“We like the philosophy of the Hereditary Disease Foundation that monies raised go directly to support research and that scientists from around the world are encouraged to collaborate and share their work. We've devoted ourselves to being supporters and research partners, and we have not been disappointed. The research is vibrant with possibilities.”

Sandy Fox
Member, Board of Directors
Hereditary Disease Foundation
# HEREDITARY DISEASE FOUNDATION RESEARCH GRANTS

The Hereditary Disease Foundation provides funding for research that advances the discovery and development of treatments for Huntington's disease and other brain disorders. We are passionate about finding and funding the most promising, creative and paradigm-changing research possible. Data generated with HDF grants allows researchers to apply successfully for major long-term funding from other sources, including the National Institutes of Health.

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Astrocytes are one of the major non-neuron cell types in the brain and control a large number of neurological processes. Huntington’s disease likely changes astrocytes in a way that contributes to the neurological problems of patients with HD. Even though HD is caused by a mutation that is present in all brain cells, some brain regions are more affected than others.

Dr. Al-Dalahmah hypothesizes that astrocytes can either have protective effects on neurons, or become dysfunctional and lose their protective effects. He will test whether the “functional” astrocytes are more enriched in the “resilient” less affected brain regions, and whether the “dysfunctional” astrocytes are more enriched in the “vulnerable” more severely affected regions.

Nuclei in the cells contain our genetic material, DNA, which harbors many functional units called “genes.” These genes encode proteins which serve many functions in the cells. For proteins to be made, DNA must be first transcribed into another intermediate genetic material called RNA, which carries the information needed to make the proteins.

Dr. Al-Dalahmah is using a new technique that involves isolating cell nuclei from human brain tissue that has been frozen and stored. He then isolates and sequences RNA from individual nuclei from “vulnerable” areas that are severely affected in HD and “resilient” areas that are less affected. This method allows him to determine which genes are expressed in single cells in a human brain, in both vulnerable and resilient regions. This knowledge allows him to understand what biological processes underlie functional, likely protective, astrocytes, and what biological processes underpin dysfunctional astrocytes.

Discovering how astrocytes in the HD brain are changed during the disease, in vulnerable and resilient regions, will help develop therapeutic strategies for overcoming and possibly reversing these deleterious changes.
Anne Ast, Ph.D.

Mentor: Erich E. Wanker, Ph.D.

Institution: Max-Delbrück-Center for Molecular Medicine, Germany

Project Title: Manipulating seeding activity and proteotoxicity of amyloidogenic HTT aggregates by targeted amino acid exchanges

Every protein needs a specific architecture in order to execute its duties within the cell. In Huntington’s disease, the disease-causing huntingtin protein has lost its original folding instruction and forms stable protein clumps. These clumps operate as templates and pass on their corrupted folding pattern to other normally folded huntingtin molecules. Dr. Ast suspects that this process could be a driving force in HD development and progression. Therefore, she wants to understand the connection between templated protein misfolding and toxicity and find a way to manipulate this process as a therapeutic approach.

Kristina Becanovic, Ph.D.

Institution: Karolinska Institutet, Sweden

Project Title: Towards the discovery of genetic modifiers and targets for future Huntington’s disease treatments

We all have the same genes with only minor differences on individual sites that affect the activity of genes and how much we have of a particular gene product in the body. These small genetic differences make us unique and different from one another and they are also the reason HD manifests itself differently in different people. In this research study, Dr. Becanovic wants to understand why people with the same number of CAG repeats sometimes have very different ages of symptom onset. The goal of this study is to identify the genetic variants that affect disease onset, so called “genetic modifiers.”

If we succeed in identifying these genetic modifiers, we will be able to use this knowledge to develop better drugs. These would, unlike today’s medicines, not just treat symptoms, but primarily protect the brain and slow down the development of the disease.
Lauren Byrne, Ph.D.
Mentor: Edward Wild, M.D., Ph.D.
Institution: University College London, England
Project Title: Advancing biofluid biomarkers for disease-modifying trials in Huntington's disease

Neurofilament-light-protein (NfL) is a protein found in brain cells and can be measured in blood as a biomarker of neuronal health. Dr. Byrne and her colleagues previously showed that NfL increases with Huntington's disease progression. Her current work aims to advance HD drug development and patient care by determining how, early in life, we can detect NfL changes and how NfL changes over the lifetime of a person who has the expanded HD gene. With lots of hope around potential disease-modifying therapies for HD, the information gained from this work could be used to guide clinical trials or treatment decisions presymptomatically.

Rivka Dikstein, Ph.D.
Institution: The Weizmann Institute of Science, Israel
Project Title: Unraveling the role of Spt4/Spt5 in inherited neurodegenerative diseases using newly discovered pharmacological tools

Trinucleotide Repeat Expansion Diseases (TREDs) consist of about 20 genetic diseases caused by a defective gene that lead to neurological pathology. Presently for most cases no effective cure is available. Gene expression involves the transcription of a DNA section into RNA which is then converted into proteins. Transcription is regulated by a special group of proteins called transcription elongation factors. One such factor is Spt4/Spt5, which has a special role in transcribing mutant genes of Huntington's disease and amyotrophic lateral sclerosis (ALS). Dr. Dikstein's team discovered the first Spt4/Spt5 inhibitors called SPIs and found that SPIs selectively inhibit the transcription of abnormal but not the normal huntingtin gene. They plan to develop further SPIs as a therapeutic approach against the inherited neurodegenerative disorders and to elucidate the mechanisms underlying the regulation of the mutated genes by Spt4/Spt5.
Dr. Leslie Thompson and Dr. Steven Finkbeiner, members of the HDF's Scientific Advisory Board, are both established researchers in the Huntington's disease field. Leslie and Steve are longtime collaborators and were founding members of a consortium established by the National Institutes of Health. The consortium received funding from HD organizations, including the HDF, to develop human neuron models of HD by reprogramming patient cells to be stem cells and then directing those stem cells to become neurons.

The two investigators developed a collaborative project for the HDF to evaluate genes that may modify the age of onset of HD in individuals, called modifier genes. Genes are “spelled” with different arrangements of 4 letters (C, A, G, T), which make up the genetic code that is translated into protein. Different individuals can have the same gene with slightly different spellings, creating natural variation in the population by influencing the amount of protein produced from that gene. Scientists have been looking at spelling differences in many genes to determine if they modify the course of HD. It’s been shown that different spellings or “sequences” of specific genes can influence age of onset; two of those are ALFY and FAN1, which are involved in clearing proteins from cells and fixing damage to DNA, respectively.

Leslie is using sophisticated techniques to look globally at how those genes affect the expression of all genes and proteins in cells. Steve is using special robotic microscopes he invented to test whether modulation of ALFY and FAN1 affects degeneration of human HD neurons. These special microscopes let him follow individual cells, much like patients in a clinical trial, and he has found that these two potential HD modifier genes have dramatic effects on neurodegeneration in patient HD neurons which are now being followed up for gene and protein changes in Leslie’s lab. The results from the two approaches will be brought together for a deeper understanding of how other genes besides the HD gene affect the course or the age of onset of HD. This will potentially provide a better understanding of HD and how to test potential HD modifiers that can lead to new treatments.
**Brent Fitzwalter, Ph.D.**

**Mentor: Myriam Heiman, Ph.D.**

**Institution: Broad Institute of MIT and Harvard**

**Project Title:** Neuroprotection in Huntington's Disease

In Huntington's disease, the nerve cells of the brain, called neurons, are vulnerable to stress caused by the toxic huntingtin protein. Turning on certain genes in neurons that provide protection from this stress may halt the progression of the disease. Foxo3 is a gene that has been shown to protect neurons and slow ageing, but its importance in Huntington's disease isn't well studied. Using powerful molecular tools in the laboratory of Dr. Myriam Heiman, Dr. Fitzwalter will uncover how Foxo3 is neuroprotective and test if turning on the Foxo3 gene is beneficial to prevent Huntington's disease progression.

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**Richard Hickman, M.D.**

**Institution: Columbia University Medical Center**

**Project Title:** Generation of Striatal Neurons from HD patient-derived fibroblasts: a feasibility study with direct correlation to human neuropathology

As a neuropathologist at Columbia University Medical Center, Dr. Hickman works alongside one of the leaders of HD neuropathology, Dr. Jean-Paul Vonsattel, to study Huntington's disease by carefully examining the brains that are generously donated for research. These precious gifts allow researchers to visualize this inextricably human disease and collaborate with other researchers to get a better understanding of the condition and to find novel treatments. Richard is currently investigating the feasibility of a new technique that allows the culturing of neurons from donor skin cells and dura. He intends to see how well the cultured neurons capture a patient's disease process by comparing with the neuropathology of the donated brain. This important validation step will pave the way for developing personalized neuronal cultures for patients living with HD and potentially lead to novel treatment discoveries.
Ali Khoshnan, Ph.D.

Institution: California Institute of Technology

Project Title: Editing of gut bacteria to reduce brain pathology in Huntington's disease

Bacterial communities living in the human gut bidirectionally communicate with most organs including the nervous system. These interactions have evolved to prevent disease and maintain well-being. Changes in the abundance of specific gut bacteria are linked to the development of various human disorders such as Parkinson's disease.

Dr. Khoshnan's laboratory is exploring the role of gut bacteria in the progression of HD. Data suggest that inflammatory bacteria in the gut of HD animal models worsen disease phenotypes. He is expanding on these findings and further examining whether changes in the activity of gut bacteria with novel prebiotics delay the onset of HD-like symptoms and reveal novel therapeutic targets.

Alejandro Mas-Monteys, Ph.D.

Institution: University of Pennsylvania
Children's Hospital of Philadelphia

Project Title: Novel approaches for knock down control

Sustained expression of therapeutic molecules for targeting mutant Huntingtin may result in unintended side effects. Dr. Mas-Monteys' project tests a new strategy that can turn on or off the expression of these therapeutic molecules using a re-purposed drug.

Importantly, this drug can reach the brain when given orally. He will test the utility of the approach in cells cultured from HD patients as well as in mouse models of HD.
**Christopher Ng, Ph.D.**

**Mentor:** David Housman, Ph.D.

**Institution:** Massachusetts Institute of Technology

**Project Title:** Characterization of genetic variants that modify age of onset in Huntington’s disease

David Housman helped pioneer the discovery of the genetic marker for Huntington’s disease. The Housman lab now studies how the rest of the human genome controls the age at which a patient with the Huntingtin mutation becomes symptomatic for the disease. A postdoctoral fellow in the Housman lab, Christopher Ng plans to identify other genetic markers that modify HD age of onset by using the extensive resources of patient samples and clinical data collected over a 23 year period from the world’s largest HD family in Venezuela. He plans on characterizing dysfunction of the proteins encoded by these genetic variants in HD patient samples and mice models. Further, his goal is to discover the role of modifier variants in the pathology of the disease by genetic manipulation in patient-derived cells and mice models. Understanding how these genetic variants alter the course of the disease will distinguish the molecular pathways that are most capable of modulating Huntington's onset. By going from genetic to molecular insights, he hopes to target these modifier pathways to develop protective therapies capable of slowing HD pathology.

**Katerina Oikonomou, Ph.D.**

**Mentor:** Michael Levine, Ph.D.

**Institution:** University of California, Los Angeles

**Project Title:** Targeting Perturbed Neuronal Ensemble Activity and Calcium Signaling for the Treatment of HD

Calcium signaling plays a central role in a plethora of cellular processes, including neuronal development, neurotransmission, energy metabolism and intracellular signaling cascades involved in memory formation. Dysregulation of calcium homeostasis in Huntington’s disease contributes to the degeneration of cortical and striatal neurons and leads to neurological abnormalities observed in both HD patients and mouse models. In this study, Dr. Oikonomou hypothesizes that perturbations in calcium handling in cortex and striatum from HD mice of different disease stages contribute to the progression of the phenotype using a combination of optical, electrophysiological, pharmacological and behavioral approaches. To monitor neuronal ensemble activity in mice, she utilizes
a new technique using miniaturized microscopes in tandem with viral expression of genetically encoded calcium indicators in specific neuronal subpopulations. Results from these experiments will shed light on the role of calcium in cortical and striatal alterations and potentially provide new targets for therapeutic intervention for this devastating disease.

**Ellen Penney, M.D., Ph.D.**

**Institution: Massachusetts General Hospital**

**Project Title: R-loops in HD: Somatic Expansion and DNA Repair**

Abnormal DNA/RNA structures, R-loops, have recently been described in several neurodegenerative diseases. These structures are predicted to form at the HD gene. R-loops are known to interact with factors that modify HD onset and progression. Dr. Penney believes that abnormal R-loop formation may be a pathogenic process that occurs early in HD and ultimately leads to cell dysfunction and death. She is studying how R-loops occur in HD and working to identify mechanisms that can regulate their formation. She hopes this work will lead to the identification of therapeutic targets for HD and other neurodegenerative disorders in which abnormal R-loop formation occurs.

**Anna Pluciennik, Ph.D.**

**Institution: Thomas Jefferson University**

**Project title: Crosstalk between DNA repair pathways in Huntington’s disease**

Huntington’s disease is caused by an expansion of an unstable DNA tract composed of CAG repeats located within the huntingtin gene. Genomic analyses of HD patients have revealed that a number of DNA repair genes influence the age of onset of the disease, presumably due to their effect on the CAG repeat length. How the proteins encoded by these genes conspire to cause CAG repeat expansion is not well understood. Dr. Pluciennik established biochemical assays to isolate protein complexes that recognize and handle DNA structures formed by CAG repeats. She will use such approaches to study cell type specific protein complexes that assemble on such structures. Modulation of such assemblies may represent a viable therapeutic strategy for treating HD.
Paul Ranum, Ph.D.

Mentor: Beverly Davidson, Ph.D.

Institution: Children’s Hospital of Philadelphia

Project Title: *High throughput quantification of gene expression and mRNA structure from single-cells in the HD brain*

Cells are the building blocks that make up the human brain. We want to understand how individual cells are impacted by Huntington’s disease and use this information to build smarter, more focused therapeutic strategies to combat HD. A key feature of the progression of HD is something called “transcriptional dysregulation.” Transcriptional dysregulation is a breakdown in the process used to make proteins from DNA. To learn more about how this breakdown impacts the brain, Dr. Ranum hopes to discover which cell types in which parts of the brain contribute to this dysfunction. With this data he can map the affected locations and types of cells, informing the design and delivery of therapies for Huntington’s disease.

Piere Rodriguez-Aliaga, Ph.D.

Mentor: Judith Frydman, Ph.D.

Institution: Stanford University

Project Title: *Structural differences between the pathogenic and non-pathogenic Huntingtin: a single-molecule approach*

The risk of developing Huntington’s disease is tightly linked with the length of a specific region within the Huntingtin protein (Htt). Mutations can make this region longer than normal—more than 36 amino acids—producing a mutant Htt with characteristics that induce neuronal decay. The underlying mechanism behind this length-dependent toxicity remains largely unexplored, mainly because of two major technical barriers in the study of Htt: 1) its insolubility and high aggregation propensity, which hinders the ability to perform experiments under physiological conditions, and 2) Htt’s remarkable conformational heterogeneity, which makes it very difficult to obtain structural information with high resolution because current methods only detect the average conformation of a giant numbers of molecules. To circumvent these technical barriers, Dr. Rodriguez-Aliaga uses a novel single-molecule approach to study with unprecedented resolution the structures of pathogenic and non-pathogenic Htt variants—one molecule at the time. His preliminary results—which are being validated with additional experiments—seem to indicate structural
differences between the pathogenic versus non-pathogenic Htt variants, which have not been detected previously. This project will provide information about Htt structure not accessible through traditional methods, which is central for the identification of novel therapeutic targets and the development of new drugs against mutant Htt toxicity.

Matthew Scaglione, Ph.D.

Institution: Duke University School of Medicine

Project Title: Analysis of a novel class of molecular chaperones that suppress polyglutamine aggregation

In Huntington’s disease the huntingtin protein forms into clumps due to a very long string of the amino acid glutamine. These protein clumps are toxic to cells and result in cell death. Dr. Scaglione has recently found that an amoeba normally has very long strings of the amino acid glutamine in many proteins, yet these proteins don’t form clumps. He also found that this amoeba contains a protein that is responsible for its resistance to protein clumping. His preliminary results also show that putting the protein from the amoeba into human cells makes human cells resistant to protein clumping. He will work to determine how this new protein prevents protein clumping and also determine if this protein has therapeutic potential in a mouse model of Huntington’s disease.

Charlene Smith-Geater, Ph.D.

Mentor: Leslie M. Thompson, Ph.D.

Institution: University of California, Irvine

Project Title: PIAS1 network in HD induced pluripotent stem cells – Dressing Huntington

The mistake in the protein that causes Huntington’s disease can be very subtle! Imagine that the HD protein starts out as a person undressed and deciding what clothing to put on. The protein needs to go out and work – what to wear? The protein wants to go out and party – what to wear? The protein has different dress options! It is the same underneath, but can wear different outfits – called “post-translational modifications” – that fit with where it needs to go and what it needs to do. Depending on how the huntingtin protein is dressed and where it is going, the protein can act as it should or
misbehave in the presence of the HD mutation. How one is dressed and where one is taken can make a difference in whether or not one gets sick and how sick one gets.

SUMO is a protein which is used as an “item of clothing” on the huntingtin protein that influences the balancing act of protein stability in cells. One of the “fashion designers,” called PIAS1, will dress proteins with SUMO, changing how proteins behave.

The Thompson lab previously showed in HD mice that decreasing the amount of PIAS1 helps to slow the progression of HD. Now Dr. Smith-Geater will evaluate whether the promising results seen in the HD mouse model translate to nerve cells derived from human HD patients. To do this, she uses an amazing technology that allows skin cells from HD patients and healthy individuals to be “reprogrammed” into stem cells, which can form any cell type of the body. They are then made into neurons, the cells that are severely affected in HD. Using these cells, she will see how reducing the presence of PIAS1 affects many different processes in HD neurons to gain an understanding of how we can use the system to develop new treatments for HD. This will be done in 2D, growing neurons in a dish, and in 3D using more complex systems that recapitulate some aspects of human brain structure.

Joan Steffan, Ph.D.

Institution: University of California, Irvine

Project Title: Analysis of how the Huntingtin protein helps clean up cellular trash

Dr. Steffan’s laboratory is studying how the Huntingtin protein, mutated in Huntington’s disease, functions as part of the cell’s garbage collection system. Huntingtin is a large protein that can function in a process called “autophagy” as a scaffold for cellular trash, helping to target it to the cellular garbage dump, called the lysosome, where it is chewed up and recycled to make nutrients for the cell during stressful times. Trash is tagged by the cell to be carried to the lysosome by a small protein called ubiquitin.

The Steffan laboratory is investigating how the Huntingtin protein interacts with the ubiquitin-tagged trash in order to scaffold it to the lysosome for degradation and to figure out what kinds of trash may be cleaned up by Huntingtin.

Dr. Steffan hypothesizes that mutation of Huntingtin may inhibit its autophagic function, allowing cellular trash to build up and be toxic to neuronal cells in the brain, contributing to Huntington’s disease pathogenesis. Her work will help define this autophagic role of Huntingtin so that therapies can be created to improve mutant Huntingtin function to keep the cell clean.
**Nicholas Todd, Ph.D.**

**Institution:** Brigham and Women's Hospital

**Project Title:** Targeted Delivery of HD Gene Therapeutics

Every drug being developed for the treatment of Huntington's disease faces a significant challenge: getting the drug into the brain. The difficulty arises due to the blood-brain barrier, a protective layer of cells that prevents toxins in the bloodstream from entering the brain but also excludes essentially all large molecule therapeutics. To address this problem, Dr. Todd's laboratory uses the technology of focused ultrasound to non-invasively and temporarily disrupt the blood-brain barrier in a targeted region and thereby allow drugs to penetrate into the brain. The technology of focused ultrasound blood-brain barrier opening has recently entered clinical trials for the treatment of brain tumors and Alzheimer's disease, but no work has been done to date on HD. In this research project, Dr. Todd and his team will use focused ultrasound to demonstrate that they can safely and effectively deliver a HD gene therapy treatment into the mouse brain. Their goal then is to obtain funding that would lead to a human clinical trial.

**Ray Truant, Ph.D.**

**Institution:** McMaster University, Ontario, Canada

**Project Title:** DNA Damage Repair Links to Energy Metabolism Defects in HD: Defining New Therapeutic Targets

Dr. Truant’s research is to understand the recent transformational genetics studies from the Genetic Modifiers of Huntington's Disease (GeM-HD) consortium and others to tell us that DNA repair is an important reason why the age of onset of HD is so different among those with HD.

The excitement around this work is that these proteins and enzymes have been deeply studied by the cancer research community for 50 years, and there are drugs sitting on shelves that may be directly repurposed to Huntington's disease. The Truant lab discovered in 2017 that huntingtin was part of the DNA repair machinery, and others have since shown in clinic that DNA repair is going wrong in HD very early, even before disease appears. Ray's 2018 published work indicates drugs are possible in this area that have real impact in mouse models, and hopefully soon in humans. In the bigger picture, an increasing number of neurodegenerative diseases are emerging with defects in fixing DNA damaged by the effects of aging. This gives us confidence with the help from those with HD working with researchers that we are on a new and exciting track.
**Gong-Her Wu, Ph.D.**

*Mentor: Wah Chiu, Ph.D.*

**Institution: Stanford University**

**Project Title:** *Deciphering mutated huntingtin aggregates and cellular architecture in Huntington’s disease neuron by cryogenic electron microscopy*

Dr. Wu’s research focuses on studies using patient-derived stem cells to observe progression of HD and aims to discover the early-stage pathological protein structures to improve disease diagnosis and identify potential therapeutic targets for HD treatment. Dr. Wu will apply cryo-electron microscopy (cryo-EM) technology, a recent Nobel Prize-winning biological structure imaging system, to record early formation and distribution of the protein that caused HD.

Cryo-EM is a powerful tool in observing protein structure without artificial chemical disruption. It also provides details at resolution higher than traditional microscopy. His study will also cover cellular organelle and cytoskeleton structures inside disease neurons to study how the huntingtin protein causes neuron cell death. Dr. Wu’s research aims to uncover the pathological protein structures and mechanisms of disease-related neuron cell death. The success of this project will provide better understanding of the disease for therapeutic strategy development.

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**X. William Yang, M.D., Ph.D.**

**Institution: University of California, Los Angeles**

**Project Title:** *Novel FAN1 Knock-in Mice to Study the Role of FAN1 in Normal Brain Function and HD Pathogenesis*

Recent genetic studies reveal that distinct variants of the FAN1 gene can either accelerate or delay the onset of Huntington’s disease. FAN1 is involved in DNA repair and kidney function, but its role in the brain and how FAN1 variants affect HD remain unclear. Dr. Yang will use a novel model that tags the mouse FAN1 protein with a fluorescent protein, which allows him to detect where FAN1 is located in the brain cells of normal and HD mouse models, and to identify the functional partners of FAN1. Dr. Yang’s studies may identify novel FAN1-related therapeutic targets for HD.
Andrew Yoo, Ph.D.

Institution: Washington University School of Medicine

Project Title: Testing the Role of Genetic Modifiers of Huntington's Disease with Directly Reprogrammed Patient Neurons

Much of our understanding of human diseases of the brain is often gained post mortem – after death. The study of neuropathology has been an extremely powerful means to gain insight into how diseases such as Huntington’s disease give rise to the devastating symptoms for which they are known. Although neuropathology has also given us insight into how the diseases began, it has been difficult to test these ideas, because these studies require the study of live human brain cells.

Scientists, including Dr. Yoo, recently have shown that human brain cells can be generated by converting human skin cells, a process known as direct neuronal reprogramming. Using this approach, Dr. Yoo has created brain cells from skin cells collected from HD patients. He has found that these brain cells also recapture features that were previously only described post mortem.

Using this powerful approach, Dr. Yoo will determine if the recently identified modifier genes that alter the course of HD also alter the disease-related features in his system. This will give scientists unprecedented insight into how the different pathologic features of the disease might influence actual disease outcome.

“We are very excited that our lab recently received a $1,766,800 five-year grant from the National Institute of Neurological Disorders and Stroke, NIH. The goal of our grant is to investigate a new way to potentially treat Huntington’s disease.

We are especially grateful to the HDF for realizing the importance of our work. It was their funding that enabled us to collect the preliminary data necessary to obtain this multi-million dollar NIH grant.”

Matthew Scaglione, Ph.D.
Duke University School of Medicine