Huntington's Disease Society of America

2014 Research Investor's Report

Huntington's Disease Society of America

2014: Two Steps Forward...One Step Back

This year marked another busy year for the Huntington's Disease Society of America (HDSA) and the global HD community. In 2014, we saw the commencement of several exciting new trials for HD from major pharmaceutical companies and the completion of the First-HD and ARC-HD trials. However, we also heard of the unfortunate termination of the two largest trials ever conducted for HD, 2CARE and CREST-E. Without a doubt, the most exciting news of the year came when it was announced that Isis Pharmaceuticals will officially begin its first clinical trial for a huntingtin lowering drug in 2015. While this is just the beginning for this drug, it marks a moment long in the making by scientists and even longer in waiting by HD patients and families. For the first time ever, a drug, specifically designed for Huntington's disease, will finally get its chance in the clinic.

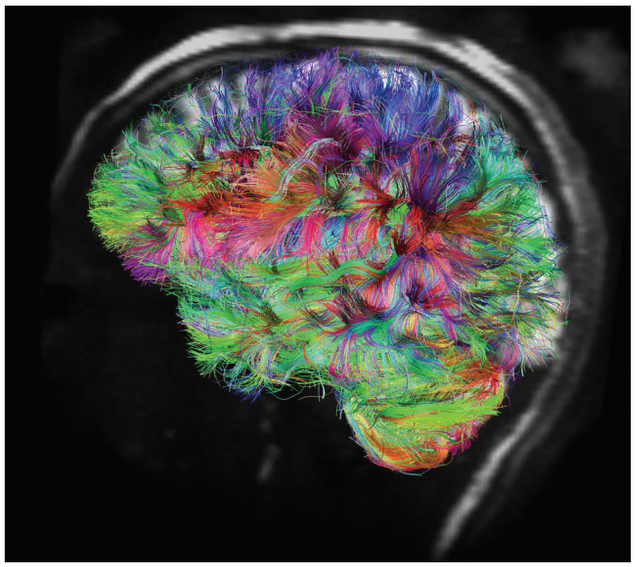
Scientists, clinicians and HD families from around the world came together at many large meetings in 2014 to hear about the latest in HD research. Large crowds of people attended the CHDI Foundation Therapeutics Conference in Palm Springs, the European HD Network meeting in Barcelona, the Huntington Study Group meeting in Minnesota and the Society for Neuroscience in Washington, DC. Last, but certainly not least, in June, the HDSA held our 29th Annual Convention in Louisville, Kentucky. Approximately 900 people came to hear the latest in research, education, care and advocacy for HD and have a little fun too!

This year, HDSA significantly expanded our flagship research initiative, the HD Human Biology Project. In this report you will see summaries of the eight new research projects HDSA has begun to support. In addition, exciting data are now beginning to emerge from the labs of the 2013 Human Biology Project winners.

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 HDSA Centers of Excellence with the goal of studying HD in humans. 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 hunt for therapies for HD will be those made in people actually affected by HD.

In February of 2014, the HDSA Board of Trustees made a strong statement to the community by formally endorsing the Enroll-HD study that is organized by the CHDI Foundation. Never before has HDSA endorsed a clinical study, but the organization felt strongly that the scope and potential impact of Enroll-HD required its full support. Enroll-HD, is a global, multi-faceted research platform that will help guide drug development, clinical trials and HD patient care for years to come. HDSA is encouraging all HD impacted families to consider getting involved.

As 2014 comes to a close, we hope that you will see in this edition of our Research Investor's Report that HDSA and the research community have made tremendous progress towards 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

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HDSA Endorses Enroll-HD

On February 19th, 2014, the Huntington's Disease Society of America (HDSA) announced its endorsement of the Enroll-HD prospective registry study, a global effort to collect a common set of clinical data and biological samples that will help scientists better understand the disease and support recruitment for clinical trials of potential new therapeutics for HD. Additionally, data collected from Enroll-HD will also help inform the standards of medical care for HD families. Never before has HDSA formally endorsed a clinical study for HD.

Enroll-HD seeks to collect a common set of clinical data for all participants across all sites around the world. Enroll-HD will also collect 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 truly is a groundbreaking initiative 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. When all is said and done, within five years, the goal is to have between 25,000 and 30,000 people in the Enroll-HD study.

"Enroll-HD has the potential to revolutionize HD science and accelerate development of therapies," said Steven V. Seekins, HDSA Chairman of the Board of Trustees. "In our mission to improve the lives of everyone affected by HD and their families, Enroll-HD distinguished itself as the platform from which future HD science will launch. It's simply too important to the lives of the HD community for us not to champion it and the potential it brings."

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 nearly 4000 subjects in 89 recruiting sites internationally, 45 of which are in the United States.

"Unlike other clinical studies that are testing potential drugs or observational studies that are smaller in scale, Enroll-HD is unique in scope and size," noted George Yohrling, PhD, Director of Medical & Scientific Affairs at HDSA. "A global repository of the most rigorously collected clinical data and samples offers countless opportunities to both academic and industry scientists."

Louise Vetter, CEO of HDSA stated that "In order to test potential therapies so that safe and effective drugs stop HD in its tracks, we need many thousands of HD family members participating in the scientific process. HDSA believes that Enroll-HD is a new breed of patient registry, with the highest levels of management, patient protection and commitment to sharing its data with scientists that can help make sure we understand HD better, test potential drugs more quickly and ensure that we are providing the highest quality of care for HD families."

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 an army of clinical trial-proven doctors ready to run the trials. Luckily for HD, CHDI Foundation has created such a platform. Enroll-HD is a global longitudinal, observational study of Huntington's disease that will enable all companies interested in pursuing HD as an indication.

To support its endorsement, HDSA will be launching an educational campaign on Enroll-HD across its network of 53 Chapters and Affiliates nationwide. Clinical trial education is already a critical component of HDSA's educational, research and advocacy work. The Society's 170 support groups, 40 social workers and specially trained Clinical Trial Diplomats and Research Ambassadors provide ongoing education to HD families about the role of observational and clinical trials in finding treatments for HD.

For a list of all current sites and more information about Enroll-HD, visit www.enroll-hd.org.

HDSA Awards HD Human Biology Project Fellowships

On October 20th, 2014, the Huntington's Disease Society of America (HDSA) announced that eight new research grants were awarded under the Society's largest research initiative, the HDSA Huntington's Disease Human Biology Project. Totaling $795,000, 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.

"With this year's awards, HDSA not only continued, but significantly expanded our financial commitment to foster innovative patient-focused research to help the HD research community better understand the biology of Huntington's disease as it occurs in people", said George Yohrling, PhD, Director of Medical and Scientific Affairs at HDSA. "The broad impact these HDSA supported studies can have on aspects of HD drug discovery and clinical development is enormous."

HDSA received nearly 30 applications from researchers from twelve different countries. Ultimately, grants were awarded to eight research fellows, from seven different institutions, in four countries (USA, Canada, The Netherlands and Germany). The winning projects include development of a human stem cell neuromuscular model, sleep assessment in HD patients, biomarker development, improved brain imaging data to enable better and faster clinical trials and unbiased "big data" approaches to better understand disease pathology and identify potential drug targets for HD.

Uniquely, the HD Human Biology Project requires that all awardees propose to work in collaboration with at least one of the 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 in the area of Huntington's disease.

"The Human Biology Project is a testament to HDSA's extraordinary commitment to support promising HD research," said Louise Vetter, Chief Executive Officer of HDSA. "We take pride in providing the world's finest HD services to the families we serve, but we also play an integral role in finding a cure for this devastating disease."

The winners and titles of the 2014 HDSA HD Human Biology Project Grants are:

- **Dr. Barbara Calamini,** Research Scientist, Duke University: *Human Stem Cell-Derived Neuromuscular Co-culture Platform for Assessing Peripheral Manifestation of Huntington's Disease,* ***Amy Bradshaw Humphrey Memorial Award Winner***
- **Dr. Dawn Loh,** Research Associate, UCLA: *At-Home Monitoring of Sleep/Wake Cycles of Huntington's Disease Patients,* ***Amy Bradshaw Humphrey Memorial Award Winner***
- **Dr. Eleni Mina,** Post-doctoral Fellow, Leiden University Medical Center, the Netherlands: *A Novel Systems Medicine Approach for HD Biomarker and Therapeutic Target Discovery*
- **Dr. Shihao Shen,** Post-doctoral Fellow, UCLA: *Transcriptome Isoform Networks in Huntington's Disease*
- **Dr. Eun Young Kim,** Post-doctoral Fellow, University of Iowa: *Developing a Robust Segmentation Pipeline that Allows for Consistent Trajectory Estimation of Huntington's Disease Gene Positive Individuals Across Multiple Longitudinal MRI sites*
- **Dr. Sonia Podvin,** Post-doctoral Fellow, University of California at San Diego: *Proximal Mutant Huntingtin Protein Interactions that Occur in a Polyglutamine Length-Dependent Manner in Human HD Brains*
- **Dr. Giulia Cisbani,** Post-doctoral Fellow, University of Laval (Quebec): *Microvesicles: Biomarker and Vehicle for the Propagation of Mutant Huntingtin Protein*
- **Dr. Alexander Buntru,** Post-doctoral Fellow, Max Delbrueck Center for Molecular Medicine (Berlin, Germany): *Development of a Novel FRET-based HTT Aggregation Assay as a Diagnostic Tool for Huntington's Disease.*

Thanks to the kind generosity of the Pittsburgh community, two of this year's top scoring Human Biology Project proposals from Dr. Barbara Calamini (Duke University) and Dr. Dawn Loh (UCLA), were given the additional honor of being named winners of the Amy Bradshaw Humphrey Memorial Award. Sadly, Amy passed away earlier this year after a long battle with HD.

HDSA would also like to acknowledge the generosity of the Gies Foundation and CHDI Foundation. Their support of the 2014 Human Biology Project allowed HDSA to double the number of awards made in 2013. Most importantly, their support will enable more high-quality, impactful human HD research.

Huntington's Disease Society of America

Summaries of 2014 HDSA - funded HD Human Biology Projects

In Their Own Words

Dr. Alexander Buntru,

Post-doctoral Fellow,
Max Delbrueck Center for Molecular Medicine, Berlin, Germany

Title: Development of a Novel FRET-based HTT Aggregation Assay as a Diagnostic Tool for Huntington's Disease.

Huntington's disease (HD) is an inherited neurodegenerative disease caused by a mutant huntingtin (HTT) protein containing an abnormal expansion of the amino acid glutamine. Above a threshold of 40 glutamine repeats the age of onset of HD is inversely correlated with the length of the glutamine stretch. Similarly to prion and other protein misfolding diseases, the formation of aggregates is strongly associated with cellular toxicity and neuronal decay. The neuronal decay in HD manifests in cognitive, psychiatric and motor impairments. Currently, there are no drug based therapeutic strategies available to combat this devastating disease. Unfortunately, a reliable biomarker to monitor HD progression is still not available. We have developed a novel fluorescence-based assay that allows the amplification and quantification of minute amounts of HTT aggregates in biological samples. First, we will optimize our assay using brain tissue homogenates of HD model mice and healthy wild-type control mice. We aim to examine whether our assay is suitable to detect HTT aggregates in human derived samples including brain tissue and cerebrospinal fluid (CSF). Using our novel fluorescence-based approach, we aim to develop novel diagnostic methods with high sensitivity and specificity. In the longer term our studies should provide the basis for the development of a sensitive, diagnostic biochemical test for HD.

Dr. Barbara Calamini,

Research Scientist,
Duke University, Durham, NC

Title: Human Stem Cell-Derived Neuromuscular Co-culture Platform for Assessing Peripheral Manifestation of Huntington's Disease

Huntington's disease (HD) is a genetic neurodegenerative disease caused by a mutation in a protein known as huntingtin. This protein is expressed in all tissues, and although the disease is classified as a neurodegenerative disorder affecting the brain, hallmarks of the disease have also been detected in other organs, including skeletal muscles. It is possible that treating these peripheral organs, such as muscles, could have a therapeutic benefit in HD patients. In addition, since sampling human brain for drug testing is not possible, more accessible tissues, such as blood, skin and muscle might provide alternative substitutes for research and drug discovery. The aim of these studies is thus to investigate the suitability of skeletal muscle for HD research using stem cells coaxed to become muscle cells. Genea Biocells, an Australian stem cell company that had previously derived HD human stem cells, has recently developed a proprietary method for making human skeletal muscles. Dr. Calamini will collaborate with Genea Biocells to study stem cell-derived muscle cells and compare them with muscle cells biopsied from HD patients. If successful, these human stem cell-derived muscle cells will provide an alternative resource for drug screening and offer a substitute for difficult to obtain patient tissues and organs.

Dr. Giulia Cisbani,

Post-doctoral Fellow,
Centre Hospitalier Universitaire de Québec Research Center, Université Laval, Quebec, Canada

Title: Microvesicles: Biomarker and Vehicle for the Propagation of Mutant Huntingtin Protein

To date, the problem in Huntington's disease (HD) has been thought to be due to nerve cells producing their own, genetically coded for, abnormal mutant huntingtin protein (mHtt), which then causes them to dysfunction and die. In recent years, there has been evidence to suggest that other cells, such as those involved in inflammation, may also contribute to the loss of neuronal cells. However, such cells have only been thought of as having indirect effects and not central to the disease process. Recently, though, we have found in HD patients -

who were transplanted with fetal tissue designed to replace cells lost to the disease process - that the abnormal mHtt could be seen in the transplant. This mHtt could only have gotten into the transplant from the patient as the grafted tissue was from unaffected donors. This unique observation forms the basis of this application as we now investigate the theory that mHtt can be transferred between cells from circulating immune cells that can get into the brain via leaky blood vessels. If true, this new theory would have wide ranging implications for HD, and similar diseases, and bring with it a totally new therapeutic approach to this currently incurable condition.

Dr. Eun Young Kim,
Post-doctoral Scholar, University of Iowa, Iowa City, IA

Title: Developing a Robust Segmentation Pipeline that Allows for Consistent Trajectory Estimation of Huntington Disease Gene Positive Individuals Across Multiple Longitudinal MRI Sites

This study aims to improve the brain imaging measures that can be used in future Huntington's disease clinical trials. We expect that our improved measures will reduce the number of participants necessary to conduct a clinical trial to determine whether an experimental treatment impacts disease progression. It is well established that accelerated morphological brain changes exist in HD-gene positive individuals. Researchers often characterize disease progression by monitoring these brain changes using MRI scans. Given that HD is a rare disease, studies often require multicenter collaborations in order to have sufficient sample size. Inevitably, longitudinal measures are highly inconsistent due to scanning environment fluctuations over time. These scanner fluctuation effects can be modeled as 'noise' presented in MRI measurements. The noise is often influenced by non-biological factors such as difference in MRI manufacturers, scan sequences, and field strength. We will directly address these noises algorithmically. While several approaches have enhanced gross comparison between groups, their high variability within a single participant limits personalized analysis of a participant's visits over time. We need consistency in MRI-driven measurement to better understand the trajectory in HD gene positive individuals. We have developed a new segmentation approach to simultaneously reduce variability within subjects and between multiple centers. We demonstrate encouraging preliminary results from the software prototype–The method reduces within-subject variability from longitudinal data selected to have a high degree of heterogeneity. The current prototype implementation is so computationally burdensome that it would be impractical for direct application. We will implement an optimized and automated version of the segmentation approach that maintains robustness and will be applicable to large-scale multicenter data sets. Finally, we will validate that the longitudinal brain imaging outcomes are more sensitive to tracking known clinical variables such as motor, cognitive, and behavioral measures. Based on our pilot study, automation of our new protocol will provide a more powerful brain imaging outcome that allows efficient and economical clinical trials.

Dr. Dawn Loh,
Research Associate, UCLA, Los Angeles, CA

Title: At-Home Monitoring of Sleep/Wake Cycles of Huntington's Disease Patients.

Poor sleep is a common complaint of HD patients. Complaints of poor sleep may stem from an inability to fall sleep, difficulty in staying asleep in bed, and tiredness during the day, with the resultant outcome of

feeling unrested and with possible side effects on mood and cognition (e.g. memory and task performance). The daily cycle of sleep and wake is controlled by the circadian system (circa=about, dian=a day), which we and others have determined is highly disrupted in animal models of HD, suggesting that the genetic cause of HD leads to disrupted circadian rhythms of sleep and wake. A disrupted circadian rhythm not only leads to poor mood and memory, but also has a negative impact on important bodily functions like cardiovascular function and metabolism. We therefore feel it is critical to seek evidence of circadian disruption in HD patients to corroborate our animal model observations. We propose to record daily rhythms in sleep and wake in HD patients and their caregivers using wristwatch-like devices (actiwatch) equipped with sensitive motion detectors that log activity. Patients will be given sleep survey forms and asked to wear the water-resistant actiwatches in their normal daily routine

for 2 weeks. What is particularly unique about our proposal is that we will concurrently ask patients to wear commercially available wristband devices with motion detectors that cost one-tenth of the research-quality actiwatches, auto-update to smartphones, and critically, graph their daily activity on smartphone applications. While these devices are not recommended for clinical diagnoses, they will make it considerably easier for patients and clinicians to get a rapid and accurate image of the sleep-wake cycle. What will be critical is to perform such measurements as early as possible in the HD diagnostic process and take steps to prevent sleep-wake and circadian disruption from further affecting the HD disease progression.

Dr. Eleni Mina,

Post-doctoral Fellow,
Leiden University Medical Center,
Leiden, The Netherlands

Title: A Novel Systems Medicine Approach for HD Biomarker and Therapeutic Target Discovery.

Huntington's disease (HD) is a neurodegenerative disease with the most prominent pathology in the brain. The disease is still lacking a treatment although huge research efforts have been made within the past 20 years that have led to various medication and therapies that can at least help to manage symptoms. This research is mainly based on HD cell and animal models because brain tissue is obviously not easily accessible, cannot be isolated from living patients and does not allow for longitudinal measurements. Peripheral (non-brain) abnormalities, such as weight loss and skeletal-muscle wasting, have been described extensively in HD, both in patients but also in animal models. Studying those changes may give suggestions for the underlying disease mechanisms and for potential biomarkers that can be of use to track disease progression, develop new therapies and measure response to therapy. In this project we follow a novel way of analyzing and integrating diverse kinds of data and reusing existing information to come up with new hypotheses for mechanistic links between the brain and peripheral pathology. In particular, we analyze blood and brain gene expression data from HD patients and controls to identify common signatures for being able to use a highly accessible tissue such as blood for studying the extensive neurodegeneration that occurs in brain. We link significant HD signatures to additional biological and pharmacological knowledge sources to prioritize biomarkers based on their potential as drug targets. Successful employment of samples from living HD patients for the study of disease progression and response to treatment will have a profound impact on the HD research and patient community. Developing a framework for prioritizing hypotheses that will be able to evaluate the potential efficacy of an experiment is of high importance before investing in long and expensive experiments.

Three Students Awarded the 2014 HDSA Donald A. King Summer Research Fellowships Awarded

Scientists at Keck Graduate Institute, Massachusetts General Hospital and Northwestern University awarded fellowships to work on Huntington's disease projects

HDSA believes there is a continual and important need to continue to train the next-generation of scientists with research expertise in 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.

In 2005, HDSA established the Donald A. King Summer Research Fellowship program 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.

This year, HDSA received many outstanding proposals from students around the country. Thanks to the generosity of donors HDSA was able to award three fellowships in 2014. It is our hope that in 2015 and beyond we can continue to grow this important program. The 2014 winners of the Donald A. King Summer Research Fellowship were:

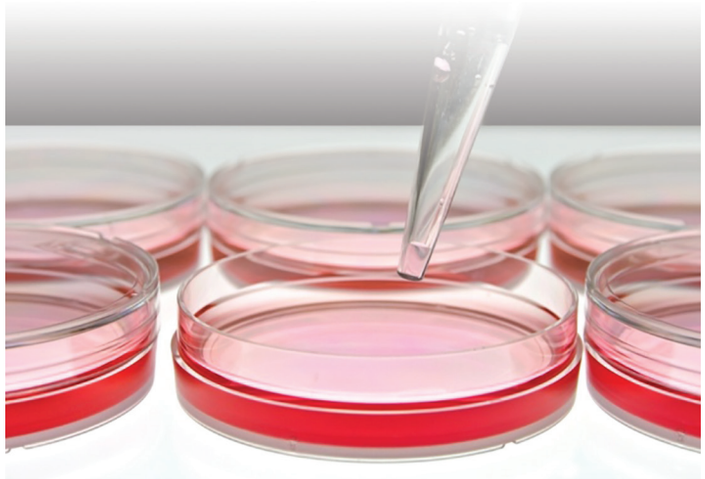
- **Courtney Hanlon** (Keck Graduate Institute)
- **Wenli Dai** (Northwestern University)
- **Varsha Prabhakar** (Smith College)

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.

Ms. Courtney Hanlon of the Keck Institute worked at the Keck Institute of Applied Life Sciences under the guidance of Drs. Animesh Ray and M. Ian Phillips on a project entitled "Gene editing of human neuronal stem cells at the Huntington's locus by targeted homologous recombination". Courtney's project aims was to see if HD can be successfully modeled in a human stem cell that was altered to contain the mutant huntingtin gene.

Ms. Wenli Dai of Northwestern University worked with Dr. Rick Morimoto on a project entitled "Direct chaperone transduction approach to Huntington's disease treatment". Wenli's project involved testing to see if the addition of a protein called Hsc70 could rescue cellular functioning in an HD neuronal model. Hsc70 acts as a chaperone to make sure other proteins behave properly.

Ms. Varsha Prabhakar from Smith College spent her summer working under the guidance of Dr. Ghazaleh Sadri-Vakili from Massachusetts General Hospital on a project entitled "NeuroSteriodal MicroNeurotrophins (NSMN) as novel therapeutics for the treatment of Huntington's disease". NSMNs are a novel class of compounds that can penetrate the blood-brain barrier and bind neurotrophic receptors. Certain neurotrophic receptors are found in the brain and, when activated, they help support the survival of existing neurons, and encourage the growth and differentiation of new neurons. When NSMNs bind to brain neurotrophic receptors, it was hypothesized that they would have a neuroprotective effect on the brain by activating pro-survival signaling pathways and thereby prevent cell death in HD brains.



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Donald King Summer Research Fellow Spotlight:
Courtney Hanlon

Courtney Hanlon attended Amherst College where she was a member of the Woman's Ice Hockey team that won two NCAA championships and is currently a graduate student at Keck Graduate Institute (KGI) in Claremont, CA. KGI is the first American graduate institution devoted solely to bioscience education and discovery, and is the seventh and newest member of the Claremont Colleges consortium. As a pre-medical student with a background in translational research, Hanlon became interested in HD through the mentorship of her faculty advisors, Dr. Animesh Ray and Dr. Ian Phillips.

"KGI emphasizes the study of rare diseases, and in finding new and valuable therapies for such diseases," says Hanlon. "In learning of HD and of the large unmet clinical need for HD patients, I decided to apply to the HDSA Donald A. King Summer Research Fellowship in hopes of clarifying some part of what are largely unknown HD pathways."

During her summer fellowship, Hanlon's group successfully edited human neuroblastoma cells at the Huntington's disease locus (HTT) via targeted homologous recombination. The team used newly discovered CRISPR/Cas9 gene editing techniques to successfully insert the HD mutation into a wild type neuroblastoma cell, a feat with important implications for future HD research. "There is currently no human cell-based model in which to reliably study HD," Hanlon explains. "By creating isogenic cell lines of human wild type and mutant cells, we aim to construct a human model to study the biological mechanisms leading to disease and cell death."

After completing her fellowship, Hanlon has elected to continue HD research throughout the academic year at KGI. Her group aims to build on their findings to successfully edit the exact cells effected by HD—human medium spiny neurons. Hanlon is now in her second year at KGI and will complete her master's degree in pharmaceutical discovery and development this spring. She is currently applying to medical schools, and has recently been accepted to the Geisel School of Medicine at Dartmouth. She plans to matriculate in fall 2015 and continue HD research as a medical student.

HDSA Launches First "HD News" App

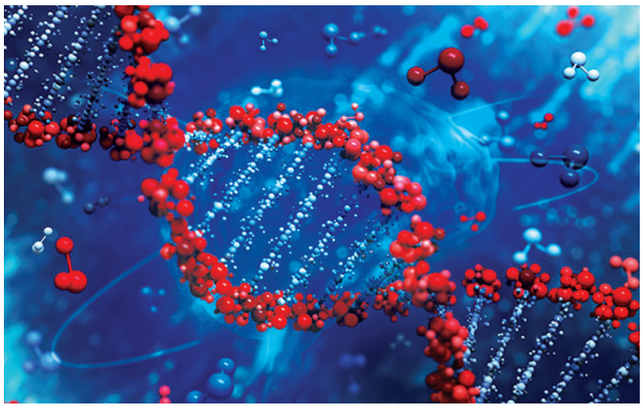
At the 29th Annual HDSA Convention, HDSA launched its new Huntington's disease (HD) news app that is available for all mobile devices. Titled "HD News" and available through iTunes and Google Play, the free app provides up-to-date news and event information from HDSA.org, research summaries from HDBuzz.net, as well as the latest news related to HD drug discovery and development from Science Daily and Medical News Today. The best way to find the app is by simply searching for "HDSA".

"HD News is one stop shopping for everyone who follows Huntington's disease science and related news," said Louise Vetter, CEO of HDSA. "We're excited to be able to provide the first customized news app for the HD community as we continue to look for new ways of bringing valuable information and support for families affected by Huntington's disease."

The app was custom designed for HDSA for Apptomics and made possible by an education grant from Auspex Pharmaceuticals.

HD Researchers Heat up Palm Springs at the 9th Annual CHDI Therapeutics Conference as the Rest of Country is Stuck in Never-ending "Polar Vortex"

This year, CHDI Foundation returned to its home away from home, The Parker Hotel in Palm Springs, California to host their 9th Annual CHDI Therapeutics Conference. CHDI Foundation, a private, not-for-profit biomedical organization funding HD science, hosted 300 HD researchers from academia, non-profit, biotech, pharma and the government for four days of detailed scientific discussions. This was the highest attended conference in the nine year history of the event. While there are many HD relevant meetings, this meeting remains 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.



As has become customary, the conference commenced with an uplifting and motivational start. Sarah Winckless, an Olympic medalist and world champion rower from Great Britain shared her inspirational story with the entire conference. Sarah spoke of growing up with an intense and innate desire to race and compete. When she turned 18, Sarah was dealt a devastating blow when she found out she had inherited the gene mutation that causes HD from her mother. Instead of falling into despair, Sarah became more motivated than ever to pursue her athletic dreams. After numerous physical setbacks due to the strain she put on her body while training, Sarah's dreams were realized when she won a bronze medal in the 2004 Summer Olympics in Athens, Greece in the double sculls rowing competition for Great Britain. She followed her bronze medal with World Championship titles in the women's quad in 2005 and 2006. Despite her family's legacy of HD, Sarah has persevered and refuses to let HD slow her down.

Unlike previous CHDI conferences, there were no formal presentations from scientists from the pharmaceutical or biotech industries about their internal drug discovery programs. These programs were discussed in detail just 10 months prior at the 8th Annual CHDI Conference in Venice, Italy. Instead, the focus of this meeting was to highlight the tremendous amount of work going on in areas such as biomarker development that will help prepare the field for disease-modifying treatments that are under development. Exciting new results that highlighted the next potential drug targets for HD were presented, as were basic research discoveries that shed light on how different cells, circuits and systems talk to each other in the presence of the mutant huntingtin gene. All of these are critically important for researchers to elucidate if we want to truly understand the biological underpinnings of HD and develop more HD specific therapies.

The scientific portion of the CHDI Conference was kicked off on day 2 by a session dedicated to new target opportunities for HD. Dan Lavery, PhD from CHDI co-chaired the session with Marcy MacDonald, PhD from MGH who is also a member of the HDSA Scientific Advisory Board. Dan introduced a new web-based tool that CHDI is making openly available to the research community. It is called HDPerturbDB. This is a database of HD data that has been collated by scientists at CHDI over the course of many years. It includes publically available data from academic groups and data from CHDI initiated research projects. Much of the data in the new HDPerturbDB was also included www.hdresearchcrossroads.org, which was recently decommissioned.

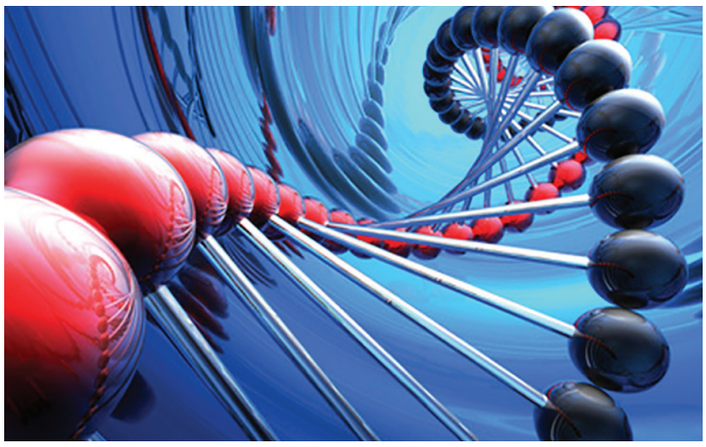
William Yang, MD, PhD from UCLA spoke about efforts in his lab to discover and validate new molecular targets for HD using a mouse model of HD created in his lab called the BAC-HD mouse. William highlighted work on a protein involved in the aging and stress response in humans called ataxia telangiectasia mutated, or ATM. ATM is a massive enzyme, almost as large the huntingtin protein that phosphorylates several key proteins that initiate activation of the DNA damage response. The Yang lab is reporting that when his HD mice were mated to mice lacking one copy of the ATM gene, this resulted in improved phenotypes in the HD mice and significantly decreased huntingtin aggregation. Studies are now being extended in HD mice to see if small molecule inhibitors of ATM will have a similar effect, as the genetic knock-down approach for ATM is not a viable path forward drug development in humans.

In the same session, Ernest Fraenkel (MIT) and Jim Rosinski (CHDI) discussed different approaches being tried to develop a new model of HD from a biological pathway or "systems' perspective. Integration of a massive amount of data being generated using HD animal models and HD patient samples is currently underway. By harnessing the

power of computation modeling, we hope that this process will identify new biological pathways that are most proximal and relevant to the HD mutation. These pathways may identify a new entry point for scientists to design new drugs for HD.

Finally, Jim Gusella, PhD (MGH) discussed exciting findings coming out of the HD Genetic Modifiers Consortium. The search for genetic modifiers is of critical importance in HD. While CAG length can account for 50-70% of HD age of onset and the rate at which HD progresses, CAG length alone cannot predict these with 100% certainty. There are naturally occurring genetic differences in people that either positively or negatively affect the rate of HD pathogenesis. If one could identify those genetic variations that are associated with a decreased rate of HD progression or delayed onset of symptoms, it is possible that scientists could target these genes with therapies to have an impact on HD. To date, no previously suggested modifiers have been reproduced. This is likely because the studies were underpowered with too few subjects. However, in a study incorporating over 4000 HD samples from people of European decent, Dr. Gusella and his collaborators have identified areas on chromosome 15 and chromosome 3 that may be home to genes that appear to be associated with a delayed age of onset of HD. One of the genes in the interesting region (loci) on chromosome 3 is called MLH1. MLH1 was previously shown by Vanessa Wheeler, also from MGH, to be involved in HD.

The afternoon session of day 2, co-chaired by Dr. Ramee Lee (CHDI) and Dr. Robert Friedlander (University of Pittsburgh) covered novel therapeutic approaches being tested in mice and humans for the treatment of HD. A wide-range of topics from electrical brain stimulation to immune system interventions were discussed. Jan Vesper, MD from the University of Dusseldorf in Germany presented data on a pilot study in man to test the effectiveness of deep-brain stimulation (DBS) to treat the chorea associated with HD. Dr. Vesper reported that bilateral implantation of stimulating electrodes into an area of the brain called the globus pallidus resulted in a significant, 50% reduction in chorea and all patients reported improvements in their activities of daily life. These promising results will be confirmed in a larger, multi-center European trial called HD-DBS.



Dr. Gill Bates (King's College London) presented data on a truly novel approach to target the peripheral (non-brain) pathology of HD. Dr. Bates has observed severe muscle pathology in numerous mouse models of HD. They propose that one could prevent or delay the muscle pathology by preventing a protein called myostatin from binding to its endogenous (native) receptor called ActRIIB. Working in collaboration with Se-Jin Lee (Johns Hopkins University), Dr. Bates' team tested an ActRIIB receptor decoy protein that was created by the Lee lab. By blocking myostatin binding with the ActRIIB decoy protein, they observed increased muscle mass in both normal and HD mice. This resulted in improved motor phenotypes in the HD mice. While still early days for this target, Dr. Bates reminded the audience that large pharmaceutical companies such as Eli Lilly, Novartis and Pfizer all have myostatin signaling drugs or antibodies in development or in clinical trials for other disorders. Thus, if the myostatin biology shown in HD mice plays out in humans with HD, drugs may already exist to target this area of HD pathology.

Dr. Chris Colwell (UCLA) presented data from HD mice showing profound circadian and sleep disruptions in HD mice. Sporadic reports of circadian dysfunction have been reported in HD, but more detailed and controlled studies are required. The possibility of the use of melatonin or melatonin receptor agonists in HD was discussed and resurfaced again during the last session of the conference. Finally, Beth Stevens (Children's Hospital, Boston) presented work from her lab involving the complement cascade, the first line of defense the body has against pathogens. The proteins that make up the complement cascade effectively tag dying or apoptotic cells or foreign pathogens for rapid elimination from the body. Several of these proteins C1q, C4 and C3b are up-regulated in late stage HD, as well as in mouse models of the disease. The current hypothesis being tested is that inhibition or blockade of the complement proteins will ameliorate HD pathology in mice. To test this, Dr. Stevens is collaborating with Dr. Yang (UCLA) to breed C1q and C3 knockout mice to the Q175 and BAC-HD mouse models to see if lowering the amount of these two different complement proteins positively impacts disease. These mice are currently breeding, so we shall stay tuned.

Day 3 was a scientifically intense day dedicated to the study of cells, neuronal circuits and systems involved in HD. The Session was chaired by Dr. Michael Levine of UCLA and Dr. Robert Rogers (CHDI). HD has long been thought of as a disease of the striatum because of the significant atrophy observed in this region of the brain in HD patients. However, Dr. Levine reminded us all not to forget that the striatum does not work alone. It receives critical input from other brain regions, most notably, the cortex. It is possible that mutant

huntingtin is causing detrimental physiological changes in the cortex causing it to misfire such that the striatum in HD is simply a "victim of the cortex". Baljit Khakh of UCLA expanded upon this theme by showing how HD mice exhibit dysfunction in other cells in the brain besides neurons. Dr. Khakh and his lab are interested if astrocytes, a non-neuronal cell type in the brain, are dysfunctional in HD. His lab wants to know if one corrects problems solely in astrocytes will it change the course of HD.

The striatum is part of amazing circuit in the brain called the basal ganglia. It is comprised of multiple brain regions working together to control different aspects of movement. Dr. Mark Bevan (Northwestern University) discussed the latest electrophysiological data from HD mice suggesting that another region in the basal ganglia called the subthalamic nucleus (STN) has disrupted electrical activity. Aberrant STN activity can result in decreased inhibition of the thalamus. This will result in excessive body movements from an uncontrolled cortex.

George Rebec (Indiana University) closed out the session with a talk on his research to investigate the dysfunction in the neurons that project from the cortex to the striatum (cortico-striatal circuit) in HD mice. It should come as no surprise that this circuit is dysfunctional in HD. What was most interesting was that they were able to use a genetic trick to selectively knock out mutant huntingtin expression in the cortex only and when they did this they found that the striatum got better. This suggests that Dr. Levine's earlier comment that the striatum may just be a victim of the cortex is not far from the truth. Understanding how these circuits and different cell types work together in the presence and absence of the mutant huntingtin gene is an essential step in the scientific process of better understanding HD physiology and could provide clues on better ways to intervene in the disease process.

The conference ended with two fantastic sessions dedicated to the research going on around the world that is paving the way for disease-modifying trials of the future. The morning session was devoted to hearing about huntingtin lowering biomarkers. Identification of pharmacodynamic (PD) biomarkers that correlate with huntingtin levels is an essential task for the field as therapies like the Isis antisense oligonucleotides (ASOs) and other gene silencing technologies get closer and closer to the clinic. A good PD biomarker for HD should correlate with huntingtin levels, be minimally invasive to the patient, be reliable and reproducible across all clinical sites and be able to be resolved over time. As co-chair, Dr. Lamya Shihabuddin (Genzyme) pointed out in her opening comments, becoming a validated biomarker for disease is not easy. The literature has reported over 150,000 different biomarkers over the years, yet just 100 are currently used in the clinic for all human diseases. To date, there are no validated biomarkers for diseases of the brain.

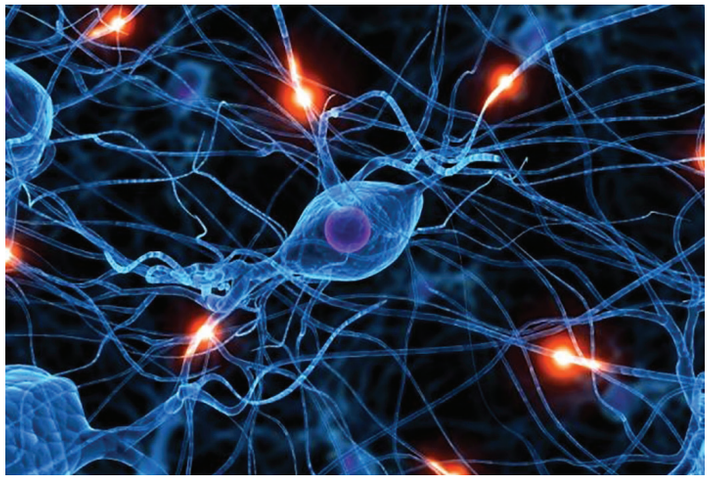
The huntingtin biomarker session commenced with a presentation by Dr. Andreas Weiss (IRBM Promidis). Dr. Weiss and his colleagues at Promidis, a small biotechnology company in Italy, are making use of novel analyte detection technologies to develop assays (tests) to allow researchers to reliably detect mutant huntingtin in human body fluids such as plasma and cerebral spinal fluid (CSF). In Palm Springs, Promidis shared their preliminary, yet very exciting data from CSF taken from control, pre-symptomatic HD, early to moderate HD and advanced, stage 3 HD patients. They reported strong huntingtin signal in CSF from all patients, even CSF that was stored in a freezer for nearly 10 years! The levels of huntingtin appears to correlate to HD disease burden, with highest levels being recorded in the most advanced patients. With financial assistance from a research grant from HDSA, Promidis is also developing an assay in collaboration with HDSA Centers of Excellence to detect the full-length mutant huntingtin protein in CSF and other body fluids.

Another biotechnology company called Kinemed is working with CHDI Foundation to develop kinetic biomarkers that could also be used for future huntingtin lowering strategies. Kinetic biomarkers are readouts that can measure the change of a pathway or biological function over time. Kinemed is making use of a technology that involves administering radioactive ("heavy water") to animals or people to track the activity of different pathways during the course of different diseases. Kinemed's Dr. Patrizia Fanara reported data from a mouse model of HD called the Q175 that their assay can detect microtubule and axonal transport dysfunction in the cortex and striatum of the HD mice. This system is important in moving cargo from one place to another in a cell. The Q175 mice have the full length human huntingtin gene with approximately 175 CAG repeats placed into the same spot in the mouse chromosome that normally houses the mouse huntingtin gene. Of particular interest was that when these HD mice were infused with an Isis ASO that lowers both the mutant and normal huntingtin allele, the axonal transport deficits were corrected to levels seen in the wild type mice. When ASO treatment stopped, the deficits returned. It is promising that this assay should be easily translatable and safe for humans.

The biomarker session concluded with talks from Dr. Stephen Morairty (SRI International) and Dr. Kevin Conley (University of Washington). Dr. Morairty showed recent data where his group is monitoring the electrical activity the brains of two different HD mouse models using electroencephalography (EEG). Dr. Conley showed preliminary data in humans assessing the mitochondrial functioning in HD patients. Using a technique called magnetic resonance spectroscopy (MRS), which can be used to study the metabolism of different organs, electrodes were placed on a patient's leg muscle to obtain biochemical information about the patient in a non-invasive way (without the need for a biopsy). Levels of different chemicals produced in the mitochondria can be determined and this can provide insight into the overall functioning of the specific organ being probed. They showed that levels of nicotinamide adenine dinucleotide (NADH) per mitochondria are significantly elevated in the 10 HD patients they tested. High NADH levels can indicate low metabolism and can result in an increase in oxidative stress to the body. It is hoped that huntingtin lowering strategies might correct this NADH imbalance.

The conference concluded with a session entitled "Clinical Discovery: Paving the Road to Therapeutic Trials" led by co-chairs, Dr. Jang-Ho Cha (Merck) and Dr. Beth Borowsky (CHDI), both of whom serve on the HDSA Scientific Advisory Board. Four presentations were given on research that occurred on HD patients on very different areas of HD biology. Dr. Nellie Georgiou-Karistianis (Monash University) discussed results from a functional neuroimaging study called Image-HD. The Image-HD is using fMRI to probe how different regions of patient's brains operate when performing different memory related tasks. This study is tracking 36 pre-HD, 36 early-HD and 36 controls over the course of 30 months and should be coming to an end in 2014.

Andrea Varrone, MD, PhD from the Karolinska Institutet in Sweden presented human HD data using another non-invasive methodology to probe deep within the brain, called positron emission tomography (PET). Using PET, the team tried to determine the amount of an enzyme called phosphodiesterase 10A (PDE10A) in the striatum of HD patients. PDE10A is predominantly expressed in the striatum, the region of the brain that selectively affected in HD. In a small group of 5 early stage HD patients compared to 5 controls, they found that PDE10A levels are markedly decreased in HD. Companies such as Pfizer, Omeros, and Lundbeck are currently developing drugs to inhibit PDE10, as there is increasing evidence that decreasing the activity of PDE10A in HD may have beneficial effects on HD motor and cognitive symptoms by helping to restore the cortical-striatal circuitry in HD patients. In fact, just before the CHDI Conference, Omeros announced that they have officially started what will eventually be an 11 site North American trial to test their clinical PDE10A inhibitor candidate in HD patients.



Finally, Alpar Lazar, PhD (University of Cambridge) and Tom Warner, PhD (university College London) presented data related to the interrogation of sleep and metabolism pathways in HD patients. We all know a good night's sleep is important to your well-being. Sleep deprivation has a huge impact on cognitive function and many HD patients report issues with both. Therefore, concerted efforts are underway to better understand what aspects of sleep are disrupted in HD. In a small study of 32 pre-manifest HD patients and 25 control subjects, Dr. Lazar's study found that HD patients had more fragmented and unstable sleep patterns. They also found that a subset of HD patients closest to motoric onset had decreased energy expenditures compared to those further from onset. Dr. Warner looked at a large number of peripheral markers of metabolism in pre-manifest HD and more advanced, Stage II-III HD patients. While Dr. Warner found very few differences in any of the parameters he tested, he did observe that the synthesis of melatonin was blunted in HD patients. In addition, there appears to be unfavorable changes to how the remaining melatonin is released. These data suggest that manipulation of the melatonin pathway could provide benefit to HD patients. However, it is essential that further research to determine if melatonin supplementation or the use of novel melatonin receptor agonists will positively impact the sleep habits and overall quality of life of HD patients.

The drug discovery and development path from idea to regulatory approval is long and riddled with pot holes that must be avoided. Within this process there are biomarkers that must be validated, technologies to be developed, and basic biology to be understood. The data presented at the 9th CHDI Therapeutics Conference can provide the community with a great deal of hope that dedicated researchers from around the globe are working together to tackle these important issues now to help ensure that future HD clinical trials achieve our collective goal of finding safe and effective therapies to slow or delay HD.

The Blood-Brain Barrier: Could Ultrasound and Bubbles be the Key to Open the Brain's Security Gate?

The human body is an amazing thing. However, when it comes to getting drugs into the brain, maybe it is simply too amazing. In order to protect your brain from foreign invaders, your body has developed a nearly impenetrable gate around it called the blood-brain barrier, or BBB. The BBB is a highly selective permeability barrier that separates the circulating blood from the fluid in the central nervous system (CNS). The BBB is formed by capillary endothelial cells and astrocytes, which are connected by tight junctions. The BBB allows the passage of water, gases, and fat soluble molecules by passive diffusion, as well as the transport of molecules such as glucose and amino acids that are crucial to proper brain function. Typically, large molecules such as antibodies or other drugs with a molecular weight greater than ~500 Daltons (a standard unit that is used for indicating mass on a molecular scale) are kept out of the brain by the BBB.

Neurodegenerative diseases, such as Huntington's disease (HD) represent a major public health issue affecting at least 20 million children and adults in the United States alone. While there are drugs available to treat the symptoms associated with HD, drugs to stop or delay the progression of any neurodegenerative disease simply do not exist. Development of these disease modifying drugs is the ultimate goal of all HD drug hunters. One of the hurdles drug hunters must overcome is the fact that 98 percent of all potential pharmaceutical agents ever made are prevented from reaching the brain because of that stinking BBB.

Many attempts have been made to deliver drugs across the blood-brain barrier using methods such as osmotic disruption and implantation of catheters into the brain; however, these methods are temporary and prone to infection and dislodgement. When the partnership between Isis Pharmaceuticals and Roche to develop antisense oligonucleotides (ASOs) for HD was announced in 2013, it was suggested that Roche will take advantage of their proprietary "Brain Shuttle" technology to help the huntingtin lowering ASOs get into the brain.

It is important to remember that not everything must stay out of the brain. A healthy brain requires nutrients from the outside world, so humans have evolved some interesting shipping routes to get them there. One of those routes involves a protein called transferrin which binds iron in the blood, then binds the transferrin receptor (TfR) on one of the epithelial cells that make up the BBB. The Roche Brain Shuttle works by hijacking the transferrin receptor (TfR) that resides on the surface of epithelial cells to get antibodies (or perhaps other large cargo like ASOs) across the BBB. The TfR gets encapsulated, is transported across the cell membrane to the other side, and is then spit out to the brain side of the BBB. It is possible that huntingtin lowering ASOs could be combined with a portion of a TfR antibody to trick the BBB so that the ASO could get better access to the brain.

In 2014, a very exciting technology was described by Chen and Konofagou in the Journal of Cerebral Blood Flow and Metabolism. The researchers detailed how focused-ultrasound (FUS) applied to the skull of mice could temporarily open the BBB in a non-invasive way. The data suggest that FUS in combination with the use of microbubbles could serve as a novel, reversible and safe strategy for enhanced delivery of therapeutic agents into the brain. Microbubbles are gas-filled bubbles coated by protein or fat shells. When microbubbles encounter FUS, they oscillate and eventually collapse. When this happens, the microbubbles can push and pull on the tight junctions that form the BBB (see figure 2) to stretch it and can gain access to the brain to release their contents.

Ultrasound Treatment *No Ultrasound Treatment*

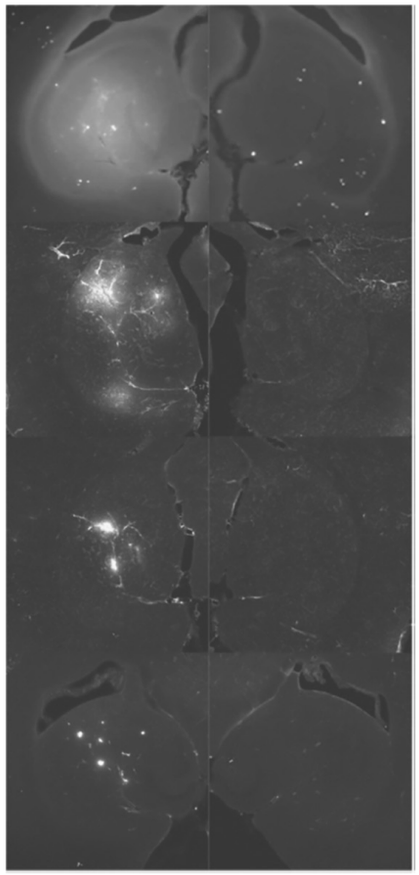


Figure 1 (from Chen and Konofogou, 2014): *Brain sections on left were treated with focal ultrasound (FUS) before administration of fluorescently-labeled dextrans and those on the right did not receive FUS.*

Chen and Konofogou applied focused ultrasound waves through the intact scalp and skull of mice. After the ultrasound was applied, mice were given intravenous injections of microbubbles containing dextrans of 4 different sizes. Dextrans are simply complex glucose (sugar) molecules. The dextrans were all coupled to a fluorescent dye to enable the detection of the dextrans in the brain. They found that by increasing the acoustic pressure of the ultrasound waves, they could successfully deliver molecules to the brain of mice that otherwise would not have succeeded in reaching its target.

Similar technology is being developed using a technique that has a slightly different approach, bathing the brain in ultrasound waves rather than creating focal defects. Specially designed headsets have been created to expose the entire brain to low-intensity ultrasound waves for an hour-long treatment session. After that large sized drugs can be administered, allowing them to freely pass the BBB. The effect has been shown to be temporary, with the blood-brain barrier returning to a functional state within a few hours.

No matter how much we understand the biology of HD, the HD research community must address the long standing issue of safe delivery of potential therapeutics to the brain. It is innovative research like this that could one day help deliver therapeutics to the brains of patients with HD and other neurological diseases.

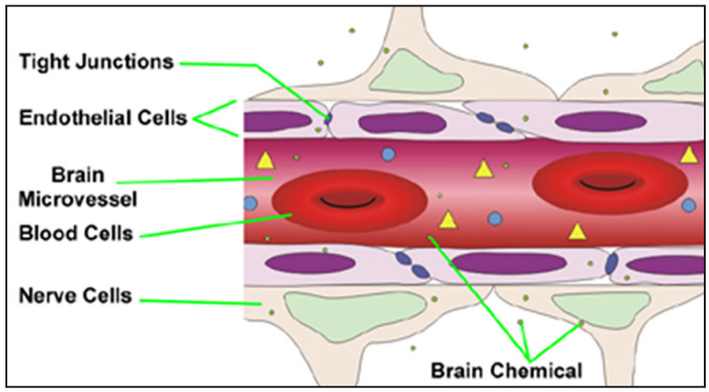


Figure 2, The Blood-Brain Barrier (BBB): *Tight junctions between astrocytes and endothelial cells prevent passage of most molecules into the brain.*

HDSA Research Webinars Open New Dialogue with Researchers

In an effort to increase research communication between HD families, patients and scientists around the world, HDSA continued the HD Research Webinar Series in 2014. Each month, HDSA hosts a webinar on current 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 gene silencing, HD animal models, new target validation, clinical trial results and new clinical study opportunities. If you missed one, don't worry. Each Research Webinar has been recorded and archived in the Research section of the HDSA website. To date, HDSA Research Webinars have been viewed over 3500 times. Sign up for email alerts from HDSA to stay informed of more great webinars starting again in January 2015!

HDBuzz That's Cool, but What Does That Mean to Me?

Stay informed on the latest HD news on HDSA.org

HDSA believes that clear and effective communication of scientific data should be a mandatory and fundamental requirement for all researchers. We take great pride sharing information to the HD patients, families and caregivers is done quickly and well. This is why HDSA continues to be 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 perfected the ability to sort through the hype and provide the community with concise explanations of the work and tell what it REALLY means to the HD community. If reading is not your thing, in October, HDBuzz released its first Podcast of many that can be enjoyed to at your leisure. HDBuzz.net 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 and through the HDSA HD News App.

HD Researchers, Clinicians, Patients and Families Turn Out in Records Numbers in Barcelona for the European Huntington's Disease Network (EHDN) Conference

This September, the HD research world converged in Barcelona, Spain for the 8th Plenary EHDN Conference. The conference began with a session dedicated to the natural history of HD. Dr. Sarah Tabrizi (University College London) led things off by highlighting results from TRACK-HD that has been critical for identifying changes that occur in pre- and early-manifest HD patients. Her very first slide summed up the HDSA research strategy when she stated, "We have to understand disease in humans if we want to effectively treat HD." Roger Barker (University of Cambridge) followed by reminding us all that animal models of HD cannot have symptoms of HD. His rationale is that because animals cannot speak, they cannot tell you how they feel. It is better to suggest that animal models of HD have "signs" of HD. Not all signs of HD can be mimicked in an animal, but we are making progress in translating some of these signs into things we can track in humans in the clinic.

Bernhard Landwehrmeyer (University of Ulm and CHDI) provided the community with an update on the progress to date and future plans for Enroll-HD. Enroll-HD is many things rolled into one. It is intended to be an enabling platform, acting much like a computer operating system. Enroll-HD has 3 goals: to enable clinical research/trials, to help us better understand HD, and finally to help improve the quality of care for HD patients. Enroll-HD has come a long way since its first patient was enrolled in August 2012. As of October 2014, approximately 50% of the sites slated to become Enroll-HD sites are now active and have recruited over 3200 patients and family members. In North America, there are 57 sites which represents 90% of the total goal. Within 5 years the goal of Enroll-HD is to have between 25,000 and 30,000 people enrolled.

Undoubtedly the most exciting scientific breakthrough was discussed in the next session of "Disease Modifiers". For years, the HD research community has been searching the human genome of HD patients for genetic modifiers. Modifiers are like "mother-nature variations" in our DNA that could either positively or negatively impact the course of a disease. In our case, we want to find variations in our DNA (researchers call these single nucleotide polymorphisms or SNPs) that can be associated with people having a delayed age-of-onset of HD. If we can identify these genes, they provide us with human validated targets which drug hunters can exploit and try to design drugs to modulate them.

Many genes have been suggested in the past, but none of them have panned out. However, Jong-Min Lee and colleagues from Massachusetts General Hospital (MGH) may have identified the first true genetic modifiers of HD. Using samples from 4,050 HD subjects with a CAG repeat between 40 and 55, they have identified regions of DNA on chromosomes 8 and 15 that contain candidate genes that could be acting as modifiers of HD. In one case, people with a particular SNP on Chromosome 15 have symptoms ~ 1.5 years later than other HD patients, while a second SNP on chromosome 15 is significantly associated with an age of onset that is 6 years earlier than others. One of the candidate genes in chromosome 15 is called FAN1 and is a DNA repair gene. Further validation of FAN1 and other genes on the 2 implicated chromosomes is underway to see if the SNP can affect signs of HD besides age-of-onset!

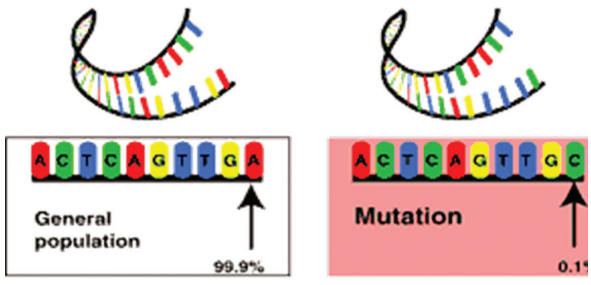


Figure 1: What is a SNP? *About 90% of human genome variation comes in the form of single nucleotide polymorphisms, or SNPs (pronounced "snips"). As their name implies, these are variations that involve just one nucleotide (A, C, G or T). Any one of the four DNA nucleotides may be substituted for any other—an A instead of a T, a T instead of a C, a G instead of an A, and so on.*

The highlight of Day 2 was the session dedicated to updating the community on the ongoing and planned clinical trials for HD. The first speaker, Juliana Bronzova (The Netherlands), discussed the clinical trials task force that has been created at EHDN to serve an advisory role for any external partners in interested in pursuing HD. Bernhard Landwehrmeyer then updated us on the Pride-HD trial being run by Teva Pharmaceuticals. The Pride-HD trial is a dose finding study for safety and efficacy of pridopidine (also known as Huntexil or ACR-16). This drug was the focus of 2 HD clinical trials called HART-HD and MermaiHD. These trials showed that pridopidine treatment resulted in a 3 point improvement in Total Motor Score (TMS), but TMS was not the primary endpoint of either trial so additional studies of this drug are required for approval. The Pride-HD study is a 26 week Phase 2b study that hopes to complete recruitment of the 400 patients necessary to finalize the study by early 2015.

A non-traditional approach for treating the chorea associated with HD was discussed by Jan Vesper of Germany. Dr. Vesper is leading the charge of a clinical study involving 40 HD patients to test the benefit of deep-brain stimulation (DBS). DBS has been around for over 25 years and has been used in Parkinson's disease patients to effectively manage their motor symptoms. In this study, 40 HD patients will receive a surgical procedure to implant electrical stimulatory devices into a region of their brain called the globus pallidus (GP). An earlier, smaller study showed that patients that received bilateral electrical implantation reported improved outcomes in their activities of daily life and showed a 50% reduction in chorea. This study will confirm these findings in a larger group with the primary endpoint being a beneficial change in the UHDRS Chorea score. This study will begin in 2014 and should end in 2017.

A second HD clinical study being sponsored by Teva is called the Legato-HD study. The study involves the use of a drug called laquinimod. Laquinimod is believed to work by working as an anti-inflammatory drug for the brain. There are data to suggest that the mutant huntingtin protein promotes microglial activation in the brain and that dampening this immune response could provide a clinical benefit to HD patients. Legato-HD is a 12 month study that will require 400 patients that will receive either placebo, 0.5, 1.0 or 1.5 mg/day of laquinimod. The primary endpoint of this Phase 2 trial will be TMS improvement, however other secondary endpoints such as brain atrophy (shrinking) and cognition will be assessed.

Cristina Sampaio, the Chief Clinical Officer of CHDI provided a brief overview of the 2 clinical studies underway testing the utility of a class of drugs known as Phosphodiesterase 10a (PDE10a) inhibitors. Many pharmaceutical companies have PDE10a inhibitors as they were thought to be a very promising target for schizophrenia. These drugs have already been tested in Phase 1, safety trials and have been found to be safe and well-tolerated. Two companies, Pfizer and Omeros, are both sponsoring separate clinical trials to test their PDE10a inhibitors in HD patients. The Omeros trial will be run only in the US, whereas the Pfizer study (to be known as the Amaryllis Study) will be a global study that will test 2 doses of drug versus placebo in 90 patients per group.

Finally, the session closed with a moment for which we have all been waiting. Dr. Sarah Tabrizi, has been named as the principal investigator responsible for managing the upcoming antisense oligonucleotide (ASO) trial for Isis Pharmaceuticals. This trial will testing the safety of Isis-HttRx, the ASO designed to lower both mutant and normal huntingtin. This trial will need a small number of patients in just a few clinical sites in Canada and Europe. The drug will be given to patients via a lumbar puncture and patients will be assessed for the occurrence of adverse events or side effects from the drug and method of administration. This is the first step required to move this huntingtin lowering agent along the clinical development pathway towards approval for HD. Isis is on track to commence this study during the first half of 2015. If Isis-HttRx is deemed safe, larger trials to test for effectiveness will then begin. As information on this and all other trials become available, you can turn to www.hdsa.org or the HD News App to stay informed.

Huntington's disease can strike down families all across the world as the mutation that causes HD has no boundaries. What was so promising to see at this meeting was that the global HD research family is working in such an open and collaborative fashion to try to accelerate every aspect of HD drug discovery and development. The data and clinical trial progress that was presented at the 8th EHDN Conference should act to provide the community with a great deal of hope that dedicated researchers from around the globe are working together to tackle these important issues now to help ensure that future HD clinical trials achieve our collective goal of finding safe and effective therapies to slow or delay HD.

Figure 2: *Outgoing Chairman of the EHDN, Dr. Bernhard Landwehrmeyer takes a pie in the face for HD, courtesy of Drs. Jeff Carroll and Ed Wild of HDBuzz.*

HD CLINICAL TRIALS UPDATE

Two of the Largest Clinical Trials Ever Conducted for HD Were Terminated in 2014

Coenzyme Q10 and Creatine "very unlikely" to show significant benefit in HD

In July and October of 2014 came the unfortunate announcements from the Huntington Study Group (HSG) that the 2CARE and CREST-E Phase III clinical trials for Huntington's disease were being terminated due to "futility". Both the 2CARE and CREST-E studies were randomized, double-blind, placebo-controlled studies testing the nutritional supplements coenzyme Q10 and creatine, respectively, as potential therapies to improve HD symptoms. Interim analyses of the data from both trials were conducted by each study's Data and Safety Monitoring Board and revealed that both drugs were very unlikely to demonstrate any clinical benefit in HD patients even if the studies were allowed to run to completion.

CoQ10 is an antioxidant which has an important role in mitochondrial function. Creatine is a molecule that serves as a precursor for adenosine triphosphate (ATP) which is made by your mitochrondria, or energy producing organelle, and is what your body uses for energy. Both oxidative stress and mitochondrial (energy) dysfunction have been implicated as potential contributors to Huntington's disease pathology.

The 2CARE study, which studied CoQ10, was the largest trial ever conducted in HD. Beginning in March 2008, the trial enrolled 609 individuals with HD in 48 sites in Australia and North America. Data collection was scheduled to end in August 2017. While disappointing, the data for HD are consistent with prior trials of CoQ10 for neurological disorders such as Parkinson's disease, in which the QE3 phase III trial of CoQ10 was also halted prematurely for futility in 2011.

Despite the failure of CoQ10, the study's leaders (Drs. Merit Cudkowicz and Karl Kieburtz) believe that the data collected in the study will prove useful in future research. The dataset from this study will be made available to all HD researchers to mine for new ideas about HD.

The CREST-E (CREatine Safety, Tolerability and Efficacy) study was also conducted by the Huntington Study Group (HSG) under the leadership of Dr. Steven Hersch of Massachusetts General Hospital and Dr. Giovanni Schifitto of the University of Rochester School of Medicine. The CREST-E study enrolled 551 research participants with early Huntington's disease from 46 sites throughout the United States, Canada, Australia, and New Zealand. Participants were randomized to receive up to 40 grams per day of active creatine or matching placebo for a treatment period up to four years in duration. While there were no safety concerns with such high doses of creatine, data analysis showed with high confidence that it was unlikely that the study would be able to show that creatine was effective in slowing loss of function in early symptomatic Huntington's disease patients. These results prompted the Huntington Study Group (HSG) and trial sponsor, the National Institute of Health's Center for Complementary and Alternative Medicine (NIH/NCCAM) to announce on October 29th that the CREST-E clinical trial should be discontinued early because of futility.

For more information on the termination of the 2CARE and CREST-E trials you may call the HSG directly at 800-487-7671. We also encourage all community members to read the articles about both these trials on HDBuzz.net.

While unfortunate, the two HDBuzz articles put this news into context and discuss other exciting HD clinical trial opportunities that are now available to the HD community. While no one likes to see a trial for HD fail, the HD research community will learn from these trials and our resolve will remain as strong as ever to find effective therapies to delay the onset or improve the symptoms of HD.

Enrollment in Huntington's Trial Suspended Pending Further Assessment of Preclinical Data

This October, Omeros provided an update on OMS824, the company's phosphodiesterase 10 (PDE10) inhibitor in development for the treatment of Huntington's disease. Much like the Pfizer compound that is being studies in the Amaryllis Trial, OMS824 selectively inhibits PDE10, an enzyme expressed in areas of the brain linked to a wide range of diseases that affect cognition. Omeros announced it suspended its Huntington's clinical trial as it further evaluates an observation from a non-clinical study in rats. The observation occurred in several of the rats receiving the study's maximum dose of OMS824, a dose that resulted in OMS824 free-plasma concentrations being higher than those that have been measured in patients.

Earlier this year, Omeros initiated the Phase 2 trial of OMS824 in patients with Huntington's disease. That trial is a sequential-cohort dose-escalation study that evaluates the safety and tolerability of OMS824 dosed for four weeks in patients with Huntington's disease. After reporting the unexpected rat results to the FDA, the FDA recommended that Omeros suspend the ongoing Huntington's disease trial, and requested that Omeros further evaluate the nonclinical data from the rat study, as well as nonclinical studies that did not yield the observation in order to characterize it more fully prior to reinitiating the clinical trial.

If and when the Omeros trial is re-started, we will be sure keep the community informed of any developments.

Huntington's Disease Society of America

Pfizer- PDE10 inhibitor trial (The Amaryllis Study) Begins

What is PDE10 and what does it have to do with Huntington's disease? PDE10 stands for phosphodiesterase 10. There are several different types (isoforms) of PDEs. The most well-known is referred to every Sunday during NFL commercial breaks. The popular drugs for erectile dysfunction, Viagra and Cialis are inhibitors of PDE5. There is another "flavor" of PDE called PDE10 that is primarily expressed 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.

In the 2013 Research Investors Report we reported that a Phase 2 clinical trial to investigate the use of Pfizer's PDE 10A inhibitor (PF-2545920) at the ICM, part of La Pitié-Salpêtrière Hospital, in Paris, France began. The primary endpoint of this trial was safety, however functional MRI (fMRI), behavioral and motor tasks will also be assessed in these patients to look for hints of efficacy.

In September of 2014, we can report that Pfizer has officially begun a Phase 2 clinical trial of their PDE10A inhibitor in the United States, Canada, Poland, United Kingdom and Germany. 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 will be recruiting 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 the clinical trial section of the HDSA website. The goal of this study is to complete recruitment by early 2015.

Raptor Pharmaceuticals Announced Phase 2/3 Clinical Trial Results with Cysteamine (RP103) in Huntington's Disease

Raptor Pharmaceuticals announced results from a planned 18 month analysis of an ongoing 3 year Phase 2/3 clinical trial of RP103 (delayed-release cysteamine) for the potential treatment of Huntington's disease (HD) in 2014. In HD animal models, there is evidence to suggest cysteamine may exert its beneficial effects by increasing the secretion of brain-derived neurotrophic factor (BDNF) in the brain. BDNF levels are diminished in HD and increased secretion of BDNF could be neuroprotective. The same drug tested being tested by Raptor for HD has been approved by the FDA for the treatment of a kidney disease called nephropathic cystinosis.

In the Raptor HD trial (CYST-HD) which took place in France, 96 patients with HD were randomized to treatment with RP103 or placebo. The objective of the study was to evaluate the effectiveness, safety and tolerability of RP103 in modifying Huntington's disease progression. RP103 appeared well-tolerated compared to the placebo group. However, 6 patients in the RP103 arm of the study discontinued treatment, while just 1 patient in the placebo arm dropped out of the trial. The primary efficacy endpoint of the study was the change from baseline in the Total Motor Score (TMS) sub-scale of the UHDRS at 18 months of treatment in the placebo and RP103 treated groups. Analysis of all 96 patients enrolled in the trial showed a positive trend towards slower progression of TMS in patients treated with RP103 vs. those patients on placebo, the primary endpoint of the study. TMS progression was 32% slower in patients treated with RP103 vs. those treated with placebo after 18 months treatment (however this effect was not statistically significant).

Since this is a 3 year study, patients were allowed to continue their baseline medication regime, including antidepressants and tetrabenazine. Patients were not randomized in the study based on concomitant medications. To confirm that the TMS results were not influenced by a potential treatment effect of tetrabenazine on chorea (a sub-score of TMS) the subset of patients not receiving tetrabenazine were analyzed for TMS. In these 66 patients (32 under placebo and 34 under RP103), RP103 treatment caused a statistically significant 58% slower progression in TMS of 2.84 points compared to 6.78 points for placebo (p=0.03) at 18 months. Slower progression was seen across all TMS sub-score measurements including eye and hand movements, balance and gait, as well as maximal dystonia and maximal chorea. Adverse events were similar in the two groups and were comparable to what has been observed in other studies in this patient population.

Raptor is currently in discussions with the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) to determine what additional clinical studies will be required before RP103 would be considered for approval for the treatment of HD. Results from the 3 year study should be made available in mid-2015. Stay tuned to www.hdsa.org for more information on the next steps.

Prana Announces Results of REACH2HD Huntington Disease Trial

The long awaited clinical trial results for the REACH2HD study run by the Huntington Study Group for Prana Biotechnology were announced in February 2014. The REACH2HD study assessed the safety and tolerability of 2 doses (100 and 250mg) of Prana's investigational drug, PBT2 over the course of 26 weeks. PBT2 is a compound that is thought to act by binding metals commonly found in the body, such as copper and iron, and redistributing them to where they are needed. For example, the redistribution of copper has been shown in cellular and animal models of HD and Alzheimer's disease to reduce toxic protein accumulation.

PBT2 appeared to be both safe and tolerable to the small group of 74 study participants that received the drug. In addition, they report a statistically significant improvement in one of their eight secondary efficacy tests called the Trail Making Test Part B. This test requires subjects to connect numbers to letters with a line (1, A, 2, B, 3, C…) as quickly as possible. The test is commonly used to examine executive functioning and mental flexibility in people. The safety, significant improvement in the Trail Making Test and encouraging pilot data using brain imaging as a readout have prompted Prana to announce they will advance PBT2 into a larger Phase 3 clinical trial for HD soon.

Auspex's First-HD and ARC-HD Trials Complete Enrollment

This year saw an exciting announcement from the Huntington Study Group (HSG) and Auspex Pharmaceuticals that they successfully completed enrollment for both the First-HD and ARC-HD Phase 3 clinical trials. The First-HD was a Phase 3 clinical research trial of an investigational drug called SD-809 Extended Release (ER) in persons who have a diagnosis of Huntington disease (HD).

SD-809 has the same biological mechanism of action as tetrabenazine. The First-HD and ARC-HD Trials were conducted by the HSG under the leadership of Samuel Frank, MD, Principal Investigator, (Boston University School of Medicine) and Claudia Testa, MD, PhD, Co-Principal Investigator (Virginia Commonwealth University).

SD-809 ER 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 ER is compared to placebo (inactive drug) in reducing chorea. First-HD recruited approximately 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.

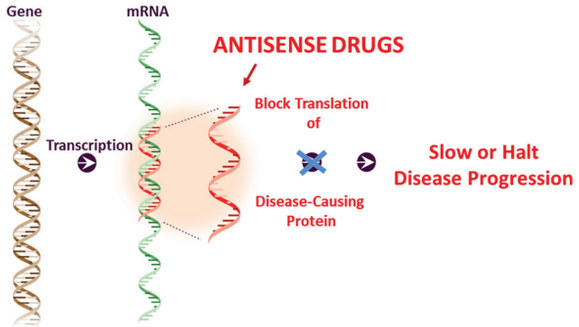
The ARC-HD trial was an open-label long-term safety and tolerability clinical research trial of SD-809 ER in persons who have a diagnosis of HD. ARC-HD also assessed safety, tolerability and effectiveness of SD-809 ER in HD participants. One group was comprised of participants who completed the First-HD 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-809ER.

We expect to hear about the data from these pivotal studies in December 2014. If the data indicate the drug is safe and efficacious in managing the chorea associated with HD, the Federal Drug Administration (FDA) may approve SD-809 for use in HD patients.

The First Huntingtin Lowering Drug to be Tested in Patients in 2015

Without a doubt, the most exciting news to break in 2014 was that Isis Pharmaceuticals will start a Phase 1b safety study of their antisense oligonucleotide (ASO) drug (Isis-HttRx) in the first half of 2015. This was a landmark announcement. Never before has a drug gone into clinical trials for HD that was designed specifically for HD. To date, all other drugs that have gone into clinical trials for HD were developed with a disease in mind other than HD. The Isis drug has been designed to bind to the mRNA (message) that is transcribed from the DNA that encodes the huntingtin gene (see figure).

The initial trial, to be led by Dr. Sarah Tabrizi from the University College of London, will be small and involve just a handful of sites in Canada and Europe to assess the safety of this new class of drugs.



The recruits for this trial will be people in the early stages of HD. The specific enrollment criteria, locations and timing have not been formally announced. If the drug is found to be safe, larger trials to investigate the ability of Isis-HttRx to lower huntingtin and correct other clinical features of HD will likely begin.

There is reason to be cautiously optimistic that the huntingtin ASO will be found to be safe. ASO's from Isis that were designed to target genes known to be involved in other degenerative diseases, such as ALS (Lou Gehrig's disease) and SMA (Spinal Muscular Atrophy) have already been tested in patients and thus far they appear safe. Fingers crossed the same will be true to the ASO directed against huntingtin.

A Special Thanks to the HDSA Scientific Advisory Board

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

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 scientifi¬cally 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
- **Melissa M,** Community Representative
- **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 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.

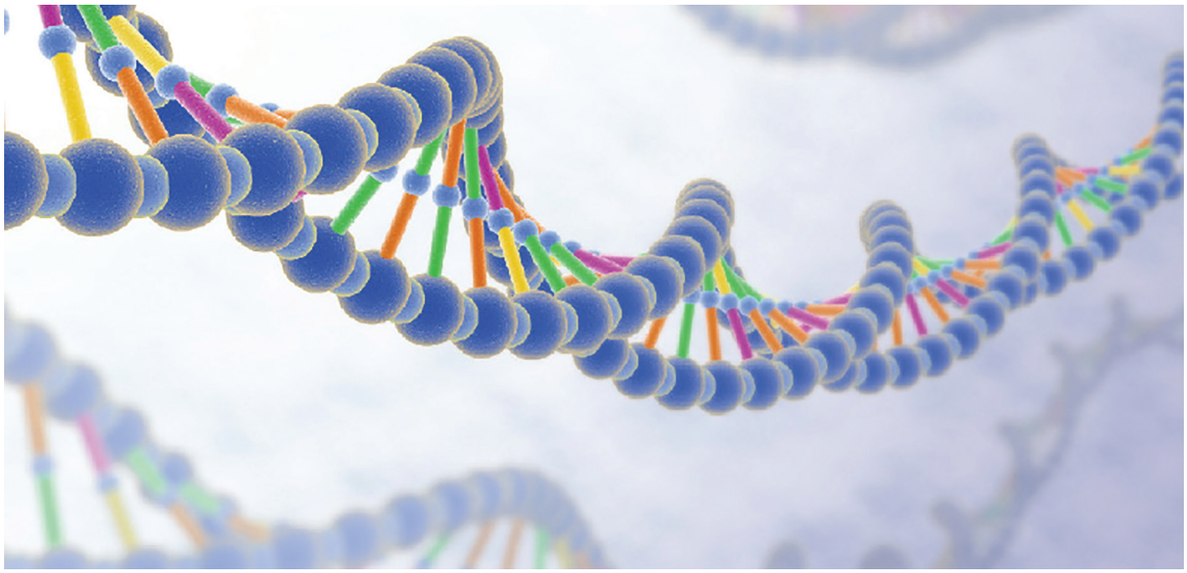
Final Thoughts

This past year was an exciting one for the Huntington's Disease Society of America (HDSA) and the entire HD research community. HDSA successfully expanded our support for ground-breaking research, through the Human Biology Project that will shape future HD drug discovery and clinical development. We also grew our Donald King Summer Research Program in an effort to ensure a robust pipeline of talented and passionate physicians and scientists for the HD field. Finally, while some HD clinical trials may have failed, other more exciting trials were there to take their place. Our understanding of HD biology and technologies have advanced to a point that we now have the first HD-specific drug (the Isis antisense oligonucleotide) being transitioned into clinical trials. This is a monumental moment in the history of HD and one that we have all been dreaming of for years.

Every clinical trial, whether it meets its planned goals or not, informs us on how to better run clinical trials for HD treatments in the future.

While financial investment is critical, dollars alone will not help us meet or goal. The continued involvement of the HD patients and families 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 of clinical trials slows approximately 85% of all drug trials. These unnecessary delays discourage drug makers from exploring drug development in diseases that have difficulty recruiting. We must ensure HD does not follow the crowd of slow recruitment. HD families cannot afford to wait.

HDSA understands that HD families are often under such enormous emotional, physical and economic pressures that participation in research studies is often too much to consider. However, if we are to meet our collective goal of a world free of HD, we must all rise to the challenge and be active participants in the drug development process whenever possible. Enroll-HD is truly a family study of HD and is recruiting family members and spouses who are not even at-risk for HD. The data collected will become valuable informative to gauge the progression of disease symptoms, help identify new biomarkers of HD and accelerate the development of future HD therapeutics. In short, by taking part in clinical trials you will be playing the most important and heroic role in the search for treatments for HD.



Our Vision: A World Free of HD

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

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 that causes Huntington's disease. Today, there are 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease.

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

Across the United States HDSA supports 53 volunteer-led Chapters & Affiliates, 20 Centers of Excellence, 40 social workers and 170 support groups.

Huntington's Disease Society of America

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