# RESEARCH GRANTS 2017-2018

# HEREDITARY DISEASE FOUNDATION RESEARCH GRANTS

**Kristina Becanovic, Ph.D.**

**Institution: Karolinska Institutet, Sweden**

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

Huntington's disease is a disease in which nerve cells die in the brain leading to severe symptoms such as movement difficulty, cognitive impairment with learning and memory difficulties, severe mood disturbance and sleeping problems. However, symptoms vary from person to person with HD. In this research study, Dr. Becanovic wants to understand why some patients become more ill than others and why some patients develop symptoms earlier or later than others. The goal of this study is to identify the genetic factors that contribute to these differences.

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 differences mean that we all are unique and different from each other and they are also the reason HD manifests itself differently in different people. If researchers succeed in identifying these genetic factors, they 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.

**Marie-Françoise Chesselet, M.D., Ph.D.**

**Institution: David Geffen School of Medicine at UCLA**

**Project Title: *Preclinical evaluation of D-PUFAs as a therapeutic intervention for HD***

Marie-Françoise Chesselet, a long-time HDF Scientific Advisory Board member, was awarded HDF funding to test compounds (known as D-PUFAs) in mice for their ability to protect brain cells from HD damage. D-PUFAs are of interest because they reduce an alteration observed in cells affected by HD. Moreover, they have been given to humans in many studies with no apparent ill effects.

If the results of Dr. Chesselet's experiments are positive, the compounds could be tested relatively quickly as a dietary supplement in humans.

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**Yoon H. Cho, Ph.D.**

**Institution: University of Bordeaux**

**Project Title: *Sleep as a window for a therapeutic clue against Huntington's disease***

People with Huntington's disease often have difficulty sleeping. Mice which have been genetically modified to have the HD gene sleep as poorly as humans with HD do. Recording the brain activity of these mice while they slept using an electroencephalographic (EEG) technique, Yoon Cho and her team discovered a strange brain activity. This was caused by a large number of neurons firing abnormally in synchrony. This activity was not present at all in normal mice. To understand where in the brain this activity was coming from, Dr. Cho and her group first tried to modulate this abnormal activity with drugs that modulate sleep and wake cycles. They found that a new sleeping pill significantly improved the HD mice's aberrant brain activity and other sleep disturbances. The pill, which blocks the chemical activity of orexin, is important for maintaining wakefulness.

Cho's current project, funded by the Hereditary Disease Foundation, is testing if the sleeping drug also corrects behavioral and cognitive impairments in these HD mice as it did the atypical brain activity and sleep disturbances. Because the drug is already available in the U.S. and Japan, this work, if validated, could lead very rapidly to a clinical trial targeting the alleviation of symptoms of Huntington's disease.

**Steve Finkbeiner, M.D., Ph.D.**

**Institution: J. David Gladstone Institute**
**University of California, San Francisco**

**Leslie Thompson, Ph.D.**

**Institution: University of California, Irvine**

**Project Title: *Assessment of WGS-derived genetic modifiers in differentiated HD-derived iPSCs***

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 Hereditary Disease Foundation to evaluate genes that may modify HD. Potential modifying genes will be analyzed in human neurons from HD patients and their effects will be studied. Leslie will use sophisticated techniques to look globally at how those genes affect the expression of other genes in cells. She will specifically look at whether modulation of potential HD modifier genes affects the gene expression changes that she previously found were associated with HD neurons. Steve will use special robotic microscopes he invented to test whether modulation of potential HD modifier genes affects degeneration of human HD neurons. These special microscopes let them follow individual cells, much like patients in a clinical trial, to sensitively measure effects of potential HD modifier genes on specific cellular pathways and neurodegeneration. The results from the two approaches will be integrated into a deeper molecular and cellular understanding of how other genes besides the HD gene affect HD. This will provide a better understanding of how HD occurs and the identification of therapeutic targets that could lead to new treatments.

**Charlene 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 Huntingtin's disease 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. Geater previously showed in HD mice that decreasing the amount of PIAS1 helps to slow the progression of HD. Now she 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 or increasing 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.

**Ben Hoffstrom, Ph.D.**

**Institution: Fred Hutchinson Cancer Research Center**

**Collaborating with Ai Yamamoto, Ph.D., Columbia University**

**Project Title: *Creating a monoclonal antibody against Alfy***

Important for understanding how a protein might work is to see where it lives in a cell and to measure how much of it might be there. This can be achieved by creating a tool, known as an *antibody*, against the protein of interest. This tool originates from a system possessed by many animals, including humans, to protect themselves: an immune system. The immune system combats objects that are considered foreign to the body, such as viruses. To eliminate viruses when they invade our bodies, we must be able to label them so that they can be found and destroyed. The label the immune system creates is an antibody. In science, we take advantage of the immune system of animals, such as rats and chickens, to create antibodies against proteins we are studying. Given that these antibodies can be exquisitely specific, this permits us to see reliably and confidently where a protein might reside in a cell, or how much of it might be present at any given time. This proposal by Dr. Ben Hoffstrom is to create antibodies so that we can study the protein Alfy.

Alfy is a very large protein that is involved in eliminating protein clumps by a powerful recycling system within the cell, known as *autophagy*. Previous work by the Simonsen lab (University of Oslo) and Yamamoto lab (Columbia University) has found that Alfy is necessary for cells to be able to eliminate protein clumps, including those that are created in Huntington's disease. Given the size and structure of Alfy, it has been very difficult to create many of the necessary tools to study this important protein, including a reliable antibody that will enable us to see Alfy. Dr. Hoffstrom uses state of the art technology to create antibodies against proteins that are known to be difficult to detect. The immune system creates multiple antibodies against a given target, and these antibodies range in how well they work. For scientific exploration, it is necessary to find antibodies that are extremely specific, given that different proteins can be very similar to one another. To be certain we are studying Alfy and not a similar protein, Dr. Hoffstrom uses methods that permit him to test the efficiency of an extremely large number of antibodies at once, with accuracy. This makes this otherwise very laborious process much more tenable, and will make this important tool available to the HD community much faster.

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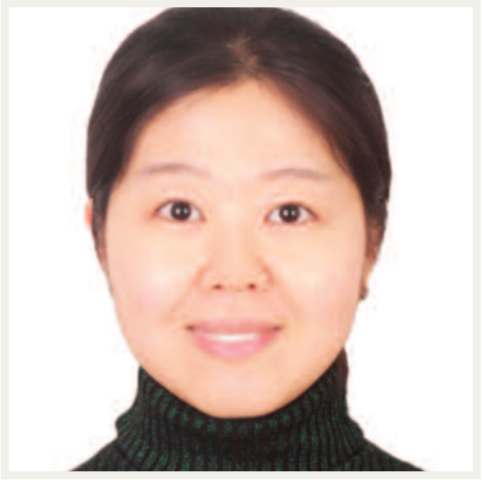
**Pan Li, Ph.D.**



**Mentor: Russell Margolis, Ph.D.**

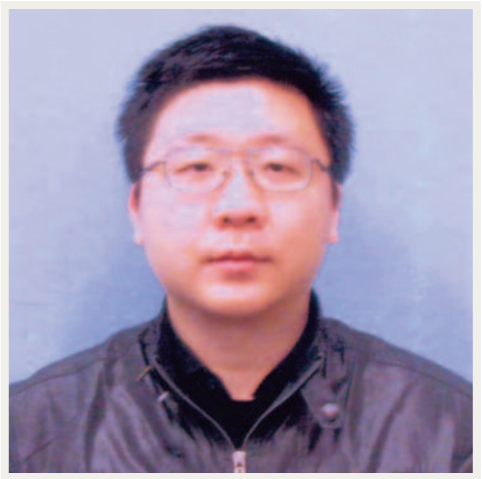
**Institution: Johns Hopkins University**

**Project Title: *A high throughput screen for small molecules enhancing the expression of HTTAS-a novel therapeutic strategy for HD***

Russell Margolis' group identified a piece of RNA (the recipe for making proteins) that is widely expressed at low levels in the brain. When this RNA is overexpressed, it lowers the amount of the protein that causes HD. They hypothesize that this RNA will provide novel therapeutic targets for suppression of the abnormal HD protein and, therefore, will be an effective treatment of HD.

Funded by the Hereditary Disease Foundation, Pan Li's research will explore the mechanism and magnitude of the effect this RNA has on the expression of the HD protein. She will use skin cells, stem cells and mouse models of HD to quantify these findings. This strategy provides an alternative approach to suppress the HD-causing protein, which may have considerable therapeutic potential.

**Boxun Lu, Ph.D.**



**Institution: Fudan University, Shanghai, China**

**Project Title: *Validation of a Gpr52 antagonist's effect on mHTT levels and toxicity***

Huntington's disease is a devastating hereditary disorder that causes neuronal death in specific brain regions, motor functional deficits and psychological symptoms, and eventually premature death. HD is caused by mutation in a single gene called huntingtin, which expresses the abnormal huntingtin protein that is toxic to the neurons. This then leads to abnormal neuronal death via complicated and unclear mechanisms. An effective approach to treating HD is lowering the abnormal protein, which may suppress all kinds of its downstream toxicity. While this could be achieved by several large biological molecules targeting the protein, the delivery of these molecules into the brain is highly challenging and expensive, prohibiting their accessibility to most HD patients. Thus, small molecule compounds that may lower the abnormal protein are highly desired.

The ultimate goal of Dr. Lu's work is to look for safe compounds that can lower the abnormal protein to treat HD. In order to achieve this, he needs to identify potential drug targets to regulate protein levels.

Lu's previous work identified a few such proteins. In this project, Lu plans to validate one of them, Gpr52, which has the highest potential for drug discovery. He will use a virus to deliver reagents that can decrease Gpr52 in HD mice and test whether the abnormal protein is lowered and the pathology is rescued.

As one of the few HD labs in China, Dr. Lu's lab also is interested in serving as a connection hub for Chinese HD research to the rest of the worldwide HD research community.

**Jose F. Moruno-Manchon, Ph.D.**

**Mentor: Andrey S. Tsvetkov, Ph.D.**

**Institution: The University of Texas McGovern Medical School**

**Project Title: *Sphingosine kinase 2 and DNA damage in neurons – A lipid kinase, DNA damage and Huntington's disease***

Maintaining genome stability is critical for cell life. Every day, our cells are exposed to stimuli that attack DNA. To repair the injured DNA and stabilize the genome, cells have various mechanisms, in which multiple molecules participate in a well-organized sequence of events. First, specific molecules detect the damaged sites, then transmit the location, attracting other molecules that repair DNA. In the human brain, defects in DNA damage repair are associated with several neurodegenerative disorders such as Huntington's disease. Identifying new molecules involved in DNA damage and repair may potentially lead to designing drugs that will mitigate neurodegeneration in HD patients. Sphingosine kinase 2 (SK2) is an enzyme that synthesizes a fat-like molecule that regulates a variety of cellular properties. Dr. Moruno-Manchon found that SK2 is overactive in HD, and it is toxic for neurons. Importantly, neurons with active SK2 have more DNA damage. An inhibitor of SK2 reduces neurodegeneration and DNA damage in neurons. Using a novel fluorescence microscopy system and neuronal models of HD, he plans to identify DNA repair proteins that are regulated by SK2, and determine how they participate in DNA damage and repair, and survival of HD neurons. A better understanding of SK2's role in DNA damage and repair could help to develop treatments for HD.

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**Christian Neri, Ph.D.**

**Institution: INSERM, Paris, France**

**Project Title: *Modeling the role of extracellular vesicles in HD pathogenesis***

Christian Neri received HDF funding for a project that extends his lab's seminal research on how a cell's ability to cope with stress is altered very early on in HD. In this project, Dr. Neri is examining the function and cargo of tiny sacs (known as *exosomes*) which can carry stress-signaling molecules to cells in different locations.

The project is expected to identify a new mechanism that could lead to new therapies to protect key areas of the brain affected by HD. The studies may also lead to the discovery of new markers useful for monitoring the effects of other drugs designed to regulate stress responses.

**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. Currently 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.

# HEREDITARY DISEASE FOUNDATION RESEARCH GRANTS

**Ghazaleh Sadri-Vakili, Ph.D.**

**Institution: Massachusetts General Hospital, Harvard University**

**Project Title: *Alterations in Hippo/YAP signaling as a pathogenic mechanism in Huntington's disease***

To develop new therapies for Huntington's disease, it is essential first to understand the exact cellular mechanisms that are not functioning properly. The key to this understanding is the way in which cells "communicate" within themselves and with each other, in particular through signaling pathways. The "Hippo" pathway is one such pathway and is of special interest because it regulates cell survival and death. For this reason, it has been the focus of much research in the field of cancer biology, which is characterized by rapid tumor growth.

Through preliminary work, the Sadri-Vakili laboratory has discovered that the Hippo pathway, particularly the subcomponents referred to as MST1/2 and YAP, is significantly altered in the brains of Huntington's patients. Additionally, similar changes were also measured in mouse models of HD.

It is not yet clear, however, if these changes are responsible for the death of neurons, a hallmark of HD. The goal of this project, therefore, is to clarify, through a series of experiments in cellular and mouse models, the role of Hippo signaling in HD.

In addition, Dr. Sadri-Vakili will determine, through a HD mouse model, if fingolimod, a drug already approved by the FDA for the treatment of multiple sclerosis, can reverse and restore the brain cell damage and changes in Hippo signaling present in Huntington's patients. If her studies demonstrate that the dysfunction of Hippo signaling contributes to neuronal death in HD, then she will have identified a new and valuable target for the development of future therapies.

**Anne Simonsen, Ph.D.**

**Institution: University of Oslo, Norway**

**Project Title: *Alfy at the Battlefront against Huntingtons Disease***

First identified by the work of Dr. Anne Simonsen, Alfy is a very large protein that targets protein clumps, known as *aggregates,* to a recycling pathway within the cell known as *autophagy*. Autophagy captures and then recycles many

different things in the cell. Alfy works by telling autophagy to specifically capture and recycle aggregates, and therefore can potentially help fight diseases such as HD.

Recent work on Alfy shows that if the amount of Alfy is increased in the cell, autophagy can capture and recycle more aggregates more quickly. Recently, work led by Drs. Nancy Wexler and David Housman identified a series of patients from the Venezuelan cohort who showed a delayed age of onset of HD by up to 23 years. These patients all possessed a subtle change in the Alfy gene.

Dr. Simonsen proposes to use her expertise in understanding whether this subtle changes causes the amount of Alfy in the cell to increase. In addition, she also proposes to identify how Alfy levels are increased, so that therapeutics can be designed to bring about similar changes to all HD patients.

**Joan Steffan, Ph.D.**

**Institution: University of California, Irvine**

**Project Title: *Analysis of an ubiquitin-binding domain within Huntingtin – 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 being funded by the Hereditary Disease Foundation to investigate 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. 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. Dr. Steffan's 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.

# HEREDITARY DISEASE FOUNDATION RESEARCH GRANTS

**Mary Wertz, Ph.D.**

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

**Institution: Broad Institute / Massachusetts Institute of Technology**

**Project Title: *In vivo genome-wide genetic screening for modifiers of mutant Huntingtin toxicity***

Although the gene linked to Huntington's disease, Huntingtin, was discovered over twenty years ago, to date there is no cure or fully effective treatment for this terrible disease. Thus there is a pressing need for basic studies to reveal new therapeutic targets.

Towards this goal, Dr. Wertz's project will perform a 'genetic screen' – a way of systematically testing the effects of each gene in the genome – to identify genes that change the toxicity of the mutant Huntingtin protein. Although such screens have been conducted before, they have not been conducted before in the context of nerve cells in the brain.

With Dr. Wertz's "in brain" genetic screen, and optimizations of it made possible by HDF funding, she has already identified many potential modulators of mutant Huntingtin toxicity. Many of these candidate modulators are novel to HD biology, giving hope that they will be able to soon elucidate a new class of HD therapeutic targets.

**Ai Yamamoto, Ph.D.**

**Institution: Columbia University**

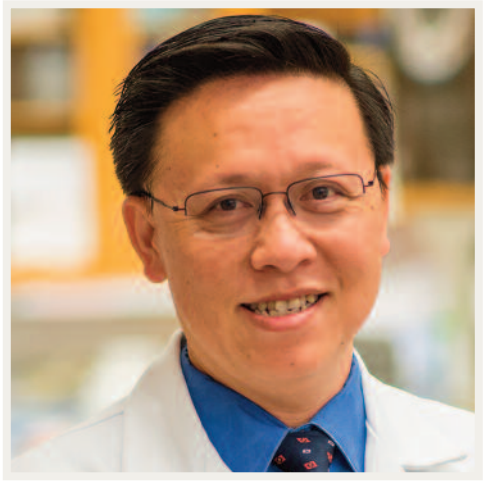
**Project Title: *ALFY-mediated Degradation and HD***

Ai Yamamoto was awarded Hereditary Disease Foundation funding to better understand how brain cells are able to remove abnormal huntingtin, the protein that causes damage in HD. Her focus is a protein called Alfy that helps to package up and dispose of clumps of harmful litter in the brain. In HD animal models, clearing away abnormal huntingtin deposits has led to improvements in symptoms, and Alfy plays an important role in cleanup.

This project aims to closely examine the huntingtin removal process by lowering or boosting levels of Alfy in HD mouse models, and testing how it affects their behavior. A better understanding of Alfy's function could help to identify therapeutic approaches to speed the elimination of damaging debris in HD brain cells.

# HEREDITARY DISEASE FOUNDATION RESEARCH GRANTS

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



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

**Project Title: *Novel Fan1 Knockin Mice to Facilitate Huntington's Disease Genetic Modifier Research***

Huntington's disease is a progressive neurodegenerative disorder caused by a genetic mutation consisting of CAG trinucleotide repeat expansion in the Huntingtin gene. The length of the abnormal DNA repeat is inversely correlated with the age when the patients become first affected by motor symptoms of HD, but other genetic and environmental factors can also contribute to the disease onset. Two recent genetic analyses of HD patients, one focusing on patients with European heritage, and another on those from Venezuela, have identified genetic variants that can either accelerate or delay the onset of HD symptoms. Importantly, both studies suggest a genetic locus containing the DNA repair pathway gene Fan1 may be involved in modifying the age of disease onset in HD. Fan1 was originally discovered as a component of a multi-protein complex that is involved in repairing DNA lesions. The role of the Fan1-containing protein complex has been extensively studied in cell types outside the brain (e.g. in the blood or kidney), but its role in normal brain development, function, and in neurodegeneration in HD remains unclear.

In this project, Dr. Yang will use mouse models to probe the role of Fan1 in normal brain function and in the pathogenesis of HD. First, he will examine if a deficiency of Fan1 could alter the molecular and pathological phenotypes in an HD mouse model expressing intact mutant Huntingtin. Second, he will study mouse models carrying Fan1 genetic variants derived from HD patients to assess if such variants can alter the phenotypic course of HD mouse models. Finally, he will create new mice expressing Fan1 with a protein tag, which will facilitate the visualization Fan1 protein in intact brain cells. The latter model may help to pinpoint the precise role of Fan1 in the healthy brain, and determine how Fan1 function may intersect with HD disease processes. Together, this study will provide novel resources and deeper knowledge on the role of Fan1 in HD, and insights from this study should bridge the gap between the identification of human genetic modifiers of HD and mechanistic insights that can inform novel therapeutic development.

*"The Hereditary Disease Foundation creates a culture of creativity, excellence, collaboration, and a sense of community and shared purpose, which helps to attract generations of scientists to join and stay in the field. Looking back at my 15 years of independent scientific career, it all started with my very first grant from HDF."*

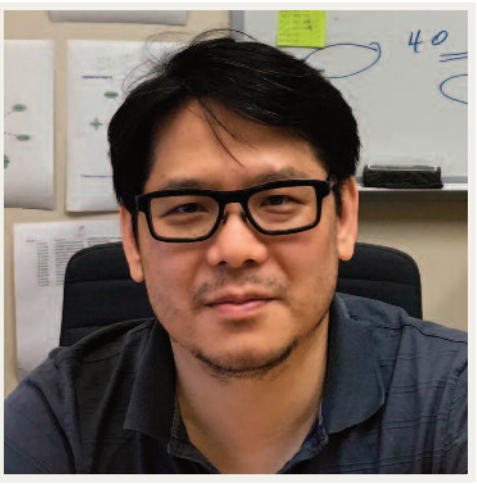
X. Willam Yang, 2017

# HEREDITARY DISEASE FOUNDATION RESEARCH GRANTS

**Andrew Yoo, Ph.D.**

**Institution: Washington University School of Medicine**

**Project Title: *Modeling Huntington's Disease with Patient Neurons Generated by Direct Neuronal Reprogramming***



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 through which we have been able 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 have begun, it has been difficult to test these ideas, given that these studies require the study of live human brain cells.

Recently, scientists, including Dr. Yoo, have shown that human brain cells can be created from human skin cells. 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 genes identified by Drs. Nancy Wexler and David Housman and others to alter the course of HD 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.

"If one looks back in the development of human genetics... I think the Hereditary Disease Foundation played really the same role that the Rockefeller Foundation played in the 30's and 40's, when it permitted the development of molecular biology.

It was a small group of people who were not waiting around, but rather were giving money to the right people, with the thought that it was sensible."

James D. Watson, Ph. D.
Nobel Laureate
Chancellor Emeritus
Cold Spring Harbor Laboratory