Calming the storm

A new drug under development could alleviate symptoms of irritability among HD patients.
Features

4
Update from Enroll HD
The first-ever Enroll-HD Congress was held in May.

10
New Leadership
The Huntington Study Group welcomes a new chair and co-chair.

14
COVER STORY
Calming the Storm
A new drug under development could alleviate symptoms of irritability among HD patients.

DEPARTMENTS

HD BY THE NUMBERS
Statistical highlights

INSIGHTS OF THE YEAR
Most influential papers in HD research

CLINICAL TRIALS
Find a HD clinical trial

HD THERAPEUTIC PIPELINE
Status of HD clinical trials

INSIGHTS OF THE YEAR
The editors and editorial board of HD Insights have selected key papers published within the year that are among the most impactful in the field of Huntington disease research. The authors of these papers are invited to present their research at the Huntington Study Group annual conference, where they are presented with an Insight of the Year Award. This year, two papers were selected. See page 20.

FIND OUT MORE ONLINE
HUNTINGTONSTUDYGROUP.ORG/HD-INSIGHTS
“I am increasingly convinced that the HSG is a unique organization, that stands out from its peers.”  

DANIEL CLAASSEN, MD  
Associate Professor of Neurology  
Vanderbilt University  

New look, new insights  

It is my great privilege to continue working with the Huntington Study Group (HSG) in the capacity as editor of HD Insights, replacing Ray Dorsey in this position. I have been an HSG investigator for almost eight years, and I am increasingly convinced that the HSG is a unique organization, that stands out from its peers. I don’t know of many groups that have such a strong interest in welcoming new investigators, supporting the educational development of the HD community, and providing a voice to coordinators, all with a singular focus on advancing therapeutic options for patients with HD. It is my hope that HD Insights will continue to reflect this energy, and provide a unique source of information to this community.

Along with Sara LaJeunesse, my deputy editor, we have made several changes to the periodical, and we hope you like them. Ultimately, our goal is to provide in-depth topical stories and news briefs that are relevant to clinical trials and HD. In this issue, we discuss the STAIR-HD study and integrate aspects of drug development, NeuroNEXT, clinical manifestations of irritability in HD, and the challenges of identifying outcome measures for these symptoms. In addition, we highlight recent events in the HD world—such as the ENROLL-HD Congress held recently in Quebec City. We will continue to offer HD Insights of the Year awards, and are pleased to introduce Sarah Gregory, et al. and Qiang Guo, et al. as this year’s award winners.

We also have invested in redesigning the print version of the periodical to make it more appealing for sharing in locations, such as your laboratory coffee table, patient waiting room, and office. You can help support us by increasing distribution to your peers, and sharing the Internet version across your department.

In the future, we will start to integrate interviews across social media platforms and provide clinical topics of interest to the community. I am also hopeful that we can create a clinical trial coordinator section, which will engage our colleagues who coordinate these studies.

Again, I want to thank Ray Dorsey and the HSG for this opportunity to serve as editor of HD Insights, and I hope you enjoy the first edition of HD Insights 2.0.
The first ever Enroll-HD Congress was held from May 20-22, 2018 in Quebec City. Enroll-HD is a worldwide observational study for HD families that monitors how the disease appears and changes over time in different people. People from all over the world—Enroll-HD principal investigators and site staff, the Enroll-HD study team, industrial colleagues, Huntington disease researchers, and patient advocacy colleagues—participated in the Congress where everyone had the opportunity to connect, learn, and share ideas and experiences among the global Enroll-HD clinical community.

Enroll-HD is evolving to meet the research challenges of 2025 and, over the course of the Congress, attendees listened to presentations describing modifications and innovative initiatives added to the Enroll-HD platform and observational study, advances in HD clinical research, and new scientific findings in HD pathophysiology.

HD clinical research is entering a new and exciting phase, and not since the discovery of the HD gene 25 years ago has there been such hope in our community. Antisense oligonucleotides that aim to lower huntingtin are now in full clinical development and were described by the keynote and featured speakers, Rachelle Doody from Roche and Blair Leavitt from the University of British Columbia. Other potential disease-modifying interventions are also fast approaching the clinical stage, and the extended HD community—families, clinicians, researchers—has all contributed to reaching this point. However, the takeaway message from the Congress is that there remains much more to do, and the Enroll-HD platform is primed to serve the HD community for most of its research needs.

The big data era brings with it methodologies that can reveal patterns, associations, and other information from large datasets in a way that was not possible before. Enroll-HD—along with its predecessors, Registry and COHORT, as well as other observational studies such as PREDICT, Track-HD/Track-On, and ImageHD—contributes to the current wealth of HD clinical data that are available to researchers. These datasets have been integral to the development of descriptive and predictive disease models, as well as to fundamental genome-wide association studies that have identified modifier genes, and several of these were presented at the Congress.

THE C-PATH ESTABLISHES HD CONSORTIUM

The Critical Path Institute (C-Path), a nonprofit organization experienced in building precompetitive consortia that work with regulatory authorities to map efficient pathways to approval of new therapeutics, has recently established such a consortium for HD. The first product of the Huntington Disease Regulatory Sciences Consortium is the Clinical Data Interchange Standards Consortium (CDISC) data standards for HD. These standards are required for regulatory submissions.
Strategic changes are currently underway to better position Enroll-HD to meet the challenges of near- and mid-term HD clinical research. The dedication and commitment of the numerous HD clinicians, study coordinators, and other site staff worldwide, as well as the participants and their families, are responsible for the enormous success of the Enroll-HD platform. Find out more about these changes on page 6.

The big data era brings with it new data analysis and statistical methodologies that can reveal patterns, associations, and other information from large datasets in a way that was not possible before.

The Congress resource fair was an opportunity to learn about these datasets and other resources, including the extensive collection of HD biosamples now available for researchers to test new ideas. This substantial base of over a million aliquots of biomaterial is expanding with the collection of new sample types such as cerebrospinal fluid and plasma from HDClarity, fibroblasts from the Multi-Tissue Study, plasma from Enroll-HD, and sperm from the Origin-HD study that will soon begin. Combined with deep phenotypic and morphometric data, these biosamples are a rich and easily accessible source of material for exploration that researchers are encouraged to access.

Enroll-HD is a unique clinical research infrastructure that has now reached maturity. It is being used to develop the tools that HD clinical research urgently needs—drug development biomarkers and more sensitive clinical assessments tailored to different stages of HD. Now, more than ever, the HD research community must work together and use our resources effectively across many fronts to deliver key tools that will expedite the development of therapeutics for HD.

The Fairmont Hotel Le Chateau Frontenac in Quebec City, Canada—venue for the first Enroll-HD Congress—is illuminated in blue to observe HD Awareness month.
Enroll-HD: Evolving to meet the research challenges of 2025

Enroll-HD was designed to be an integrated infrastructure to facilitate the execution of HD clinical studies and to generate high-quality biomedical data. The Enroll-HD platform includes several ongoing and planned interconnected studies, with the Enroll-HD study being the largest and the clinical pillar of the platform that encompasses collection of longitudinal phenotypic data and blood-derived biosamples. Its current protocol and overall structure closely follow its direct predecessors, COHORT and Registry. Participants from Registry who consent continue to seamlessly transition to Enroll-HD, linking the longitudinal data collected in Registry to Enroll-HD study data. The first participant entered the Enroll-HD study on July 23, 2012, and now there are more than 16,000 active participants from 19 nations and 168 clinical study sites. After six years of growth, the Enroll-HD platform now needs to be adapted to meet the challenges of the new HD clinical research and development environment that we have all shaped. These changes have three overarching goals:
Now in its 6th year, strategic changes to Enroll-HD are being introduced to meet the current and future HD clinical research landscape.

OPTIMIZE THE COMPOSITION OF THE ENROLL-HD COHORT

Enroll-HD began as an open-ended, prospective, natural-history study without pre-defined constraints on participation. Transitioning Registry participants over to Enroll-HD significantly increased the total population as well as the longitudinal depth of data. Overall, the current cohort mainly comprises individuals with manifest disease (55%), a population with a low dropout rate (~5% annually). Current forecasts indicate that, left unchanged, over the next ten years the cohort would be heavily skewed towards the later disease stages. However, it is clear that future clinical studies and trials will require participants in early-manifest and premanifest disease stages. Additionally, successful conduct of clinical studies in these earlier stage populations will require the development of well-validated prognostic, predictive, and responsive biomarkers. A large cohort of study-ready premanifest and early-manifest participants will be needed to meet the requirements of upcoming clinical trials and biomarker studies.

TWO MAJOR INITIATIVES TO RESHAPE THE COMPOSITION OF THE ENROLL-HD COHORT ARE CURRENTLY UNDERWAY:

- **Modify recruitment and retention strategy to increase the number of premanifest and early-manifest participants**
  This involves working with lay associations and genetic-counseling centers to identify eligible participants, establishing recruitment targets, refining forecast modeling, and assessing new technologies such as mobile technology.

- **Enroll-HD Lite, a study protocol that caters to moderate- to advanced-stage participants**
  This new protocol will reduce participant burden while maintaining continuity of critical Enroll-HD data by offering a lighter assessment battery and, whenever possible, assessments specific for moderate- to advanced-stage HD participants.
CREATE NEW RESOURCES FOR RESEARCH

Enroll-HD will continue to provide researchers with innovative resources to develop and test novel hypotheses. Two new projects will augment the current extensive biosample collection and phenotypic datasets. The first will build a large, longitudinal, high-quality plasma sample collection spanning all disease phases (and including family controls and gene-negative family members) to fully explore the growing interest in peripherally expressed biomarkers to use in mechanistic and discovery research. Currently, high-quality HD plasma collections are scarce and being quickly depleted.

The second project will look for unusual or extreme phenotypes, since such anomalous cases could be the key to understanding new molecular mechanisms or environmental exceptions. Two distinct approaches have been used in such analyses: a statistical approach that defines outliers based on specific distributions and a more qualitative method that relies upon clinical experience and insight to identify uncharacteristic traits. We will introduce what we are calling a blue-card system (in reference to the UK’s adverse-reaction reporting yellow card system) to flag unusual clinical cases in the EDC and enable in-depth review by a team of expert clinicians and geneticists to gauge whether the individual merits further study, namely whole-genome sequencing.

TWO NEW PROJECTS:

- **Build a high-quality plasma collection**
  A longitudinal plasma collection of approximately 2,000-3,000 participants (spanning all disease stages, including control participants) for a minimum of five consecutive years.

- **Identify unique phenotypes — blue-card system**
  A system to flag unusual or extreme phenotypes for review and potential further study.

Enroll-HD will continue to provide researchers with innovative resources to develop and test novel hypotheses.
AUTOMATE, COMMUNICATE, AND REORGANIZE FOR BETTER EFFICIENCY

Several projects are underway to reduce the resources needed to operate and manage the study and enhance overall data quality.

IMPORTANT CHANGES INCLUDE:

► Provide timely feedback to sites
Sites need timely feedback to improve performance. New easy-to-read site report cards that highlight the most critical aspects of study management—recruitment, retention, safety, and data quality—will soon be introduced.

► Statistical monitoring and EDC changes to enhance data quality
Using statistical algorithms to check all data points, combined with revisions to several forms in the EDC and added edit checks, will further enhance data quality and reduce queries to sites.

► Reorganize Enroll-HD governance
Consolidating Enroll-HD governance maximizes productivity of committees without undue burden to the members or detracting from the resources needed to run the platform. The reorganization also incorporates a structured process of membership rotation.

New easy-to-read site report cards highlighting the most critical aspects of study management—recruitment, retention, safety, and data quality—will soon be introduced.

Enroll-HD aims to involve as many as 20,000 people from families affected by HD

169 clinical sites worldwide
Huntington Study Group Welcomes New Leaders

Andrew Feigin, MD, and Elise Kayson, MS, ANP, have been elected as the chair and co-chair, respectively, of the Huntington Study Group (HSG). Both Feigin and Kayson have dedicated their careers to the clinical care of patients and families and to research in HD.

Feigin and Kayson began their four-year term as chair and co-chair May 1, 2018, succeeding Ray Dorsey and Blair Leavitt, who along with Julie Stout, Joni Steinman, and Shari Kinel, expertly led HSG through the last four years. The pair was democratically elected by HSG’s worldwide membership of more than 500 investigators, coordinators, and other researchers and care providers.

Feigin, professor of neurology at NYU Langone Health and co-director of the Marlene and Paolo Fresco Institute for Parkinson’s and Movement Disorders, has been involved in the care of HD patients and research since his participation in the Venezuela Collaborative Research Group, which isolated the HD gene 25 years ago.

His independent research has focused on the development of novel imaging biomarkers that could be used as outcome measures for HD clinical trials. He has served in many HSG leadership positions over the past 20 years, including as a member of the Executive Committee, chair of the Program Committee for the HD Clinical Research Symposium for five years, and chair of the Clinical Research Advisory Committee.

Feigin is the principal investigator (PI) of the SIGNAL trial and a co-PI of LEGATO-HD, and has served as a site PI on numerous other HD trials.

“It’s an exciting time to be involved in clinical research for HD because of the novel therapies that are entering clinical trials,” says Feigin. “The HSG is important because it fills a critical niche in the development of novel therapies for HD. I want to make sure we continue to be at the forefront of HD clinical research.”

Kayson, director of clinical and strategic initiatives at the University of Rochester’s Center for Health + Technology (CHEt), has been involved in the care of HD patients and clinical trial research since the inception of the HSG and was one of the founders of the organization.

Prior to leading CHEt’s Clinical and Strategic Initiatives, Kayson was the director of project management for the Clinical Trials Coordination Center (CTCC) at the University of Rochester and previously worked in industry.

In addition, her long involvement in all aspects of more than 50 clinical trials, including the FDA approval of the only two drugs for HD gives her a deep understanding of clinical trial design, organization and conduct, and insights into and appreciation of HD clinical trials from the perspective of study participants to coordinators, investigators, and sponsors. She has served in many leadership positions in HSG, including as a member of the Executive Committee, co-chair of the HSG Credentials Committee, and co-chair of the HSG Educational Committee.

“It is exciting to be part of the momentum of research in HD. I am honored to serve as the HSG Co-Chair and look forward to reaching the goal of finding treatments that make a difference for our patients and families,” says Kayson.

Feigin and Kayson have ambitious plans for their tenure as chair and co-chair. One of their goals is to increase HSG’s education and outreach to patients and their families. For example, they would like to help individuals understand the importance of staying in clinical trials until they are completed. “If patients don’t stay in these trials, we won’t be able to address the scientific questions and obtain robust outcomes, which are critical for submissions to the FDA,” says Kayson.

In addition, the team aims to expand its focus on innovation; for example, by promoting in its clinical trials the use of tele-visits, along with wearables and sensors, for monitoring patient information in real-time.

Feigin and Kayson also plan to lean more heavily on the HSG research community for assistance with meeting their goals. “We have the leading clinical trial experts from all over the world as part of the HSG,” says Feigin. “We need to better utilize that expertise.”

One way the pair is soliciting the help of the HSG members is by calling on them to serve on a research advisory board. The board will help in the development of protocols and studies that improve the care of patients with HD and lead to the development of novel therapies.

“What sets the HSG apart from other similar organizations is its composition as a group of researchers, clinicians, nurses, and care providers who have come together to find better treatments for HD,” says Feigin. “The HSG fills a unique and important niche in the conduct of HD clinical trials.”
### HD: By the numbers

<table>
<thead>
<tr>
<th>500+</th>
<th>The number of HSG members including investigators, coordinators, and researchers and care providers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>The number of years since the Huntington Study Group was founded.</td>
</tr>
<tr>
<td>12 WEEKS</td>
<td>The total duration of dosing with SRX246 in Azevan Pharmaceutical's clinical trial.</td>
</tr>
<tr>
<td>27</td>
<td>Lauren Steffan’s age when she was diagnosed with Huntington Disease.</td>
</tr>
<tr>
<td>30,000</td>
<td>Approximate number of Americans who have Huntington disease.</td>
</tr>
<tr>
<td>24 months</td>
<td>The time when a pig animal model under development develops demyelination in the brain, indicating premanifest HD.</td>
</tr>
<tr>
<td>16,982</td>
<td>Number of active participants in Enroll-HD.</td>
</tr>
<tr>
<td>5</td>
<td>Number of continents with countries currently participating in Enroll-HD</td>
</tr>
</tbody>
</table>
To create a novel model of Huntington disease (HD) a group used bilateral intrastratal injections of AAV vector serotype DJ expressing the first 171 amino acids of huntingtin (Htt) with either 18Q (wt) or 82Q (mutant) into mice. When injected with mutant Htt, this model shows motor deficits 4-5 weeks post injection and shows HD behavioral dysfunction and selective neuronal degeneration. Due to the selective neuronal degeneration the group hopes this model will be a tool for studying striatal neuropathology that is not characteristic of other murine models.

Another porcine model from the Li group was described in a recent issue of Cell. This was a knock-in model expressing full-length endogenous Htt, with exon 1 from human mHtt (150Q) replacing porcine Exon 1 Htt and created using CRISPR/Cas9 technology. At the protein level this model expressed full-length mHtt, as well as fragments and cleavage of the protein that was not apparent in the wild-type controls. This model had clear phenotypic deficits with abnormal walking steps, respiration difficulties, and decreased pulmonary function. A key finding in this KI model is that the neuropathology mimics classic HD with robust and selective neurodegeneration.

Peripheral blood mononuclear cells (PBMC) are an easy-to-access source of biological material that can be mined for biomarkers. In a study published in Scientific Reports, nuclear DNA (nDNA) damage in PBMC’s was found to have a four-fold increase in Huntington disease (HD) patient samples when compared to controls. Interestingly, the quantifiable levels of nDNA damage were correlated with stage of disease based on patient total functional capacity score, indicating that this should be further investigated as a biomarker for HD. This body of work additionally confirms mutant huntingtin (mHtt) involvement in DNA repair pathways as well as its negative impact on peripheral cell types.

To investigate mHtt function, the Pan group took the approach of expressing a fragment of mHtt in primary cortical neurons and investigated gene expression changes. Twist1 is a transcription factor required for embryogenesis and is normally expressed in low levels in quiescent neurons. In this study, Twist1 was upregulated in the presence of mHtt. This overexpression was recapitulated in HD mouse models and existing human data. Knockdown of Twist1 RNA in mHtt expressing neurons reversed altered expression of some of the genes involved in neuronal function, and abrogated neurotoxicity and attenuated epigenetic changes associated with aberrant BDNF expression, indicating this TF may be a key regulator of pathogenesis.

Most studies investigating Htt function focus on protein interaction with the N-terminus of Htt. An additional manuscript from Scientific Reports investigated interactions of the Htt C-terminal by performing co-immunoprecipitation of this region from rab11-enriched mouse brain endosomes. Htt immunoprecipitated and co-localized with Kalirin, a Rac1 activator. mHtt had a stronger interaction with Kalirin, leading to a reduced capacity to activate Rac1. This interaction needs to be further investigated as a mediator of HD-associated cytotoxicity.

Without a current treatment for Huntington disease (HD), searching for new and known compounds that modulate HD neuropathology and symptoms is an active area of research.

Dr. Ray Truant’s group is known for demonstrating the disease relevance associated with the phosphorylation state of the first 17 amino acids (N-17) of huntingtin (Htt). In a recent manuscript the group performed a high-content, blinded, image-based screen built on the phospho-N17 status of N-17\(^2\). The most interesting hit was N6-Furfuryladenine (N6FFA) which modulated the state of N17 phosphorylation in a disease-dependent manner and promoted cell viability by acting on DNA repair pathways. This compound had beneficial effects on motor phenotypes and mHtt levels in YAC128 mice, implicating the DNA repair pathway as a targetable pathway for modulating HD.

Another interesting compound for attenuating HD symptoms was explored in a recent *Biomedical Research* manuscript\(^2\). The compound *Rhodiola rosea*, a root extract traditionally used to improve mood and mental stamina, was tested in an HD *Drosophila* model. In this model, administration prevented neurodegeneration, locomotive phenotypes, and increased lifespan. Since it is an approved compound with a good safety record it should be further explored in other models for beneficial effects on HD phenotypes.

An additional treatment for HD was explored recently in a paper by Liu et al.\(^3\); the potential of IV-based immunoglobulin (IVIg) for attenuating symptoms of HD was tested in a mouse model. This is an approved therapy for treating different autoimmune and neurological disorders and involves delivering polyclonal serum of IgG pooled from multiple donors. In the R6/2 mouse model, IVIg prevented neurodegeneration by reducing levels of mutant Htt with the mechanism of action being through inhibition of the NF-kB pathway. This is an additional promising compound for use in the treatment of HD.


Irritability affects about half of patients with HD and is a significant source of distress for patients and their caregivers.
Lauren Steffan was just a girl when her mother began to have episodes of uncontrollable anger. “I remember a time when she completely destroyed the house; she was throwing things and tearing up old photos and journals,” says Steffan. “I thought it was normal for my mom to lose her cool, but now I know that her anger was related to her Huntington disease.”

Steffan herself tested positive for Huntington disease (HD) in 2016 at the age of 28. “When you face a diagnosis of HD, your mind goes to dark places,” she says. “Once you find out you have the disease, it’s hard not to be irritable.”

Indeed, receiving a diagnosis of HD causes a range of extreme emotions, and rightfully so. “There is a lot to be angry about in Huntington disease,” says Karen Anderson, associate professor of neurology and psychiatry at Georgetown University Medical School. “People have often grown up seeing their parents or other family members affected by HD, and they know what’s coming for them; they know it’s a debilitating illness.”

And yet, as the disease progresses, much of the irritability associated with HD is due to biological changes that take place in the brain.

“There is a clear neurodegenerative basis for profound behavioral changes among HD patients,” says Steven Hersch, professor of neurology at Harvard Medical School and senior director for clinical development at Voyager Therapeutics who is collaborating with Azevan on its HD clinical trial. “The incidences of irritability and behavioral dyscontrol are just so high among these individuals.”

Characterized by poorly controlled anger and often elements of verbal or physical aggression, irritability affects about half of patients with HD and is a significant source of distress for patients and their caregivers. Often patients behave normally most of the time, with irritability occurring in intermittent bursts.
A new drug developed by Azevan Pharmaceuticals could help to alleviate symptoms of irritability among HD patients. Called SRX246, the drug has been shown in preclinical studies to reduce aggression and fear responses, both of which are part of human irritability. The drug also produces antidepressant and anti-anxiety effects in animal models.

Vasopressin in the Brain

SRX246 works by attaching to the vasopressin V1a receptor, thus blocking the hormone vasopressin from attaching to this receptor, which is the major form found in the human brain. “There is a long history of recognition of a relationship between the effect of vasopressin in the central nervous system and the expression of aggressive behavior,” says Michael Brownstein, senior vice president for drug development at Azevan Pharmaceuticals. “Elevated vasopressin is strongly associated with increased levels of aggression. In our preclinical studies in mice, we showed that SRX246 blunted aggressive behavior markedly.

The Azevan team also used functional magnetic resonance imaging (fMRI) to observe the changes taking place in the rats’ brains in response to SRX246. That study involved housing a male and female rat together until they bonded. The male was placed in an MRI scanner, was able to see and smell his mate, and then a strange male rat was put into the cage with the female. “When we added a strange male, the MRI showed a significant increase in activity in circuits involved in aggression in the original resident,” said Brownstein. “If the males were treated with SRX246, those changes were blocked.”

While the drug proved to be successful in animal models, its administration for use in the brain wasn’t so easy. “Exploiting the vasopressin system as a target for CNS disorders was problematic because previously available vasopressin antagonists did not cross the blood-brain barrier after oral administration,” says Neal Simon, CEO of Azevan. “We eventually solved the problem through a combination of good luck and good chemistry. Our vasopressin antagonists, including SRX246, are very specific in their action on the vasopressin V1a receptor. Consequently, we don’t expect them to have significant side effects.”

The researchers then proceeded to conduct an imaging study with healthy human volunteers. “We found that the drug lowered the effect of vasopressin on brain circuits that were activated in response to pictures of angry or threatening faces, a standard protocol for eliciting emotional responses,” says Brownstein. “These experimental medicine results, in particular, enabled us to attract additional funding to continue development of the compound.”

Support Network

One source of the team’s additional funding came from the National Institute of Neurological Disorders and Stroke’s (NINDS’s) Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT). According to Walter Koroshetz, director of the NINDS, “the goal of NeuroNEXT is to facilitate the rapid development and implementation of promising new treatments for people with neurological disorders.”

“NeuroNEXT focuses on supporting biomarker-informed phase II trials in humans, which are trials that have built into them what we call ‘go/no go’ criteria,” says Koroshetz. “In other words, you don’t go on to the expensive phase III trial unless you see what is predicted in the phase II trial.”

Koroshetz has firsthand knowledge of the importance of under-taking careful phase II trials. As an expert in HD, Koroshetz spent his research career prior to working at NINDS investigating the nature of the cell death that occurs in the brains of HD patients. Specifically, he studied the ability of coenzyme Q10 to lower lactic acid in the brain. It turned out that one of the Huntington Study Group team’s trials that he was involved with showed a trend toward benefit of coenzyme Q10, although non-significant; another trial showed nothing. “It’s pretty clear that we jumped into the phase III clinical trial without the kind of evidence we needed,” he says. “All the pieces of the puzzle were not in place.”
Koroshetz believes that NeuroNEXT’s emphasis on requiring phase II trials to be conducted in a rigorous, systematic fashion across multiple centers makes projects more successful down the road.

Koroshetz believes that NeuroNEXT’s emphasis on requiring phase II trials to be conducted in a rigorous, systematic fashion across multiple centers makes projects more successful down the road. He notes that SRX246 was considered by the study section to be a good candidate for NeuroNEXT support because it already had demonstrated efficacy and lent itself well to the network’s format.

The Azevan Pharmaceuticals team received funding from NeuroNEXT in September, 2015, and enrolled the first of 106 patients beginning in June 2016. The study was conducted at 22 locations across the United States. “Spreading the study sites across the United States is important,” says Anderson, who helped to design the study, because it reduces the potential for bias. “You don’t have one particular investigator enrolling subjects who may assess a patient’s irritability and aggression in a certain way.”

Specifically, the researchers assigned subjects to take 80 mg of SRX246 twice daily for two weeks, followed by 120 mg twice daily for four weeks. One group of subjects continued to take 120 mg of SRX246 twice daily for an additional six weeks, while the second group increased their dose to 160 mg twice daily for six weeks. Subjects in the placebo group were given a similar number of capsules that were identical in appearance to the capsules that contained SRX246 during the trial. The total duration of dosing was 12 weeks. The last patient was assessed in September, and the data analysis was undertaken right away.

An Unmet Need

Everyone involved in SRX246, from the researchers to the funding agency to the patients, are hoping for positive results and rapid progress to approval. “Currently, people with HD who have irritability that interferes with their well-being have limited options for treatment,” says Koroshetz. Anderson notes that HD patients often are prescribed drugs that
were originally approved for psychosis, schizophrenia, and bipolar disorder. “These drugs have not been tested in a careful way to see if they actually work for people with HD and to characterize their side effects,” she says. “There is a black-box warning for antipsychotic medications because of the risk of cardiovascular issues, strokes, and even death. We know there is a potential for really serious side effects with these drugs, but when the family is calling you at 10:00 at night on a Saturday because someone is tearing up the house you have to do something to help them.”

Anderson remembers a particular patient who was a manager at the company where he worked. “He had people skills and interacted well with others,” she says, “but he became increasingly difficult to deal with at work because he was irritable. He began to feel that all of his employees were lazy and weren’t listening to him. He would throw the stapler or kick the trashcan across the office if someone brought him bad news on a project. Eventually, he had to stop working, which made things worse for his wife and two small children because he was home more often. Once, one of his kids left his bike outside in the rain. My patient was so angry, he ran over the bike with his truck. It’s difficult for everyone when those kinds of things happen.”

As HD progresses, it affects many parts of the brain, including the frontal lobe, which is responsible for putting the brakes on our behaviors and getting us to think about the consequences of our actions, explains Anderson. “In the case of Huntington disease, the brakes are off and you just act on impulses; unfortunately a lot of those responses are aggressive and angry,” she says.

Anderson notes that not everyone with HD has symptoms of irritability, but when they do occur they can be very serious. Indeed, a safe, well-tested drug to reduce irritability is greatly needed in the HD community.

“When you experience firsthand the courage of the patients and their family members, you become really attached to trying to do something that can make a big difference in this disease,” says Koroshetz.

Looking to the Future

Currently, the Axovant team and their collaborators in the NeuroNext network are preparing to analyze the results of the phase II clinical trial.

“This isn’t just about developing a drug,” says Simon. “We talk to patients and listen to their stories, and we hear them asking for help. We need to maintain our objectivity in this study, and we have. While we are currently blind to treatment conditions, the data to date strongly suggest that the drug is well tolerated and safe. We will know about behavioral effects in a few months. I wish we had a cure for Huntington’s disease, but right now this is one way we may be able to help patients and their families.”

According to Simon, the team expects to complete analysis of its topline data by late in the fourth quarter of 2018 or early 2019. “If the data show positive behavioral effects, we will meet with the FDA to determine a path for remaining studies to secure approval. We hope that the HD community will help support our efforts once the results are in hand.”

Lauren Steffan may be among them. Given her mother’s history of HD-induced irritability, she knows what could be on the horizon. A mother of two young children, she says she is doing her best to manage the irritability she already is feeling. “So far, I am handling it well,” she says. “I’m just trying to be a good mom and live my life to the fullest.”

Meet the Advocate

PARTICIPATING IN DRUG TRIALS GIVES HD PATIENT LAUREN STEFFAN HOPE FOR THE FUTURE

Diagnosed with Huntington disease (HD) in 2015, Lauren Steffan, like many individuals with HD, struggles to balance her feelings of bitterness and anger with her optimism that researchers will discover a cure in time to save her life, along with the large community of patients who are also at risk or diagnosed positive and are desperate for reliable drug treatments.

Her mother currently battles HD from the confines of a nursing home. She is in the later stages of the disease, and Steffan considers her to be the ultimate fighter.

Now 30, Steffan says she has good days and bad. “When you face a diagnosis of HD, your mind goes to dark places,” she says, but she urges fellow patients to not let the darkness take over. She notes that although researchers still are only at the beginning stages of effective drug development, patients should live their lives to the fullest. “Do not neglect to seek medical treatments now, see an experienced neurologist, use diet and exercise to the best of your abilities, and create a strong support group,” she says.

Steffan, who lives in Houston, Texas, immediately enrolled in clinical drug trials after receiving her diagnosis. “It was a no brainer for me because the risk was better than the alternative,” she says. “Participating in clinical trials gives me hope for the future. I do it because I want to help further our understanding of the disease pathology and how it can be treated effectively in the near future. And I want to help other people with HD understand that we don’t have all the answers, but by participating in trials, we can get there. Without participation we will never find an effective treatment.”

Steffan says she now feels cautiously hopeful. “I feel like I’m on the edge of the Grand Canyon, looking over,” she says. “The solution is there. We can do this.”

Steffan believes that the key to finding effective treatments and even a cure lies in the abilities of researchers and clinicians to collaborate with each another and share proprietary information. In addition, she urges researchers and clinicians to be honest and open with each other. “Working hand in hand, they should reinforce the importance of unity,” she says.

She adds that she is particularly interested in the promise of several current research strategies that have led to clinical trials that are either enrolling or in the pipeline. For example, Roche/Genetch, Wave Life Sciences, UniQure, Vaccinex, and many more companies have therapies that are in development. “This is very exciting and none of it would be possible without the great care and teamwork of patients, scientists, neurologists, social workers, clinical trial coordinators, the Huntington Study Group and other non-profit groups, patient advocates, and caregivers, just to name a few,” she says.

Meanwhile, Steffan graduated from the University of Houston-Downtown last May with a bachelor’s degree in communication studies. She is a dedicated patient advocate for the HD community, all of whom she considers as family. She is a mother and spends her time raising her children whom she adores dearly. In her free time, you can find her at a hot yoga studio or digging into a great book.

Her final advice to fellow patients is find their passion and embrace it. “Do not live in fear,” she says. “Turn your anger into passion, for passion is alive and well in all of us. Stay educated and aware. And most importantly make friends along the way and never be afraid to share hugs.”
“Participating in clinical trials gives me hope for the future.”

LAUREN STEFFAN
THE AWARDS

Each year, the editors and editorial board of HD Insights select key papers published within that year that are among the most impactful in the field of Huntington disease research. The authors of these papers are invited to present their research at the Huntington Study Group annual conference, where they are presented with an Insight of the Year Award. This year, two papers were selected to receive this award, and summaries of this work are provided here.

Testing a Longitudinal Compensation Model in Premanifest Huntington Disease

BY SARAH GREGORY

Compensation is assumed to account for normal function in the presence of neuronal loss during the earliest stages of Huntington disease (HD). Despite being a recognized phenomenon, the neuronal mechanisms underlying compensation are not well understood. This is mainly due to the absence of a well-defined characterization and corresponding model for empirical investigation. We developed a model comprising three components needed for compensation: brain activation (measured by task-based and resting state fMRI), behavior, and pathology (MRI-based volume measurements), where each component has a specific trajectory across three phases of HD progression. During the earliest phase, function is maintained by increased brain activation; in the second, brain activation decreases as function begins to deteriorate; and finally, both brain activation and function decrease rapidly in the presence of steadily increasing neuronal loss. Using data from the premanifest-HD Track-On HD cohort, our conceptualization of compensation was partially realized. Cognition was maintained by an increase in connectivity between the left and right dorsolateral prefrontal cortex, while both UHDRS-Total Motor Score and quantitative motor behavior were supported by increased connectivity between the left and right premotor cortex. As such, our model can be used to test for compensation in neurodegenerative disease with similar patterns to HD.


PUBLISHED WORK

Sarah Gregory’s paper was published in the July 2018 issue of Brain: A Journal of Neurology.
The Cryo-EM Structure of Huntingtin

BY RUBEN FERNANDEZ-BUSNADIEGO

Huntington disease is caused by a mutation in the gene coding for the Huntingtin (HTT) protein. Despite decades of intense research, the native function(s) of HTT remain poorly understood, partly due to the limited structural information available on this protein. In this paper, we used cryo-electron microscopy to determine the structure of HTT in complex with HAP40, a known HTT interactor. The overall resolution of 4 Å allowed de novo building of an atomic model of the HTT-HAP40 complex. HTT is eminently α-helical and consists of three large domains: the N- and C-terminals domains are rich in HEAT (huntingtin, elongation factor 3, protein phosphatase 2A, and lipid kinase TOR) repeats arranged in a solenoid-like fashion. These domains are linked by a smaller bridge domain, containing multiple non-HEAT α-helical repeats. HAP40 occupies a cleft formed by the three HTT domains, binding all of them simultaneously. This structure represents an important step toward the elucidation of the physiological functions of HTT and its role in Huntington disease.


ARCHITECTURE OF THE HTT–HAP40 COMPLEX

a–d, The reconstructed density map filtered according to local resolution is shown as a translucent surface. The atomic model is superimposed in ribbon representation, with domains colour-coded as follows: HTT N-HEAT domain, blue; HTT bridge domain, yellow; HTT C-HEAT domain, maroon; HAP40, purple. a–d show different views of the complex as indicated. e, Schematic of the domain organization of HTT and HAP40. (Figure courtesy of Nature.)

PHASES OF FUNCTION

Figure courtesy of the guarantors of Brain from the original article “Testing a longitudinal compensation model in premanifest Huntington’s disease.” The main components of compensation are a performance outcome (Y), an activation signal compensator (C), and brain volume (X), which are tracked over time. Three phases are depicted for Huntington disease progression. Phase 1 is compensation, where brain activation increases in reaction to brain deterioration, and the increased activation causes performance to be maintained; in Phase 2, disease effects start to overwhelm compensation, which results in an activation plateau and the initiation of performance deterioration; and Phase 3 shows relentless disease effects with brain activation starting to decrease and performance deterioration accelerating. Brain volume is expected to steadily decrease over time regardless of phase.
### CURRENTLY ENROLLING

**Sponsor**: Azidus Brasil  
**Identifier**: NCT03252535  
**Agent**: Cellavita HD  
**Phase**: II  
**Contact**: Joyce Macedo, PI  
joyce.macedo@azidusbrasil.com.br  
**Design**: First in human, dose-escalation study to evaluate the safety of the stem-cell based therapy Cellavita HD in HD  
**Length**: 5 years  
**Sites**: None listed

**Sponsor**: Hôpitaux de Paris  
**Identifier**: REVHD  
**Agent**: Resveratrol  
**Phase**: III  
**Contact**: Fanny Mochel, MD, PhD  
fanny.mochel@upmc.fr  
**Design**: Randomized, placebo-controlled study to evaluate the therapeutic potential of Resveratrol on caudate volume in HD patients, using volumetric MRI  
**Length**: 1 year  
**Sites**: France

**Sponsor**: Institut National de la Santé et de la Recherche Médicale  
**Identifier**: TRIHEP3  
**Agent**: Triheptanoin oil  
**Phase**: II  
**Contact**: Fanny Mochel, MD, PhD  
fanny.mochel@upmc.fr  
**Design**: Randomized, double-blind, controlled study of Triheptanoin oil, an anaplerotic therapy, in early manifest HD  
**Length**: 1 year  
**Sites**: France and Netherlands

**Sponsor**: Vaccinex Inc.  
**Identifier**: SIGNAL  
**Agent**: VX15/2503  
**Phase**: II  
**Contact**: Andrew Feigin, MD, Huntington Study Group  
800-487-7671  
**Design**: Randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of VX15/2503 in individuals with late prodromal and early manifest HD  
**Length**: 12 to 21 months  
**Sites**: 30 total: United States and Canada

**Sponsor**: Wave Life Sciences Ltd  
**Identifier**: PRECISION HD1  
**Agent**: WVE-120101  
**Phase**: I/II  
**Contact**: Clinical Operations  
855-215-4687  
clinicaltrials@wavelifesci.com  
**Design**: Randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of WVE-120101 in adults with early manifest HD  
**Length**: 2 years  
**Sites**: Toronto, Ontario Canada

**Sponsor**: Wave Life Sciences Ltd  
**Identifier**: PRECISION HD2  
**Agent**: WVE-120102  
**Phase**: I/II  
**Contact**: Clinical Operations  
855-215-4687  
clinicaltrials@wavelifesci.com  
**Design**: Randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of WVE-120102 in adults with early manifest HD  
**Length**: 2 years  
**Sites**: Toronto, Ontario Canada

### ACTIVE

**Sponsor**: Azevan Pharmaceuticals  
**Identifier**: STAIR  
**Agent**: SRX246  
**Phase**: I/II  
**Contact**: Neal Simon, PhD  
610-419-1057  
ngsimon@azevan.com  
**Design**: Randomized, placebo-controlled, double-blind, 12 week, 3-arm dose escalation study of SRX246 in individuals with irritability and early symptomatic HD  
**Length**: 12 weeks  
**Sites**: 22 total: United States

**Sponsor**: Ionis Pharmaceuticals  
**Identifier**: NCT03342053  
**Agent**: IONIS-HTTRx  
**Phase**: II  
**Contact**: Ionis Pharmaceuticals  
800-679-4747  
patients@ionisph.com  
**Design**: An open-label extension study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IONIS-HTTRx for patients who participated in prior IONIS-HTTRx studies  
**Length**: 74 weeks  
**Sites**: 9 total: Canada, Germany, and the UK

**Sponsor**: Teva Pharmaceutical Industries  
**Identifier**: NCT02215616  
**Agent**: Laquinimod  
**Phase**: II  
**Contact**: Sarah Boe, Teva  
610-727-3486  
**Design**: Randomized, double-blind, placebo-controlled, parallel-group study evaluating efficacy and safety of Laquinimod (0.5 or 1.0 mg/day) in HD  
**Length**: 12 months  
**Sites**: 52 total: Worldwide

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**Sources**: www.clinicaltrials.gov and apps.who.int/trialsearch
HD THERAPEUTIC PIPELINE

TREATMENT TYPE
- Disease-modifying therapies
- Symptomatic treatments
- Gene-targeting therapies

Sources: www.clinicaltrials.gov, HDSA’s Therapies in the Pipeline, and company/developer websites.

To patients
- Deutetrabenazine (Teva)
- Tetrabenazine

Phase 3
- SRX246 (Azevan)
- Laquinimod (Teva)
- VX15/2503 (Vaccinex)
- Varenicline
- Pridopidine (Teva)
- IONIS-HTTRx (Ionis)

Phase 2
- AAV-miRNA (uniQure)
- AAV-RNAi (Voyager/Genzyme)
- AAV-shRNA (Spark Therapeutics)
- WVE-120101 (WAVE Life Sciences)
- WVE-120102 (WAVE Life Sciences)

Phase 1
- Preclinical
Teva Pharmaceuticals is working every day to make quality healthcare accessible around the world. As a manufacturer of specialty and generic pharmaceuticals, Teva provides both new therapies and greater access to quality, affordable medicines.