

# Research Report 2016



## 2016: The Momentum is Building...

Some years are less about headlines and more about steady progress towards goals. 2016 was clearly one of those years. As our work to support new therapies and curative treatments for Huntington's disease continues, our patience continues to be tested, even as our hope builds. The breakthroughs in HD care that we seek are still on the horizon, but they are closer than ever which is why we want to reflect on all the progress and momentum that has been built in the HD research community over the past 12 months.

In just this last year, three HD clinical trials - from Teva, Pfizer and Vaccinex - all completed their recruitment. The Enroll-HD registry and observational platform enrolled its 10,000th participant. Teva submitted a novel new drug application to the FDA for approval to combat the motor symptoms associated with HD. Ionis Pharmaceuticals announced that they have started administering the highest and final dose of their antisense oligonucleotide (ASO) to early stage HD patients in the first of its kind study to investigate a huntingtin lowering drug. Finally, a new study was initiated by Azevan here in the US to see if their drug, SRX-246 can improve irritability and aggression in HD patients.

Research and care programs at Huntington's Disease Society of America (HDSA) demonstrated great progress in 2016 as well. HDSA expanded their network of Centers of Excellence to 39 comprehensive care centers across 30 states. We continued to expand our patient-focused research commitments and launched a new call center to complement the HDTrialfinder and further accelerate the clinical development of new HD drugs.

Since 2012, HDSA has awarded over \$3 million to the HD Human Biology Project. The Human Biology Project is a critical piece of HDSA's mission to support impactful HD research that will help guide us closer to effective therapies. The research we support is all patient-centric and done in collaboration with HD clinics from around the globe with the goal of understanding HD in the only place it occurs, in *humans*. In this report, you will see summaries of the nine new research projects HDSA is supporting as of November. In addition, the first HDSA Berman-Topper Family HD Career Development Fellowship, was awarded in 2016 to provide a bright young scientist with the time and resources to allow transition into an independent HD investigator.

These achievements all have one thing in common. They could not have been achieved without the participation of HD families. We are indebted to the brave HD research Heroes around the world who volunteer selflessly so that we will not have to wait another generation for effective HD treatments. Thank you for being the engine that is literally powering HD science!

Today, there are approximately 10 companies actively pursuing different approaches to reduce huntingtin, the root cause of HD. While the technologies hold great promise, the only way to figure out if they will work for HD is to study them in people. 2017 and beyond will provide many additional opportunities to get involved in HD clinical trials. I have no doubt that the HD community will continue to rise to these challenges.

As I look back on the last year, I am inspired by the progress that has been made and the momentum that continues to build. While it's taking longer than anyone wants, I am more confident than ever that a day when we can change the course of HD to treat and stop it is closer than ever. May 2017 be the year when we can bring relief and hope to you – our HD families.

Thank you,



~ George Yohrling, PhD  
HDSA Senior Director, Mission & Scientific Affairs



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## HUNTINGTON'S DISEASE SOCIETY OF AMERICA AWARDS \$930,000 TO NINE NEW HD HUMAN BIOLOGY FELLOWS

This November, the Huntington's Disease Society of America (HDSA) announced that nine research grants have been awarded under the Society's largest research initiative, the HDSA Huntington's Disease Human Biology Project. Totalling \$930,000, these grants represent HDSA's patient-centric research focus which brings basic and clinical researchers together to facilitate Huntington's disease (HD) science in the human condition, instead of in animal models, with the direct participation of people affected by HD.

"Now in its fourth year, the HD Human Biology Project is the perfect combination of innovative patient-focused research

and development of the world's brightest young scientists to ensure a robust pipeline of researchers for the future", said George Yohrling, PhD, Senior Director, Mission and Scientific Affairs at HDSA. "This year's fellows represent the best in pursuits of novel HD human biology from all around the globe, and their research will push the boundaries of HD knowledge to inform vital topics such as Juvenile-onset HD, biomarker identification, stem cell technology and symptomatic treatment."

HDSA received applications from researchers from all around the world. Ultimately, grants were awarded to nine research fellows, from the US, Canada and Spain.

The winners and titles of the 2016 HDSA HD Human Biology Project Grants are:

- **Dr. Madeleine Sharp**, Assistant Professor, McGill University, Canada: *Striatal-dependent reward processing: A substrate for early behavioral symptoms in Huntington's disease*
- **Dr. Wasim Malik**, Assistant Professor, Harvard Medical School/ Massachusetts General Hospital: *Oculomotor assessment as a potential biomarker for Huntington's disease*
- **Steven Marinero**, Graduate Student, Duke University: *Brain infiltration of peripheral blood mononuclear cells in driving neurodegeneration in Huntington's disease*
- **Dr. Natalia Pessoa Rocha**, Research Fellow, University of Texas Health Science Center at Houston: *Microglial activation in HD: A structural and functional study*
- **Alan Phipps**, Graduate Student, Indiana University: *Efficacy of tDCS for improving gait in HD*
- **Dr. Rocio Gomez-Pastor**, Research Fellow, Duke University: *Prevention of subnormal degradation of the neuronal protective factor HSF1 in Huntington's disease*
- **Dr. Lisa Salazar**, Assistant Project Scientist, University of California at Irvine: *Molecular and cellular assessment of huntingtin lowering in differentiated patient-derived HD iPSCs*
- **Charles Mosier**, Research Associate, University of California at San Diego: *Proximal Huntingtin Protein Interaction Networks in Human Juvenile and Early Adult HD Brains Analyzed by Proteomics and Systems Biology*
- **Dr. Veronica Ines Brito**, Research Fellow, University of Barcelona Medical School: *Study of mitochondrial outcomes as biomarkers of Huntington's Disease progression and/or readouts of pharmacological interventions*

"HDSA is proud to support these talented individuals who are bringing their curiosity and insights into the HD field," said Louise Vetter, Chief Executive Officer of HDSA. "The HD Human Biology Project is a unique and important research program which continues our tradition of moving HD science forward so that improved care and potential cures can be made available to families affected by HD as soon as possible."



# Summaries of 2016 HDSA- funded HD Human Biology Projects *In Their Own Words*

## **Dr. Madeleine Sharp,**

Assistant Professor,  
McGill University, Canada

*Title: Striatal-dependent reward processing: A substrate for early behavioral symptoms in Huntington’s disease.*



Huntington’s disease affects a part of the brain called the striatum that we know is very important for controlling behavior. The striatum sends signals about the ‘rewards’ experienced in our environments to the rest of the brain. These rewards can be anything: a delicious meal, attaining a goal, a nice hug, or a good grade. The ability to properly send signals about these rewards is critical because most of what we think, remember, learn and do is controlled or guided by reward: we remember positive experiences, we learn from good outcomes, we strive to do well and we pay attention to what matters. In the early stages of HD, most of the disease in the brain is in the striatum. If the striatum is so important for informing the rest of the brain about reward, could reward signaling be impaired in patients with HD? Also, we know that the majority of people with HD experience behavioral symptoms like loss of motivation or a tendency to perseverate on certain ideas or actions. Since these symptoms happen even in the early stages of the disease, can these symptoms be explained by an inability of the striatum to properly signal rewards? In fact, we know that in people with other diseases that involve the striatum such as Parkinson’s disease, these symptoms are related to abnormal reward signals in the striatum. But this has never been tested in HD. The goal of this project is to determine if reward signaling is impaired in people with HD. We think that this could help us design better treatments for behavioral symptoms.



## **Dr. Wasim Malik,**

Assistant Professor, Harvard  
Medical School/Massachusetts  
General Hospital

*Title: Oculomotor assessment as a potential biomarker for Huntington’s disease.*



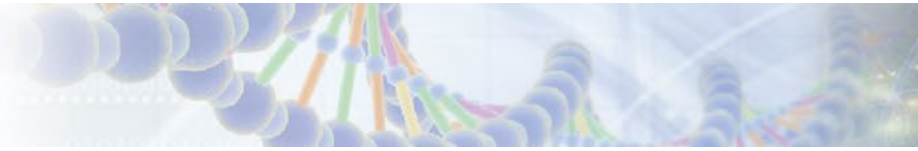
The goal of our research is to develop a novel eye-movement technique to aid the diagnosis and progression monitoring of Huntington’s disease (HD). We will conduct a pilot study using a portable eye-tracking system, with custom-developed analysis software. We will identify abnormal eye-movements that may indicate the presence and severity of HD. We will then use state-of-the-art techniques in machine learning and big data analytics. These analyses are inspired from great successes in real-world medical problem-solving also used by Google, IBM Watson and others. By analyzing the unique data through innovative artificial intelligence approaches, we expect that work will lead to a better way for HD’s early diagnosis and to monitor its progression. Ultimately, this technique may be used to improve clinical trials and clinical management in HD.

## **Steven Marinero,** Graduate Student, Duke University

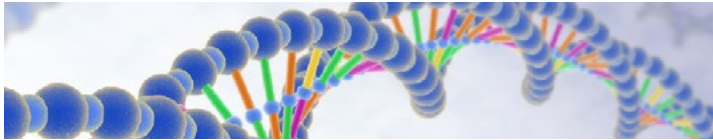
*Title: Study of CAG repeat expansion impact on huntingtin mRNA cellular localization for a rational design of next generation oligonucleotide-based therapeutics.*



While much study has been devoted to genetic “triggers” of CNS neurodegeneration—notably mutant Htt in Huntington’s disease (HD)—such inherited triggers are typically expressed from early fetal development and are fundamentally inaccessible to timely clinical intervention. In contrast, later and significant “drivers” of the forward rate and extent of disease pathogenesis may present as more favorable and effective therapeutic targets. In this context, the present proposal focuses on neuroinflammation as a likely significant driver of later stages of HD disease progression. Peripheral macrophages are especially favorable targets because of their location in an easily drug accessible



compartment, namely the blood, prior to their infiltration into the brain in later stages of disease. Yet defining relative roles for infiltrating peripheral blood monocyte-derived macrophages (MDMs) vs. endogenous microglia in CNS disease has been challenging. Here, we will take an *ex vivo* engraftment strategy which will give us a unique opportunity to investigate the role of MDMs in a *bona fide* brain tissue setting where the identities of infiltrating MDMs vs. endogenous brain microglia can be clearly distinguished. In particular, we will be able to ask the critical question of whether MDMs from HD patients have altered functional impact on HD neurodegeneration, enabled by support and collaboration from the HDSA Center of Excellence at Duke.



**Dr. Natalia Pessoa Rocha,**

Research Fellow, University of Texas Health Science Center at Houston

*Title: Microglial activation in HD: A structural and functional study.*

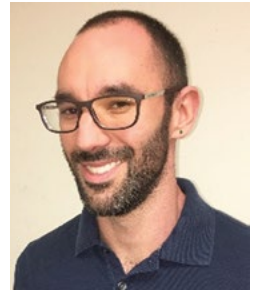


The objective of this study is to investigate (try to figure out) the role played by microglia in different stages of Huntington's disease (HD). Microglia are the brain immune cells. They play an important role as mediators of inflammatory response to infection and injury inside the brain. For this, we intend to do a positron emission tomography (PET) scan and blood analyses. A PET scan is a type of imaging test. It uses a radioactive substance called a tracer to look for some characteristic in the body. In this study, we will use a radioactive substance to trace microglia in the brain. In addition, we will collect peripheral blood in order to analyze the profile of blood immune cells. Then, we will try to analyze whether inflammation in the brain (through PET scans) is associated with inflammation in the blood (through blood exams). This will help the study doctors (researchers) to understand the immune / inflammatory mechanisms that are involved in HD. The results obtained from patients with HD in different stages will be compared with controls (i.e., individuals with no neurological disorder). The researchers expect to increase the understanding of physiological changes associated with HD (mainly immune system-related changes). Our results can foster the development of new therapeutic interventions targeting inflammation in HD.

**Alan Phipps,**

Graduate Student,  
Indiana University

*Title: Efficacy of tDCS for improving gait in HD.*



Impaired gait has a tremendous impact on the lives of Huntington's disease (HD) patients, limiting their ability to safely navigate their surroundings. This deficit puts HD patients at an increased risk of falling. Such difficulties in gait may result from the over-excitability of the brain's motor cortex that occurs after degeneration of certain basal ganglia pathways in HD. Here we propose to investigate the potential of transcranial direct current stimulation (tDCS) to improve gait and brain excitability in HD patients. tDCS is a safe, noninvasive brain stimulation technique that can painlessly increase or decrease the excitability in a targeted region of the brain. Current research shows that tDCS is effective in improving motor function and brain excitability in stroke and Parkinson's disease patients. This would be the first study to investigate the potential benefits of tDCS in HD patients. To assess gait, subjects will walk on a motorized treadmill for 10 minutes.

While walking, footswitches placed in the subject's shoes will allow us to determine foot placement timing during gait. Additionally, electrical activity from several lower limb muscles will be recorded during gait by taping electrodes to the skin. We predict that inhibitory tDCS in HD patients will decrease brain excitability and improve gait. If so, this would suggest that tDCS could be used to counteract over-excitability of the motor cortex in HD patients, yielding improved gait. With no cure for HD available, treatment goals are to limit symptom management, frequently by pharmacological means. Unlike medications used to manage HD, tDCS has no side effects. This study may have important implications for daily functioning and fall risk in HD patients by reducing brain excitability and therefore improving gait.

**Dr. Rocio Gomez-Pastor,**

Research Fellow, Duke University

*Title: Prevention of subnormal degradation of the neuronal protective factor HSF1 in Huntington's disease.*



HD is caused by a variation in the HTT gene that encodes a protein (huntingtin) that misfolds, thereby causing dysfunction and death of neurons



and muscle cells. Under normal conditions cells possess molecular machinery, orchestrated by the master regulatory protein HSF1 that prevents protein misfolding and maintains cell function and viability. However, in cellular and mouse models of HD, and most importantly, in HD patients, this machinery is impaired. We have identified why the HSF1-dependent cellular protection mechanism is defective in HD, not only in the brain, but also in small biopsies taken from the leg muscle. We have demonstrated that inhibition of the HSF1 degradation process has potential for HD therapy in mice and that the inappropriate HSF1 degradation machinery is conserved from mouse HD models to a limited number of human HD patient samples. This project proposes to determine if the HSF1 degradation machinery is found in tissues from both postmortem HD patient brain, and in living HD patient muscle, skin and fat to validate the involvement of this pathway in Human HD patients. Since we have demonstrated that modification of the HSF1 degradation pathway improves symptoms in a mouse HD model, demonstrating the conservation of this pathway in humans will provide a strong foundation for developing therapies through the HSF1 protective mechanism in humans.

### **Dr. Lisa Salazar,**

Assistant Project Scientist,  
University of California at Irvine  
*Title: Molecular and cellular assessment of huntingtin lowering in differentiated patient-derived HD iPSCs.*



Huntington's disease (HD) is a devastating neurodegenerative disease that strikes in the prime of life. Patients experience progressive impairment of motor and cognitive function, as well as other symptoms, and treatments to slow disease progression remain elusive. Because disease is caused by mutation of the huntingtin (HTT) gene, one strategy for disease intervention, now in clinical trials, is to reduce production of the HTT protein. Using HD patient-derived stem cells, we are generating cell lines in which total or mutant HTT levels can be reduced at the stem cell stage, or any time during their development into mature neurons. This will allow us to evaluate the consequences of



reducing total HTT compared to those of preferentially lowering mutant HTT. This is important because the question remains whether decreasing expression of wild-type HTT will have more subtle adverse effects. This strategy will further enable us to begin to identify which disease characteristics can be rescued, especially when intervention is given to more mature cells, as it would be in patients. Specifically for the proposed studies, we will examine the ability of HTT lowering to rescue gene expression, cell viability and metabolic function, resulting in the identification of relationships between gene expression and cell function that might inform benefits and side effects of HTT lowering treatments and provide signatures amenable to rescue that can be targeted in small molecule screens.

### **Charles Mosier,**

Research Associate, University  
of California at San Diego  
*Title: Proximal Huntingtin Protein  
Interaction Networks in Human  
Juvenile and Early Adult HD Brains  
Analyzed by Proteomics and  
Systems Biology.*



Huntington's disease (HD) is caused by trinucleotide repeat (CAG) expansions in the HTT gene, encoding huntingtin (Htt) protein with increased polyglutamine (polyQ) tract. Juvenile HD patients with >60 repeats display early age of onset in children compared to adult HD patients with ~38-55 repeats, while normal patients have 10-35 repeats. The tremendous difference in age of onset of juvenile and adult HD predicts differences and similarities in mutant Htt protein interactions that lead to neurodegeneration and deficits. Therefore, the goal of this human-focused project is to investigate human juvenile HD brains for Htt interacting proteins that will be evaluated for mediating mutant Htt-induced neuronal cell death. Data will be compared to parallel studies on human adult HD brain tissues (including early stages of the HD disease process) for Htt protein interactions. This research will assess the hypothesis that juvenile HD involves distinct and similar sets of proteins interacting with mutant Htt in a polyQ-length dependent manner to initiate molecular pathways leading to neuronal cell death, compared to human early adult HD. Results will define differences and/or similarities in mechanisms for early onset juvenile HD compared to adult HD. Findings will logically lead to new drug target opportunities to address the unmet need for effective therapeutic drugs to improve the lives of juvenile and adult HD patients.



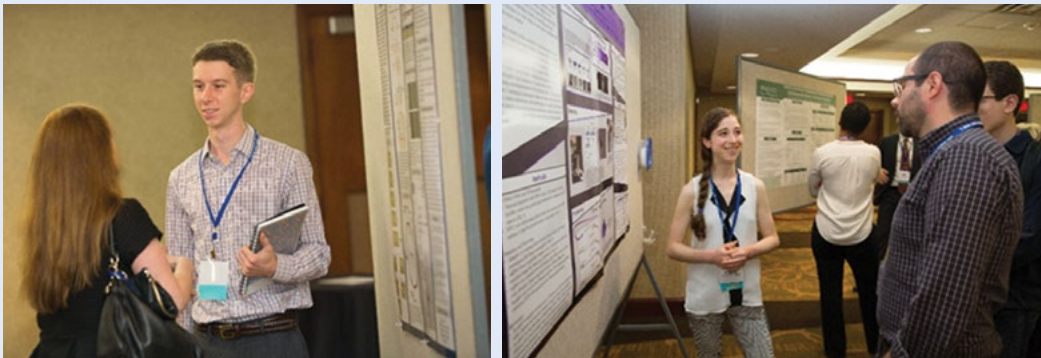
**Veronica Ines Brito,**  
 Research Fellow, University of  
 Barcelona Medical School  
*Title: Study of mitochondrial outcomes  
 as biomarkers of Huntington's Disease  
 progression and/or readouts of  
 pharmacological interventions.*



In people carrying the HD genetic abnormality, many brain cells become damaged and eventually die even before the main outward symptoms appear. Thus, timing of the brain changes and the outward symptoms of HD are completely disconnected. Therefore, HD treatment success requires intervention at early disease stages before extensive brain cell loss. To achieve proper neuroprotective therapies we need tracking tools known as biomarkers to monitor the status of the disease and the early brain changes. Among different pathological processes there is much evidence implicating mitochondria alterations in cell problems since mitochondria produce the

vast majority of energy but also damage and highly reactive molecules. Moreover from research in HD and other human diseases there is growing evidence that the same mechanisms of disease can be shared by the brain and peripheral tissues. Importantly, in HD the mutant protein is expressed in almost all cells. With this in mind, we would like to explore and identify in dermal fibroblast obtained from control and HD patients' biopsies (pre-symptomatic and symptomatic) different signs of mitochondrial dysfunction. We will focus in mitochondrial processes previously described to be altered in HD brain such as mitochondrial dynamics, bioenergetic and oxidative stress and we will correlate these outcomes with different clinical characteristics. Moreover we will explore for alterations in the expression of newly DNA-like molecules (miRNAs) that can affect mitochondrial function in these peripheral tissues. This part of the study has the potential to find novel aberrant miRNAs associated to mitochondrial dysfunction but also to identify other miRNAs in dermal fibroblast that could reveal specific targets for treatment or biomarkers of disease progression.

## HDSA held the 3<sup>rd</sup> Annual Donald King Research Session at the 2016 Convention in Baltimore, Maryland



**2015 Donald King Fellows, Rogan Grant (top left), Brianna Bibel (top right) and Patrick Hogan (bottom left) are shown presenting the findings of their research to the attendees of the 2016 HDSA Convention in Baltimore, Maryland**



**2016 HDSA Research Forum Keynote Address Speakers Dr. Walter Koroshetz, Director of the National Institute of Neurological Disorders and Stroke (left) and Dr. Robert Pacifici, Chief Scientific Officer of CHDI Foundation (right) address the approximately 950 attendees of the 2016 HDSA Convention in Baltimore, Maryland.**





# HDSA Announced the Winners of 2016 Donald A. King Summer Research Fellowship

## Scientists working at University of Iowa, Institute for Systems Biology and Children’s Hospital of Philadelphia awarded fellowships to work on Huntington’s disease projects

In April 2016, the Huntington’s Disease Society of America (HDSA) announced the recipients of the 2016 Donald A. King Summer Research Fellowships, a vital program to train the next-generation of scientists with research expertise in neurodegenerative disorders, especially Huntington’s disease. The HDSA Scientific Advisory Board carefully reviewed and scored the proposals using several criteria such as: the quality of the candidate’s academic achievements, mentoring plan for candidate, scientific rigor of the experimental design and feasibility to achieve significant deliverables in a short summer timeframe.

Three impressive students were selected as recipients of the 2016 Donald A. King Summer Research Fellowship:

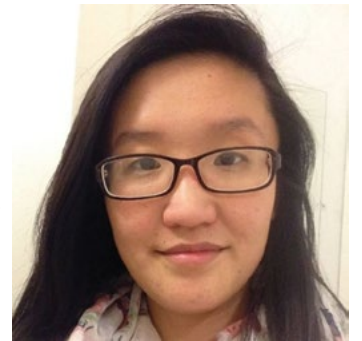
- **Mr. Lance Heady** (University of Iowa) worked at the University of Iowa with Dr. Andrew Pieper. Lance utilized a *Caenorhabditis elegans* (worm) model of HD to study the effectiveness of a novel class of neuroprotective compounds.



- **Ms. Dani Bergey** (Montana State University). Dani spent the summer working with Dr. Nathan Price at the Institute for Systems Biology in Seattle, Washington on a project entitled “Characterization of transcriptional networks underlying tissue selectivity in HD neurodegeneration”. She used computational analyses of gene expression data to try

to understand why neurodegeneration is seen first in the striatum of HD patients.

- **Ms. ShuJuan Zheng** (University of Pennsylvania). ShuJuan worked under the guidance of Dr. Beverly Davidson, a leader in the field of gene therapy for HD, at the Center for Cell and Molecular Therapy at the Children’s Hospital of Philadelphia. Her project assessed the ability of different viruses that are used to deliver gene silencing drugs to spread in the different cellular populations in the brain.



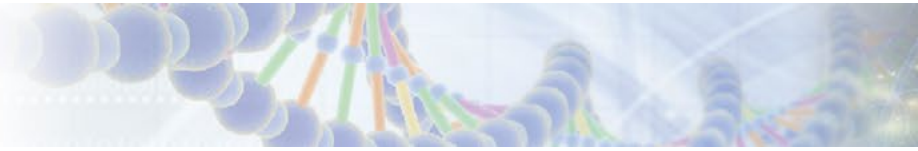
HDSA established the Donald A. King Summer Research Fellowship program in 2005 in honor of Donald King who passed away in 2004. Don was a tireless advocate for HD families and served as HDSA’s Chairman of the Board from 1999 to 2003. The purpose of this fellowship program is two-fold: first, to attract the brightest young scientists into the field of Huntington’s disease research and secondly, to facilitate meaningful HD research to clarify the biological mechanisms underlying HD pathology.

We look forward to hearing about their promising research at the 2017 HDSA Convention.



Renaissance Schaumburg Hotel & Convention Center





## Donald King Summer Research Fellow Spotlight:



### **Dani Bergey**

Dani Bergey is a Research Associate at the Institute for Systems Biology. She works in the labs of Dr. Nathan Price and Dr. Lee Hood where she performs research on neurodegenerative disorders including Huntington's disease (HD). Dani enjoys doing neuroscience research in groups that utilize the capabilities of

math and statistics. Her background is in Cell Biology and Neuroscience with a minor in Mathematics from Montana State University in Bozeman, MT. For her undergraduate research, Dani studied Familial Dysautonomia in Dr. Frances Lefcort's developmental neuroscience lab. Having a family friend with HD motivated Dani to study neuroscience in college and to pursue HD research following her coursework.

Dani was awarded a 2016 Donald A. King Summer Research Fellowship. With the funding from this award, she was able to pursue valuable training in programming and statistical modeling in the context of brain disease. Under the leadership of Dr. Nathan Price and Dr. Seth Ament, Dani used RNA-sequencing data from a mouse model of HD to characterize gene expression changes in brain regions and cell types throughout disease progression.

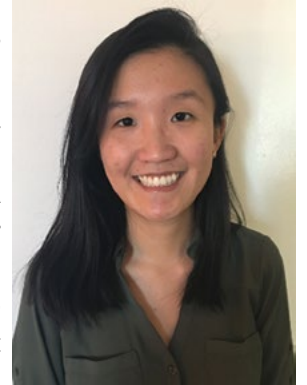
The type of cells that undergo the most dramatic degeneration in HD are neurons that reside in the striatum. Her results support the notion that along with neurons, glial cells hold an important role during disease progression. In particular, she found a specific group of cells that undergo significant gene expression changes in the same time frame as striatal neurons. This trend is not limited to the striatum, but also occurs dramatically in the cortex. Her summer research contributes to understanding the unique responses of various cell types and tissues to the mutant huntingtin protein.

When not in the lab, Dani is a soccer enthusiast and an artist. This past year, she illustrated a mini textbook for a health sciences program called BioScience Montana, with topics spanning neuroscience, metabolomics, and infectious diseases. She is considering graduate programs in biomedical

visualization or a research track in computational neuroscience. Dani strives for a career that joins science education and outreach, human disease, and the arts.

### **ShuJuan Zheng**

ShuJuan Zheng is currently a senior at the University of Pennsylvania, majoring in biology with a concentration in neurobiology. This summer, with the support of HDSA through the Donald King Summer Research Fellowship, she was able to conduct a project evaluating the transduction efficiency of different adeno associated viruses (AAV)



serotypes in the striatum and in neuronal populations affected by Huntington's disease (HD). This study provided further information about AAV as a gene therapy agent that can be used to treat HD in the future. This experience was significant in shaping her science career. It gave her a sense of the science that she wants to accomplish in the future.

During her last school year, Shu will be working on an independent research project evaluating the transduction of cardiotropic AAV to the heart and assessing the amino acid peptides that allow for this specificity. In addition, she is continuing the work initiated by the fellowship by quantifying the transduction of the AAV serotypes to interneurons and medium spiny neurons. Both projects are being carried out in Dr. Beverly Davidson's lab at CHOP. Shu is very grateful for the opportunity provided by the foundation to begin the project and the invaluable mentorship that Dr. Beverly Davidson has provided.

After graduation, she will take a gap year to explore possible future paths by continuing as a research assistant in Dr. Beverly Davidson's lab. She is interested in both neuroscience and genetics research. In the future, she would also like to continue contributing to research for novel cures to neurodegenerative disease such as HD. During her rare spare time away from research and classes, Shu volunteers at the Penn hospital and local community service projects. She also enjoys making home cooked meals for her roommates, and trying out new recipes.

# HDSA's HD TrialFinder Adds Live Call Center

In 2015, the Huntington's Disease Society of America launched HD TrialFinder ([www.HDTrialFinder.org](http://www.HDTrialFinder.org)), an exciting and much needed new resource for HD community. HD TrialFinder is a free, easy-to-use clinical trial matching service that connects individuals with Huntington's disease, caregivers, healthy volunteers and physicians with current studies. Powered by Emerging Med, the continuously updated database includes - interventional, observational and biomarker studies being conducted at clinical trial sites across North America.

Starting in 2016, HDSA added a live call center component to HD TrialFinder. Now, HD families can call 866-890-6612 between 9:00 a.m. and 5:00 p.m. eastern time and speak to

an HDSA-trained Clinical Trial Navigator. The Navigator is there to assist families with customer service needs related to the HD TrialFinder.org website as well as provide important clinical trial information to those who may not have access to a computer.

Currently, there are clinical research opportunities for every member of the Huntington's community to join, unlike other websites like clinical trials.gov, which are not HD patient focused, HD TrialFinder works closely with corporate and academic partners to provide information about all currently recruiting trials in lay language that is easy for HD families to understand.

## How to use HD TrialFinder:

### Step 1

Go to [www.hdtrialfinder.org](http://www.hdtrialfinder.org) to create an account or log in if you already have a username and password or, dial 866-890-6612 between 9am and 5pm EDT to speak with an HD Clinical Trial Navigator.

### Step 2

Complete a brief questionnaire about yourself or the HD impacted individual.

### Step 3

Review your clinical trial match results. HD TrialFinder will compare your unique profile to its comprehensive, continually updated clinical trial database.

### Step 4

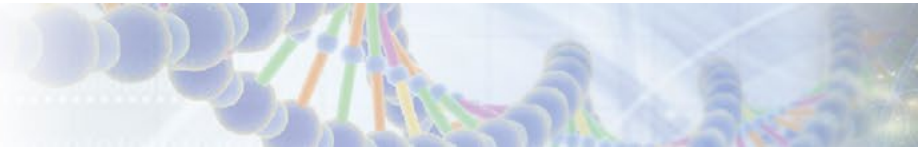
Contact your nearest HD clinical center to speak with a study coordinator and get involved. As new clinical trial sites become active in your local area, HD TrialFinder will automatically notify you.

“Recent studies suggest that more than 80 percent of all clinical trials are delayed due to the inability to recruit participants in a timely manner,” said George Yohrling, PhD., Senior Director, Mission and Scientific Affairs at HDSA. “Families have been waiting generations for the day when potential disease modifying therapies for HD would be developed. Well, that time is now upon us so we should do everything in our power to ensure no HD clinical trial is delayed.”

HD TrialFinder was created to be a resource for the entire HD community. This is evident in the fact that numerous HD organizations such as CHDI Foundation, Huntington Study Group, Huntington Society of Canada, HD Buzz and Help4HD have all joined HDSA as partners in clinical trial awareness

and education by promoting use of HD TrialFinder among their constituents.

“HD TrialFinder is one of the most valuable tools the HD community has at its disposal”, says Dr. Ed Wild (University College of London, Institute of Neurology). “As a researcher, and HDSA-supported communicator of HD research news via HDBuzz, I spend a lot of time and effort educating family members about all the cool research that’s happening, and getting them motivated and excited to take part in clinical trials. HD TrialFinder brilliantly capitalizes on that motivation, supplying up-to-date, customized research opportunities and connecting patients to researchers in a few mouse clicks. It is a critical tool for recruiting the volunteers we need to help beat Huntington’s disease.”



## HD Trialfinder

### Facts about HD TrialFinder

- Since its launch in 2015, over 2100 people have signed up for HD TrialFinder.
- There are currently 19 different HD clinical trial opportunities the HD TrialFinder database that are looking for participants.
- HD TrialFinder trial listings are updated daily to provide HD families with the most up-to-date HD clinical trial information.
- Only North American trials that are currently recruiting participants are listed in the HD TrialFinder database.
- Unlike other resources, HD TrialFinder provides direct contact information to the sites nearest you so that you have a name, phone number and email for you to reach out and get involved.
- HD TrialFinder is the only HD specific clinical trial navigation resource for HD families to offer customer support with Clinical Trial Navigators who are there to support you and follow-up with you to help you get involved.

## HDSA Community Showcased at Annual Huntington Study Group Meeting

In November, approximately 450 researchers, clinicians, advocates and members of the local HD community convened at the Gaylord Opryland Hotel in Nashville, Tennessee to discuss the latest breakthroughs in HD clinical research at the annual Huntington Study Group (HSG) conference entitled "HSG 2016: Discovering Our Future!".

The meeting kicked off with a special symposium to propose a new clinical score that could be used in future HD clinical trials aiming to slow the clinical progression in early HD patients. This new "score" is a composite score of four different aspects of the Unified Huntington's Disease Rating Scale (UHDRS). Statisticians presented compelling data to suggest that combining the Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modality Test (SDMT) and Stroop Word Test (SWT) into one score has a significantly greater signal to noise ratio than any of the 4 measurements alone. This is important because development and utilization of clinical scores with greater signal will allow trials to be run with fewer volunteers. The fewer volunteers needed, the quicker sites can recruit. The quicker sites recruit, the quicker we can complete a study and get results. Most importantly, requiring fewer volunteers will have a large impact on the lives of both patients and caregivers.

The next two days brought together clinicians and scientists that represent the HSG, EHDN and HDSA to discuss a wide range of topics such as: clinical trials results, upcoming clinical trials, development of new biomarkers for HD, clinical care models and scientific breakthroughs. The final day of the HSG conference was dedicated to the HD families. During the morning research symposium attendees got an overview

of the regulatory path for HD drugs by representatives of the FDA. In addition, updates on a number of clinical trials as well as the progress and challenges ahead as scientists aim to develop stem cell-based therapies as novel treatments for HD were shared. The conference closed with an HDSA Educational Day where local families heard from HDSA CEO Louise Vetter, superstar advocate and NYA member Havanna Lowes and got the opportunity to interact in small breakout sessions to share their experiences on talking about HD as a family, dealing with late-stage HD and genetic testing.

This year, the HSG invited the 2014 HDSA Human Biology Project Fellows (Dr. Regina Kim, University of Iowa; Dr. Dawn Loh, UCLA; and Dr. Sonia Podvin, UC-San Diego) to attend to present their patient focused research findings to the HD research community.



**Louise Vetter, CEO of HDSA and Havanna Lowes, NYA member and advocate, speak to HDSA HD Family Day attendees during the HSG Annual Conference in Nashville, TN**



# HDSA Designated Thirty-Nine Centers of Excellence in 2016

In February the Huntington’s Disease Society of America (HDSA) proudly announced that thirty-nine outstanding Huntington’s disease care facilities were awarded the designation of HDSA Centers of Excellence for 2016. Up from 29 Centers last year this represents a 34 percent increase in the reach of the program.

The HDSA Centers represent an exemplary commitment and established expertise in HD to bring more comprehensive care to more HD affected families across the United States. With 39 Centers, HD families will have more ‘boots on the ground’ support with locations in 30 US states. This year, HDSA allocated \$1,092,250 to the Centers of Excellence program which is a 38 percent increase in funding from the \$790,000 awarded in 2015.

“The expansion of the HDSA Center of Excellence program to nearly forty clinical care centers means that thousands of new families will have more resources and support in their fight against HD,” said Louise Vetter, HDSA’s Chief Executive Officer. “We are incredibly grateful for the generosity of the HD community, whose efforts make these awards possible, and thankful for the dedication and commitment to world-class care that our HDSA Centers of Excellence provide.”

The HDSA Centers of Excellence provide an elite team approach to Huntington’s disease care and research. Patients benefit from expert neurologists, psychiatrists, therapists, counselors and other professionals who have deep experience working with families affected by HD and who work collaboratively to help families plan the best HD care program throughout the course of the disease. Applications to become an HDSA Center of Excellence are open to all clinics in the United States who share HDSA’s commitment to high-quality, comprehensive care and access to clinical research.

The review of Center of Excellence applications was led by the volunteer-led HDSA Center Program & Education Advisory Committee (CPEAC). The CPEAC solicited letters of interest from all clinics in the United States who share HDSA’s commitment to high-quality, comprehensive care and access to clinical research.



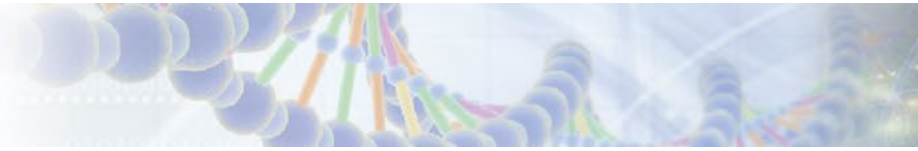
The 2016 HDSA Center of Excellence grantees is listed below alphabetically:

- Albany Medical College (NY)
- Beth Israel Deaconess Medical Center (MA)
- Cleveland Clinic (OH)
- Colorado Neurological Institute
- Columbia Health Sciences/NYS Psychiatric Institute (NY)
- Duke University (NC)
- Emory University (GA)
- Georgetown University (DC)
- Hennepin County Medical Center (MN)
- Indiana University
- Johns Hopkins University (MD)
- Massachusetts General Hospital
- Ochsner Health System (LA)
- Ohio State University
- Rush University Medical Center (IL)
- Stanford University (CA)
- University of Alabama, Birmingham
- University of California, Davis Medical Center
- University of California, Los Angeles
- University of California, San Diego
- University of California, San Francisco
- University of Colorado
- University of Florida
- University of Iowa
- University of Louisville (KY)
- University of Miami (FL)
- University of Nebraska Medical Center
- University of Pennsylvania
- University of Pittsburgh Medical Center (PA)
- University of Rochester (NY)
- University of South Florida
- University of Texas Health Science Center- Houston
- University of Utah
- University of Vermont, Frederick Binter Center for Parkinson’s Disease & Movement Disorders
- University of Virginia
- University of Washington (WA)
- Vanderbilt University Medical Center (TN)
- Virginia Commonwealth University
- Washington University School of Medicine (MO)

Blue = NEW COE for 2016

COE Coverage in 2016  
30 states





## Optimism on Display among HD Researchers at the 11<sup>th</sup> Annual CHDI Therapeutics Conference in Palm Springs

As in years past, The Parker Hotel in Palm Springs, California hosted the 11th Annual CHDI Therapeutics Conference this February. The conference brought together over 300 of the world's leading HD scientists and drug hunters for four days of intense scientific updates on the progress being made to bring effective therapies forward for HD. There are many HD relevant meetings, however, this meeting remains the only conference dedicated to providing an open forum for HD "drug hunters", pharmaceutical and biotech companies working on HD. The spirit of the entire conference is collaborative and open. There is a true sense that all are there not for themselves or their company, but to truly make a difference in the lives of HD patients.

The conference began with CHDI scientific management providing updates on their pre-clinical and clinical portfolios. Drs. Vogt, Dominguez and Sampaio of CHDI presented updates from the systems biology, chemistry and clinical teams respectively. One exciting and noteworthy project being developed by CHDI is the creation of a PET ligand to detect the huntingtin protein in the brains of HD patients. Basically, the PET ligand is a drug/chemical that recognizes the huntingtin protein and binds to it when it is administered to a patient. The chemical is tagged with short-lived radioactive molecule that would allow scientists to see where in the brain the huntingtin protein is using a Positron Emission Tomography (PET) scanner. While this drug will never be a standalone treatment for HD, it is essential to the development of all huntingtin-lowering therapies. Having such a drug would permit researchers to peer into the brains of HD patients in a non-invasive manner to determine if the huntingtin lowering treatments are doing their job.

The scientific portion of the CHDI conference took place over the course of the next three days. The conference kicked off with a session on structural insights into the huntingtin protein. Dr. Elena Cattaneo (University of Milan) provided attendees with an evolutionary lesson on huntingtin. She showed data to suggest that the huntingtin protein could be traced back thru over 800 million years of evolution. Most all organisms, large and small, have a huntingtin-like protein, but interestingly, the polyglutamine (polyQ) region of the protein that is expanded in HD is not conserved. As you travel further and further up



the phylogenetic tree the polyglutamine region gets bigger and bigger. Some say this suggests that the endogenous function of the huntingtin protein is in regulating brain development. Others in the session provided research updates on the structure and function of the huntingtin protein. By understanding the normal role of huntingtin, as well as what huntingtin does when it is expanded, researchers hope to identify new avenues for intervention.

In the next session on the huntingtin gene, Vanessa Wheeler (Mass General Hospital) presented data related to the expansion of the CAG repeat in HD. As we know, HD is caused by a triplet repeat expansion of the DNA code, CAG, in the huntingtin gene. Typically, the longer the CAG repeat in a person, the earlier the onset of symptoms will be. Long CAG repeats are also very unstable and can expand even more in certain areas of the brain, such as the striatum which is typically the first brain region to be effected in HD. This expansion could be caused by aberrant DNA repair mechanisms that take place in our cells. One DNA repair protein thought to be involved in the expansion of the CAG repeat in the huntingtin gene is called Mlh1. Mlh1 was found to be linked to altered HD age of onset in the seminal paper published last year by a large consortium of HD researchers looking for HD genetic modifier genes in people. When Dr. Wheeler and her team knock down the Mlh1 protein in HD mouse models, they are able to prevent the CAG stretch from expanding and prevent onset of HD-like symptoms in mice. Evidence is certainly converging around



the role of DNA damage and repair as playing an important role in the pathology of HD. Other researchers, such as Ray Truant (McMaster University), presented data to suggest that mutant huntingtin may be playing a role in oxidative DNA damage that could ultimately lead to HD symptoms.

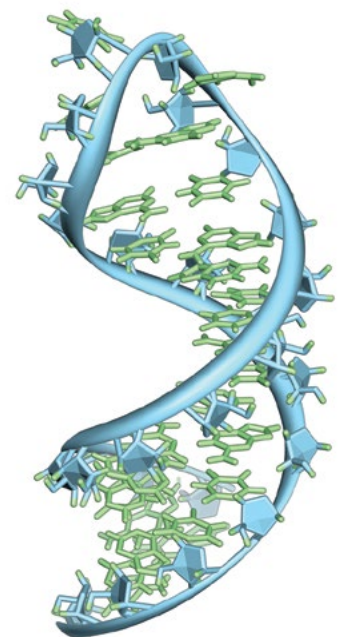
There is no doubt the most promising area of drug development right now is in the area of huntingtin lowering therapies. A great session highlighted numerous scientific approaches to both modify and measure huntingtin levels in the brains of HD patients. One exciting development is the creation of a PET ligand to detect huntingtin. The idea behind a PET ligand for huntingtin is that it could serve as a non-invasive way to monitor the levels of huntingtin in the brains of HD patients. To date, researchers do not have a way to look inside one's brain to see if the huntingtin lowering drugs are working. Preliminary data from CHDI Foundation was presented to suggest that the drug (ligand) is getting into the brain and binding huntingtin. In addition, the levels of huntingtin detected with the ligand correlate with the disease burden score suggesting this could also serve as a biomarker of disease progression.

Since we know the gene responsible for HD, it opens up a number of different avenues to target it. Drs. Konstantinova (uniQure) and McBride (Oregon Health Science University) presented updates on similar approaches to make use of viruses to deliver huntingtin-lowering RNAs to the brains of HD patients. Both researchers are developing non-allele selective reagents that will lower both the normal and expanded huntingtin protein. Meanwhile, Feng Zhang (Broad Institute) provided an overview of the CRISPR-cas9 technology that could one day be exploited to correct the huntingtin gene at the DNA level. Others presented ideas on how we could tap into our body's own protein clearance mechanisms such as autophagy ("self-eating"), to stimulate the clearance of the huntingtin protein.

While the neurons within a region of the brain called the striatum are thought to be the most effected cells in the brain, there are several other non-neuronal cells in the brain and each of them also express the huntingtin protein. One of these cell types is called *glia* (Greek word for glue). As their Greek name implies, they were once thought to simply be supportive cells that held neurons in place. As time goes on, we are finding that they do much more than that and in the case of HD, they may be playing an important role the pathology of the disease. In a session on "replacing cells and restoring networks" in HD, Dr. Steven Goldman (University of Rochester) presented his group's

latest findings involving glia. The Goldman lab has created an intriguing animal model that contains mouse neurons with a normal (non-expanded) huntingtin gene and human glia that have an expanded huntingtin gene. They found that the presence of these glia was enough to create HD-like phenotypes in the mice. Conversely, if normal human glia are transplanted into the brains of an HD mouse, they showed that they could reverse some of the behavioral, motor and electrophysiological "symptoms" in the HD mice. This suggests that glia could be a potential therapeutic target for combating HD.

Last year's start of Ionis Pharmaceutical's clinical study to test the safety of ASOs in HD patients was a landmark moment for the field. This is the first drug designed specifically for HD patients to be tested in people. The Ionis study is progressing as planned. There have been no reports of adverse side effects to date and is scheduled to be completed in late 2017. The momentum created by this trial has not been lost. In fact, the diversity of approaches to tackle HD has increased in 2016. As our understanding of HD and the technology to modify one's genome improves, researchers are creating a treasure chest of potential weapons to combat HD. Some are years away from getting their opportunity to prove themselves in the clinic, but what is certain is that their day is coming.



Overall, the data presented at the 11th CHDI Therapeutics Conference should provide the community with a great deal of optimism that collaborative researchers from around the globe are working in an unprecedented manner to rapidly find safe and effective therapies to slow or delay HD. What is clear is that no one individual will find the treatment for HD, it will take the entire HD "village" of families, patients, researchers and physicians working together to make HD history.



## Topic of the Year: Genome Engineering (CRISPR)

CRISPR. No, it is not referring to that place in everyone's refrigerator where good fruits and vegetables go to die. Instead, CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeat and has taken the global scientific community by storm!

CRISPR is quickly becoming an incredibly powerful and inexpensive laboratory tool to enable researchers to modify the genome (DNA) of organisms. Originally identified as an innate viral defense mechanism in bacteria, researchers have been able to exploit this system to specifically target any gene and make changes to it. This technology creates possibilities where we can start to treat genetic diseases, such as HD, that are caused solely by a mutation in one's DNA.

In theory, it is possible researchers could develop a CRISPR system to target the expanded huntingtin DNA (gene) and repair the CAG length to normal or shut off its expression altogether. This has been done to cells in a dish, but editing a gene in all cells in an adult is no small undertaking. The biggest challenge

to be addressed before CRISPR becomes a reality for the treatment of brain diseases like HD remains delivery. Delivery systems, such as viruses, must be optimized to achieve the

necessary levels of brain exposure of the CRISPR system components that would likely be needed to change the course of HD. Serious safety and ethical concerns must also be carefully addressed because the engineering of the human genome like this has never been done before.

Nevertheless, progress is being made at a lightning fast pace. As researchers and ethicists come up with solutions to these issues, genome engineering technologies such as CRISPR hold great promise in helping us to prevent disease from ever happening.



## HDSA Awards First-Ever Berman-Topper Family HD Career Development Fellowship to Dr. Ricardo Pinto

In May of 2016, HDSA announced that Dr. Ricardo Mouro Pinto of Massachusetts General Hospital/Harvard Medical School had been awarded the inaugural HDSA Berman-Topper Family HD Career Development Fellowship.

This prestigious new fellowship, made possible due to generosity of the Berman and Topper families, provides up to \$80,000 of funding per year for three years to young scientists and clinicians who desire to make Huntington's disease (HD) part of their long-term career plan.

"On behalf of the Topper and Berman families, I would like to congratulate Dr. Pinto on being named the first recipient of what we hope is a valuable fellowship," said Michael Berman. "With the support of HDSA, we are confident that Dr. Pinto's work will lead to greater knowledge of HD and help in our goal of finding effective therapies."

HDSA received applications from researchers from all around the world for this competitive grant. Ultimately,

the winning project will make use of the innovative genome editing technology CRISPR-cas9 to identify and validate potential new drug targets for HD

that could modify the course of the disease in people. Dr. Pinto's project is officially titled "Identification of genetic modifiers of somatic CAG instability in Huntington's disease by in-vivo CRISPR-cas9 genome editing."

"The prolonged period of stagnant NIH budgets, has increased the need for non-profit disease organizations, like HDSA, to ensure that the pipeline of HD scientists and clinicians is primed and ready for the future", said George Yohrling, PhD, Senior Director, Mission and Scientific Affairs at HDSA.







## Positive Study Data in Spinal Muscular Atrophy (SMA) Trial Provides Hope HD Patients

On August 1, 2016, Ionis Pharmaceuticals and its partner Biogen announced that they halted Phase 3 ENDEAR trial of an Ionis antisense oligonucleotide (ASO) in infants with genetic disorder called spinal muscular atrophy (SMA). They did not stop the trial because the drug was not working or was unsafe, instead they stopped it early because they found that the drug appeared to be working so well that it would have been unethical to continue the study with a placebo treatment arm!

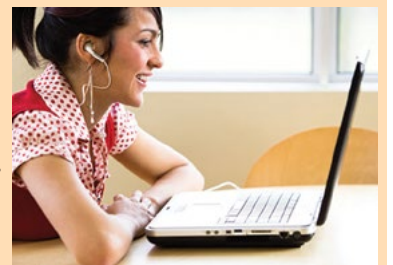
SMA is a genetic neurodegenerative disorder characterized by the loss of motor neurons in the spinal cord and brain stem that results in progressive muscular atrophy and weakness. It is caused by a mutation in a gene called SMN1. Children diagnosed with the most severe form of SMA (type 1) generally live less than two years without respiratory support and never develop the ability to sit up.

The drug, called Nusinersen, is an ASO drug, much like the Ionis ASO that is currently in clinical development for HD. Instead of lowering protein levels, like the HD ASO is designed to do, the SMA ASO works by tricking the SMN2 gene into behaving like the mutated or missing SMN1 gene and produces functional SMN, the protein essential for the survival of motor neurons. It was reported that some children that received Nusinersen were able to get out of their wheelchairs and walk!

Why is this so exciting for HD? Well, both drugs are delivered via a spinal tap (lumbar puncture) and Nusinersen was shown that it could be delivered to the brains of people. It also appeared safe and well tolerated. All these are good signs that a similar approach for HD could work. In addition, the clinical results in the ENDEAR study demonstrated that it may be possible to not only slow down progression of a neurological disease, but actually restore lost function. If true, this could assist symptomatic HD patients reverse their disease burden.

## HDSA Research Webinars Provide Forum to Hear Directly from HD Researchers

HDSA is committed to improving research communication between HD families, patients and scientists around the world. To achieve this, HDSA hosts a monthly HD Research Webinar Series. The webinars are on a variety of research topics presented by HD experts from around the globe. These webinars run for approximately 30-40 minutes, with 20-30 minutes dedicated to a question and answer session through a chat feature of the webinar software.



This year's topics included the high prevalence of reduced penetrance HD alleles, novel pathogenic mechanisms such as the role of the immune system in HD, intrabodies against huntingtin, clinical trial results and information from the FDA. If you missed one, don't worry. Each Research Webinar is recorded and archived on HDSA's YouTube channel. Make sure you sign up for email alerts from HDSA to stay informed of more great webinars starting again in January 2017!

## Science...Simplified

Stay informed on the latest HD research news on HDSA.org and HDBuzz.net

HDSA believes that clear and effective communication of scientific data should be a mandatory and fundamental requirement for all researchers. We pride ourselves in ensuring that research information is communicated to HD patients, families and caregivers in a timely manner. To assist us with this, HDSA is a proud supporter of HDBuzz.net.



HDBuzz reports on HD research in *plain language* that is written by scientists for the benefit of the global HD community. We often see press releases from institutions or companies suggesting that their



finding is a potential "cure" for HD. Unfortunately, it's not that easy and these potential "cures" are often misrepresenting the context of the science.

To help combat these false expectations, HDBuzz has perfected the ability to sort through the media hype and provide the community with concise explanations of the scientific findings and tell what they REALLY mean to the HD community. HDBuzz.net is a tremendous resource that is made available to all because of the support from HDSA and other HD organizations. HDBuzz also posts Podcasts on various research topics that can be enjoyed to at your leisure. All of HDBuzz's content is also available on HDSA.org and on the HDSA HD News App available for free on iTunes and GooglePlay.



# HD CLINICAL TRIALS UPDATE

## ENROLL-HD REACHES MILESTONE: 10,000<sup>TH</sup> PARTICIPANT ENROLLS!

So, exactly what is Enroll-HD? Enroll-HD is many things. Enroll-HD is a global longitudinal, observational study of Huntington's disease. It is a global effort to collect a common set of clinical data and biological samples that will help scientists better understand the disease. It also serves as a platform to support recruitment for clinical trials of potential new therapeutics for HD. Finally, it aims to inform us about the best standards of medical care for HD families.

Enroll-HD collects a common set of clinical data for all participants across all sites around the world.

Enroll-HD also collects blood samples for DNA and other biological samples for scientific purposes. These human samples will prove to be invaluable resources to assist researchers to uncover better drug targets for HD. All the data and samples will be made available to share with researchers. Enroll-HD will also serve as a platform to determine what interventions work to improve the care of people with HD. Conclusions from this could aid the worldwide HD patient population as new guidelines for the optimal care of HD patients should be identified. Finally, Enroll-HD will assist in the development of better, smarter and even quicker clinical

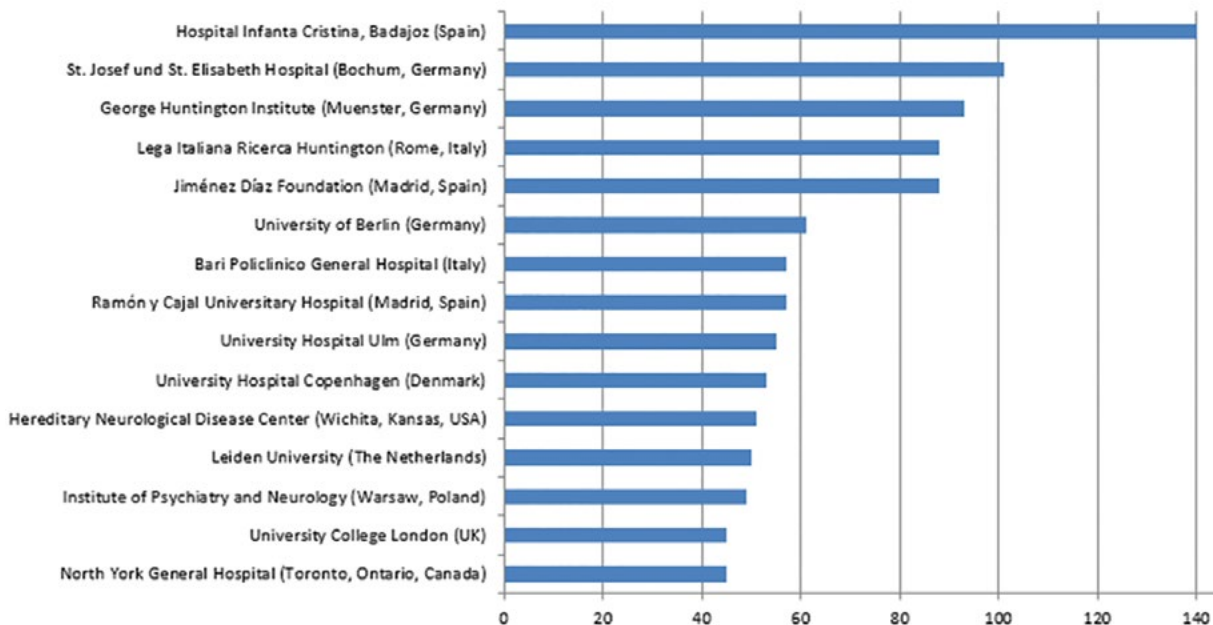


trials as we all hope the registry component of Enroll-HD will assist with the timely recruitment of clinical trial participants. If a trial is fast to recruit, it will be fast to yield data that will hopefully result in faster approval of all future HD drugs.

Enroll-HD is sponsored and managed by CHDI Foundation, a not-for-profit biomedical research organization dedicated to rapidly developing therapies that slow the progression of Huntington's disease. Launched in November 2010, Enroll-HD currently has 11,430 participants enrolled at 137 sites in 14 countries around the world. Unfortunately, North American participation has significantly fallen behind European participation. In Europe, 6,237 participants have been enrolled at 71 active sites, while just 4,501 participants have been enrolled at 56 active sites in the US and Canada. In 2016, the best recruiting US site was the Hereditary Neurological Disease Center in Wichita, Kansas. No other US site was able to crack the Top 15.

For a list of all current sites and more information about Enroll-HD, visit [www.enroll-hd.org](http://www.enroll-hd.org) or [www.HDTrialfinder.org](http://www.HDTrialfinder.org).

Top Enrolling Sites - Year to Date 2016





# Azevan Pharmaceuticals Initiates STAIR Trial to Improve Irritability and Aggression in HD Patient

Earlier this year, Azevan Pharmaceuticals, a small biotechnology company from Pennsylvania launched a new Phase 2 clinical trial in partnership with the NIH. The study, known as the STAIR trial comes from its official title of “An Exploratory Phase II Study to Test the Safety, Tolerability, & Activity of a Novel Vasopressin 1a Receptor Antagonist (SRX246) in Irritable Subjects with HD”.

The drug being tested, SRX-246, is an investigational drug that is believed to work by blocking a receptor in the brain called the vasopressin 1a (V1a) receptor. When SRX246 binds to the V1a receptor, it prevents a small protein (peptide) normally made by the body called vasopressin, from binding to the V1a receptor. SRX246 is orally bioavailable drug that can penetrate the blood-brain barrier to get access to the brain.

Blocking the V1a receptor is considered a novel mechanism of action for treating stress-related Central Nervous System (CNS) disorders. The V1a receptor is the primary vasopressin receptor in the CNS. The vasopressin peptide, made normally in our bodies, has been implicated in social and emotional behaviors. When a person makes too much vasopressin, this can be associated with irritable/aggressive behaviors.

The *primary* goal for the STAIR study will be tolerability of 2 different doses of SRX246 in HD patients. The *secondary* goal of the study is safety. A *final* goal of the STAIR Study is to explore several potential measures of irritability in HD Patients that can be assessed in the clinic to help us understand if SRX246 is helpful in decreasing the irritability in HD. Clinical measures such as the Unified HD Rating Scale (UHDRS); UHDRS Irritability and Aggression scale; Aberrant Behavior Checklist (ABC-I); Irritability Scale (IS), Cohen-Mansfield Agitation Inventory (CMAI); Clinical Global Impression Scale (CGI), Caregiver Burden Assessment, and even a novel eDiary will be used by participants in this trial.

The STAIR study is being conducted at 22 centers in the United States. They are looking to recruit 108 patients for this study. All 22 clinical sites are NeuroNEXT study sites for the National Institutes of Health. 15 of these sites are also HDSA Centers of Excellence. For a local study coordinator contact information, please visit [HDTrialfinder.org](http://HDTrialfinder.org) or call an HDTrialfinder Clinical Trial Navigator at 866-890-6612.



## Pfizer: The Amaryllis Study Concludes Recruitment in 2016

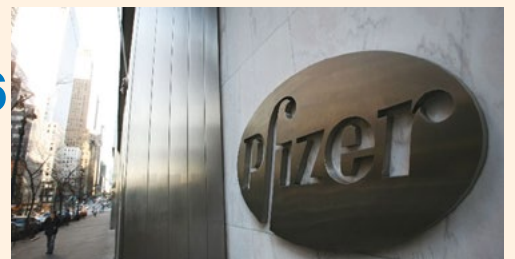
Recent evidence in pre-clinical (animal) models of HD suggests that the inhibition of PDE10 may have therapeutic benefit in HD by restoring the way neurons talk to one another. Other recent data from HD patients suggests that PDE10 levels are inversely correlated with disease progression (the less PDE10, the more advanced your HD). PDE10 stands for phosphodiesterase 10. PDE10 is primarily expressed the striatum. The striatum is the region of the brain that is particularly vulnerable in HD. In the past, many pharmaceutical companies created PDE10 inhibitor drugs for schizophrenia.



In 2014, Pfizer began a global Phase 2 clinical trial of their PDE10A inhibitor in HD patients. This study was named The Amaryllis Study,

a name familiar to all HD community members as amaryllis are the traditional flower of hope for the fight against HD. Amaryllis was able to recruit approximately 270 subjects for the 26 week study. Subjects were divided into three groups: a placebo group, a 5mg dose and a 20mg dose.

The primary endpoint for this trial is to see if the drug can positively impact the Total Motor Score (TMS). However, other clinical readouts such as cognition, behavior and brain size with the use of MRI imaging will be employed. With the study now fully recruited, we expect to hear about the results of this study in late 2016. Visit [HDSA.org](http://HDSA.org) for news updates.



## Teva Announces Pride-HD Study Results for Pridopidine at EHDN Conference



TEVA PHARMACEUTICALS LTD

Pride-HD was a Phase 2 clinical research study of an investigational drug called pridopidine in people who have a diagnosis of Huntington disease (HD). Pride-HD lasted for 52 weeks and tested 4 different doses of drug versus placebo over 400 people with varying stages of HD. The purpose of this study was to see what effect pridopidine had on movement, thinking, and behavior, compared to placebo (a capsule that looks like pridopidine but has no active ingredient), in people with HD. The primary outcome of this study was a change in the total motor score (TMS) of HD patients on the drug.



In September, Dr. Michael Hayden, the Chief Scientific Officer at Teva Pharmaceuticals presented the results from this study at the 2016 European HD Network Conference that was held in The Hague, The Netherlands. Unfortunately, the trial failed to significantly improve TMS. The study sponsors believe

that an unusually high placebo effect compared to those in other studies limited their ability to identify significant and positive drug effects on TMS. However, when

Teva looked at the data for patients with early stage HD, they observed that pridopidine had a significant impact on another common clinical readout called Total Functional Capacity (TFC). One's TFC score correlates to their ability to work, manage their finances and perform other general activities of daily living.

The potential effect on TFC with pridopidine will need to be confirmed in a separate clinical study that Teva is planning now. Dr. Hayden reiterated that Teva remains committed to bringing this and other drugs forward to help improve the lives of HD patients around the world.



### Delays for the Legato-HD Study

The primary objective of Teva's second Phase 2 clinical study is to

assess the efficacy of laquinimod 0.5, 1.0, and 1.5 mg qd (four times a day) in patients with HD after 12 months of treatment using the Unified HD Rating Scale-Total Motor Score (UHDRS-TMS). Earlier this year, cardiovascular side effects were seen in patients receiving either a 1.2 or 1.5 mg dose of laquinimod in a separate study involving multiple sclerosis patients. Because of this finding,

the Legato-HD study was temporarily paused to amend the protocol to drop the 1.5 mg dose from the study.

Laquinimod is a drug that is thought to act by decreasing the inflammatory response in the brain that is commonly observed in neurological disorders. Evidence suggests there is an increased inflammatory response in HD brain so reducing it could hold therapeutic benefit. Approximately 400 subjects are needed for this study that got underway in late 2014. The study hold has now been lifted and is once again recruiting volunteers. Visit [HDTrialFinder.org](http://HDTrialFinder.org) to find a site near you.

## A New "WaVe" of Huntingtin Lowering Approaches are Coming

In just two years, WaVe Life Sciences has gone from thinking about working on HD to preparing the necessary paperwork for the FDA to allow them to begin a clinical study in HD patients. WaVe is Massachusetts based a biotechnology company that has optimized a way of creating antisense oligonucleotides (ASOs), similar to the Ionis approach, that have unique structural properties that allow them to be more potent and have greater specificity for their RNA target.

WaVe's drug is an antisense oligonucleotide (ASO) like Ionis' Htt-Rx, however, the WaVe ASO differs in that it is targeting just the expanded (mutant) huntingtin gene. It does this by recognizing single nucleotide polymorphisms (SNPs) that are DNA coding differences commonly found in people. WaVe has identified

two SNPs that are found only on the expanded huntingtin gene. The ASOs recognize the region on the RNA where these SNPs are found, bind and then the resulting RNA/ASO duplex is degraded. This should result in less expanded huntingtin protein being formed.

Unfortunately, not everyone with HD expresses of these two SNPs. It is estimated that approximately 70% of all HD patients will express one of these SNPs and could potentially benefit from this approach. WaVe hopes to initiate a Phase 1b/2a clinical study in early to mid-stage HD patients next year.





# Thank Goodness! Isis Pharmaceuticals Becomes Ionis Pharmaceuticals

A week before Christmas 2015, Isis Pharmaceuticals officially changed their name to Ionis Pharmaceuticals. While the name may have changed, the commitment to HD at Ionis has not. The first ever clinical trial testing a drug designed specially with HD in mind (Ionis-HTT<sub>Rx</sub>) is progressing through Phase 1b safety and tolerability clinical studies.



## What is Ionis-HTT<sub>Rx</sub>?

Ionis-HTT<sub>Rx</sub> is an investigational drug being developed by Ionis Pharmaceuticals for the potential treatment of Huntington's disease (HD). Ionis-HTT<sub>Rx</sub> offers a unique mechanism to correct the underlying genetic anomaly that causes HD by preventing the production of the toxic huntingtin protein. Ionis-HTT<sub>Rx</sub> is an antisense oligonucleotide (ASO) drug designed to reduce the amount of huntingtin protein made in the brain, and without the RNA "message" available, the huntingtin protein is not made. Ionis-HTT<sub>Rx</sub> is designed to lower both the normal and expanded copy of a person's huntingtin gene. Scientists refer to this as a non-allele selective approach.

This study is designed to evaluate the safety and tolerability of multiple doses of an investigational drug, Ionis-HTT<sub>Rx</sub>, in adult patients with early manifest HD. Each patient will receive multiple injections of the drug at a specific dose with different groups of patients receiving different doses. This helps to establish the safety and tolerability profile of the drug. The study will enroll approximately 40 patients with early manifest, Stage 1 HD (defined as Total Functional Capacity of 11-13), aged 25 to 65 years, at the time of informed consent, with genetically confirmed disease by direct DNA testing, and who pass additional screening evaluations conducted at the study center to confirm eligibility. Participation in this study is expected to last for about 8 months.

## How is the study drug being administered?

Each dose of Ionis-HTT<sub>Rx</sub> or placebo, is administered as a single intrathecal injection, also commonly called a lumbar puncture or a 'spinal tap'. The dose is given as an injection into the lower back, and travels to the brain as it distributes in the cerebrospinal fluid. The study is randomized 3:1 so that three-fourths of the patients will receive Ionis-HTT<sub>Rx</sub> and one-fourth of the patients will receive placebo. This safety

study is designed with the fewest number of placebo patients as possible to meet the statistical standards necessary to adequately determine the benefit-risk of Ionis-HTT<sub>Rx</sub>. None of the patients or physicians participating in the study know whether the patients are receiving active drug or placebo (double-blind). After study completion, an open-label extension study of Ionis-HTT<sub>Rx</sub> may be implemented if this is warranted based on review of safety, tolerability, pharmacokinetic (effect of body on drug) and exploratory pharmacodynamics (effect of drug on body) findings.

## Where is the study taking place?

The Ionis-HTT<sub>Rx</sub> study is being conducted at six centers in Canada, United Kingdom and Germany only. Unfortunately, there are no sites in the USA. If the data from the study suggest the drug is safe and well tolerated, future clinical studies will be required to test for its effectiveness in treating symptoms associated with HD. These studies would likely include clinical testing sites in the USA.

## What is the latest news about Ionis-HTT<sub>Rx</sub>?

Ionis has just reported that the fourth and highest dose group (cohort) has begun. To date, there have not been any serious adverse side effects or events. The study is on track as planned and should be complete by late 2017. If analysis of the results suggest the drug is safe and well-tolerated, future trials to investigate the efficacy of Ionis-HTT<sub>Rx</sub> will be explored.

While the entire HD community is excited about the start of this study, we must remember that the sole purpose of this study is to evaluate the safety of Ionis-HTT<sub>Rx</sub> in HD patients. It will not evaluate the effectiveness of the drug to improve HD symptoms.



## A Special Thanks to the HDSA Scientific Advisory Board



***Pictured from Left to Right: Ray Dorsey, Melissa Moser, Harry Orr, Kurt Fischbeck, Louise Vetter, George Yohrling, Susan Browne, Michelle Gray, Beth Borowsky, Neil Aronin. Not pictured: Lucie Bruijn, David Howland, Marcy MacDonald, Sam Frank***

The HDSA Scientific Advisory Board (SAB) is comprised of leading experts in their fields. The Scientific Advisory Board's role is to advise the Board of Trustees and HDSA Management on a range of issues. In general, the SAB provides scientific review of research proposals to ensure that the research programs at HDSA are scientifically sound, pertinent and provide a high impact to the HD research community. The current members of the HDSA SAB are:

- **Michelle Gray, PhD**, Assistant Professor, University of Alabama-Birmingham (Chairwoman of SAB)
- **Neil Aronin, MD**, Professor and Chairman of Endocrinology and Metabolism, University of Massachusetts Medical School
- **Lucie Bruijn, PhD**, Chief Scientific Officer, ALS Association
- **Ray Dorsey, MD, MBA**, Professor, University of Rochester
- **Kenneth Fischbeck, MD**, NIH Distinguished Investigator, Chief, Neurogenetics Branch
- **Sam Frank, MD**, Associate Professor, Beth Israel-Deaconess Hospital (ex officio)
- **David Howland, PhD**, Director, CHDI Foundation
- **Blair Leavitt, MD, PhD**, Professor, University of British Columbia
- **Marcy MacDonald, PhD**, Professor, Harvard Medical School, Massachusetts General Hospital
- **Melissa Moser**, Community Representative
- **Harry Orr, PhD**, Professor, University of Minnesota
- **Susan Browne, PhD**, Director, Teva Pharmaceuticals

The Committee's specific responsibilities include:

- Periodically reviewing HDSA's medical and scientific affairs strategy and recommending funding for research grant awards.
- Significantly expanding HDSA's research commitments.
- Define and administer HDSA's research program, including RFP development, proposal review and grant oversight.

We are grateful to the SAB members who so generously donate their time and talent as volunteers!



# Final Thoughts

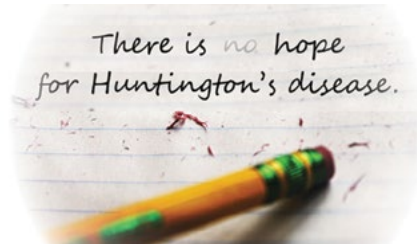
Last year, we saw the start of the first clinical study ever to test a drug designed to lower huntingtin, the protein responsible for HD. While we will not know the results of this important study until late 2017 at the earliest, families should take comfort in knowing that many other companies are working feverishly to bring similar huntingtin lowering drugs to the clinic in the near future. While families and scientists alike agree on this being the most promising therapeutic approach to date, we must not become complacent. There is still much work to be done. There is still more we must learn about HD.



To do this work will require us to get off the sidelines and into the game. Treatment of HD in the future will likely require a multi-drug approach even if the huntingtin lowering drugs become a reality. The need for effective therapies to combat the cognitive, psychiatric, behavioral and motor symptoms of HD will remain. Since 2012, HDSA's research strategy has focused solely on the one true model of HD, humans. This strategy is now being adopted across many diseases and many different organizations. This patient-focused approach is even being adopted by the FDA.

To help scientists, clinicians and regulators better understand HD and the impact the disease has on families, in 2017 and beyond I believe we will begin to see more and more experimental medicine and survey type studies that will require patient participation. While these studies may not be testing an actual drug, they are critical if we are to continue to elucidate the underpinnings of HD. They are critical to prepare us for the trials of the future and thanks to HDSA's HD Trialfinder, finding these studies has never been easier. Whether you are symptomatic for HD, at-risk or a caregiver, you will always find a study to consider.

I think there is one thing we can all agree on: we need effective treatments for HD TODAY! So, in 2017, let's continue to work together as one HD family to embrace the research opportunities presented to us so that we can make our common goal a reality.



**VOLUNTEER. EDUCATE. ADVOCATE. DONATE.**  
**hdsa.org (800)345-HDSA**



## **Our Vision: A World Free of Huntington's Disease**

### **Our Mission: To improve the lives of people with Huntington's disease and their families.**

Huntington's disease is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities starting in their prime working years. Currently, there is no cure for Huntington's disease (HD).

Every child of a parent with HD has a 50/50 chance of inheriting the faulty gene that causes Huntington's disease. Today, there are approximately 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease.

The Huntington's Disease Society of America is the premier nonprofit organization dedicated to improving the lives of everyone affected by HD. From community services and education to advocacy and research, HDSA is the world's leader in providing help for today and hope for tomorrow for people with HD and their families.

Across the United States, HDSA supports 54 volunteer-led Chapters and Affiliates, 39 Centers of Excellence, 50+ Social Workers and more than 160 Support Groups.



**Huntington's Disease  
Society of America**

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