanding of how basic research can be used to inspire the next generation of therapeutic targets. The resource fair featured pharmaceutical companies Roche, Prilenia Therapeutics and Wave Life Sciences, as well as representatives from University of British Columbia's HD Biobank and Enroll-HD.

"I am truly amazed at how HSC's research program has grown. Fifty years ago, it was all just a dream – and to see how it has become a reality is truly inspiring. It makes me see just how much of an impact a group of people can have when united by a common goal."

Ariel Walker
Co-Founder, HSC

HSC also maintains a strong presence at research-focused meetings around the world. This enables us to stay up to date on all of the latest research developments and share the important information with our community.

Other conferences HSC representatives attended this year:

CHDI's 18th Annual HD Therapeutics Conference.
April 24-27, Dubrovnik, Croatia.

Huntington Study Group's 30th Annual Meeting.
November 2-4, Phoenix, USA.

Clinical Trials Ontario Annual Conference.
November 8-9, Toronto, Canada.

2nd Annual Canadian Movement Disorder Meeting.
November 24-25, Toronto, Canada.

Updates on Clinical Trials (In Canada):

Previously approved for tardive dyskinesia, the orally administered Valbenazine (INGREZZA®) demonstrated effectiveness in a Phase 3 clinical trial called KINECT-HD, which led to its approval by the U.S. FDA for treatment of HD chorea. At the moment, outside of the USA, only trial participants will have access. Trial completed.

Sage Therapeutic's drug SAGE-718 is designed to increase activity in NMDA receptors, which are thought to be critical for cognitive functions such as memory, multitasking, and decision-making in individuals with HD. Early results led to further investigation in ongoing Phase 2 trials, and a Phase 3 open label, which evaluate the drug's impact on daily tasks. Trial ongoing.

Roche and Genentech have initiated recruitment at Canadian sites for the Phase 2 clinical trial GENERATION HD2, which focuses on evaluating the safety, biomarkers and efficacy of tominersen, a non-allele-specific antisense oligonucleotide (ASO). Targeting individuals with prodromal, or early manifest HD, this study follows the Phase 3 trial GENERATION HD1, and aims to assess lower doses of tominersen in a population with earlier stages of HD. Trial ongoing.

Wave Life Sciences have completed enrollment in a multiple-dose group of Phase1b/2a SELECT-HD trial to add to their single dose cohort. This marks a significant step forward in gathering data on how multiple doses of the ASO WVE-003 may impact biomarkers, safety and tolerability in HD. WVE-003 selectively targets the messenger RNA of the mutant huntingtin gene. Anticipated data from the multiple-dose group, along with all single-dose data, is expected in the second quarter of 2024. Trial ongoing.

Prilenia had been conducting a study on pridopidine, an orally administered drug aimed at supporting Total Functional Capacity (TFC) in individuals with HD. While the latest Phase 3 study, PROOF-HD concluded by missing its primary and secondary endpoints, pridopidine demonstrated a good safety profile. Further data analysis is ongoing to understand if this drug has any potential benefits in subgroups of study participants. Trial completed.

Updates on Clinical Trials (Outside Canada):

The PIVOT-HD trial of PTC-518, an orally administered drug developed by PTC, was initially planned as a 3-month study but has since expanded to include participants with movement and cognitive impairments and to extend the trial period to 12 months. Data from the first 3 months indicate the drug is lowering huntingtin levels, and that it is well tolerated. Trial ongoing.

Final data from a Phase 2a clinical trial indicates that the experimental therapy ANX005, developed by Annexon Biosciences, leads to the stabilization of functional capacity in individuals with early HD and with high complement system activation. The therapy, designed to suppress complement C1q, a protein implicated in neurodegeneration, demonstrated positive results, paving the way for a planned Phase 2/3 trial. The treatment was generally well-tolerated, with stable neurofilament light chain (NfL) levels, and showed promise in individuals with high complement system activation. Trial completed.

AMT-130, a gene therapy for HD delivered by brain surgery, is currently in early-stage clinical trials focusing on safety. The trials involve low and high doses of AMT-130, with careful monitoring and assessments of participants' HD symptoms, brain volume and motor functions. While early data has showed a return of the NfL spike to baseline levels after surgery and some stabilization in total functional capacity, the results are still being analyzed, and caution is emphasized due to the novel nature of this therapy. Trial ongoing.

SOM3355 is an oral VMAT2 inhibitor (vesicular monoamine transporter 2) for the symptomatic treatment of chorea movements associated with Huntington disease. SOM3355 has successfully completed Phase 2a trials in HD and shown a favourable safety profile. The program received positive results of Pre-IND (Investigational New Drug) with US Food and Drug Administration (FDA) and Scientific Advice with European Medicines Agency. Trial completed.

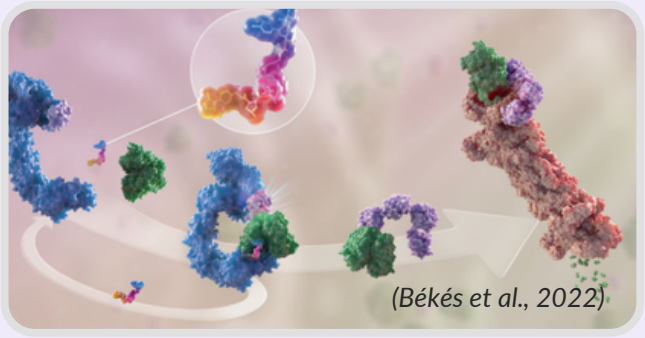
Updates on Clinical Trials (Outside Canada):

AskBio has initiated the first-in-human clinical trial for AB-1001, an experimental gene therapy developed to modulate cholesterol metabolism in the brain for individuals with HD. The Phase 1/2 trial, which was recruiting participants in Paris, aims to assess the safety of AB-1001 in up to 18 people with early-stage HD, determining the highest dose without unacceptable safety issues. The therapy, utilizing a modified adeno-associated virus to deliver the CYP46A1 gene, aims to normalize cholesterol metabolism, potentially slowing neurodegeneration in HD. Trial ongoing.

Vaccinex's pepinemab is aimed at targeting SEMA4D to address neuroinflammation. The completion of the Phase 2 SIGNAL trial, a late-stage study, indicated that while the study did not meet pre-specified co-primary endpoints, data analysis after the study showed a greater ability to detect beneficial clinical changes in patients somewhat more advanced in disease progression, suggesting the potential for cognitive benefits and slowing brain atrophy in HD patients. Trial completed.

Emerging Research Themes

New or developing concepts and ideas that are gaining recognition and significance in the HD research space



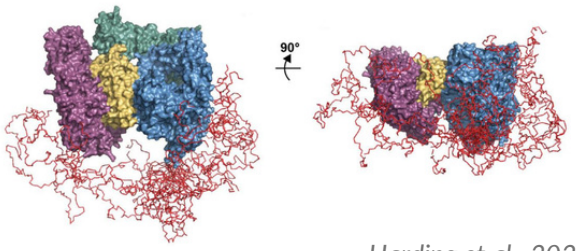
(Békés et al., 2022)

Protein Elimination:

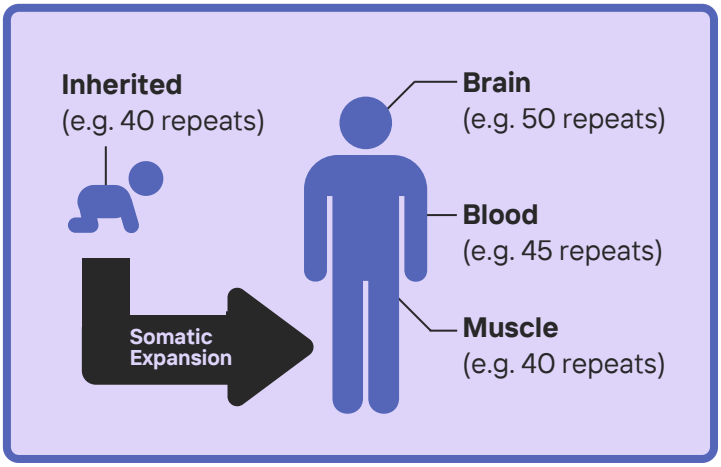
PROTACs, or Proteolysis-Targeting Chimeras, have promise in drug development by marking specific proteins, including the huntingtin protein. Similarly, innovative technologies such as VecTron are allowing companies like VectorY to better understand protein degradation techniques. VecTron introduces a unique signal that prompts the cell to break down and dispose of the targeted protein. This evolving landscape of molecular medicine is utilizing new technologies to improve cellular processes and presenting new ideas for eliminating proteins associated with various diseases.

Unravelling the Microscopic Complexity:

Leveraging technological advancements and cutting-edge applications, researchers can delve into the microscopic intricacies of the huntingtin protein in detail like never before. State-of-the-art tools, advanced imaging techniques and computational modeling enable a comprehensive exploration of the protein's structure, spatial orientation, and interactions with other molecules. This technology lets scientists unravel the complexities of how the protein folds under the influence of extended CAG repeats in Huntington disease.



Harding et al., 2021



Somatic Expansion:

Somatic expansion in Huntington disease involves an abnormal increase over time in the number of CAG repeats within the HTT gene during cell division throughout the body. This expansion contributes to the variability in symptom severity and onset among affected individuals, leading to mosaicism in the distribution of repeat lengths in different tissues. Understanding somatic expansion is important for comprehending the genetic complexities of Huntington disease and exploring potential therapeutic targets.

HSC Research Council

The Research Council of the Huntington Society of Canada is comprised of leading HD research scientists with expertise in various areas of investigation. Council members are volunteers serving without remuneration. The Council analyzes and prepares recommendations about applications received for the research funding programs and provides strategic research advice.

Dr. Mahmoud Pouladi

Dept. of Medical Genetics
University of British Columbia

Dr. Rachel Harding

The Structural Genomics Consortium
University of Toronto

Dr. Tamara Maiuri

Dept. of Biochemistry & Biomedical Sciences
McMaster University

Dr. Tiago Mestre

Dept. of Medicine
University of Ottawa

HSC Clinical Neurology Council

The Clinical Neurology Council of the Huntington Society of Canada is comprised of accomplished neurologists who specialize in the care of individuals affected by HD. These dedicated professionals volunteer their expertise to play a role in recruiting the next generation of Canadian HD neurologists.

Dr. Mark Guttman
Former Neurologist
Centre for Movement Disorders, Toronto

Dr. Tiago Mestre
Neurologist
Department of Medicine
University of Ottawa

Dr. Blair Leavitt
Consulting Neurologist
University of British Columbia
Centre for HD

Dr. Sylvain Chouinard
Neurologist
André-Barbeau Movement Disorders Unit
Centre hospitalier de l'Université de Montréal

Dr. Oksana Suchowersky
Research Chair in Neurology
Medical Geneticist
University of Alberta

> ***I look to the future and see a world of possibility. We have already taken big steps, from having a dedicated Director of Research at HSC to confirming the HSC Research Chair at Western University. Advances stemming from these initiatives will be life-changing.***
>
> **Shelly Redman**
> **CEO, HSC**

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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