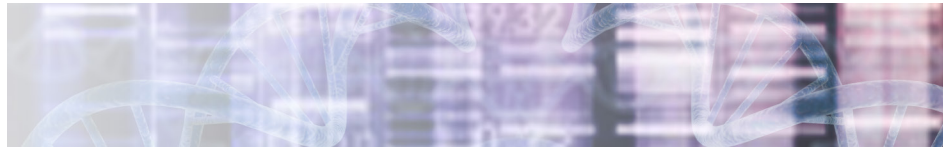




Huntington's Disease  
Society of America



2013  
Research Investor's Report



## HDSA's Renewed Commitment to HD Research

It was a busy year not only for the Huntington's Disease Society of America (HDSA), but also the global HD community. This year marked the 20<sup>th</sup> anniversary of the identification of the huntingtin gene which was a historic moment that truly transformed the way HD research is done. 2013 will also be remembered as a year of international outreach and collaboration. Instead of Palm Springs, CHDI Foundation took their annual therapeutics conference to Venice, Italy this year and the World Congress for HD was held for the first time in Latin America (Rio de Janeiro). These meetings provided valuable opportunities for researchers, patients and families to interact with HD experts they might not otherwise get to meet. Last but not least, HDSA held their 28<sup>th</sup> Annual Convention in Jacksonville, Florida. HDSA succeeded in bringing Dr. Michael Hayden, one of the world's most prominent HD researchers, to give the Keynote Address during the Research Forum. Dr. Hayden provided the entire audience with an incredible message of hope that potential new treatments for HD are on the way.

HDSA has a proud history of pioneering research, particularly the work originating from the 16 Coalition for the Cure researchers that were supported by you, the families. These scientists have played critical roles in HD research ranging from identifying the gene that causes HD to the identification of biological mechanisms that become dysfunctional during the course of the disease. While the Coalition work has concluded, in 2013 a major priority at HDSA was to execute the goals set forth in the 2012-2016 Strategic Plan to develop a new HDSA-driven research initiative. The main objective of this annual Research Investor's Report is to summarize the tremendous research progress we made in 2013, while also reviewing progress that has been made by others this year.

HDSA's Board of Trustees determined that research supported by HDSA must meet a number of criteria. First, the data and outcomes must be impactful by better informing clinicians and scientists on the design of future clinical trials. For example, this could be achieved by identifying a new biomarker in the blood of patients that could be monitored to assess efficacy of a novel therapeutic. Second, the work must not replicate research being done at other institutions, such as the National Institutes of Health and CHDI. To ensure this, we have improved lines of communication between all of the major institutions supporting HD research. Finally, the new research must involve a collaboration with one of the 21 HDSA Centers of Excellence across the United States. They are a unique and important resource not available to other HD organizations and one which HDSA must capitalize.

While incredibly innovative work is ongoing in labs across the world to develop better pre-clinical animal models of HD, there is no argument that the best and most physiologically relevant observations that will guide us in the hunt for effective therapies to slow the progression of HD are those that will be observed in HD patients. We strongly believe that observations from patients at the HDSA Centers of Excellence can significantly impact the future of HD research.

So, as 2013 comes to a close, you will see in this edition of the Research Investor's Report that HDSA and the research community have made tremendous progress towards moving closer and closer to meaningful clinical trials that will hopefully modify the course of HD and bring relief and hope to you – our HD families.

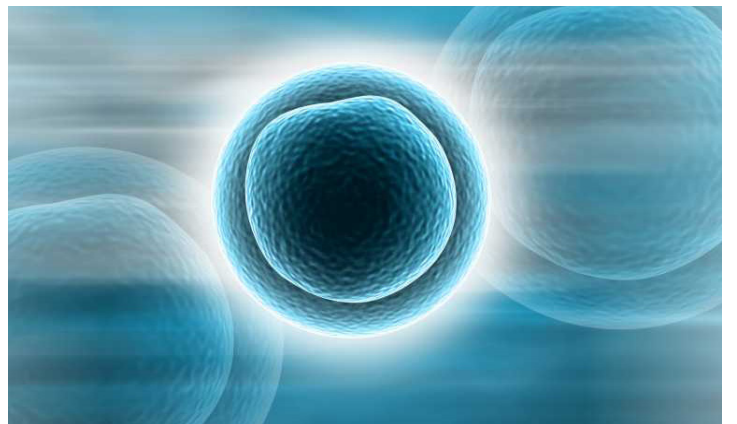


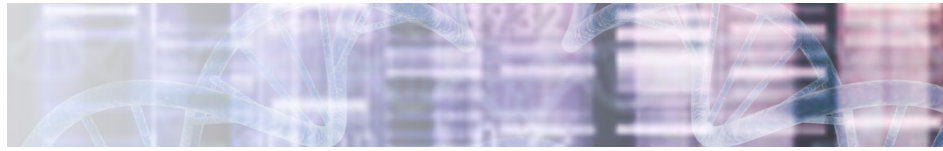
George Yohrling, PhD  
HDSA Director of Medical & Scientific Affairs



# Table of Contents

<b>4</b> New HDSA Scientific Advisory Board	<b>13</b> Zinc Finger Proteins
<b>5</b> First-ever HD Human Biology Project Awards	<b>14</b> Progress at CHDI Foundation
<b>6</b> Summaries of 2013 HDSA funded HD Human Biology Projects	<b>16</b> International HD Research Platform: Enroll-HD
<b>8</b> Donald A. King Summer Research Fellowships Awarded	<b>17</b> Pfizer-PDE10 Inhibitor Trial Prana Biotechnology Publishes Positive Results
<b>9</b> Stem Cells in HD Research and Development	<b>18</b> Auspex Pharmaceuticals Future Directions
<b>10</b> New Clues to Why Striatal Neurons are Preferentially Damaged in HD HD Buzz	<b>19</b> Final Thoughts
<b>11</b> Research Webinar Series Teva Pharmaceuticals Joins the Fight Against HD Genzyme Moving Forward	
<b>12</b> Huntingtin Antisense Oligonucleotides	





*Pictured from Left to Right: Neil Aronin, Eric Schadt, Harry Orr, Jang-Ho Cha, George Yohrling, Lucie Bruijn, Marcy MacDonald, Beth Borowsky, Michelle Gray, Louise Vetter, Sam Frank.  
Not pictured: Kurt Fischbeck, Ray Dorsey.*

## A New HDSA Scientific Advisory Board is Formed

The first step in developing an impactful new HD research program was to form a diverse and expert committee to guide the Society. The HDSA Scientific Advisory Board (SAB) is comprised of leading experts in their fields. The SAB'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:

- **Jang-Ho Cha, MD, PhD**, Director, Clinical Research, Merck (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, Boston University (ex officio)
- **Michelle Gray, PhD**, Assistant Professor, University of Alabama-Birmingham
- **Marcy MacDonald, PhD**, Professor, Harvard Medical School, Massachusetts General Hospital
- **Harry Orr, PhD**, Professor, University of Minnesota
- **Eric Schadt, PhD**, Chairman and Professor, Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine

The SAB'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.



## HDSA Announces First-ever HD Human Biology Project Awards

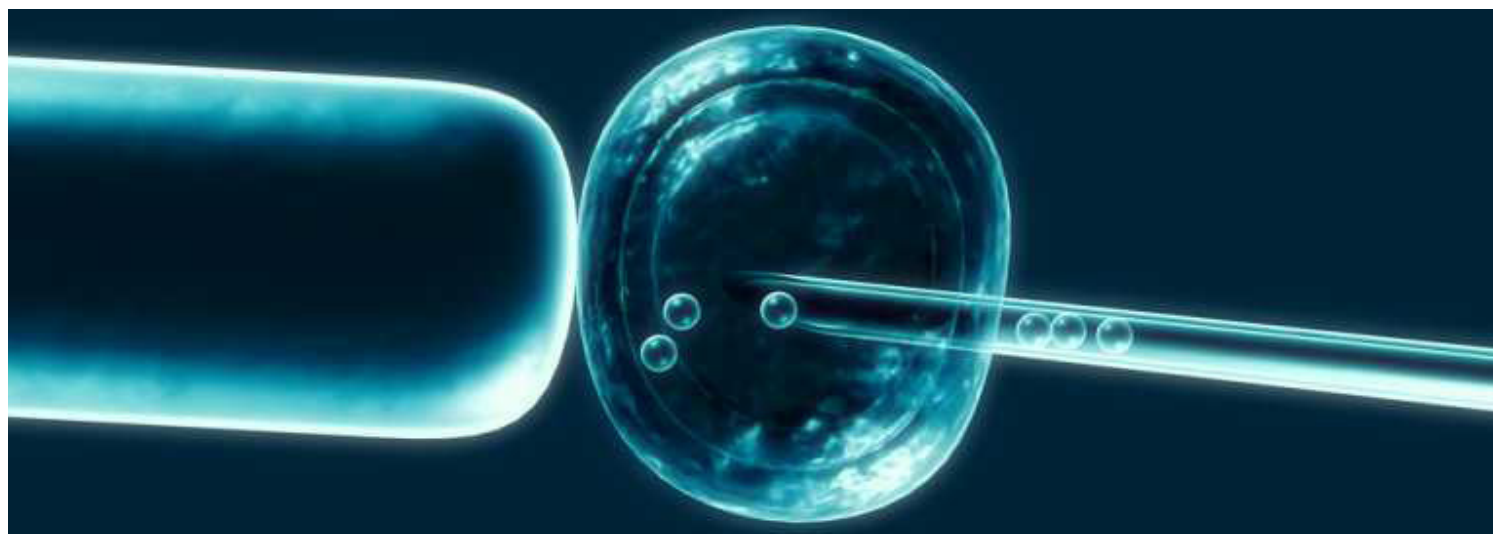
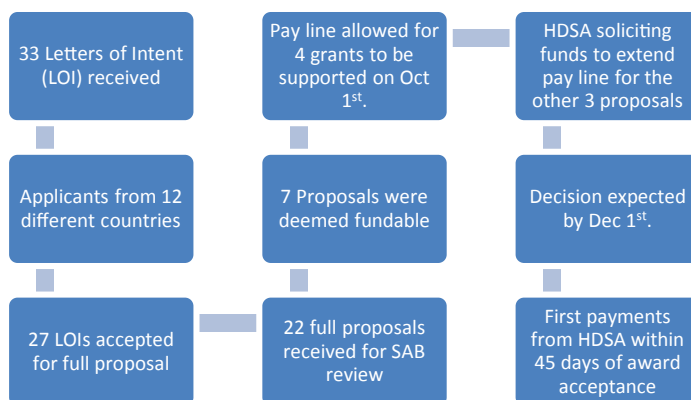
Over the course of the past year, the groundwork was laid to revitalize the HD research efforts at HDSA. HDSA established a world-class SAB representing diverse expertise in the neurodegenerative disease research and clinical functions to evaluate all scientific proposals to ensure they were of the highest scientific merit and properly addressed critical issues to help move the HD research community closer and closer to promising therapies for HD. This work culminated in October when HDSA announced that four research grants were awarded to launch the Society's new research initiative, the HDSA Huntington's Disease Human Biology Project. Totalling \$575,000, these grants emphasize the importance of bringing basic and clinical researchers together to facilitate HD science beyond animal models into human data and with the participation of HD patients.

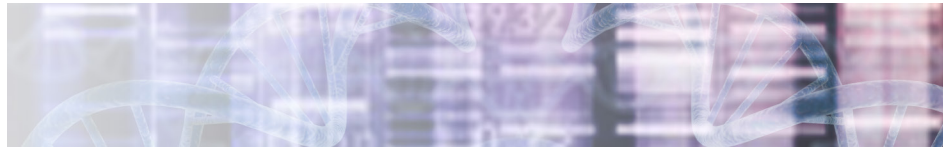
Uniquely, the HD Human Biology Project requires that all awardees propose to work in collaboration with at least one of the twenty-one HDSA Centers of Excellence across the USA. The HDSA Centers of Excellence are a select network of academic medical centers providing expert multi-disciplinary care to HD patients and families from health professionals with deep passion and experience in the area of Huntington's disease. These awards will foster innovative research to help the HD research community better understand the biology of Huntington's disease as it occurs in humans.

The Society is excited about the potential impact these HDSA-supported studies can have on assessing potential disease-modifying therapies, as well as expanding our knowledge of

the underlying causes of disease progression. To quote Louise Vetter, CEO of HDSA, "HDSA has a long history of supporting important HD science while simultaneously offering a broad catalog of programs to support families who are living with HD. Funded by the generosity of families who are committed to making a difference in the fight against HD, the Human Biology Project underscores our dedication to providing help for today and hope for tomorrow in order to bring our vision of a world free of Huntington's closer."

HDSA received top-notch applications from researchers from twelve different countries. Ultimately, grants were awarded to four research fellows (summaries below). The winning projects include statistical modeling of clinical HD data to better predict HD onset, biomarker development, and metabolic profiling of HD patient samples to better understand disease pathology.





## Summaries of 2013 HDSA- funded HD Human Biology Projects

**Dr. Roberto Boggio,**  
Senior Research Scientist,  
IRBM Promidis, Pomezia, Italy

*Title: Development of a novel, ultra sensitive bioassay for quantification of full-length mutant huntingtin in patient body fluids and analysis of different forms of huntingtin during disease progression. In collaboration with Dr. Susan Perlman, HDSA Center of Excellence at UCLA, Dr. Victor Sung, HDSA Center of Excellence at UAB, and Dr. Sandra Kostyk, HDSA Center of Excellence at Ohio State University.*

The long preclinical and clinical phases of Huntington's disease provide opportunities of early therapeutic interventions for disease-modifying therapies. A major obstacle to achieving this goal is the lack of quantitative, robust and reliable biomarkers for use in primary diagnosis, monitoring disease progression, patient stratification and evaluating efficacy of therapeutics in the clinic. Promidis is developing novel, sensitive, quantitative and robust immunoassay to enable quantification of mutant huntingtin protein levels in body fluids of patients, in particular cerebral spinal fluid (CSF) and plasma. The aim of this project is to develop a novel huntingtin immunoassay specifically recognizing "full length mutant huntingtin" and to assess the levels of huntingtin during disease progression in human bio-fluids such as plasma, Peripheral Blood Mononuclear Cells (PBMCs) and CSF in patient samples provided by HDSA Centers of Excellence.

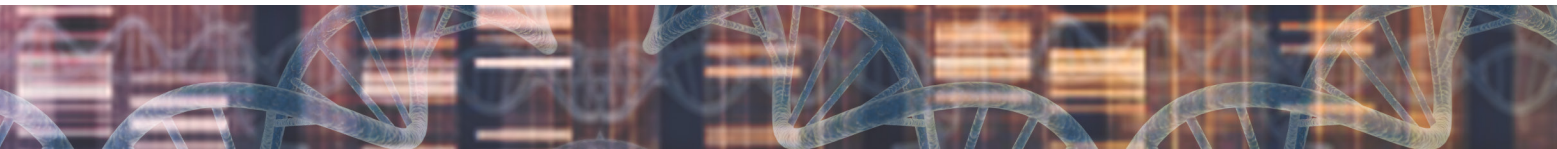
The development of ultra-sensitive assays for huntingtin can impact HD drug development on several levels: 1) Characterization of wild-type and mutant huntingtin in clinically relevant samples will provide a baseline for huntingtin levels at different stages of disease and can support stratification of patient populations for clinical trials. 2) Quantitative detection of huntingtin in the CSF (as a surrogate of brain tissue) may provide evidence of treatment efficacy of huntingtin lowering therapies in the central nervous system. 3) Assays for quantification of wild-type and mutant huntingtin (including its different structural conformations and fragments) can be used to better understand the pathophysiology of HD and may lead to the identification of novel treatment targets.

**Dr. Helen Budworth,**  
Project Scientist,  
Lawrence Berkeley National Laboratory

*Title: Metabolomic and gene expression analysis of fatty acid metabolism biomarkers of Huntington's disease. In collaboration with Dr. Chris Ross, HDSA Center of Excellence at Johns Hopkins University*

Since HD primarily affects the brain, monitoring the onset of symptoms and progression of the disease are extremely difficult. Biological markers of disease that are present in the blood of patients would be of great utility in tracking the disease and also in testing how effective prospective therapies are. Huntington's disease is known to affect a patient's metabolism. For example, patients often experience dramatic weight loss despite increased caloric intake. Therefore, we will use metabolic markers of disease that are present in the blood, such as fatty acids, to help us better track disease progression and test effectiveness of novel therapies. This metabolic profile will be integrated with a gene expression profile from the same human HD blood to create a "metabolomic signature" for HD.





**Dr. Tanya Garcia,**  
Assistant Professor,  
Texas A&M Health Science Center

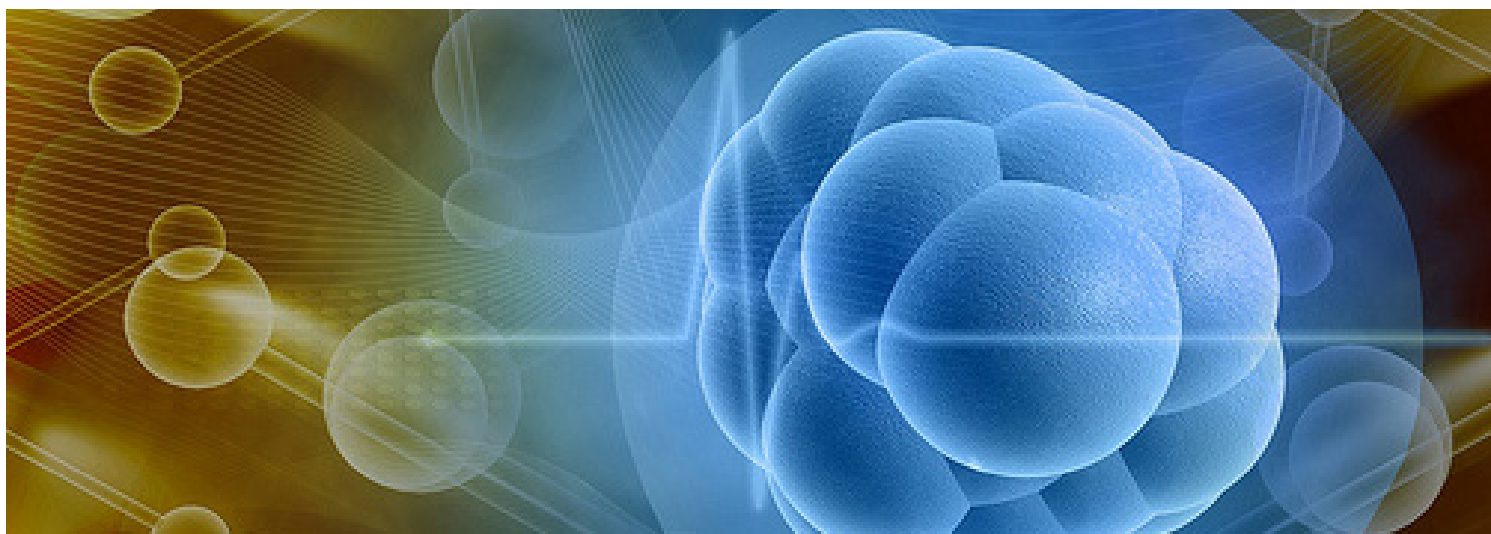
*Title: Improved Definition and Prediction of Huntington's disease motor-onset using advanced statistical models. In collaboration with Dr. Karen Marder, HDSA Center of Excellence at Columbia University*

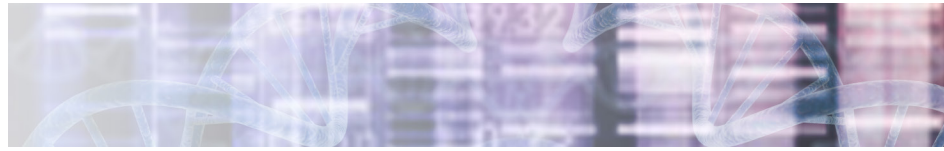
A vital area of clinical and statistical research that we will address is objectively defining disease-onset, and identifying salient biological markers that can track disease progression and predict when the disease starts. Such information will help to improve our understanding of HD, evaluate potential therapies, and provide appropriate genetic counseling to patients and their family members. Ongoing observational studies are finding promising biological markers, but no statistical model exists that comprehensively assesses the relationship between these markers and HD. To fill this gap, we will develop novel and advanced statistical models. The models will include (i) personalized motor-sign decline curves, and (ii) patient-specific factors such as genetic features, brain imaging measures, and cognitive performance. Modeling the dynamic worsening of motor-signs provides a new way to determine optimal treatment-intervention time periods, and even predict the likelihood of being diagnosed with HD in future time periods. Using modern statistical techniques, we will assess patient-specific markers so as to discover their usefulness in predicting HD motor-diagnosis. Our models will thus advance the fundamental understanding of HD, and outperform existing models in the clinical literature which only use genetic factors that determine whether, but not when the disease will begin.

**Dr. Jun Hua,**  
Postdoctoral Research Associate,  
Kennedy Krieger Institute

*Title: Functional and Neurovascular biomarkers for HD using MRI at 7T. In collaboration with Dr. Chris Ross, HDSA Center of Excellence at Johns Hopkins University*

Reliable HD markers for disease progression monitoring and potential treatment assessment in the clinic, especially those present in the early stages of the disease, are of the utmost importance to the HD community. Magnetic resonance imaging (MRI) is a non-invasive, repeatable and versatile imaging technique that is capable of measuring a number of essential physiological parameters in the human brain. We will perform functional and neurovascular measurements using novel MRI techniques at ultrahigh field strength (7T) with enhanced sensitivity in prodromal (pre-symptomatic) and early affected HD patients and age-matched healthy controls. We will evaluate the suitability of the neurovascular readouts as imaging biomarkers in the early stages of HD. These studies will refine our understanding of functional and neurovascular abnormalities in prodromal and early HD populations. Furthermore, these parameters are expected to be important measures for tracking disease progression and assessing efficacy of huntingtin lowering strategies in the clinic.





## Donald A. King Summer Research Fellowships Awarded

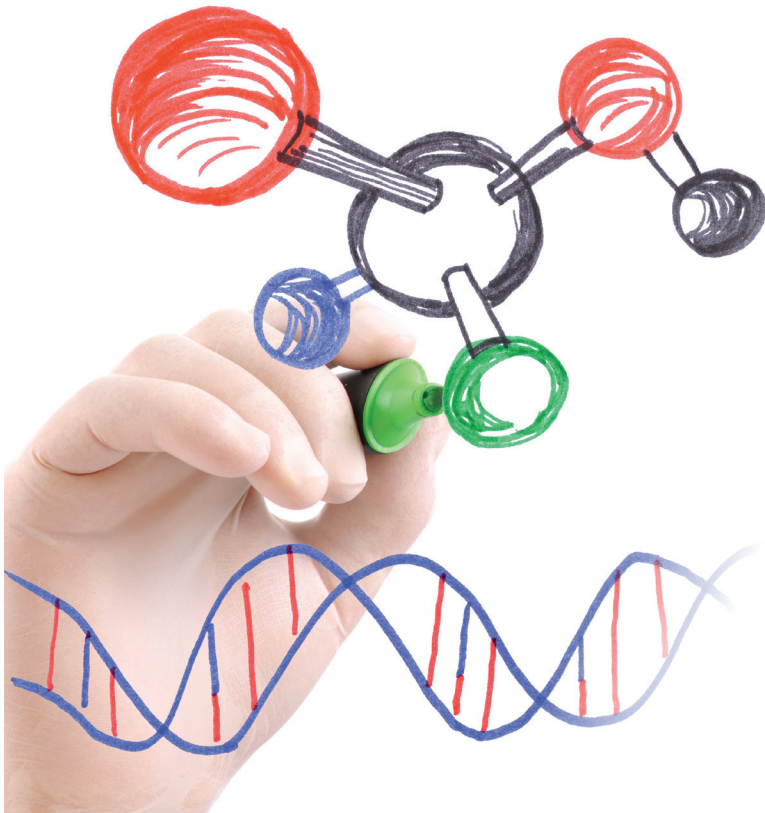
HDSA believes there is a fundamental need to continue to train the next-generation of scientists with research expertise in neurodegenerative disorders, especially Huntington's disease. The goal of the Donald A. King Summer Research Fellowship program is just that. It is our desire to attract the brightest young scientists into the field of Huntington's disease research all while facilitating meaningful HD research to clarify the biological mechanisms underlying HD pathology.

The Donald A. King Summer Research Fellowships sponsor HD investigations that are conducted over an approximate 10-week summer period. Fellowship recipients, working under the supervision of senior HD scientists, take on a project that will be helpful in future HD research and also nurture a continuing interest in HD research.

This year, HDSA received many outstanding proposals from students around the country. Unfortunately, due to financial constraints we could only select two recipients for 2013. With increased commitments from the community it is the goal of HDSA to expand this important program in 2014 and beyond. The 2013 winners of the Donald A. King Summer Research Fellowship were:



**Jenny Lin** is currently a student at MIT, but worked with Drs. William Yang and Steve Horvath at UCLA on a project entitled "A systems biology approach to analyze Huntington's disease".



**Jolene Luther** is currently a student at the University of Iowa. This summer she worked with Drs. Jane Paulsen and Hans Johnson at the University of Iowa on a project called "MRI T2 hypo-intensities as a biomarker in prodromal (pre-manifest) HD".





## Stem Cells in HD Research and Development

Stem cells are an area of research that has received a lot of attention lately from both researchers and the community. To address this, HDSA invited Dr. Jamshid Arjomand from CHDI Foundation to be the first presenter in the HDSA Research Webinar series for 2013. Dr. Arjomand is the Director of Basic Research at CHDI where he oversees a large portfolio of HD stem cell-related research activities. Dr. Arjomand presented on the use of stem cells in HD research and therapeutics.

Stem cells are unspecialized cells capable of continuous renewal and capacity to become any cell type or organ. This characteristic is referred to as pluripotency. There are several varieties of stem cells which were briefly discussed. One type of stem cell that holds great promise are induced pluripotent stem cells (iPSCs). These cells were described by Yamanaka et al in 2006 when his group discovered a way to reprogram adult skin into “pluripotent” stem cells. This “revolutionary” finding resulted in Dr. Yamanaka being awarded the 2012 Nobel Prize for Physiology and Medicine.

Several different approaches to stem cell transplantation therapies were highlighted by Dr. Arjomand. The approach currently being tested in small clinical studies involve fetal brain transplant, in which small dissections of the developing fetal brain(s) are implanted into the regions most affected in HD, with the hope that the fetal graft will replace the dying HD striatal neurons. The largest such study is the ongoing clinical trial called Multicentric Intracerebral Grafting in Huntington’s Disease (MIG-HD) being performed in France. The primary completion date of this trial was slated for mid-2013. Mesenchymal stem cells (MSCs) are another experimental option and their potential is only now being elucidated through basic mouse and rat studies. MSCs are predominantly derived from the bone marrow, and they seem to have a much more limited differentiation capacity and are thus referred to as “multipotent”. MSCs can be transplanted directly or genetically

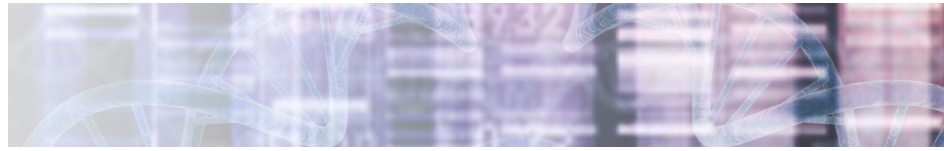
engineered to express and secrete important growth factors, such as brain-derived neurotrophic factor (BDNF), a peptide that is commonly decreased during the course of HD. Several different animal studies were illustrated in which MSCs were injected directly into the brain of HD rodent models and demonstrated potential in mediating some aspects of neuronal repair.

Another approach capitalizes on the endogenous adult stem cells found in each of our brains. Although only tested in mice, the strategy is to coerce these cells to proliferate, migrate and mature into striatal medium spiny neurons. However, these new neurons would still carry the mutation that is responsible for HD, so the long-term benefits of such an approach would need to be evaluated carefully. Finally, iPSCs can be created from an HD patient and the expanded huntingtin mutation can be corrected in a cell culture dish. In theory, these corrected cells could then be differentiated into striatal neurons and implanted into the brains of the same HD patient. However, this strategy is at this time only theoretical and many technical hurdles still need to be resolved before any clinical implementation could be considered.

While all very exciting possibilities, there are many questions that must be carefully addressed to ensure that the stem cell treatment is safe and effective for patients. Animal studies to understand the “what, where and how” of the different technologies must be performed. These unknowns do not stop some from advertising stem cells as a miracle treatment for a wide array of diseases. To address this troubling trend, the International Society for Stem Cell Research has created a website ([www.closerlookatstemcells.org](http://www.closerlookatstemcells.org)) that allows potential patients to better evaluate the claims made by some clinics offering treatment or soliciting trial participants. It also details 10 important points all people should know about stem cell treatments.

### HDSA is a Supporter of the NIH HD iPSC Consortium

In 2010, a large consortium of stem cell/HD researchers was formed to spearhead an effort around the use of iPSCs to help us better understand HD biology. This group is primarily funded by NINDS and CHDI, but other organizations, such as HDSA are also financially supporting these research efforts. The goal of the HD iPSC Consortium is not to develop a cell therapy for HD, but instead is focused on developing better and more relevant neuronal models of Huntington’s disease for basic research, target identification & validation and drug discovery efforts. The Consortium will also develop a repository of well-characterized HD stem cells and protocols that will be made available to the entire HD research community. Several of the former HDSA Coalition for the Cure researchers are members of the iPSC consortium. Each year, HDSA and other stem cell researchers attend an annual conference to hear about the latest progress using HD iPSCs. Unfortunately, due to the government shutdown, the 2013 meeting had to be rescheduled for early 2014.



## New clues to why striatal neurons are preferentially damaged in HD

HDSA-supported study also suggests activation of Nrf2 could shorten life of mutant huntingtin



Dr. Steve Finkbeiner

A long-standing question for Huntington's disease (HD) researchers is why certain nerve cells die, while others appear to be relatively spared by the mutation in the huntingtin gene. It is especially puzzling because in HD patients, the mutant huntingtin gene can be found in every cell in the body, yet it appears to preferentially strike neurons in a region of the brain called the striatum.

In a study supported by HDSA (with a gift organized by the James E. Bashaw Family) and published July 21st in the journal *Nature Chemical Biology*, Andrey Tsvetkov, Steven Finkbeiner and their colleagues from the Gladstone Institute of Neurological Disease and the University of California, San Francisco showed that differences in the rate of proteostasis may be the clue they needed in understanding why striatal neurons die first in HD. Proteostasis is a biological system the body uses to maintain essential protein levels and perform quality control of the various proteins expressed in a given cell.

To study proteostasis in a cell, the UCSF researchers developed a new technique called optical pulse labeling. It allows them to track the lifespan of the normal and mutant huntingtin proteins that they expressed in individual rat brain neurons derived from the cortex, striatum and cerebellum. They can visualize the huntingtin proteins, because they were made to also express a fluorescent marker that can be seen under a microscope. The fluorescent signal emitted from each huntingtin protein allows them to measure the time the proteins exist within each type of cell.

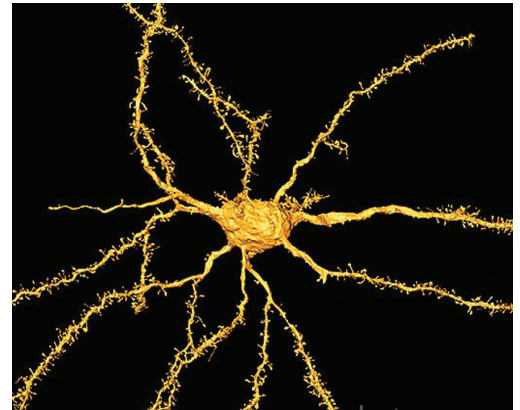
They found that the lifetime of the huntingtin protein predicted neuronal survival. In other words, shorter lifetimes of mutant huntingtin were associated with longer neuron survival. The

cellular environment of the neuron (striatal, cortical or cerebellar) was also found to play an important role in the stability of huntingtin. Striatal neurons cleared mutant huntingtin more slowly than cortical or cerebellar neurons suggesting that the efficiency of the proteostasis system in these different cell populations differs in their ability to clear huntingtin. This observation could help explain the increased susceptibility of the striatum in HD. It raises the possibility that if we stimulated the proteostasis system with experimental therapies it could help shorten huntingtin lifetime and improve neuronal well-being.

To test this idea, Tsvetkov et al over-expressed Nrf2, a transcription factor known to regulate protein processing and the antioxidant response pathway. When Nrf2 was expressed in striatal neurons expressing a mutant huntingtin with 46 polyglutamines, the mean lifetime of huntingtin was shortened, and the neuron lived longer.

Drugs that are reported to activate the Nrf2 protein are known. One of them, dimethylfumarate (Tecfidera) was recently approved by the FDA for use in multiple sclerosis. It remains to be seen if dimethylfumarate or other Nrf2 stimulating compounds will have a beneficial effect in HD, but rest assured this work is underway.

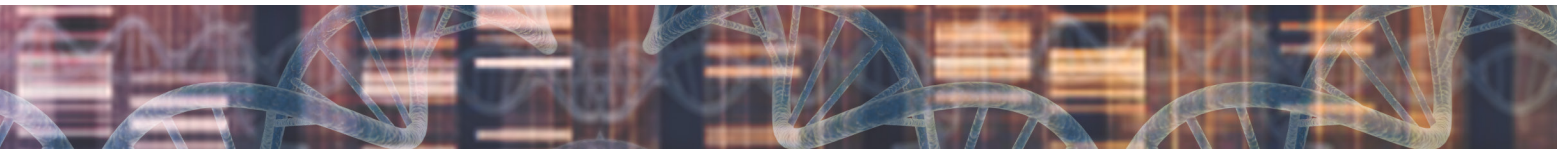
*References:*  
Tsvetkov AS et al. Proteostasis of polyglutamine varies among neurons and predicts neurodegeneration. *Nature Chemical Biology*, July 21, 2013.



### Stay "in the Know" with HDSA

Clear and effective communication of scientific data to the community they serve should be a mandatory and fundamental requirement for all researchers. HDSA takes great pride in assuring the transfer of information to the HD patients, families and caregivers is done quickly and well. This is why 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. HDBuzz has an amazing ability to sort through the hype and provide readers with concise explanations of the work and tell what it REALLY means to the HD community. If you have not already checked out this website ([www.hd-buzz.net](http://www.hd-buzz.net)), we highly recommend you do so. It is a tremendous resource that is made available to all with support from HDSA and other HD organizations. All of the HDBuzz's content is also available on HDSA.org.



## Research Webinar Series

In an effort to increase research communication between HD families/patients and the HD scientists around the world, HDSA announced a new HD Research Webinar Series for 2013. Beginning in February 2013, HDSA hosted a series of monthly webinars on current research topics presented by HD experts from around the globe. These webinars run for approximately 30-40 minutes, with 20-30 minutes available for a question and answer session through a chat feature of the webinar software. The variety of topics covered included: ASOs to lower huntingtin, stem cells, PDE10 and various HD clinical trials. Each Research Webinar is archived and available on HDSA.org. Look for exciting new webinars starting in January 2014!



TEVA PHARMACEUTICALS LTD

### Teva Pharmaceuticals Joins the Fight Against HD

In 2013, Teva Pharmaceuticals acquired the rights to the Neurosearch drug called pridopidine (aka, Huntexil or ACR-16). Pridopidine was the focus of the HART-HD and MermaiHD trials in HD patients a few years ago. While these trials did not meet their primary endpoint, there were data to suggest pridopidine may be having a beneficial effect in HD patients. In September, at the World Congress for HD in Rio de Janeiro, Brazil, Teva announced that a Phase IIb, dose range finding study in HD patients will begin in January 2014. This study will require 400 HD patients. There will be five arms to the study with 80 patients per arm. A placebo arm and four doses of pridopidine (45, 67.5, 90, and 112.5 mg twice a day) will be tested for 26 weeks. They expect the last patient to be enrolled by August 2014 and the results by 2Q2015. To be included in this trial, one must have a Total Motor Score (TMS) > 25, be 21 or older and weigh at least 50 kg.

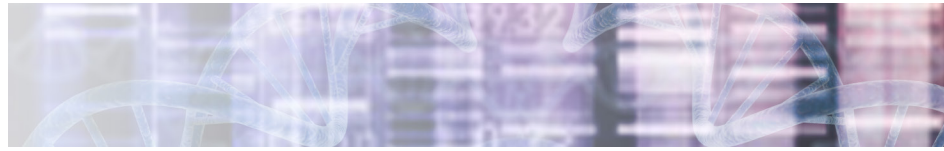
Following the pridopidine trial, Teva has plans to initiate another trial for HD. The drug they want to test is called laquinimod. It is thought to act like an anti-inflammatory drug for the brain by dampening the microglial activation that has been demonstrated to occur in HD brains. The exact date and criteria for the laquinimod trial have yet to be released.



### Genzyme Moving Forward with Viral-Mediated Gene Silencing Approach for HD

At the 2013 HDSA Convention in Jacksonville, Dr. Lisa Stanek from Genzyme (now a Sanofi Company) presented the therapeutic approach currently underway at the biotechnology giant, Genzyme. They are utilizing adeno-associated viruses (AAV) to package DNA that expresses short-hairpin-RNA (sh-RNA) that will bind and repress the expression of the huntingtin gene. These viruses can only get to the brain by direct injection. Once there, the virus should, in theory, express the shRNA to lower huntingtin forever. This is both good and potentially bad. While this could mean that only one injection procedure will be required, once in the brain, the body has no way of shutting down the expression of the shRNA against huntingtin. Chronic repression could have unwarranted side effects. The Genzyme team is making great progress in pre-clinical animal models of HD, however many questions remain to be addressed before viral delivery of gene-silencing sh-RNA can be done in HD patients.

In 2014, expect to hear more about the use of this viral-mediated gene silencing in large animal models of HD, like sheep. Studies in large mammals are essential to better understand how these therapies work in brains that are more anatomically similar to human brains than rodents.



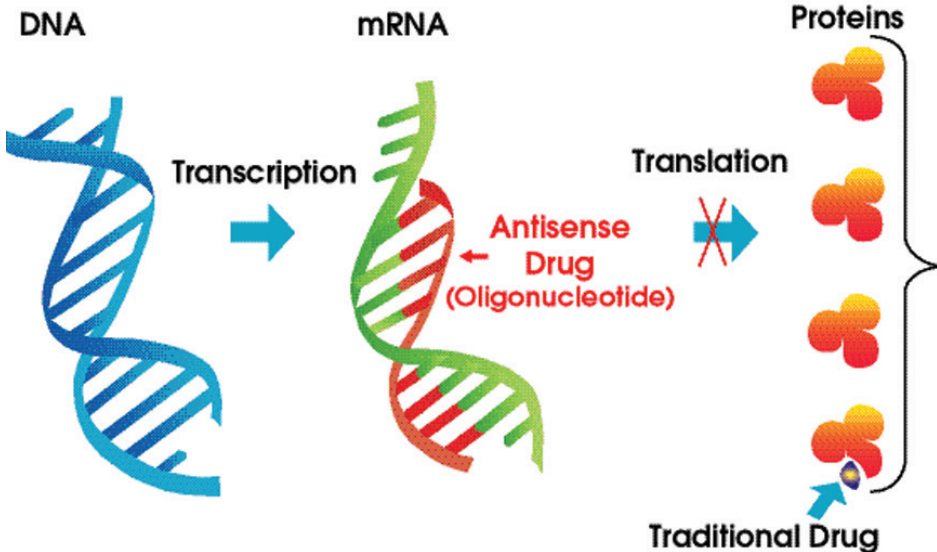
## Huntingtin Antisense oligonucleotides (ASOs) Continue to Show Promise as Potential Disease Modifying Therapy for HD

On March 19<sup>th</sup>, Dr Holly Kordasiewicz and Kristina Lemonidis from Isis Pharmaceuticals presented an update to the community on the use of antisense oligonucleotides (ASOs) to treat HD. Isis Pharmaceuticals is a biotechnology company focused on RNA targeting therapeutics. RNA is the message that encodes the synthesis of all proteins. Isis has pioneered antisense technology and as a result created a drug discovery and development company with nearly 30 drugs currently in development. They plan to add three to five new development compounds each year. It is their goal that an ASO development candidate to target huntingtin will be identified by the end of 2013.

technology, which aims to get the drugs into the brain without having to inject them into the spinal fluid.

Antisense therapy is a form of treatment being pursued for many different disorders such as diabetes, cancer, ALS and now HD. The ASOs currently being tested in animal models of HD are small, single-stranded molecules composed of between 18-20 nucleic acids. The ASOs can be designed to bind to almost any region of RNA. When the ASO binds to the RNA, the RNA is targeted for degradation. The end result of effective ASO binding to RNA is that less protein will be made. This is exactly what Isis has

shown in rodent models of HD. When the ASO directed against the huntingtin RNA is administered to HD mouse models, the levels of huntingtin mRNA and protein decrease.



**DISEASE** In addition to decreases in huntingtin levels, they also observe improvements in motor activity and coordination, anxiety, even a slowing of the loss of brain mass. Another exciting observation is that following a short two-week dosing of the mice, their huntingtin levels remain significantly suppressed for up to 12 weeks. This suggests that intermittent treatment may be possible in patients. This is so important because the ASOs do not get into the brain via the most common routes of drug administration (oral, intravenous). As of today, intrathecal (spinal cord) injections must be used to bathe the brain in ASOs.

In April of 2013, Isis and Roche Pharmaceuticals formed an alliance to work together to develop Isis ASOs for HD. The terms of the deal require Roche to pay Isis \$30 million for the development of its Huntington's disease ASO and the first Phase I clinical trial in patients. If the Phase I safety trial is successful, Roche will pay up to \$362 million to further support the development and licensing of the drug. Initially, their research will focus on Isis' lead drug candidate that blocks production of all forms of the huntingtin (HTT) protein (non-allele selective). Isis is also conducting research into treatments that specifically block production of the disease-causing forms of the HTT protein which has the potential to treat subsets of HD patients (allele-selective).

Despite the promising pre-clinical results, testing of anti-huntingtin ASOs in humans will likely not begin until late 2014. Even then, those studies will be Phase I clinical trials in a small number of people (<30) to assess the safety of the drug and to better understand how to dose the drug in Phase II and III clinical trials in HD patients. Very promising news was announced in May of 2013 when the results of a Phase I safety trial testing intrathecal dosing of an ASO against a protein known to be involved in ALS (Lou Gehrig's Disease) were reported. This is the first clinical study of intrathecal delivery of an ASO. They showed that the Isis ASO was well tolerated to ALS patients. This method of delivery is what we expect will be done in HD patients so we are hopeful this will also be safe for HD patients. While the initiation of these trials cannot come soon enough, this novel approach to silence the huntingtin gene holds great promise.

The partnership with Roche has other scientific benefits. The deal also gives Isis access to all the resources and technologies a large pharmaceutical company like Roche can bring to bear on a problem. One of these exciting resources is Roche's brain shuttle



## Zinc Finger Proteins: Novel technology to target huntingtin DNA

There is no better validated protein target to combat Huntington's disease than that of huntingtin (htt). Diversified small molecule and non-conventional strategies, such as gene therapy, are being developed to lower the expression of the mutant protein that causes HD. Over the past few years a great deal of excitement has been generated by the pre-clinical results that use non-conventional approaches to specifically silence mutant htt. The two major types of htt silencing are antisense oligonucleotides (ASOs) and short-interfering RNA (siRNA). Both work at the level of the htt mRNA and interfere with the ability of the cell to make the huntingtin protein (reviewed in Matsui and Corey, 2012).

There is another, complementary approach that is also being explored that can target the htt DNA. Researchers have found that they can engineer zinc finger proteins (ZFPs) that can bind the expanded CAG repeats in the htt DNA sequence with greater efficacy than the shorter CAG repeats found in the normal htt allele. ZFPs are small proteins that can be experimentally linked together. ZFPs are identified by their unique three-dimensional protein structure. Each ZFP has a  $\alpha$ -helical and  $\beta$ -sheet structure that contain amino acid residues that coordinate the binding of metals such as zinc. Other proteins, such as transcriptional activators or repressors can also be fused to the array of engineered ZFPs. The ZFPs can bind near the promoter of any gene and be used to either increase or decrease the transcription of the targeted gene.

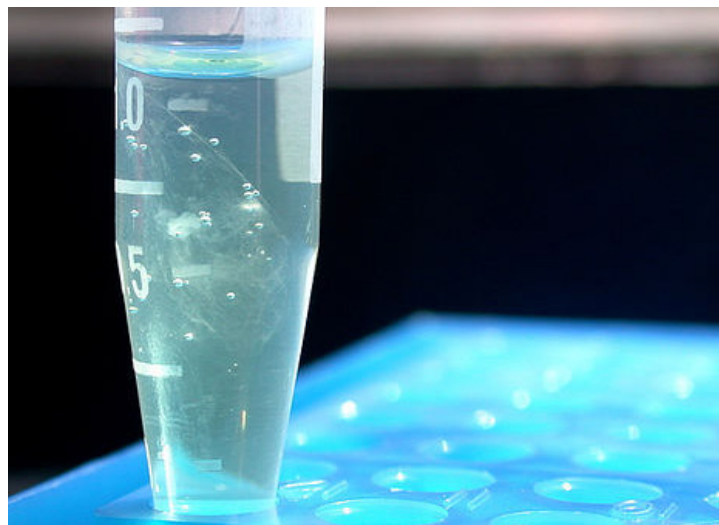
Recently published results from Garriga-Canut et al and work from Sangamo Biosciences have both used ZFPs to selectively target the mutant htt DNA in animal and neuronal models of HD respectively.

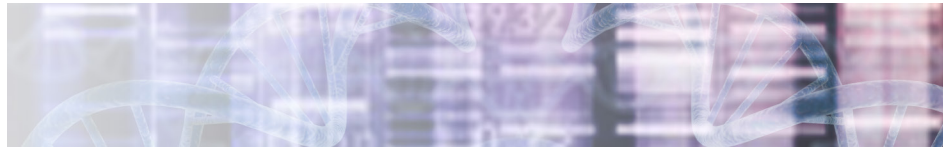
In the work from Garriga-Canut et al, they tested their most promising ZFPs in the R6/2 mouse. The R6/2 mouse is a widely used model of HD that expresses just a short fragment of the human htt protein (~3%). The ZFPs were delivered to the striatum of R6/2 mice with an adeno-associated virus (AAV) to ensure widespread delivery to the striatum. With a number of different ZFPs, they observed a selective repression of mutant htt RNA, reductions in htt protein aggregates in the striatum, and improvements in the motor deficits in the R6/2 mice. They also found that the ZFPs designed to target expanded CAG repeats in the htt gene did not repress other important CAG-containing genes. These results provide important proof-of-concept that ZFPs can be delivered to an HD animal model and can effectively repress molecular and behavioral phenotypes.

Last year, Sangamo reported exciting data using ZFPs in cell models of HD. At the November 2013 Society for Neuroscience meeting in San Diego, CA, Sangamo presented even more exciting data that demonstrate Sangamo's zinc finger DNA-binding protein ZFP gene regulation technology can be used to selectively repress the expression of the mutant and disease-causing form of the huntingtin gene (HTT) leaving the normal gene unchanged in a commonly used mouse model (R6/2) of HD. This selective repression has positive effects on both molecular markers and physical indications of disease in the animals. In the ZFP Therapeutic-treated regions of the animals' brains, scientists observed a reduction of mutant huntingtin protein aggregates, levels of which are associated with the severity of the disease in humans. Sangamo scientists also observed increased levels of biomarkers indicative of protection of critical nerve cells that are progressively lost in the brains of HD patients. Delivery of the ZFP Therapeutic to the brain of R6/2 mice resulted in a statistically significant reduction in clasping behavior compared to controls. "Clasping" is an HD-associated symptom exhibited by R6/2 animals that scientists think may relate to the motor symptoms of the human disease.

The use of ZFPs to target the mutant htt gene holds great promise. While much work remains to be done in pre-clinical animal models of HD, this new therapeutic modality could serve as another weapon in our fight against HD.

*References: Garriga-Canut M, Agustín-Pavón C, Herrmann F, Sánchez A, Dierssen M, Fillat C, Isalan M. Synthetic zinc finger repressors reduce mutant huntingtin expression in the brain of R6/2 mice. Proc Natl Acad Sci U S A. 2012 Oct 10.*





## Progress at CHDI Foundation: 8<sup>th</sup> HD therapeutics Conference in Venice, Italy

Every four years, the CHDI Therapeutics Conference takes their show on the road. Instead of meeting in Palm Springs, this year the CHDI Foundation, a global private, non-profit foundation funding HD science, hosted nearly 300 HD researchers from academia, non-profit, biotech, pharma and government in Venice, Italy for four days of intensive scientific sessions. This was the highest attended conference in the eight year history of the event. While there are many HD relevant meetings, this is the only conference dedicated to providing a 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.

On the same day the conference began, the exciting news about the Isis-Roche partnership quickly traveled to the attendees. If the Isis ASOs successfully meets their clinical trial milestones, the deal includes an additional \$362 million in payments to Isis. The large Phase III clinical studies that are required for regulatory approval can cost hundreds of millions of dollars. This makes the identification of a development partner essential for small companies like Isis. Besides the financial aspect of the deal, the partnership is also very significant because now another major pharmaceutical company also sees HD as a viable business strategy.

Just like in 2012, the CHDI conference was kicked off by a session dedicated to systems biology, which is the holistic study of an organism, which is viewed as an integrated and interacting network of genes, proteins and biochemical reactions, not individual components. CHDI's Chief Scientific Officer Robert Pacifici highlighted the importance of a systems biology approach to better understand HD, because new technologies are now



available that generate an immense amount of HD data. He described that these data sets are simply too large to be consumed and interpreted by conventional means. In addition, despite the identification of the huntingtin gene 20 years ago, scientists are finding that HD is a much more complex disease than originally suspected. Huntingtin has many biological functions.

These functions are all part of different biological pathways and networks that simply do not work in isolation. For these reasons, the HD research community is committed to building a new “map” of HD. The end results should be better therapeutic intervention points, better biomarkers and a more complete understanding of the most appropriate animal models to use in the development of HD drugs.

The afternoon session on day one addressed the hypothesis that HD is developmental disease. Elena Cattaneo (University of Milan) discussed the evolution of the polyglutamine repeat in huntingtin. She also presented data using neural stem cells that further suggests that the huntingtin protein is essential for early brain development. Peg Nopoulos (University of Iowa) presented an update on the Kids-HD research program that hopes to understand if there are behavioral and developmental alterations in at risk, gene expanded children and at-risk, non-gene expanded children aged 6-18. Dr. Nopoulos has observed loss of cerebral cortex starting as early as 7 years of age. These anatomical changes are correlated to behavioral changes in the children. However, it was discussed that more robust statistical analyses must be performed to confirm the significance of these changes.

Dr. Ali Brivanlou (Rockefeller University) presented data from human HD embryonic stem cells (hESCs). Using these cells Dr. Brivanlou has identified four, naturally occurring huntingtin mRNA isoforms. The significance of these findings will be further tested, but they could result in new huntingtin proteins with altered functions. In addition, he showed that hESCs with 48 CAGs show significant decreases in levels of bioenergetic molecules (ATP, ADP, and AMP) and aerobic glycolysis. This could provide further clues to the early biological systems that become dysfunctional early in the course of HD.

Day two focused solely on the best and most validated target for HD, mutant huntingtin. We heard from experts on the role of mutant huntingtin in HD and got updates from Phillip Gregory of Sangamo Biosciences (mentioned earlier) and David Corey of UT Southwestern Medical Center on novel approaches to target the huntingtin DNA and RNA respectively. As a review, Sangamo's technology uses zinc finger proteins to selectively target the CAG region of the mutant huntingtin DNA sequence. In Venice, they reported their latest data showing they have effectively lowered huntingtin levels by around 50% in a mouse model of HD. They will now work to study the effects of their ZFPs when expressed over time using viruses to deliver the intervention.

For HD patients and families, day three contained some of the



more exciting results. The morning session was devoted to hearing about CHDI late stage therapeutic programs. Pfizer, working in collaboration with CHDI reported new HD animal data using their PDE10A inhibitor (MP-10). Pfizer's data suggest that their PDE10 inhibitors preferentially affect the indirect pathway in the basal ganglia, the portion of the brain that is highly susceptible to degeneration in HD. The basal ganglia is critical for the normal control of many biological functions such as cognition and motor control. This pathway is thought to be preferentially effected in HD. Inhibition of this enzyme, which is predominantly localized to the striatum appears to normalize the way the synapses in the HD mice and rats fire. Planning is now underway to access the safety and tolerability of MP-10 in early-HD patients for 28 days. In addition to safety, readouts using fMRI, as well as behavioral and motor tasks will be assessed. The first patient in the Pfizer PDE10 trial was dosed in Paris in October. Pfizer does not expect a US clinical study in HD patients to begin until 2014.

Three other HD drug programs were highlighted by CHDI scientists. The KMO inhibitor program was presented by Laci Mrzljak (CHDI). CHDI has a potent, peripherally acting KMO inhibitor called CHDI-340246. They believe the drug may work by altering the balance of toxic chemicals in the brain formed by the metabolism of the amino acid, tryptophan. However, to date, the compound showed little if any beneficial effects upon chronic dosing in two different HD mouse models (R6/2 and Q175).

Efforts are also well underway at CHDI to identify small molecule inhibitors of the histone deacetylase (HDAC) class IIa family of enzymes. In this family of proteins, HDAC4 is the most promising. Genetic knock down of HDAC4 in multiple HD mouse models has been shown to positively benefit the mice. This suggests that inhibition of HDAC4 activity may provide a therapeutic benefit to HD patients. Additional studies are required to determine if targeting the catalytic site of HDAC4 is a viable approach for HD.

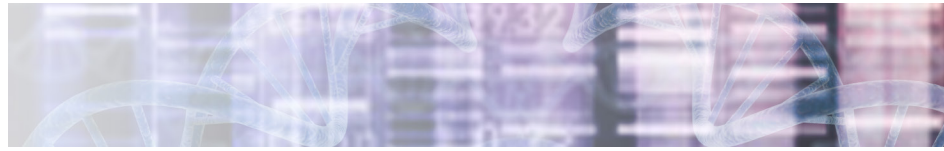
Finally, Jonathan Bard (CHDI) presented work on another collaboration with Pfizer to develop trkB agonists as a

neuroprotective strategy for HD. The hope is that activation of the trkB receptor will increase brain-derived neurotrophic factor (BDNF), an important protein that is made in the cortex and is lost in HD. The Pfizer collaboration centers around a selective trkB antibody called 38B8. Animal testing of this antibody by direct injection into the brain is planned in both HD mouse and rat models. A secondary approach to elevate BDNF levels is also being pursued by CHDI. They hope to use viruses (adeno-associated viruses) as carriers of the BDNF gene and inject them directly into brains to enhance BDNF in HD patients.

The conference concluded with a session on HD clinical biomarkers. Beth Borowsky (CHDI), who is also a member of the HDSA Scientific Advisory Board, presented important work on a proposed disease-state biomarker for HD called 8OHdG. An earlier paper reported that 8OHdG, a marker of DNA damage, was increased in the blood of HD patients. A thorough attempt was made to confirm this finding in new HD patient blood samples. They reported that there are no differences in 8OHdG at any stage of HD. Unfortunately, this suggests that 8OHdG will not be a useful disease-state biomarker.

Finally, Ken Marek (Institute for Neurodegenerative Disorders) presented exciting clinical data using the PET imaging tracer MNI-659 to monitor changes in PDE10A levels in HD patients. While the sample number is low, the preliminary data indicate that binding of the PDE10A PET ligand decreases while the UHDRS motor scores increase, and therefore could be an important biomarker. Dr. Marek presented a version of these data during the September 2013 HDSA research webinar series.

The drug development path from scientific idea to FDA approval is long. While we recognize these approvals simply cannot come quick enough, the HD community can be more optimistic than ever. Years of painstaking research is now moving us closer and closer to the initiation of clinical trials that may alter the course of Huntington's disease. While much work remains, rest assured that progress IS being made by an army of dedicated and passionate HD researchers from around the globe.



## International HD Research Platform:

# Enroll-HD



In 2012, Enroll-HD an exciting global initiative that will include families in Europe, North America,

Latin America, Australasia and parts of Asia got underway. However, in 2013 we have begun to see tremendous participation in this effort. Since this time last year, we have seen the number of Enroll-HD sites increase from 7 to 44 and the number of participants jump from 106 to over 1,300! It is a potentially groundbreaking initiative project that builds upon the knowledge gained from the COHORT study in the U.S., Canada and Australia, and the similar REGISTRY study in Europe and Asia. It has the potential to become the biggest observational trial of any disease in the world, and is possible due to the unique collaboration among HD researchers around the globe.

Enroll-HD is a global longitudinal, observational study of Huntington's disease. Enroll-HD collects a common set of data for all participants across all sites around the world. Enroll-HD also collects blood samples for DNA and cell lines. All data and samples will be available to share with researchers to answer important questions about HD. The potential impact of Enroll-HD on the community is immense.

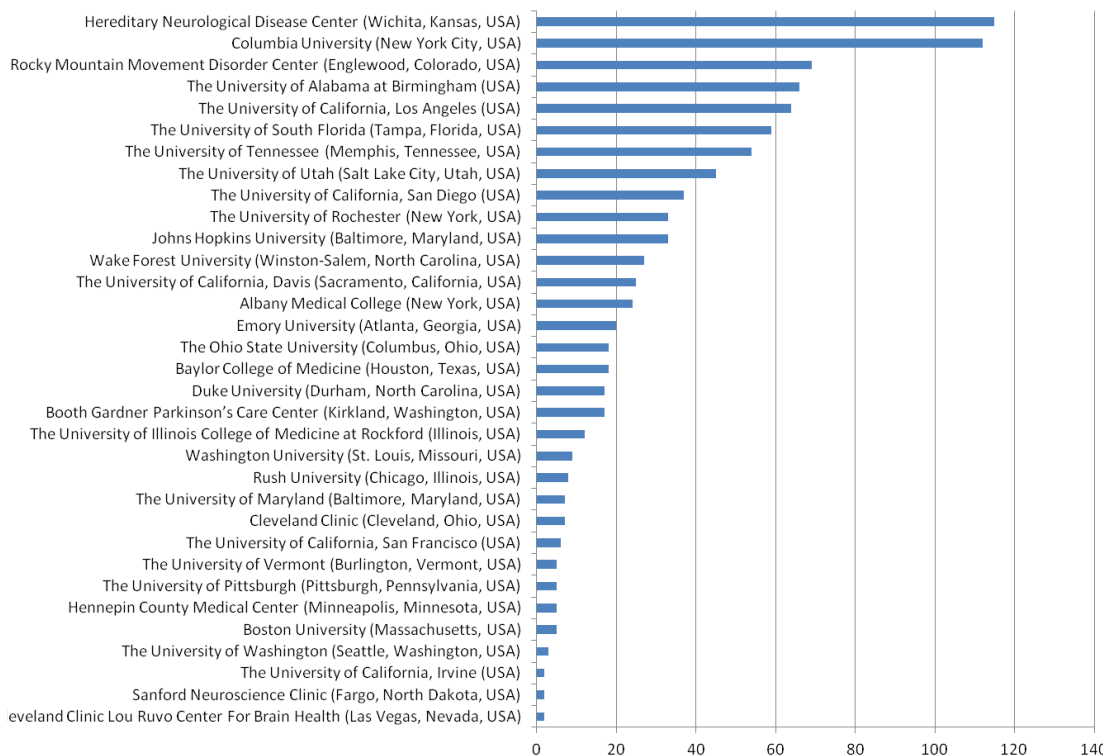
Participants in Enroll-HD will provide clinical data and biologic samples to help better understand the human biology of Huntington's disease. This is in complete alignment with HDSA's Human Biology

Project. 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.

New sites are being added weekly and growth throughout North America, parts of South America and Australian, with Europe and Asia to follow soon. The goal of Enroll-HD is to have over 200 sites in 27 countries. This would amount to over 600 individual patient visits per month. To find out more please go to [www.enroll-hd.org](http://www.enroll-hd.org) or visit [www.hdsa.org](http://www.hdsa.org).

As of November 1<sup>st</sup>, a total of **1298 participants** have been enrolled at the following 44 sites:

### US Sites - Total Enrollment







## Pfizer- PDE10 inhibitor trial in HD patients begins in Paris

In the coming years, we will all be hearing a lot about phosphodiesterase (PDE) inhibitors as a possible treatment for HD. There are several different types (isoforms) of PDEs. The most well-known is PDE5 that can be inhibited with the popular drugs Viagra and Cialis. 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. Many major pharmaceutical companies have PDE10 inhibitor programs with schizophrenia as the primary indication. However, recent evidence in pre-clinical models of HD suggests that the inhibition of PDE10 may have therapeutic benefit in HD by restoring the neuronal circuitry of the indirect pathway of the basal ganglia.

A partnership was recently formed between Pfizer and CHDI Foundation to investigate the use of Pfizer’s PDE10 inhibitor often referred to as MP-10 or PF-2545920 in HD. In rodent models of HD, the teams at CHDI and Pfizer have shown that PF-2545920 can rescue the aberrant cortico-striatal circuitry that

is observed in these animals using electrophysiological techniques. These data generated enough enthusiasm to have recently propelled PF-2545920 into a safety and tolerability study in patients with early onset HD. The first research participant was administered Pfizer’s phosphodiesterase (PDE) 10A inhibitor (PF-2545920) in the Phase 2 study at the ICM, part of La Pitié-Salpêtrière Hospital, in Paris, France. The primary endpoint of this trial is safety, however functional MRI (fMRI), behavioral and motor tasks will also be assessed in these patients to look for hints of efficacy. The results of this short 28 day trial will determine if and when additional PDE10 inhibitor trials will take place in the United States.

It is worth mentioning that other companies, such as Lundbeck and Omeros, also have active PDE inhibitor programs that they are hoping to move forward in to the clinic for the treatment of HD in the near future.

## Prana Biotechnology publishes positive results for PBT2 in animal models of HD

This year, researchers from Prana Biotechnology and UCSF have published data on the small molecule, PBT2, in two different animal models of Huntington’s disease (Cherny et al). PBT2 is a novel compound that is known to cross the blood-brain barrier, appears safe to humans and has demonstrated neuroprotective effects in various brain disease models. The purported mechanism of action of PBT2 is to act as a chaperone of metals such as iron and zinc. Both iron and zinc are thought to play an important role in the aggregation of proteins, such as huntingtin. PBT2 is thought to sequester these metals away from the mutant huntingtin protein and prevent the formation of toxic, oligomeric (multi-subunit) forms of huntingtin.

Cherny et al tested PBT2 in both a worm and mouse model of HD. While PBT2 delayed the paralysis commonly observed in the HD worm, it is interesting to note that PBT2 had no apparent effect on the aggregation of the short polyglutamine-containing protein that is expressed in their worm. This suggests that the worm model used here is not ideal for understanding the impact PBT2 has on the different forms of huntingtin.

More striking results were seen when the researchers administered PBT2 to a commonly used mouse model of HD (R6/2 mouse). The R6/2 mice express just a short fragment (3%) of the total human huntingtin protein. When dosed beginning at just three weeks of age, PBT2 had a significant impact on motor behavior, body weight, brain weight and survival of the HD mouse. They reported that HD mice treated with PBT2 lived 26% longer than the same HD mice treated with a vehicle control.

While these results are certainly encouraging they are not entirely

unexpected. Previous work from Nguyen et al in 2005 showed that clioquinol, a compound very similar to PBT2 in

terms of chemical structure and mechanism of action, improved survival in the R6/2 mouse by 20% and had a significant effect on huntingtin aggregation.

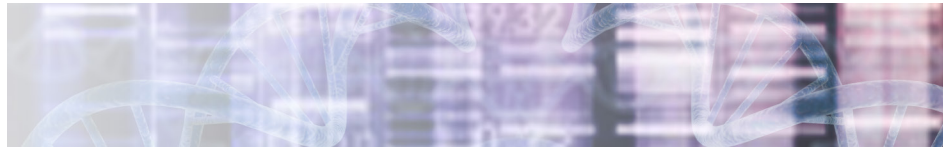
Based on these results, as well as previous data suggesting PBT2 may positively impact cognition (thinking) in Alzheimer’s disease, Prana set out to discover if PBT2 will have similar effects in HD patients. PBT2 was tested in a Phase II clinical study called Reach2HD for patients with early to mid-stage HD in Australia and the United States. The Reach2HD trial is now complete and the HD research community is anxiously awaiting the results from this pivotal study in early 2014.

### References:

Nguyen T, Hamby A, Massa SM. Clioquinol down-regulates mutant huntingtin expression in vitro and mitigates pathology in a Huntington’s disease mouse model. *Proc Natl Acad Sci U S A*. 2005 Aug 16; 102(33):11840-5.

Cherny RA, Ayton S, Finkelstein DI, Bush AI, McColl G, Massa SM. PBT2 reduces toxicity in a *C. elegans* model of polyQ aggregation and extends lifespan, reduces striatal atrophy and improves motor performance in the R6/2 mouse model of Huntington’s disease. *J Huntington’s Disease* 2012, 211-219.





## Auspex Pharmaceuticals: FIRST-HD and ARC-HD Trials Begin to Test Efficacy of Novel Form of Tetrabenazine

To date there is just one drug (tetrabenazine) that has been FDA approved for the treatment of the motor symptoms related to HD. Auspex Pharmaceuticals is currently developing a novel version of tetrabenazine (deuterated-tetrabenazine) which is also referred to as SD-809. Auspex has substituted several hydrogen atoms in the tetrabenazine molecular structure with deuterium, which is also known as heavy hydrogen because it contains a neutron in its nucleus, whereas the most common hydrogen atom does not. This simple substitution appears to have a profound effect on the way the drug is metabolized by the body. One dose can stay around for a significantly longer time than unmodified tetrabenazine. The hope is that the deuterium addition will reduce the number of doses and total dosage HD patients are required to take throughout the day. This should reduce the peak circulating blood levels of the drug. They believe this will decrease the unwanted side effects, but still be effective at reducing chorea.

To test this hypothesis, Auspex has partnered with the Huntington's Study Group (HSG) to initiate a Phase III clinical trial in persons diagnosed with HD to determine how safe, effective and tolerable this new drug will be. This study is referred to as the FIRST-HD trial. This study will require 90 patients with chorea that have NEVER taken tetrabenazine. A second clinical study is also underway with the same drug. This study is called to as the Alternatives for Reducing Chorea in Huntington's Disease trial (ARC-HD). The ARC-HD trial will determine how safe and tolerable it will be to have HD subjects currently taking tetrabenazine switch to taking SD-809. This will require 36 HD patients. Patients that have successfully completed the First-HD trial may be eligible to rollover to ARC-HD. Information about this and other HD Clinical Trials that are currently enrolling patients can be found at [www.hdsa.org](http://www.hdsa.org) or [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

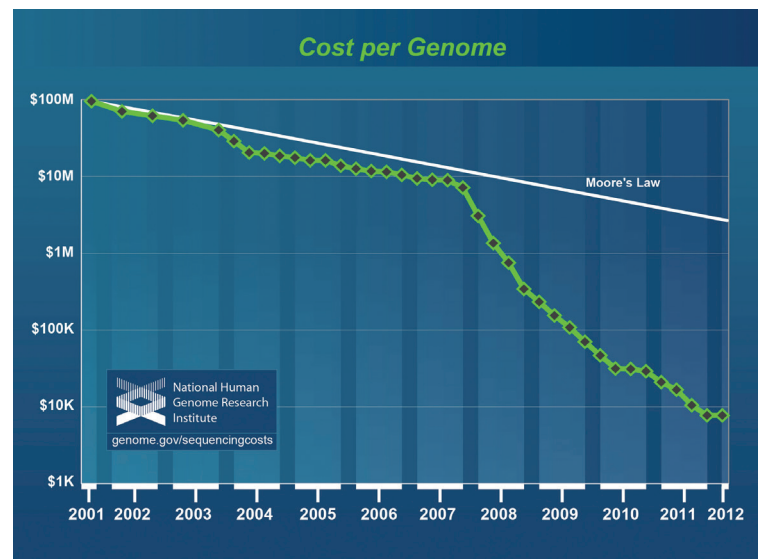
## Future Directions for HD Research: New Targets and Technology

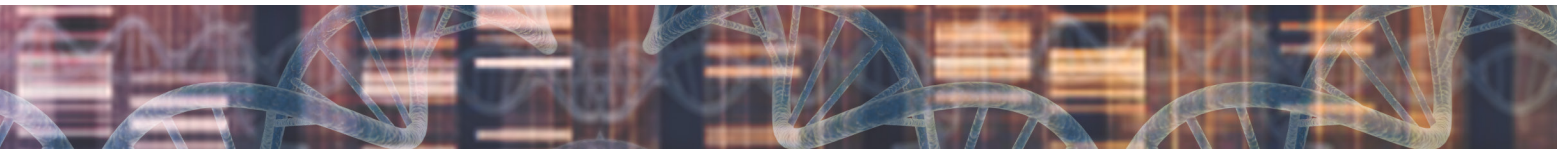
As we move closer to our ultimate goal of testing potential disease modifying therapies in the clinic for HD, the scientific community is not resting. With each day we see increasing examples of advances in new technologies that may hold promise as the next generation of HD drugs. In November 2013, there was a significant amount of press coverage about an exciting genome-editing technique called CRISPR. CRISPR stands for Clustered regularly interspaced short palindromic repeats. CRISPR was first identified in bacteria as a sort of adaptive immune system to help them fight off viral attack. The CRISPR system makes use an enzyme in bacteria called Cas9 that works to cut DNA. Scientists are now working to harness the potential of this system to modify or cut any gene of their choosing. In theory this could used on the huntingtin gene to potentially shorten the CAG repeat, however these are still very early days for this technology, but promising nonetheless.

As technology matures, we routinely see a dramatic reduction in the costs associated with them. High-definition TVs and computers are perfect examples of this. Scientific technologies are no different. Since the human genome was completed over 10 years ago, the cost of sequencing genetic material has plummeted dramatically. In 2001, the NIH estimated that the cost to sequence an entire genome was approximately \$100 million dollars. In 2013, it costs just a few thousand dollars! Couple the cost reduction with advances in computing ability and it is understandable why we have seen a boom in the discussion about "big data" and the use of unbiased computational analysis to help

us better understand disease biology. This field is commonly referred to as systems biology. Large scale efforts are underway at CHDI, the Institutes for Systems Biology and other major academic institutions to develop new models of HD biology with the hope that these models will yield viable drug targets to disrupt HD pathogenesis. As these models evolve, we are hopeful that better, more HD specific gene targets will emerge for HD.

A major issue to tackling any brain disorder is that the body has created an amazing self-defense mechanism called the blood-brain-barrier (BBB) to protect our most vital organ, the brain, from foreign invaders. The BBB is so good at its job that it makes





## Future Directions for HD Research continued

it very difficult for drugs and other therapies to penetrate it and access the brain where damage is occurring. Researchers around the world are working on innovative ways to circumvent the BBB to help treat brain disorders like Alzheimer's, Parkinson's and Huntington's disease. Companies, such as Roche, have a proprietary brain-shuttle technology that they will use to improve delivery of ASOs to the brain. In addition, other groups are making use of exosomes to get therapies across the BBB. Exosomes are created by our body. They can be harvested and packaged with gene silencing reagents, such as siRNA, and then injected into the blood stream. Genetic engineering tricks can be used to ensure that the exosomes go directly from the blood to the brain without the need for direct brain injections.

These are just a couple of the ingenious approaches being pursued around the globe to successfully target the brain. In the coming years we hope that several of these methods will bear promising proof-of-concept data in humans.



## Final Thoughts

Thank you for all you have done to help HDSA in its objective to support meaningful research programs in the search for treatments for HD. The need for high-impact investments in HD research has never been greater as the major pharmaceutical companies move away from high-risk basic research and discovery efforts to assume a lower risk late-stage drug development and marketing role. This shift has put a much greater responsibility upon non-profit organizations, like HDSA, to fund the innovative research that will eventually catch the eye of the pharma and biotech companies to bring them into the HD fight.

While financial investment is critical, dollars alone will not help us reach the finish line. The continued involvement of the HD patients and loved ones in clinical research is essential to finding effective treatments for HD. Without rapid clinical trials, drugs cannot be tested in a timely fashion. Under-

enrollment into clinical and observational trials slows the scientific process and can discourage drugmakers from pursuing HD as an indication for their drug.

So, please consider participating in a clinical study or trial. Many of the observational trials (e.g. Enroll-HD) are recruiting family members who are not even at-risk for HD. The data you provide will become valuable baselines to gauge the progression of disease symptoms, help identify new biomarkers of HD and accelerate the development of future HD therapeutics.

HDSA strives to provide **Help for Today and Hope for Tomorrow** to everyone affected by HD. We are certain you recognize the hope created by the research advances described in these pages. With your continued help we can turn that **Hope** into the reality of safe and effective therapies for HD.

## Our Vision: A World Free of HD

Huntington's disease is a hereditary, degenerative brain disorder that results in a loss of cognitive, behavioral and physical control, and for which, presently, there is no cure. More than 30,000 people in the United States are currently diagnosed with HD, and each of their siblings and children has a 50 percent risk of developing the disease. Although medications can relieve some symptoms in certain individuals, science has yet to find a means of conquering or even slowing the deadly progression of HD.

The Huntington's Disease Society of America is the largest non-profit organization dedicated to improving the lives of people with Huntington's disease and their families.

Founded in 1968 by Marjorie Guthrie, wife of folk singer Woody Guthrie who lost his battle with HD, the Society works tirelessly to provide community services, education, advocacy and research to support everyone affected by HD. With 54 Chapters and Affiliates, 21 Centers of Excellence, 40 Social Workers and more than 170 support groups, HDSA is providing **help for today, hope for tomorrow** to HD families nationwide.



Huntington's Disease  
Society of America

505 Eighth Avenue, Suite 902  
New York, NY 10018

1-800-345-HDSA | [www.hdsa.org](http://www.hdsa.org)