



Huntington's Disease  
Society of America

**2015  
Research  
Investor's  
Report**



## 2015: A Year of Unprecedented Hope

This was a landmark year for the Huntington's Disease Society of America (HDSA) and the global HD community. HDSA continued to expand their patient-focused research commitments and launched new resources, such as the HDTrialfinder to accelerate the clinical development of new HD drugs. This is essential as never before have we had so many companies pursuing HD therapies in the clinic.

Without a doubt, the scientific highlight of 2015 was that the first clinical trial for a huntingtin lowering drug began. Since the identification of the gene that causes HD in 1993, the research community has been working hard to devise ways to eliminate huntingtin at its roots. This summer, Isis Pharmaceuticals announced that a Phase 1/2a study to test the safety of their antisense oligonucleotide (ASO) that lowers huntingtin had begun. While this is just the beginning for this drug, it marks a moment 22 years in the making. This is the first time a drug, specifically designed for Huntington's disease has been administered to HD patients.

HDSA released a first-of-its kind clinical trial matching resource for the HD community, called HDTrialfinder. It matches a patient's clinical information to the criteria for HD clinical trials that are currently recruiting around the country. This resource provides families with the most up-to-date information about trials and direct lines of contact to their local study sites.

HDSA's major research initiative, the Human Biology Project, entered its third year in 2015. The Human Biology Project was launched in 2013 as 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 six new research projects HDSA is supporting. We believe this approach is critical for the acceleration of treatments for HD as everyone agrees that the most important observations to guide researchers in the quest for new HD therapies will be those made in people actually affected by HD.

The term "Genetic Modifiers" also became mainstream in the HD community in 2015. Two separate studies were published that identified potential genetic factors in one's DNA that could impact or "modify" the clinical onset of HD. One such modifier was found by Becanovic et al in a region of DNA that controls the expression of the huntingtin gene. In another study, a consortium of researchers from around the world published a groundbreaking study that identified two regions of DNA (on Chromosomes 8 and 15) that appear to alter the course of HD in people. Both studies provide clues that could assist in the development of new therapeutic approaches for HD.

As you read through the 2015 Research Investors Report, I am confident you will agree with me that 2015 was a year of unprecedented hope. HDSA and the research community have made tremendous progress towards meaningful clinical trials that will hopefully change the course of HD and bring relief and hope to you – our HD families.



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





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## HDSA Awards Six HD Human Biology Project Fellowships for 2015

This October, the Huntington's Disease Society of America (HDSA) announced that six research grants have been awarded under the Society's largest research initiative, the HDSA Huntington's Disease Human Biology Project. Totalling \$750,000, these grants emphasize the importance of bringing basic and clinical researchers together to facilitate Huntington's disease (HD) science beyond animal models and into the human condition with the participation of HD patients.

"Now in its third year, the HD Human Biology Project allows HDSA to foster innovative patient-focused research to help the HD community better understand the biology of HD as it occurs in people", said George Yohrling, PhD, Senior Director, Mission and Scientific Affairs at HDSA. "There is nothing more exciting or more relevant to HD than scientific observations made in people with the disease".

HDSA received applications from researchers from all around the world. Ultimately, grants were awarded to six research fellows, from three countries (USA, Canada, and Australia). The winning projects include the development of a sensitive test to detect huntingtin protein in spinal fluid, the use of human stem cells to understand HD phenomena, biomarker development, and a clinical study to investigate the potential of exercise and electrical brain stimulation to increase brain plasticity in HD patients.

"HDSA is devoted to enabling promising HD research and supporting scientific leaders in the quest to find a cure for Huntington's disease as quickly as possible," said Louise Vetter, Chief Executive Officer of HDSA. "The Human Biology Project is unique in its insistence that the science has immediate relevance

in helping patients and families, because simply put - there's no time to waste."

**Shown left: Sandra Hurley presenting Dr. Jang-Ho Cha with a check for \$174,000 for research.**



The winners and titles of the 2015 HDSA HD Human Biology Project Grants are:

- **Dr. Amber Southwell**, Postdoctoral Fellow, University of British Columbia: *Ultrasensitive detection of huntingtin protein in cerebrospinal fluid*, **Dr. Janis Brown Memorial Award Winner**
- **Dr. Ali Khoshnan**, Senior Research Scientist, California Institute of Technology: *Investigating the toxicity of mutant huntingtin in human induced pluripotent stem cells (iPSCs) derived from gut epithelial cell models*
- **Dr. Marie Didiot**, Postdoctoral Fellow, University of Massachusetts Medical School: *Study of CAG repeat expansion impact on huntingtin mRNA cellular localization for a rational design of next generation oligonucleotide-based therapeutics*
- **Dr. Sophie Andrews**, Research Fellow, Monash University (Australia): *Exercise and brain stimulation as modifiers of neuroplasticity 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.*
- **Dr. Changning Wang**, Instructor, Massachusetts General Hospital/Harvard Medical School: *Investigation of epigenetic mechanisms in Huntington's disease patients quantified by non-invasive PET imaging*

This year, thanks to the generosity Mrs. Sandra Hurley (Arlington, TX), this year's top scoring Human Biology Project proposal from Dr. Amber Southwell (University of British Columbia) was given the additional honor of being named winner of the Dr. Janis Brown Memorial Award. Sadly, Janis passed away in September 2014 after a long battle with HD. Janis was a strong advocate for HD research. Her cousin and caregiver, Sandra Hurley wanted to honor Janis' legacy with this award.

**Shown right: Dr. Janis Brown**





## Summaries of 2015 HDSA - funded HD Human Biology Projects *In Their Own Words*

### **Dr. Amber Southwell,**

Post-doctoral Fellow,  
University of British Columbia

*Title: Ultrasensitive detection of huntingtin protein in cerebrospinal fluid.*



### **Dr. Janis Brown Memorial Award Winner**

Huntingtin, the protein that when mutated causes HD, accumulates within cells and engages in a variety of aberrant interactions. Reducing the levels of this toxic protein should prevent all subsequent pathology and prevent or delay the onset of HD. In fact, several huntingtin lowering therapies are being developed through animal studies and rapidly approaching trials in humans. However, what is missing is a method to measure huntingtin protein levels in the human brain, a necessary pre-requisite to evaluating the success of huntingtin lowering therapies. We have overcome this obstacle using a technique called IP-FCM to measure mutant huntingtin protein in the fluid that bathes the brain, the cerebrospinal fluid (CSF) and have shown that mutant huntingtin protein in the CSF originates in the brain and is released by injured or dying brain cells. Levels of mutant huntingtin protein in the CSF increase with worsening HD symptoms, suggesting that this approach will be useful as a measure of disease progression in HD. Additionally, lowering mutant huntingtin in the brain using gene-silencing treatments results in a measurable reduction of mutant huntingtin in the CSF, indicating that IP-FCM could be used to verify and quantify changes in brain mutant huntingtin in response to experimental therapies. In ongoing work, we will continue to study our IP-FCM method to learn more about how it works and continue to use IP-FCM to learn about HD by measuring mutant huntingtin in CSF from the same patients over time to see how it changes in individuals. Additionally, we will develop similar quantitative methods to measure huntingtin



protein that cannot be quantified with the current method, such as the normal huntingtin protein, allowing comparison of mutant and normal protein levels over time in patients.

### **Dr. Ali Khoshnan,**

Senior Research Scientist,  
California Institute of Technology

*Title: Investigating the toxicity of mutant huntingtin in human induced pluripotent stem cells (iPSCs) derived intestinal epithelial cell models.*



The age of disease onset is variable among HD patients with similar polyglutamine (polyQ) length. Thus, in addition to polyQ expansion, environmental factors may accelerate the progression of symptoms. Inflammation is a potential modifier of HD pathology. The intestinal microbes contain compounds, which are known to induce inflammation and disrupt the normal function of intestinal epithelium. The expression of mutant huntingtin (mHTT) in the gastrointestinal (GI) tract cells may increase the susceptibility of intestinal epithelium to microbial insults. We propose that the inflammatory components of gut microbes enhance the toxicity of mHTT in intestinal cells and contribute to GI abnormalities in HD patients. Our preliminary data support this hypothesis. To expand on these findings and to establish a connection between gut microbes and HD pathology, we plan to develop intestinal models using patient-derived stem cells. These innovative approaches may identify novel biomarkers for diagnosis and provide strategies to develop safe biotherapies for GI-associated symptoms in HD.

### **Dr. Marie Didiot,**

Post-doctoral Fellow,  
University of Massachusetts  
Medical School

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



Oligonucleotide-based therapy that enables the direct silencing of HTT mRNA, is one of the most promising therapeutic approaches for the treatment of Huntington's disease (HD).



Our laboratory is focused on the development of novel hydrophobically modified, small-interfering RNA (hsiRNA) for the treatment of HD. We observed that any RNA-interfering (RNAi) reagents targeting HTT mRNA reach a plateau of 50-70% silencing, while the targeting of other genes usually results in more than 95% knockdown. Understanding this phenomenon is critical for the development of HTT-targeting oligonucleotide therapeutics. Based on preliminary data, we suspect that a significant fraction of Htt mRNA is nuclear (in nucleus of cell) and thus is inaccessible to regular RNAi reagents. Understanding the potential functional role of nuclear HTT mRNA is essential for a rational design of next-generation oligonucleotide therapeutics. The goal of this proposal is to investigate the impact of CAG repeat expansion on HTT mRNA intracellular localization in human-derived primary fibroblasts from healthy and HD subjects. We hope to understand how the CAG repeat expansion impacts the sub-cellular localization of HTT mRNA that impairs the silencing efficiency of oligonucleotide therapeutics. This study will also contribute to the validation of oligonucleotide therapeutics against HTT mRNA in a human HD context. Finally, we also aim to better understand the role of HTT mRNA CAG repeat expansions in HD pathogenesis.

### **Dr. Sophie Andrews,**

Research Fellow,  
Monash University (Australia)

*Title: Exercise and brain stimulation as modifiers of neuroplasticity in Huntington's disease.*



Huntington's disease is a devastating genetic condition with no cure. Drugs can lessen the symptoms but have little effect on disease progression. It has been observed that disease onset is delayed in patients with more active lifestyles. This suggests exercise is a lifestyle factor with exciting potential to delay the symptoms of neurodegenerative disease. Researchers investigating HD in mice have shown that exercise can increase brain plasticity, the brain's ability to change and

adapt. It is not yet known whether the same is true in humans, or what 'dose' (intensity) of exercise is optimal, and therefore studies are needed to determine how best to use exercise to improve brain function. We propose to address this important gap by undertaking two studies. First, we will examine the effect of exercise intensity on brain plasticity in pre-symptomatic individuals who are predisposed genetically to HD, as well as healthy control participants. We will measure brain plasticity using a safe, non-invasive and painless way to stimulate the brain ('transcranial magnetic stimulation'). Second, we will assess whether exercise can enhance the learning of new motor skills, and whether this effect can be increased using another type of non-invasive brain stimulation ('transcranial direct current stimulation'). This research is the first step towards providing individuals that are predisposed genetically to HD with evidence based advice to change their lifestyles before symptoms develop. The knowledge generated from this research will also be used to design new non-medication interventions that are most likely to be effective.

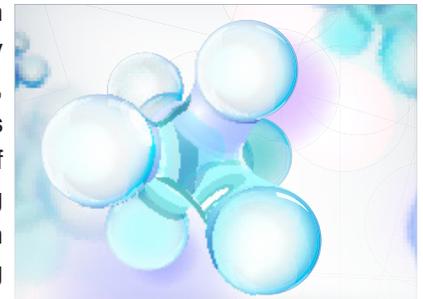
### **Dr. Lisa Salazar,**

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.

**Dr. Changning Wang,**

Instructor,  
Massachusetts General  
Hospital/Harvard Medical School  
*Title: Investigation of epigenetic mechanisms in Huntington's disease patients quantified by non-invasive PET imaging.*



To date, our understanding of HD has been dominated by HD animal model data and without tools to 'see' into the living brain, it is impossible to visualize the molecular changes that precede disease onset. Molecular imaging with techniques like positron emission tomography (PET) has proven valuable at measuring disease after onset. A key subset of this family, the class 1 Histone deacetylase (HDAC) isoforms, has been shown to be dysregulated in the brains of animal models with remarkable therapeutic potential for improving cognitive function that results from early neurodegeneration. Our lab has developed the first, and to date only, imaging agent for class 1 HDACs and has successfully progressed the imaging agent to first-in-human trials. Our experiments will answer the question, is HDAC expression altered in the human HD brain? Importantly, either positive OR negative outcomes will provide an immediate step forward in understanding HD and motivate novel drug trials.

## HDSA Researcher Honored with Prestigious "Genius" Grant

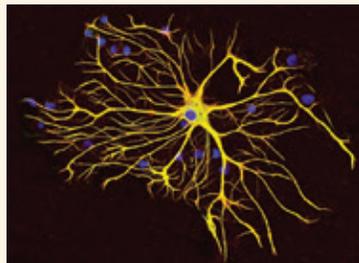
On September 29, 2015, the MacArthur Foundation announced the 24 recipients of its five-year "genius" grants. The fellowships are given annually in recognition of significant originality and dedication, and come with no-strings-attached grants of \$625,000.

Of the seven winners from this year working in STEM fields, only one is a woman: neuroscientist Beth Stevens, PhD, who studies how brain cells communicate and how miscommunication can lead to disease. Beth is Assistant Professor of Neurology at Harvard Medical School, Research Associate at Boston Children's Hospital, and an institute member at the Broad Institute of MIT and Harvard.



**Dr. Beth Stevens. 2015 Recipient of MacArthur Foundation "Genius" Grant and Principal Investigator of HDSA Human Biology Project Grant.**

Dr. Stevens' research focuses on understanding how glial cells (a.k.a. glia) interact with neurons to communicate with one another through synapses. Glia, though not as well-known as neurons, actually make up about half



of the brain. Dr. Stevens is currently mentoring Dr. Daniel Wilton on an innovative research study supported through the HDSA Human Biology Project to investigate the role of the immune system in HD.



# HDSA Announced the Winners of 2015 Donald A. King Summer Research Fellowship

**Scientists working at Gladstone Institute for Neurological Disease, University of Pittsburgh and Rush University Medical School awarded fellowships to work on Huntington's disease projects**

In April of 2015, the Huntington's Disease Society of America (HDSA) announced the recipients of the 2015 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. This year, a record number of applications from across the country were received. 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 2015 Donald A. King Summer Research Fellowship:

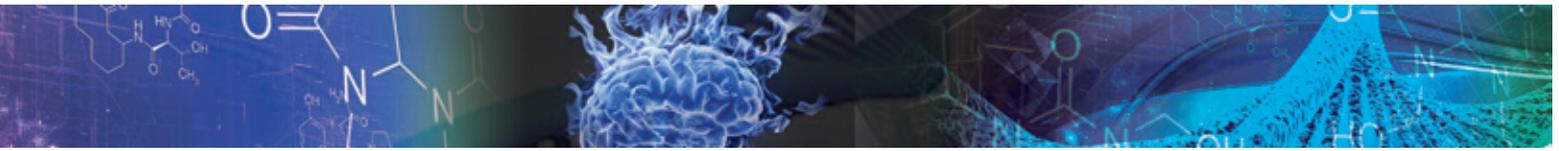
- **Mr. Patrick Hogan** (Rush University Medical Center) worked under the guidance of Drs. Kathleen Shannon and Jennifer Goldman (both from Rush University) on a project entitled "*Clinical and imaging biomarkers of neuropsychiatric features in pre-manifest Huntington's disease*". Patrick's project aimed to examine the characteristics of early neuropsychiatric HD symptoms and investigate the relationships between those symptoms and neuroimaging patterns and genetic data collected through the PREDICT-HD study.
- **Mr. Rogan Grant** (Haverford College). Rogan spent the summer working with Dr. Joseph Glorioso on a project entitled "*Development of an inducible CRISPR/Cas9 vector for huntingtin knockout*". Rogan's project involved

development of a promising genome-engineering tool called the CRISPR/Cas9 system to lower huntingtin. This huntingtin lowering tool was expressed in human HD neurons using viruses that have the potential to cross the blood-brain-barrier. Use of brain penetrating viruses could increase the chances of delivering huntingtin lowering drugs to deep regions of the brain

- **Ms. Brianna Bibel** (St. Mary's College of California). Brianna worked under the guidance of Dr. Steven Finkbeiner from the Gladstone Institute for Neurological Disease, as well as Dr. Vanessa Wheeler from Massachusetts General Hospital on a project entitled "*Elucidating the role of somatic expansion in human HD neurons degeneration with nanobiopsy and longitudinal single cell analysis*". Brianna combined the use of Dr. Finkbeiner's automated microscopy technology and nanobiopsy of human HD neurons to determine if the number of CAG repeats in individual HD neurons expands over time and whether this expansion happens before neurodegeneration occurs.

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.





# Donald King Summer Research Fellow Spotlight:

## Rogan Grant

Rogan Grant is a recent graduate of Haverford College, where he studied molecular biology and neuroscience. In his senior thesis research, Rogan investigated the potential neuroprotective effects of argon gas and 17 $\beta$ -estradiol following ischemic stroke, and it was during this time that he developed a deep appreciation for biomedical neuroscience. Spurred by this experience, Rogan resolved in his senior year to dedicate his career to work toward the understanding and eventual cure of one or more neurological disorders.

Thanks to the Donald A. King Summer Research Fellowship, and a chance meeting with Dr. Joseph Glorioso at the University of Pittsburgh, Rogan was able to make early progress toward this goal. In the Glorioso laboratory, he developed and tested several CRISPR/Cas9 expression vectors for huntingtin gene knockout, which will one day inform the development of a herpes-simplex-virus-based gene therapy vector for Huntington's disease. He cites this experience as a major milestone in his early scientific career.

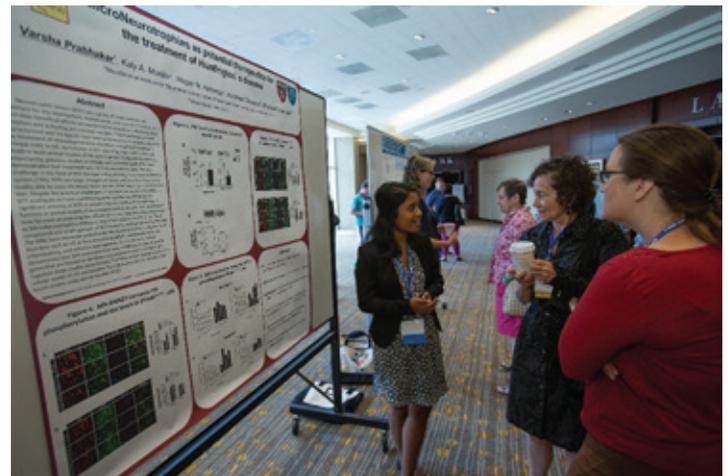
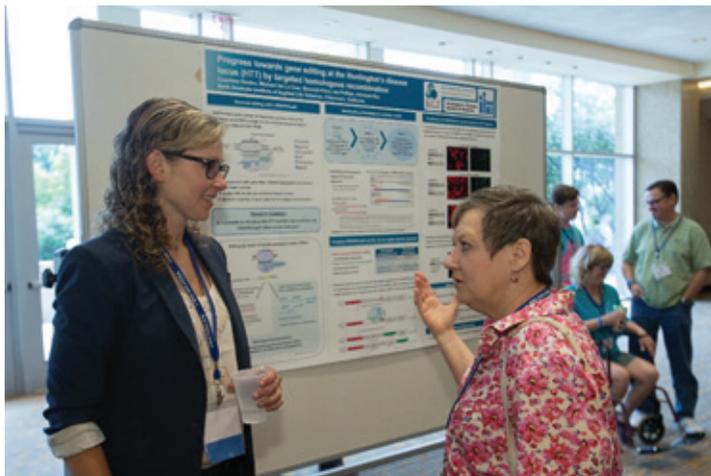
Rogan is now a research associate in the Barth laboratory at Carnegie Mellon University, where he is helping to develop

a novel imaging technique to study the connectome (defining what proteins interact with each other in the body). It is hoped that this tool will soon be used to study alterations in neuronal circuitry in various disease states, which will provide key insight into the systems-level pathology involved in diseases of the brain. Rogan aims to use this opportunity to further hone his research skills before pursuing a PhD in neurobiology.



In his rare moments not devoted to scientific research, Rogan takes time to run, bike, and ski, and continues to pursue the perfect cappuccino. In the near future, he would like to work to encourage scientific literacy in the general population, and hopes to make this an integral part of his career. Regardless of his ultimate career path, Rogan hopes to continue to contribute to the HD community.

# HDSA held the 2<sup>nd</sup> Annual Donald King Research Session at the 2015 Convention in Dallas, Texas



*2014 Donald King Fellows, Courtney Hanlon (left) and Varsha Prabhakar (right) are shown presenting the findings of their research to the attendees of the 2015 HDSA Convention in Dallas, Texas*



## HDSA's HD TrialFinder Connects People with Clinical Studies in Their Area

In April of 2015, the Huntington's Disease Society of America launched HD Trialfinder, 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. The continuously updated database includes both interventional, observational and biomarker studies being conducted at clinical trial sites across North America.

The trial listings in the HDSA HD TrialFinder come from publicly available sources, such as [clinicaltrials.gov](http://clinicaltrials.gov) from the National Institutes of Health. In addition, direct outreach is made to researchers and trial sites across the country to include their HD related clinical research studies in the HD TrialFinder database. All HDSA supported clinical research is required to be placed in the HD TrialFinder database.

"Currently, there are clinical research opportunities for every member of the Huntington's community to join," said Louise Vetter, Chief Executive Officer at HDSA. "From global initiatives to understand the disease to trials to evaluate the efficacy of specific treatments for HD symptoms, the field of HD science is providing an open door for families to help bring cures closer and we encourage everyone to get involved."

### 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.

#### 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

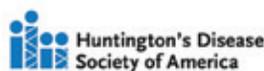
Contact your nearest HD clinical center to speak with a study coordinator and get involved. As new clinical trial sites become active in your local area, HD TrialFinder will automatically notify you.

"Through clinical trials, researchers are hoping to find new

ways to detect, treat and prevent Huntington's disease," said George Yohrling, PhD., Senior Director, Mission and Scientific Affairs at HDSA. "Recruiting individuals to participate in research in a timely manner is the greatest obstacle to developing the next HD treatment."

The HDSA HD TrialFinder only lists trials and studies that have Institutional Review Board (IRB) approval. Studies are also subject to additional review by the HDSA Scientific Advisory Board prior to being listed to ensure that listings only include credible trials and investigators.

"HDBuzz is focused on bringing high-quality information about Huntington's disease research to HD families around the world," said Jeff Carroll, PhD., Assistant Professor at Western Washington University and co-founder of HDBuzz.net. "HD TrialFinder is another key piece of the puzzle, and will serve as a great resource to connect HD families to ongoing trials. Improving the rate at which trials fill up brings closer the day that we're all waiting for – effective treatments for HD."



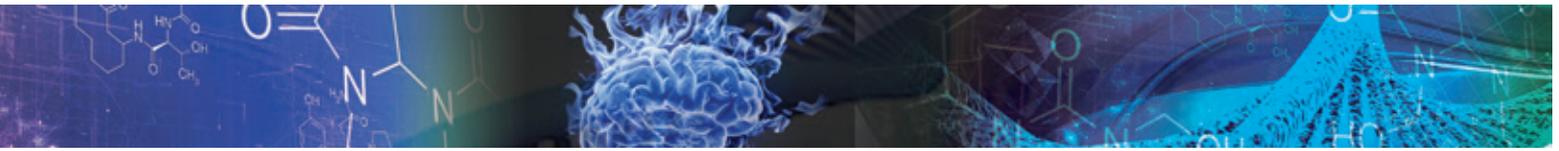
# HD Trialfinder

### Facts about HD Trialfinder

- Since its launch, over 1000 unique profiles have been created on the HD Trialfinder.
- HD Trialfinder trial listings are updated daily to provide HD families with the most up-to-date HD clinical trial information.
- Only trials that are currently recruiting participants are listed in the HD Trialfinder database.
- HD Trialfinder empowers patients and families to initiate a research conversation with their physician.
- HD Trialfinder is an important tool to help accelerate the HD drug development process.

The technology and platform for the HDSA HD TrialFinder is provided by EmergingMed.





## Huntington's Disease Society of America Adds Call Center Component to HD TrialFinder

The Huntington's Disease Society of America is pleased to announce that it has added a phone-based service to its repertoire of resources for the Huntington's disease community. HD TrialFinder is the only comprehensive, constantly updated database of institutional review board-approved HD trials taking place across North America.

HD TrialFinder is now a web and phone-based clinical trial matching service that connects individuals with Huntington's disease, caregivers, healthy volunteers and physicians with current studies. The trial listings in the HDSA HD TrialFinder come from publicly available sources, such as [clinicaltrials.gov](http://clinicaltrials.gov) from the National Institutes of Health, and are supplemented by HDSA's direct outreach to researchers and trial sites across the country to include their HD related clinical research studies in the HD TrialFinder database. Additionally, all HDSA-supported clinical research is now required to be placed in the HD TrialFinder database.

"HDSA is proud to launch this family-centered call center with EmergingMed," said Louise Vetter, Chief Executive Officer at HDSA. "We hope that the addition of the Clinical Trials Navigator resource will help make the process of getting involved in clinical trials less overwhelming for HD families."

In addition to the full suite of online resources, individuals can now call HDSA-trained Clinical Trial Navigators from 9:00 a.m. -5:00 p.m. eastern time. These "Navigators" answer questions about the trial process and connect individuals with trial sites based on their unique profile. Patients and caregivers will be encouraged to share their trial matches with their healthcare professionals to help decide whether a clinical trial is appropriate. Navigators will not recommend or endorse particular trials. Their role is to help individuals navigate HD clinical research opportunities by providing educational support.

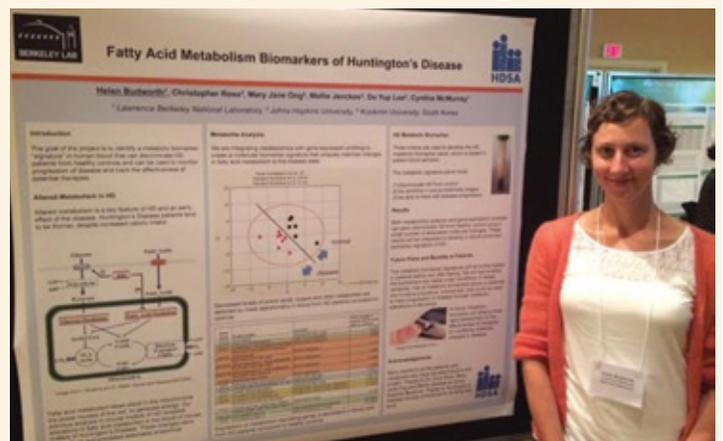
"HD TrialFinder is an important tool to help empower the HD community to start a conversation with their physician about the clinical trial options available to them," said George Yohrling, PhD., Senior Director, Mission and Scientific Affairs at HDSA, "We know that access to the novel research and treatments currently in development can provide hope to families that may feel there is none."

HDSA's HD TrialFinder can be accessed at [www.HDTrialfinder.org](http://www.HDTrialfinder.org) or by calling toll-free, (866) 890-6612. The technology and platform for the HDSA HD TrialFinder is provided by EmergingMed.

## HDSA Human Biology Project Fellows Highlighted at Annual Huntington Study Group Meeting

This year, the Huntington Study group (HSG) invited the 2013 HDSA Human Biology Project Fellows (Dr. Tanya Garcia, Texas A&M; Dr. Helen Budworth, Lawrence Berkeley National Lab; and Dr. Jun Hua, Johns Hopkins University) to attend to present their patient focused research findings to the HD research community.

In October, approximately 400 researchers, clinicians, advocates and members of the local HD community convened in Tampa, Florida to discuss the latest breakthroughs in HD clinical research at the annual HSG conference entitled "HSG2015: Building our Future". Dr. Michael Hayden, the Chief Scientific Officer at Teva Pharmaceuticals presented the Keynote address. Dr. Hayden is one of the world's leading HD researchers. Under Michael's guidance, Teva has launched two clinical trials for HD (PRIDE-HD and LEGATO-HD) and acquired Auspex Pharmaceuticals, the company responsible for the clinical development of SD-809 (Austedo) for HD. Dr.



**Dr. Helen Budworth, a 2014 HDSA Research Fellow, presents her research findings at the HSG 2015 Conference in Tampa, FL.**

Hayden reminded that audience that Teva remains committed to helping to provide "care on the road to a cure for HD".



## HD Researchers at the 10th Annual CHDI Therapeutics Conference in Palm Springs Heat Things up as East Coast stuck in Deep Freeze

This February, The Parker Hotel in Palm Springs, California was host to the 10th Annual CHDI Therapeutics Conference. CHDI Foundation, a private, not-for-profit biomedical organization funding HD science, hosted approximately 300 HD researchers from academia, non-profit, biotech, pharma and the government for four days of detailed scientific discussions. While there are many HD relevant meetings, this meeting remains the only conference dedicated to providing an open forum for HD “drug hunters”, pharmaceutical and biotech companies working in HD, to share ideas and discuss their progress in the push to develop effective therapies for HD. Due to the unique non-profit nature of CHDI, there are no competitors for CHDI, just collaborators.

This year's conference began with CHDI scientific management providing updates on their pre-clinical and clinical portfolios. Dr. Robert Pacifici, the Chief Scientific Officer at CHDI got things started by highlighting just a few of the many drug discovery programs they are currently considering as potential programs to combat HD. Several different translational programs at various stages of maturity were discussed.

A very common observation in many HD models is that a protein called brain-derived neurotrophic factor (BDNF) is depleted in the brains of HD patients. If one could boost levels of this important factor, or trick the brain into thinking that more of this factor were present, researchers believe this could potentially interfere with the course of HD. BDNF binds to a receptor in the brain called the TrkB receptor. While the discovery of small molecules that can act as TrkB specific agonists has been problematic, CHDI and their partner Pfizer and are considering an alternative approach. This involves the use of a TrkB antibody to bind the receptor to mimic activation. This could have neuroprotective consequences and is currently being tested in HD animal models.

Another area under investigation at CHDI is the kynurenine pathway. The kynurenine pathway is responsible for the metabolism (breakdown) of the essential amino acid, tryptophan. Evidence across HD models ranging from cells, flies and mice suggest that this pathway is overactive in HD. One enzyme in this pathway is called kynurenine monoxygenase,



or KMO. A result of too much KMO can be the generation of excess amounts of neurotoxic tryptophan metabolites, such as quinolinic acid. CHDI has created a small molecule that can inhibit KMO with the hopes that it can decrease the production of these toxic metabolites and potentially slow down the progression of HD. The drug, referred to as CHDI-246, is still in the pre-clinical development stage, but may one day get an opportunity to test its effectiveness in human testing.

Cheryl Fitzer-Attas, VP of Clinical Research at CHDI then presented several projects within the clinical portfolio at CHDI. The overarching goals of the CHDI Clinical Team are to better understand the mechanisms that cause HD, validate biomarkers, support HD clinical trials and develop new clinical tools/assessments to improve and accelerate clinical testing. For the latter, CHDI and their collaborators are focusing on the development of an HD Tool Kit that is a collection of relevant and validated assessments of clinical HD research. There is a clear recognition that cognitive and psychiatric symptoms of HD cause the most functional disability. The new clinical assessments are trying to better quantify this disability. One such test is called the Cognitive Assessment Battery (CAB). The CAB is comprised of 6 tests, 3 are computerized and 3 are paper and pencil tests. This is the first battery created for late pre-manifest HD and early HD trials. Another rating scale being developed is called FuRST2.0. This is a functional rating scale that aims to assess the activities of daily living of HD patients.





CHDI is interested in better understanding the economic consequences of HD. CHDI is collaborating with IMS Health to develop a burden of Illness Cost Model of HD to try and quantify the economic burden of HD. Preliminary data suggests that between \$17,500 and \$34,000 per year can be saved if an HD patient can be stabilized in stage 1 HD. A new survey will be introduced to the community through the Enroll-HD research platform to look at the indirect costs associated with HD.

Speaking of Enroll-HD, this enormous effort being coordinated by CHDI was the final project highlighted by Dr. Fitzer-Attas. Enroll-HD now has over 7,700 participants around the world with the goal of 25,000 or more within five years. The Enroll-HD platform has three main goals:

1. To improve our understanding of HD and find out what factors influence the progression
2. To foster good clinical care and improve the health of the participants
3. To enhance the design and expedite the conduct of clinical trials



At this conference, CHDI announced a brand new website ([www.Enroll-HD.org](http://www.Enroll-HD.org)) has been released and the very first dataset from 1437 Enroll-HD participants has been extracted and can now be accessed by HD researchers around the world. To gain access to these data, researchers must submit an application form to CHDI through the new portal at Enroll-HD.org. As more people join Enroll-HD, the dataset will become richer in information that could better inform scientists about the biology of HD.

As has become customary, the first evening of the meeting culminates with an uplifting and motivational speech. Dr. Jeff Carroll provided the attendees with a much anticipated Keynote Address. Jeff is an Assistant Professor at Western Washington University and researches metabolic alterations in HD. In addition to being an HD researcher, Jeff comes from an HD family and is positive for the gene mutation that causes HD. Jeff took the audience on a journey through his life. From the beginning when he first learned HD was in his family through today where he is now an independent HD researcher working tirelessly to defeat the disease that took his mother and affects three of his siblings and himself.

The scientific portion of the CHDI conference took place over the course of the next three days. Topics ranging from harnessing the power of flies, to unbiased “Big Data” analytical approaches, to existing clinical trials for HD were all addressed. Another exciting topic that was covered was an update on the search for genetic modifiers of HD. Of particular interest to many HD families is the question of why one person in a family with 42 CAGs develops symptoms of HD at 30 years of age while another person in the same family with 42 CAGs develops symptoms at 70. If both people have the same exact mutation, what can account for the wide range in the age of onset? The answer likely lies with what scientists call genetic modifiers. These are inheritable factors, besides the huntingtin gene, that when inherited along with the expanded huntingtin gene could either accelerate or delay the onset of the disease. If we could identify the factors at play that are causing the person with 42 CAGs to first develop symptoms at 70 instead of 30, it is possible that researchers could exploit that observation into a drug for the people to potentially delay the disease onset.

Jong-Min Lee (Massachusetts General Hospital) presented that they have identified regions on two different chromosomes (8 and 15) that appear to be associated with both earlier and later age of onset. Within these regions of each chromosome there are a number of different genes expressed. Next steps are to start narrowing down which gene, if any, in these suspicious regions of DNA are truly having a disease modifying effect.

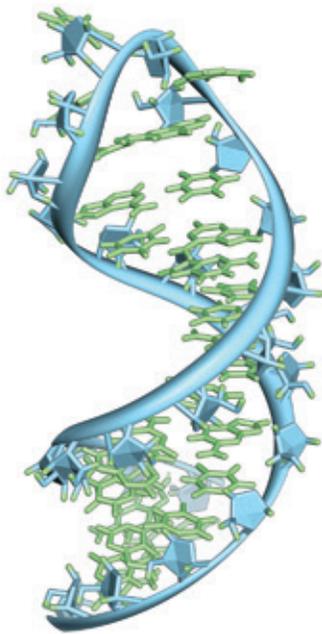
An entire session was dedicated to the advancement of huntingtin lowering therapies. We heard from Dr. Frank Bennett of Isis



Pharmaceuticals about their plans for a Phase 1/2a safety study of their ASO to lower huntingtin (Htt-Rx). This trial has now begun! In a separate Isis ASO trial with the goal of increasing the amount of the SMN2 protein that is decreased in spinal muscular atrophy (SMA), Dr. Bennett reported data from three infants with SMA that received their ASO. In all three children, the drug got into the brain and increased the levels of the SMN2 protein as desired. While these are not HD patients, these data do provide great hope that their huntingtin selective ASO may get to the brain and positively affect the levels of the huntingtin protein when administered via a spinal tap.

ASOs are not the only therapeutic strategy being investigated for HD. In this exciting session we heard from Dr. George McAllister at BioFocus about their approach to screen for more traditional small molecule drugs (such as ones that could be taken orally) to lower huntingtin levels. Dr. Lisa Stanek of Genzyme (a Sanofi company) showed incredibly exciting pre-clinical data in monkeys using their approach to use viruses to deliver huntingtin lowering agents to the brain. Using something called an Adeno-Associated Virus (AAV), Genzyme was able to demonstrate that they could achieve widespread distribution of their AAV in the cortex (70-90% coverage). This is very exciting because one of the major concerns of the viral approach to date has been the poor distribution of the virus within the brain. Finally, Dr. Geoff Nichol from Sangamo Biosciences

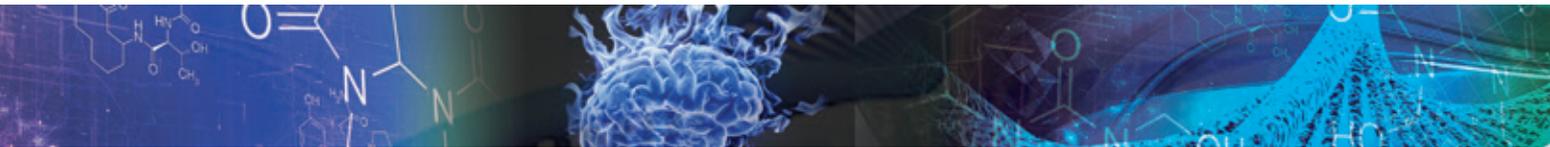
presented an update on their allele-selective approach to target huntingtin at the DNA level. Like Genzyme, Sangamo uses AAVs however their cargo is much different. Sangamo uses AAVs to deliver Zinc Finger Proteins (ZFPs) that can bind specifically to expanded CAG repeat lengths such as in the expanded huntingtin DNA. The viruses also contain what is referred to as a transcriptional repression domain. When these ZFPs bind to the CAG repeat in huntingtin, the viruses will also express the transcriptional repression domain that will prevent the huntingtin DNA from being “transcribed” into RNA. RNA is basically the recipe the



body uses to make the huntingtin protein. Unlike the current Isis Pharmaceutical approach, Sangamo will target only the expanded huntingtin DNA with hopes of leaving the normal huntingtin protein unchanged. The Sangamo approach is still in the pre-clinical phase of development, but plans are being made for a Phase 1 safety study in symptomatic HD patients.

In order to run a clinical trial one must have readouts that can accurately and reproducibly tell you if the drug is having the desired effect. We also need readouts that can better predict the onset and progression of HD. These readouts are referred to as biomarkers and an entire scientific session was dedicated to cover the latest innovative approaches being tested for HD. New brain imaging studies are underway to investigate new targets, such as the cannabinoid receptor and serotonin receptor (5-HT2a) to see how they change over time in HD patients. A biomarker study called CLARITY-HD will make use of human cerebral spinal fluid (CSF), to search for protein changes in HD patients. Investigation into CSF is important because it is an accessible human sample that may serve as a surrogate to what is going on in the brain. Finally, scientists from IBM presented how they will use the power of computers (i.e. Watson) to perform an automated speech analysis in HD patients to try and detect early changes in vocalization that could potentially predict the onset of psychoses in HD.

While there is never a good time to have HD, it is certainly an exciting time in the HD research community. Never before have so many drugs been in the HD pipeline than now. This year's start of the Isis Pharmaceuticals clinical study to test the safety of ASOs in HD patients marks a monumental point for the field. This is the first drug designed specifically for HD patients to be tested in humans. We hope this study will help enable many other huntingtin lowering drugs in the near future. Overall, the data presented at the 10th CHDI Therapeutics Conference should act to provide the community with a great deal of hope that dedicated researchers from around the globe are working in an unprecedented manner to ensure that future HD clinical trials achieve our collective goal of finding safe and effective therapies to slow or delay HD. No one person will find the cure for HD, it will take the entire HD community (families, patients, researchers and physicians) working together until HD is history.



# Huntington's Disease Society of America Announces 2015 HDSA Centers of Excellence

In February 2015, HDSA announced that twenty-nine outstanding Huntington's disease care facilities were awarded the designation of HDSA Centers of Excellence for 2015. Competition for the grants was intense with forty-two applications received from top-notch medical institutions around the country.

The 2015 HDSA Centers of Excellence represent a 45% increase from the twenty Centers awarded in 2014. The roster of Centers share an exemplary commitment to bringing more comprehensive care to more HD affected families across the United States, including a new 'boots on the ground' presence in at least ten states where the Center of Excellence program did not previously have reach. These include Delaware, Nebraska, North Carolina, North Dakota, Oregon, Pennsylvania, South Dakota, Tennessee, Vermont and West Virginia. In total, nearly \$800,000 was provided to HDSA Centers of Excellence this year.

"HDSA is excited to recognize twenty-nine exceptional clinics in 2015 and directly support their comprehensive approach to helping families manage the challenges of Huntington's disease," said Louise Vetter, HDSA's Chief Executive Officer. "These awards are made possible by the incredible generosity of the HDSA community, who are united in their commitment to bring help and hope to more families, in every corner of the United States."

The HDSA Centers of Excellence provide an elite team approach to Huntington's disease care and research. At these world-class facilities, 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.

This year's program marks a turning point in HDSA's effort to increase access to expert, multi-disciplinary care for HD families. The grant program expanded to support both regional collaborations and smaller, developing clinics, in addition to the classic, one-site centers. At all levels of the program, a commitment to clinical research is expected, as is the expectation of family support through ancillary services and social workers.

This review was led by the HDSA Center Program & Education Advisory Committee (CPEAC) and culminated with the launch

of a new Center grant program in July 2014 (publicly available at HDSA.org) with requests for proposals open to all clinics in the United States who share HDSA's commitment to high-quality, comprehensive care and access to clinical research.



The 2015 HDSA Center of Excellence grantees is listed below alphabetically:

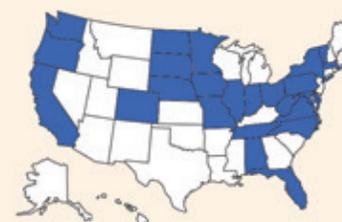
- Boston University Medical Center (MA)
- Cleveland Clinic (OH)
- Colorado Neurological Institute
- Columbia Health Sciences/NYS Psychiatric Institute (NY)
- Duke University (NC)
- Hennepin County Medical Center (MN)
- Indiana University
- Johns Hopkins University (MD)
- Massachusetts General Hospital
- Ohio State University
- Rush University Medical Center (IL)
- Stanford University
- 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 Florida
- University of Iowa
- University of Nebraska Medical Center
- University of Pittsburgh Medical Center (PA)
- University of Rochester (NY)
- University of South Florida
- 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 2015

COE Coverage in 2014  
17 states



COE Coverage in 2015  
25 states





## Topic of the Year: Genetic Modifiers of HD

### Scientists identify genetic factors that alter the clinical onset of HD

Twenty-two years after the publication of the paper that identified the gene that causes Huntington's disease, the collaborative and innovative nature of the HD research community is at it again! Published this summer in the prestigious journal, *Cell*, scientists have identified regions of the human genome that can either delay or accelerate the onset of HD.

Specifically, they found that the expression of genetic variants within chromosomes 15 and 8 could accelerate HD onset by 6 and 1.6 years respectively, while expression of a separate variant, also in chromosome 15, could delay HD by 1.4 years.

The data also suggest that the body's DNA repair mechanisms (specifically a gene named MLH1) may play an important role in the disease process. In all, these data provide us with strong evidence from humans that the course of HD can be modified. It is hoped that further investigation of the regions of chromosomes 15 and 8 that contain the genetic variants associated with altered HD onset could result in the identification of novel therapeutic targets for HD drug development that could possibly slow the onset of disease.

This study is a result of the efforts of hundreds of scientists and clinicians from around the world that make up the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium, as well as the participation of thousands of HD patients. Proof again that HD families are making important HD science possible. Thanks to everyone for their time and dedication!

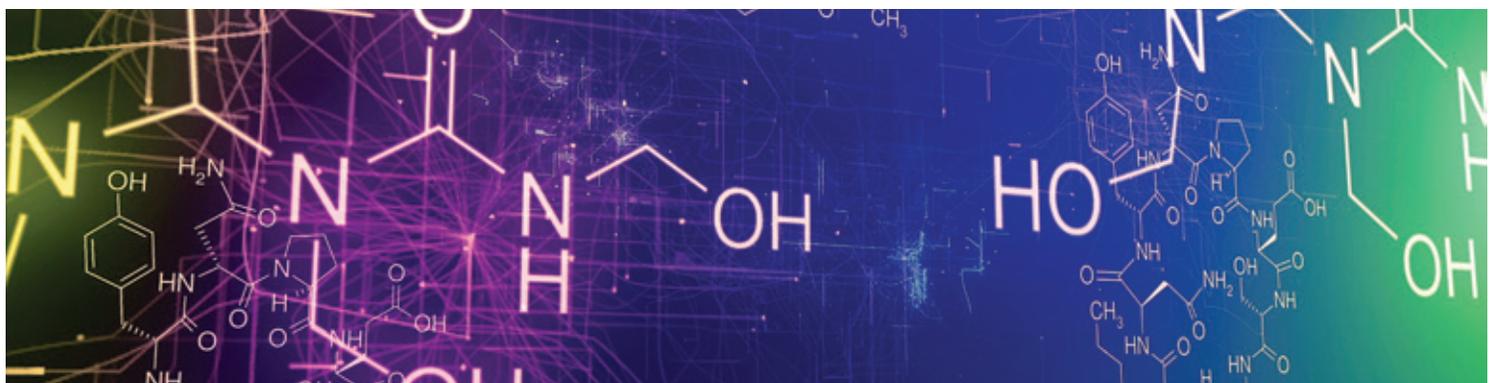
While discussing the potential impact of these findings, Dr. James Gusella, the corresponding author on this landmark paper was quoted as saying, "What we can say for sure is that the modifier variants located on these chromosomal regions affect the disease process prior to the appearance of symptoms.

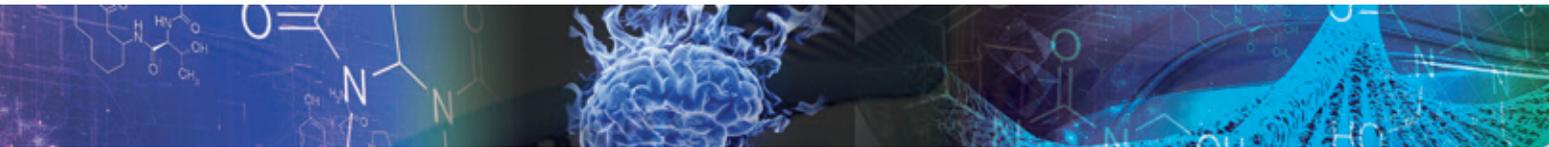
Figuring out the exact DNA sequence variations responsible and how they influence the disease process should provide us with a guide for developing drugs that we hope could have a much larger effect than the one to six years produced by the natural variations, possibly even preventing symptom onset altogether. We believe that we are closer to finding such therapies, but it's impossible to predict a specific timeline."



***This is referred to as a Manhattan Plot. The purple dots above the dotted line show the highly significant genome-wide peak that was found on Chromosome 15 by the GeM-HD Consortium***

In a separate study, researchers from the University of British Columbia identified a genetic variation (called a single nucleotide polymorphism or SNP) in a region of DNA that codes for the huntingtin promoter. The promoter resides just upstream of the huntingtin gene and is ultimately responsible for the levels of the huntingtin RNA and protein made by the body. When the SNP is located on the non-expanded huntingtin DNA promoter, it results in an earlier age of onset for HD patients. However, when the SNP was associated with the expanded (mutant) huntingtin promoter, it resulted in a significant delay in the age of onset for HD patients. This effect was particularly strong when the CAG repeat length was between 41 and 45 CAG. When the SNP was found on the promoter for a huntingtin gene with 41 CAG repeats, it was associated with a greater than 17 year delay in the age of onset of motor symptoms of HD!





# HD CLINICAL TRIALS UPDATE

## ENROLL-HD: A Global Platform to Enable Future HD Drug Development

There are over 7000 rare diseases, like HD, in the world. Patients affected by rare diseases often ask, “How do we get pharmaceutical companies to pay attention to our disease?” The suggestion most commonly given is to build a global registry of patients, with longitudinal clinical data and ensure you have a network of clinical trial-proven doctors ready to run the trials. Luckily for HD, CHDI Foundation has created such a platform that will enable all companies interested in pursuing HD as an indication.

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 will support recruitment for clinical trials of potential new therapeutics for HD. Finally, it will undoubtedly help inform the 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 currently has over 7700 subjects in more than 120 recruiting sites internationally, 49 of which are in the United States. Within five years, the goal is to have between 25,000 and 30,000 people in the Enroll-HD study.

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).

## Pfizer: The Amaryllis Study Hopes to Conclude Recruitment in 2016

What is PDE10 and what does it have to do with Huntington’s disease? PDE10 stands for phosphodiesterase 10. There are several different types of PDEs. The most well-known is referred to every Sunday during NFL commercial breaks. The most well-known is in popular drugs for erectile dysfunction, Viagra and Cialis are inhibitors of PDE5. There is another “flavor” of PDE called PDE10 that is primarily expressed in 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. While that may not have panned out, 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).

In 2014, Pfizer began a global Phase 2 clinical trial of their PDE10A inhibitor in HD patients. This study has been 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. This study is trying to recruit 270 subjects for 26 weeks. Subjects will be divided into three groups: a placebo group, a 5mg dose and a 20mg dose.

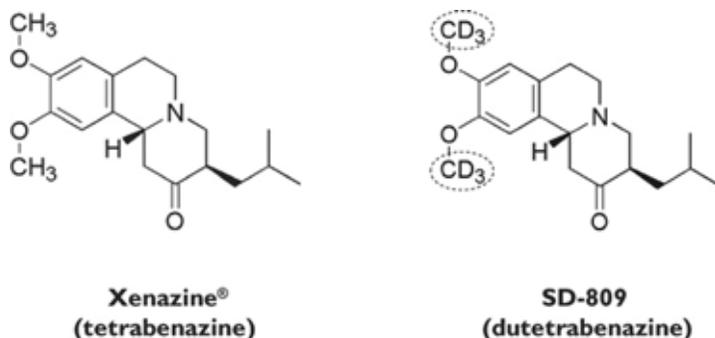


The primary endpoint for this trial will be to see if the drug can positively impact the Total Motor Score (TMS). However, other clinical readouts such as cognition, behavior and brain size with the use of MRI imaging will be employed. All the US study sites can be found in [HDTrialfinder.org](http://HDTrialfinder.org). The goal of this study is to complete recruitment by early 2016.

## Auspex's First-HD and ARC-HD Trials Meet Their Primary Endpoints

Just after the 2014 Research Investors Report went to press, Auspex Pharmaceuticals announced positive topline efficacy and safety results from its Phase 3 registration trial (First-HD) that evaluated SD-809 for the treatment of chorea associated with Huntington's disease (HD). The primary efficacy endpoint for First-HD was the change from baseline to maintenance therapy in the Total Maximal Chorea (TMC) score of the Unified Huntington's Disease Rating Scale (UHDRS). In addition to meeting the primary efficacy endpoint, significant improvements in both patient and clinical global impressions of change and quality of life were observed. The study demonstrated a favorable safety and tolerability profile, including low rates of depression, somnolence, restlessness and anxiety. Finally, Auspex also announced results from an analysis of the completed four-week Switch portion of the ARC-HD study, which also has an ongoing long-term safety component. Data from the ARC-HD study showed that patients who switched from the current standard of care, tetrabenazine, to SD-809 maintained chorea control at both week one and week four.

SD-809 has the same biological mechanism of action as tetrabenazine. SD-809 is thought to positively impact chorea by inhibiting the packaging and release of an important neurotransmitter in the brain called dopamine. High dopamine levels in the brain are often associated with uncontrolled movements. First-HD investigated how safe, tolerable and effective SD-809 is compared to placebo (inactive drug) in reducing chorea. First-HD successfully recruited 90 participants at approximately 30 sites across North America who had been diagnosed with HD and who have not taken tetrabenazine in the past 6 months.



**Figure: Minor chemical modifications to tetrabenazine result in significantly improved pharmacodynamic properties of SD-809.**

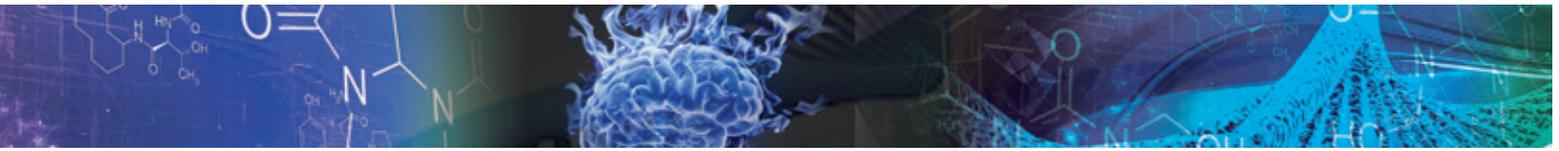
The ARC-HD trial was an open-label long-term safety and tolerability clinical research trial of SD-809 in persons who have a diagnosis of HD. ARC-HD also assessed safety, tolerability and effectiveness of SD-809 in HD participants. One group was comprised of participants who completed the First-HD study and were then “rolled over” into the open-label trial. The second group (Switch) consisted of patients taking tetrabenazine who were willing to “switch” from tetrabenazine (Xenazine) to SD-809.

Following word of the positive clinical data, Auspex submitted a New Drug Application (NDA) to the Food and Drug Administration (FDA) for approval of SD-809 in HD. In a move to bolster their neurologic pipeline, Teva Pharmaceuticals purchased Auspex in May of 2015 for \$3.5 Billion! The HD Community should expect a decision on the Auspex NDA by early 2016. If approved, SD-809 will provide physicians with another tool for their arsenal to combat the chorea associated with HD.

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

It is a goal of HDSA to improve 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 allele-specific ASOs, novel pathogenic mechanisms in HD, and new clinical study opportunities. If you missed one, don't worry. Each Research Webinar is recorded and archived on HDSA's YouTube channel so you can view at your leisure. Make sure you sign up for email alerts from HDSA to stay informed of more great webinars starting again in January 2016!





# Teva Currently Testing Two Different Drugs in Clinic for HD



TEVA PHARMACEUTICALS LTD

## Pride-HD Completes Enrollment

Pride-HD is a Phase 2 clinical research study of an investigational drug called pridopidine in people who

have a diagnosis of Huntington disease (HD). The purpose of this study to see what effect pridopidine has 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 will be a change in the total motor score (TMS) of HD patients on the drug.

Pridopidine, the investigational drug being studied may have an effect on some of the symptoms of HD that depend on dopamine. Dopamine is a substance that is naturally made

by the human body. It is made in many areas of the brain, and affects how people behave, think and move. It has been suggested that changes in the way dopamine works in HD creates signs and symptoms of the condition. This study is being conducted to determine if pridopidine helps with the signs and symptoms of HD.

Pride-HD is a joint collaboration between the Huntington Study Group (HSG) and the European Huntington's Disease Network (EHDN). 400 participants have now be enrolled globally at approximately 51 study sites. Participants are receiving either pridopidine or placebo for 26 weeks. The Pride-HD successfully met its enrollment goals and is no longer accepting participants. We expect to hear about the results of this study in early 2016.



## Legato-HD Still Recruiting Patients

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 UHDRS-TMS. Laquinimod is a small molecule 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. Approximately 400 subjects are needed for this study that got underway in late 2014. The current goal is to have the study completed in 1Q2017. In addition to HD, laquinimod is currently being investigated as a potential therapy for multiple sclerosis (MS).

## What do all those big words really mean to me and why should I care?



Stay informed on the latest HD research news on HDSA.org and the HD News App

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, "cures" don't

just fall from the sky! 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.



# And they're off! Isis Pharmaceuticals Transitions Antisense Oligonucleotide (ISIS-HTTRx) Into Clinic for HD



eligibility. Participation in this study is expected to last for about 8 months.

## How will the study drug be administered?

Each dose of ISIS-HTTRx or placebo, will be 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, an intrathecal injection, and travels to the brain as it distributes in the cerebrospinal fluid. The study will be randomized 3:1 so that three-fourths of the patients will receive ISIS-HTTRx and one-fourth of the patients will receive placebo. This safety

## What is ISIS-HTTRx?

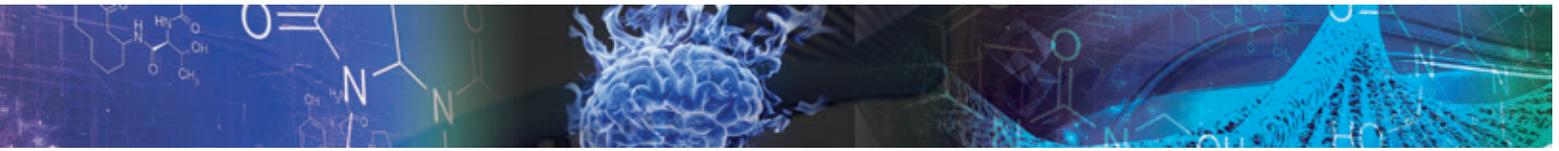
ISIS-HTTRx is an investigational drug being developed by Isis Pharmaceuticals for the potential treatment of Huntington's disease (HD). ISIS-HTTRx offers a unique mechanism to correct the underlying genetic anomaly that causes HD by preventing the production of the toxic Huntingtin protein. ISIS-HTTRx, is an antisense 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.

This study is designed to evaluate the safety and tolerability of multiple doses of an investigational drug, ISIS-HTTRx, 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 36 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

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 ISIS-HTTRx. None of the patients or physicians participating in the study will know whether the patients are receiving active drug or placebo (double-blind). After study completion, an open-label extension study of ISIS-HTTRx 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.

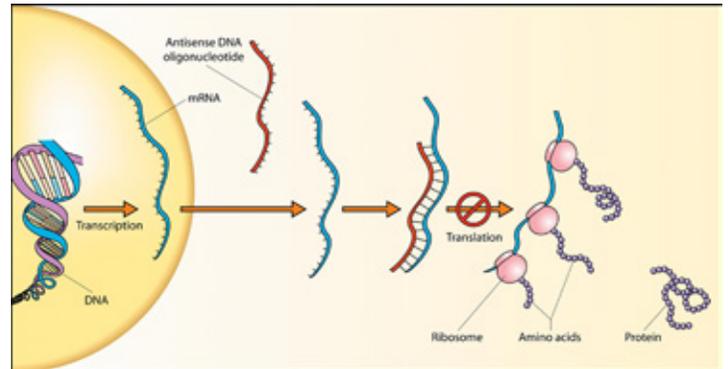
## Where will the study take place?

The HTT-Rx study will be conducted at six centers in Canada, United Kingdom and Germany only. There are no sites in the USA. If the data from the HTTRx 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.



For the ISIS-HTTRx study, you are required to live near a study center and travel distance in this study has been limited to within 4 hours of ground travel. Eligibility will be determined by the clinical trial investigator at each site, who may consider factors such as travel distances, medical insurance and their specific institutional policies regarding international patients.

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 ISIS-HTTRx in HD patients. It will not evaluate the effectiveness of the drug to improve HD symptoms.



*From ipbrief.net. ASOs (shown in red) work by binding to RNA and preventing the RNA from being translated into the toxic huntingtin protein*

## HDSA Announces New Career Development Fellowship

The Huntington’s Disease Society of America is now accepting letters of interest for a new research fellowship program specifically designed to develop new scientific leaders in the quest to better treat and one-day cure Huntington’s disease. The Berman/Topper Family Huntington’s Disease Career Development Fellowship is a three-year grant for young scientists to work collaboratively with their mentors and other committed HD health professionals to help develop the fellow into an independent HD leader.

HDSA partnered with the Berman/Topper Family to launch this new program in response to the desperate need for career development mechanisms for young HD researchers and the stagnant budget at the National Institutes of Health, which had been a traditional grant funder of new scientists.

“HDSA is grateful for the partnership of the Berman and Topper Families who share our goal to ensure that the pipeline of passionate and bright HD scientists and clinicians remains full,” said Louise Vetter, Chief Executive Officer at HDSA.

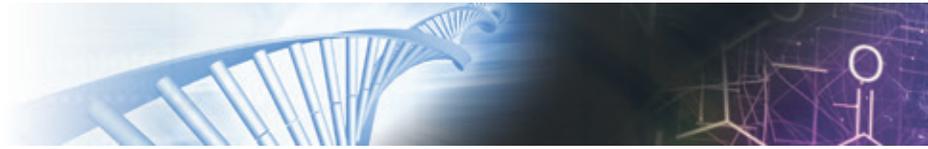
“This Career Development Fellowship program is a unique commitment to developing the next generation of passionate and innovative HD scientists.”



“We are excited to work with HDSA to provide an opportunity to attract new minds to the battle against HD. We hope that each person involved in this program will in some way contribute to greater knowledge of the disease and ultimately to causing a cure,” said Michael Berman, speaking on behalf of the Berman and Topper families.

Scientists and clinicians who are no more than five years removed from obtaining their PhD or completing their residency/fellowship and who are interested in a career in Huntington’s disease research or care are invited to apply for the Berman/Topper Family Huntington’s Disease Career Development Fellowship. Applicants cannot have their own laboratory and must identify an individual who will serve as their mentor and supervisor throughout the duration of the three-year award. Each award three-year award provides up to \$80,000/year of which \$75,000 is designated for salary and research support, plus an additional \$5,000 for travel/education related to the fellowship.

To submit an application to the Berman/Topper Family Huntington’s Disease Career Development Fellowship or to download the detailed Request for Proposal, please visit [www.hdsa.org](http://www.hdsa.org). Completed applications must be received by HDSA no later than Monday, February 29, 2016, at 5:00 pm (EDT). For more information, contact Dr. George Yohrling, HDSA Senior Director, Mission and Scientific Affairs, at [gyohrling@hdsa.org](mailto:gyohrling@hdsa.org).



## 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, 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 (Chairman of SAB)
- **Neil Aronin, MD**, Professor and Chairman of Endocrinology and Metabolism, University of Massachusetts Medical School
- **Beth Borowsky, PhD**, Director of Translational Medicine, CHDI Foundation
- **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)
- **Marcy MacDonald, PhD**, Professor, Harvard Medical School, Massachusetts General Hospital
- **Melissa Moser**, Community Representative
- **Harry Orr, PhD**, Professor, University of Minnesota
- **Susan Browne, PhD**, 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.

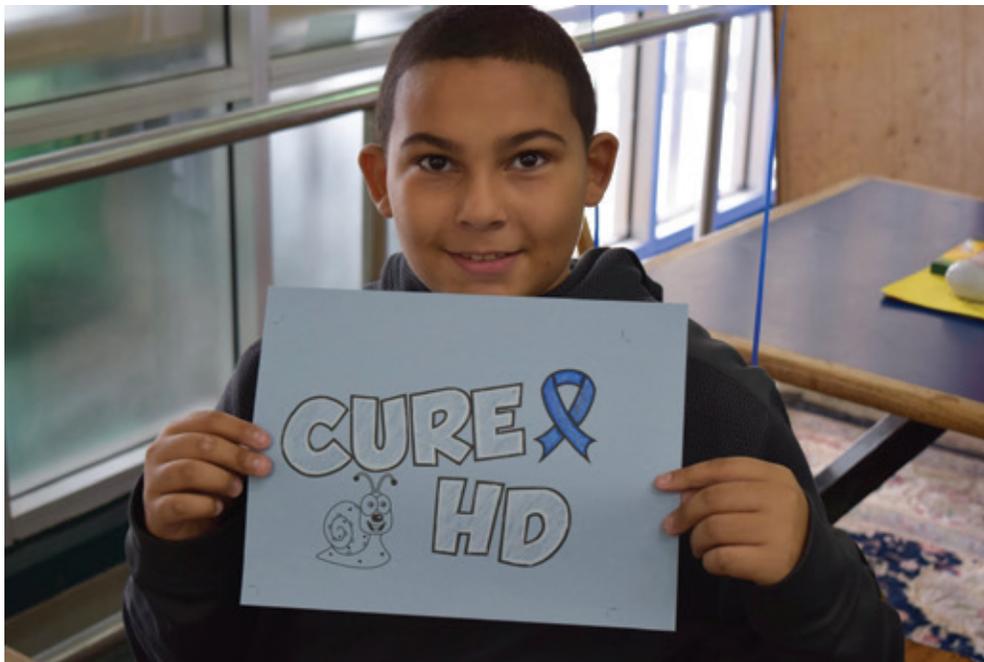


## Final Thoughts

Not since the gene that causes HD was identified in 1993 has the scientific community been so excited and hopeful about the prospects of making a positive impact on finding treatments for HD than they are in 2015. This year brought the start of the much anticipated huntingtin lowering trial from Isis Pharmaceuticals. This study marks the beginning of our scientific journey to hit back at the root cause of HD. While the goal of this study is solely to evaluate safety and tolerability of the gene silencing drug, it will no doubt serve as a beacon for all future huntingtin lowering trials.

We have also seen the number of companies interested in HD grow in 2015 to numbers we have never experienced. With this comes large commitments of corporate resources to the fight against HD. While financial investment in research and development is critical, dollars alone will not help us meet our goal of a world free of HD. The continued involvement of the HD patients and families in clinical research is essential to finding effective treatments for HD. Years ago, patients had no options if they wanted to participate in a clinical trial. That has certainly changed. Many patients now have several trial options available and with the launch of HDSA's HD Trialfinder, they now have a valuable resource that provides up-to-date clinical trial information at their fingertips.

For year's families have asked "when are the drugs to treat HD coming?" The answer is: they have arrived. We must continue to work together as one HD family to seize the clinical opportunities presented to us so that we can make what was once thought to be impossible, possible!



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



**Our Mission:  
To Improve the Lives of Everyone  
Affected by Huntington's Disease  
and their Families.**

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

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 during their prime working years and has no cure. HD is known as the quintessential family disease because every child of a parent with HD has a 50/50 chance of carrying the faulty gene. Today, there are 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease. Many describe the symptoms of HD as having ALS, Parkinson's and Alzheimer's – simultaneously.

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 & Affiliates, 29 Centers of Excellence, 60 social workers and more than 170 support groups.



**Huntington's Disease  
Society of America**

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