HD SUFFERERS SEEK SUPPORT FROM THE VATICAN

VOLUME 18, FALL 2017
Last spring, a colleague of mine alerted me to a job opening at the Huntington Study Group as the deputy editor of *HD Insights*. “Fantastic!” I thought. “I’m skilled at managing publications, and I have a background in biology from the University of Tennessee and the University of Georgia. But what is Huntington disease?” I’d heard of it, but I admit I had to look it up before deciding to apply for the position.

I quickly learned about the devastation that HD has on patients and their families. But I also learned that researchers around the world are attacking the disease from every possible angle, motivated by the intellectual challenge that HD presents, but more importantly by finding treatments and eventually a cure for patients.

Unfortunately, I wasn’t alone in my ignorance of HD; much of the lay public is equally uninformed. But that is changing through the efforts of those involved in HD research and outreach. Take Charles Sabine, for example. His work to bring awareness to HD by soliciting the recognition of Pope Francis is described on page ## in this issue of *HD Insights*.

Also in this issue, Dr. Xiao-Jiang Li of Emory University, talks about his work to inactivate the mutant huntingtin gene in adult mice using the CRISPR/Cas9 system (page 21). In addition, Katherine High, president and chief scientific officer at Spark Therapeutics, discusses her company’s efforts to use gene therapy to treat congenital blindness, which has implications for HD (page 4).

Coincidentally, a few weeks before learning about the deputy editor position at *HD Insights*, a man at a local park caught the attention of my young daughters. The man seemed to be twitching uncontrollably. “What’s wrong with him?” my youngest daughter asked. “I don’t know, sweetie,” I responded.

But now I do know, and I am determined to provide you, the readers of *HD Insights*, with the best possible source of information about HD, including current research findings, an inside look at ongoing clinical studies, and stories about the people who are searching for a cure.

After browsing this issue of *HD Insights*, I invite you to view the periodical’s new website at hdinsights.org. There, you will find an online form on which to submit your story ideas for a future issue of HD Insights, or you can email me directly at HDInsights@hsglimited.org. I look forward to hearing from you!
MEET THE COMPANY
Katherine High discusses Spark Therapeutics’ gene therapy work.
Pages 4-7

MEET THE NEXT GENERATION
A new generation of HD researchers is taking the field in exciting directions.
Pages 8-14

HIDDEN NO MORE
Pope Francis lends hope to HD sufferers.
Pages 20-21

MEET THE TECHNOLOGY
Xiao-Jiang Li uses CRISPR/Cas9 to delete the mutation that causes HD.
Pages 22-24

BY THE NUMBERS

2,000
The number of attendees at the HDdennomore event at the Vatican, which aimed to bring awareness to HD.

$2.36
The market value (in billions) of Spark Therapeutics’ outstanding shares.

1993
The year the gene for HD was discovered.

9
The ripe old age (in months) of mice whose HD neuropathology and behavioral phenotypes were reversed by Xiao-Jiang Li, et al. using CRISPR/Cas9-mediated gene inactivation (see page 21).

40+
The number of CAG repeats within the HTT gene that almost always results in HD.
MEET THE COMPANY

SPARK THERAPEUTICS
Dr. Katherine High, president and chief scientific officer at Spark Therapeutics, and Emeritus Professor of Pediatrics at the University of Pennsylvania’s Perelman School of Medicine, spoke with HD Insights about the company’s program to develop and acquire FDA BLA approval for a gene therapy to treat a rare form of congenital blindness. The therapy has implications for HD.

**HD INSIGHTS:** Dr. High, congratulations on your biologics license application (BLA) to the FDA. [A BLA is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce.]

**HIGH:** Thank you very much. This is a milestone for Spark, but as a former president of the American Society of Gene and Cell Therapy, I can tell you it is also a milestone for American gene therapy because it is the first application filed for an adeno-associated virus (AAV) vector for a genetic disease, in this case a rare form of congenital blindness.

For those of us who work in gene therapy for genetic disease, creating therapeutic options for people who are born with inherited diseases, many of whom have had very restricted therapeutic options, has been a long-standing goal. To file an application for an AAV product for a rare form of congenital blindness is very exciting for us.

**HD INSIGHTS:** This is the first FDA BLA application for a gene therapy to be eventually approved for use for a genetic condition?

**HIGH:** Yes, in the USA. The European Medicines Agency has approved two applications for gene therapy for genetic disease. One was an AAV vector approved in 2012 for lipoprotein lipase deficiency, a very rare lipid disorder, and the other was a retroviral vector for ADA SCID, a rare form of immunodeficiency.

But neither of those therapies are FDA-approved in the USA, therefore, this BLA for the rare form of congenital blindness, if granted, will be the first FDA-licensed product for gene therapy for a genetic disease. For me, that would be the fulfillment of a career spent trying to establish a basis for gene therapy for genetic diseases.

**HD INSIGHTS:** Can you tell us about this genetic therapy and how it might be applicable to HD?

**HIGH:** This genetic therapy is developed for a rare form of inherited blindness. There are more than 220 genes involved in vision, and mutations in any one of those genes might interfere with vision. This particular gene encodes an enzyme that is needed to regenerate 11-cis retinol, a critical component of a light-sensing molecule required in the photoreceptors to convert light energy to an electrical signal.

Continued, page 6
HIGH: When light strikes the retina, a reaction occurs that changes cis-retinal to trans-retinal. But that trans-retinal must then be regenerated to the cis form, and that occurs under the activity of the regenerative enzyme, RPE65, (which stands for retinal pigment epithelial 65 kilodalton protein), an isomerohydrolase. A mutation in this enzyme leads to loss of activity of the enzyme, and a break in the visual cycle.

An attractive feature of this disease for gene therapy is that normal retinal anatomy is preserved for a long period of time, so that if the normal gene can be introduced, and the visual cycle restored before there has been extensive degeneration of the retina, vision can be restored.

"...this BLA for the rare form of congenital blindness, if granted, will be the first FDA-licensed product for gene therapy for a genetic disease."

The work that underlies all this was first conducted in a naturally occurring dog model of the disease. Dr. Jean Bennett in the Department of Ophthalmology at the Perelman School of Medicine of the University of Pennsylvania had shown that subretinal injection of an AAV vector expressing the isomerohydrolase would restore vision in the dogs. That was the basis of the clinical studies in 12 subjects, which began in 2007 at the Children’s Hospital of Philadelphia. Child and adult patients who met all the entrance criteria for the study would have the worse of their two eyes injected. Using several different visual endpoints, we were able to show that their vision improved.

The next study we did was to inject the contralateral eye. At the beginning, we were concerned this might generate an immune response, like a prime and boost of a vaccine, because the patients’ immune system had now been exposed to the vector—but that did not occur. Based on the safety data from injecting the first eye, and then the second eye a couple of years later, we were able to move forward to a Phase Three study, which began in 2012 and read out toward the end of 2015. We spent 2016 and the first part of 2017 preparing the BLA, which we filed in May 2017.

Additionally, we have preclinical programs going on in diseases that target the CNS—one is Batten’s disease, a pediatric neurodegenerative condition, and the other is HD.

These programs are still at preclinical stages, and there is relatively less clinical experience with introducing AAV vectors into the CNS, although the PD trials have been going on for some time, and there is experience in a couple of other indications as well. There has been an early trial for Batten’s disease that involved focal intraparenchymal injections of AAV. We are looking at a different approach where we are hoping to get more extensive global distribution of the gene product.

HD INSIGHTS: The idea that you could have a one-time injection and cure a retinal disease, and that you could have a one-time injection and maybe not cure, but at least have substantial benefit for HD patients, is very appealing. Can you tell us about the status of your work in HD?

HIGH: We have been collaborating for some time now with Dr. Beverley Davidson from the Children’s Hospital of Philadelphia, and we have worked to develop a convincing package of safety data in dogs as well as preclinical efficacy data in mouse models.

Continued, page 7
HIGH: Much of the work in the mouse models is already published. Some of the safety data in non-human primates has been presented in various forums. Dr. Jodi McBride at Oregon Health and Science University has done a lot of that work. Dr. Davidson’s group and ours have worked together to generate additional data in non-human primates.

HD INSIGHTS: Can you estimate when you expect Sparks’ therapeutic compounds to go to clinical trials for HD?

HIGH: I cannot give you a date for that. As you know, once we believe that we have a convincing package of safety and efficacy data, we would need to submit that to both FDA (an IND application) and local regulatory groups (the clinical protocol and supporting documents to the local IRB, details of the vector to the local Institutional Biosafety Committee), and get their agreement. We have not yet completed all the studies required to be ready to submit to the FDA.

HD INSIGHTS: As you look at HD from an outside perspective, what is missing? What would make it easier to develop a new drug for HD?

HIGH: I will tell you what I think are the good things about HD as an indication for gene therapy. While working with neurologists, I have been very impressed that the clinical rating scales, and the natural history data in HD seem very robust. And you guys have impressive genotype-phenotype correlation data. I think that the endpoints for such a study have been well studied. All those things are important.

When I contrast that with these rare blindness conditions, as in the situation when we started our work, there were no FDA-approved pharmacologic products for the treatment of any of those conditions. That means that you have to really think about what you would use for endpoints. In the case of RPE65 deficiency, we had to develop a new endpoint, in the form of a mobility test that assesses functional vision, and then validate it.

One of the advantages of HD is that you have good natural history data, and in the UHDRS, an outstanding clinical rating scale that can be used across multi-site studies. This gives confidence that the UHDRS can be used to follow the effect of any kind of therapeutic intervention.

In terms of gene therapy, I think another good thing about HD is that we are contemplating focal delivery to the CNS, at least in the initial studies. I think there are very good safety data from the PD trials about focal delivery of AAV to the CNS.

A bigger challenge for situations where you want to have global delivery to the CNS is that there is less experience with that. I think that initial studies in HD will probably involve focal delivery to the CNS, and then you have some reasonable expectation that if you can knock down the mHTT without having any off-target effects, you can see clinical benefit from that.

HD INSIGHTS: Dr. High, thank you very much for your time, and congratulations again on your application to the FDA. I know this is a great moment for you, and it reflects not only your leadership at Spark, but also a long career as a successful academic and researcher pursuing gene therapies. We look forward to the day of celebrating the success of the first application to the FDA for a genetic therapy for HD.
MEET THE NEXT GENERATION

From the use of super-resolution imaging techniques to study brain synapses to the use of antisense oligonucleotides to silence genes, the new generation of HD researchers is taking the field in exciting directions. Those whose research is particularly remarkable have been invited by the HSG to attend the November 2017 HSG Annual Meeting in Colorado. Here, they will present their backgrounds, their current work, and their vision for the future of HD research.
AMBER SOUTHWELL, PhD

EDUCATION:
• BS, Biochemistry, University of Texas at Austin, Austin, TX
• BS, Molecular Biology, University of Texas at Austin, Austin, TX
• PhD, Neurobiology, California Institute of Technology, Pasadena, CA
• Postdoctoral Fellowship, University of British Columbia, Vancouver, Canada

CURRENT POSITION:
Assistant Professor of Neuroscience, University of Central Florida, Orlando, FL

CURRENT RESEARCH INTERESTS:
My research focuses on developing experimental therapies for neurodegenerative diseases, with a focus on HD. Our goal is to bring therapies from conception through to clinical translation. In addition to therapeutics, we also develop model systems and companion biomarkers to make this possible.

REASONS FOR INTEREST IN HD RESEARCH:
I became interested in therapeutic research for neurodegenerative diseases because I saw how medical science was increasing longevity, but not quality of life, due to the increasing prevalence of these intractable diseases. I focused on HD because it is the most common genetic neurodegenerative disease, allowing for genetic model system development, as well as preventative therapeutic strategies.

HOPES FOR THE FUTURE OF HD RESEARCH:
Like most of us, my hope is that a truly preventative therapy will be developed to protect those with the HD mutation from developing the disease. At one time, people thought about the possibility of eradicating the HD mutation through family planning, but now that we know how common new mutations are, and how many people in the general population carry a reduced penetrance allele for HD, it has become apparent that we will never eliminate the HD mutation. Now, our hope is that a positive genetic test for HD is followed by an effective, preventative treatment regimen.

HOBBIES AND INTERESTS:
My main hobby is neuroscience, even outside of the lab. I love reading about the brain and all the cool things it can do, and all the truly weird things that go wrong when it is not working correctly. I also love cooking, dancing, SCUBA diving, and playing with my amazing kids.
MEET THE NEXT GENERATION

DANIEL WILTON, PhD

EDUCATION:
• BS, Biochemistry, University of Birmingham, Birmingham, UK
• PhD, Neuroscience, University College London, London, UK

CURRENT POSITION:
Postdoctoral fellow, Stevens Lab, F.M. Kirby Neurobiology Research Center, Boston Children’s Hospital, Boston, MA

CURRENT RESEARCH INTERESTS:
My research focuses on how the nervous and immune systems interact to facilitate synapse elimination during developmental pruning windows, as well as how these processes become dysregulated in HD. I use a number of transgenic mouse models, which parallel many aspects of disease progression in humans and enable investigation of specific circuits through the selective elimination of mHTT from different brain regions. In conjunction with stereotactic surgeries to label specific neural connections, I use super-resolution imaging techniques to study the role of microglia-synapse interactions in HD. In parallel, I use a number of molecular and pharmacological approaches to dissect the signals involved in cross-talk between complement and microglia, and the mechanisms that lead to the targeting of vulnerable synapses. My ongoing studies are aimed at discerning the molecular and cellular mechanisms involved in the region-specific neurodegeneration observed in HD.

REASONS FOR INTEREST IN HD RESEARCH:
The glial cells I study are the resident immune cells of the brain; therefore, my research has led me to look at the role of the immune system in HD pathogenesis. I believe this is a particularly underexplored research area, and one that is potentially very important, given that some of the earliest quantified changes in HD relate to perturbations in the immune system.

HOPES FOR THE FUTURE OF HD RESEARCH:
Last year, I attended the HDSA annual conference and presented some of my current work, which gave me the opportunity to meet some of the families affected by HD, and witness the courage, generosity, and strength of this community. My own work has personally benefited from the willingness of people burdened by this terrible disease to step forward and participate in research efforts. I am very grateful for this, and I am hopeful that the work we are doing in the Stevens Lab will help to move our understanding of the disease forward, and eventually enable the development of useful therapeutics.

HOBBIES AND INTERESTS:
I enjoy playing a number of sports, including soccer and tennis. I also enjoy learning languages, reading, and cooking.
LISA SALAZAR, PhD

EDUCATION:
- BS, Biology and Chemistry (Mathematics Minor), College of Saint Mary, Omaha, NE
- PhD, Biological Sciences, University of California, Irvine, CA

CURRENT POSITION:
Assistant Project Scientist, laboratory of Dr. Leslie Thompson, Department of Psychiatry and Human Behavior, University of California, Irvine, CA

CURRENT RESEARCH INTERESTS:
I have dedicated my scientific career to understanding the molecular processes that regulate normal cellular function, and how these processes are altered in disease. These studies reach across multiple fields, including the immunological signals involved in chronic transplant rejection; fibroblast growth factor signaling in cancer; and, more recently, HD, with a focus on altered gene expression in the presence of mHTT. Through my HDSA Human Biology fellowship, I am evaluating the potential of total versus mHTT lowering to correct cellular and gene expression changes in neurons derived from HD patient stem cells. My goal is to systematically determine the specific, and potentially complex, alterations to normal neuronal function and gene expression when total HTT is reduced, as well as the differential effects of preferentially reducing mHTT compared to total HTT knockdown. A major part of this work involves the generation of iPS cell lines derived from unaffected and affected individuals that can be induced to reduce total HTT or mHTT at any point along the path from stem cells to mature neurons. These studies also include determining the effects of total HTT—lowering following treatment with ASOs or siRNA delivered using a highly effective lipid nanoparticle system. Results from these studies will further inform clinical HTT-lowering treatments.

HOPES FOR THE FUTURE OF HD RESEARCH:
It is an exciting time in HD research, with the advent of nucleotide-based HTT-lowering strategies holding great promise as a possible disease-modifying treatment. It is my hope that HD research will continue to identify rational therapies that modify disease progression, improving the prognosis and quality of life for HD patients and those who care about them.

HOBBIES AND INTERESTS:
Hiking, spending time with family and friends, volunteering in therapeutic horseback riding lessons, and working to improve the lives of people with disabilities.
MEET THE NEXT GENERATION

SHOULSON SCHOLARS

FILIPE BROGUEIRA RODRIQUES, MD, MSc

EDUCATION:
• MD, Faculty of University, University of Lisbon, Lisboa, Portugal
• MSc, Faculty of University, University of Lisbon, Lisboa, Portugal

CURRENT POSITION:
Clinical Research Fellow, UCL Huntington Disease Centre, London, United Kingdom; Honorary Neurology Registrar, National Hospital for Neurology & Neurosurgery, London, United Kingdom

CURRENT RESEARCH INTERESTS:
I am a clinical academic with a medical background, currently developing my skills and knowledge in statistics and research methodology. My areas of academic interest are research synthesis and methodology, and outcomes measures and biomarkers in HD. My field of clinical interest is neurodegeneration and neurogenetics with a special focus on HD.

REASONS FOR INTEREST IN HD RESEARCH:
I have been clinically and academically involved with HD since 2013, when I started applying my research techniques to HD, and began to evaluate participants for the REGISTRY study in Lisbon, Portugal, under the supervision of Professor Ferreira. In 2015, I joined the UCLcHuntington Disease Centre led by Professor Tabrizi and Professor Bates, where I work under the supervision of Dr. Wild. My research focus has been on the systematic evaluation of new therapeutic interventions, optimization of clinical trials’ designs, and development of new outcomes measures.

HOPES FOR THE FUTURE OF HD RESEARCH:
During my short, but rich, involvement with the HD community, I have grown to learn that every step regardless of its size is important in the fight against this condition. I am firmly convicted that we have never been closer to find an intervention with the power to change the course of the disease as we are today, and that there is still a lot to be done in the symptomatic intervention’s domain, where investment is needed both research- and clinically-wise.

HOBBIES AND INTERESTS:
Sports, gastronomy, and contemporary art.
ERIC KELLER

EDUCATION:
Currently working on undergraduate degree, biotechnology major (animal option), biochemistry minor, Rutgers University, Newark, NJ

CURRENT POSITION:
• Undergraduate Researcher, Samuel L. Baily Huntington Disease Family Service Center, Rutgers New Jersey Medical School, Newark, NJ
• Undergraduate Researcher, Structural Biology Laboratory, Rutgers University, Newark, NJ

CURRENT RESEARCH INTERESTS:
I am currently interested in learning how the HTT aggregates transfer from cell to cell. The lab I am in is trying to figure out the mechanism that mutant HTT uses to pass into other cells. We are also interested in visualizing the many different forms of mHTT via cryo-em and 3D tomography.

REASONS FOR INTEREST IN HD RESEARCH:
Huntington disease runs in my family, and now I possess enough knowledge to research the subject further.

HOPES FOR THE FUTURE OF HD RESEARCH:
I’d like to explore the possibilities of CRISPR/Cas9 and other recent biotechnology developments, and apply them to HD research.

HOBBIES AND INTERESTS:
I am very passionate about soccer and am a fan of the Tottenham Hotspurs. When I am not in the lab or at work, I like to play Frisbee and video games, and watch movies.
CURRENT RESEARCH INTERESTS:
I am concerned about the lack of psychiatric support available to those with Huntington disease, especially when a more complex clinical presentation is evident. The service provided in our tertiary outpatient clinic was evaluated, and the aim will be to use this to evidence the utility of neuropsychiatry services and create a benchmark for future standards of clinical care.

REASONS FOR INTEREST IN HD RESEARCH:
In 2008, I met my first patient with Huntington disease after having been persuaded to experience an HD clinic at Queen Square by Professor Sarah Tabrizi. I was intrigued at how a disease due to one clearly defined genetic mutation could result in such varied psychiatric presentations, and I was in awe of how the families and caregivers coped.

HOBBIES AND INTERESTS:
I love playing the piano and listening to classical music. I also enjoy the great outdoors and downhill skiing. This year, I finally have found the time to improve my French.
MEET THE INVESTIGATOR

STEVEN HERSCH, MD, PhD
MEET THE INVESTIGATOR

NAME: STEVEN HERSCH

CURRENT POSITION: Senior Director for Clinical Development, Voyager Therapeutics, Cambridge, MA, USA and Professor of Neurology, Harvard Medical School, Boston, MA

EDUCATION: PhD, Boston University, Boston, MA; MD, Boston University School of Medicine, Boston, MA; Residency, Emory University Hospital, Atlanta, GA; Fellowship, Emory University Hospital and Wesley Woods Geriatric Hospital, Atlanta, GA

Dr. Steven Hersch, professor of neurology at Harvard Medical School and senior director for clinical development at Voyager Therapeutics, speaks with HD Insights about the HD therapies he is pursuing through his work with Voyager Therapeutics.

HD INSIGHTS: Today, we have the pleasure to speak to Dr. Steven Hersch, who is the senior director for clinical development at Voyager Therapeutics, as well as a professor of Neurology at the Harvard Medical School. Dr. Hersch, can you tell us about Voyager Therapeutics?

HERSCH: Voyager was founded almost four years ago, bringing together all-stars in neuroscience, clinical development for neurologic disorders, RNA interference, AAV vector engineering and manufacture, and CNS targeted gene therapy delivery. The goal of the company is to develop gene therapies for major unmet needs in neurology, with neurodegenerative diseases being a particular emphasis. Voyager’s Parkinson’s disease program, which uses an AAV vector to deliver AADC to the putamen in patients with advanced PD, is progressing to pivotal phase 2-3 and has provided a foundational clinical experience for HD. Voyager’s pipeline also includes programs in ALS, Friedreich’s ataxia, frontotemporal dementia and Alzheimer’s disease, and severe, chronic pain.

HD INSIGHTS: Voyager recently announced that it had selected its lead candidate for RNA silencing for HD. Can you tell us about that program?

HERSCH: The clinical lead, VY-HTT01 is composed of an adeno-associated virus (AAV) capsid and proprietary transgene that harnesses the RNA interference pathway to selectively knock down the production of HTT messenger RNA (mRNA). The clinical lead was carefully selected from a large number of candidates using experimental and bioinformatic approaches to optimize potency and selectivity and minimize off-target effects. In preclinical models, a single administration of VY-HTT01 was well-tolerated and resulted in robust, dose dependent, and widespread knockdown of HTT messenger RNA in disease-relevant regions of the non-human primate central nervous system. Its pharmacology and safety continue to be studied.

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**MEET THE INVESTIGATOR, continued**

**HD INSIGHTS:** As I understand it, the therapeutic approach would involve a one-time surgical injection of the therapy into the brain of HD patients. Can you tell us about that approach, its benefits and limitations?

**HERSCH:** We intend to build on Voyager’s experience in the intraparenchymal delivery of gene therapy treatments using MRI-guided convection-enhanced delivery, which enables highly controlled administration that is especially important in the atrophying HD brain. Since the clinical morbidity of HD is due to widely distributed neurodegeneration, one of the major challenges with this approach is to obtain a sufficiently broad distribution to achieve a significant clinical benefit.

**HD INSIGHTS:** Other companies seem to be taking similar approaches to gene-silencing treatments, including Wave, Spark Therapeutics, and Ionis. Can you briefly compare or contrast your approach to others?

**HERSCH:** Each of these programs are developing treatments intended to reduce huntingtin levels in the CNS by targeting the huntingtin mRNA. Ionis and Wave are utilizing anti-sense oligonucleotides that are administered to the CSF by lumbar puncture. Repeated delivery is required to maintain the pharmacologic effects of these molecules. Spark and UniQure have AAV-based huntingtin-lowering gene therapy programs that are likely to have some similarities to Voyager’s, though our viral vector optimization and delivery methods may offer some differentiation. For the HD community, it is certainly beneficial to have multiple companies working on these complicated but promising approaches.

**HD INSIGHTS:** Can you tell us about your timeline, such as when you expect to see your therapy for HD entering clinical trials?

**HERSCH:** We announced a lead candidate selection for this program in June of this year, which means we have selected a preclinical candidate to move into humans, following additional work on the pharmacology and delivery of VY-HTT01 in animal studies, which would be followed by the IND enabling toxicology needed to proceed to clinical trials.

**HD INSIGHTS:** You have been a leader in HD research for at least the last 20 years. You have an active lab at Harvard Medical School. You were the co-chair of the Huntington Study Group, and you recently accepted a full-time position at Voyager. Can you tell us what attracted you to join Voyager?

**HERSCH:** I began by consulting for Voyager on a limited basis through an agreement between Voyager and the neurology department at MGH. I have found it really rewarding and exciting to apply my knowledge and experience in HD toward developing a gene therapy with great clinical potential. I also enjoyed learning much more about gene therapy and commercial approaches to drug development. By the time joining Voyager full-time became a possibility, I had become so invested in the program that it was an easy decision to make. Now I have the bandwidth to play a more extensive role in the HD program and to become involved in the early clinical development of some of the other Voyager programs. I am also pleased that Harvard and MGH are allowing me to maintain my appointment and continue some of my ongoing academic clinical and research efforts.

**HD INSIGHTS:** When you are not working at Voyager and still working as an academic, how do you like to spend your time?

**HERSCH:** Our family loves spending time together on Martha’s Vineyard in the summer.

**HD INSIGHTS:** Steve, many thanks for all your efforts, and for taking time to talk to us about the promising therapies for HD.

**HERSCH:** Thank you.
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<td>Randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of intravenously administered IONIS-HTRx in patients with early manifest HD</td>
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<td>ACTIVA® PC neuro-stimulator</td>
<td>II</td>
<td>Susanne Harnisch +49 6421 2866553 <a href="mailto:susanne.harnisch@kks.uni-marburg.de">susanne.harnisch@kks.uni-marburg.de</a></td>
<td>Randomized, double-blind, parallel-group, sham-controlled, multi-centre trial of Globus Pallidus Deep Brain Stimulation in individuals with HD</td>
<td>3 months</td>
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<td>Triheptanoin oil</td>
<td>II</td>
<td>Fanny Mochel, MD, PhD <a href="mailto:fanny.mochel@upmc.fr">fanny.mochel@upmc.fr</a></td>
<td>Randomized, double-blind, controlled study of Triheptanoin oil, an anaplerotic therapy, in early manifest HD</td>
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<td>II</td>
<td>Karl Kieburtz, MD, MPH</td>
<td>Open-label, single-group assignment study to assess the long-term safety of 45 mg of pridopidine in HD participants</td>
<td>2 years</td>
<td>12 total - United States and Canada</td>
<td>Enrollment complete, study ongoing</td>
</tr>
<tr>
<td>Teva Pharmaceutical Industries</td>
<td>LEGATO-HD</td>
<td>Laquinimod</td>
<td>II</td>
<td>Sarah Boe, Teva 610-727-3486</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group study evaluating efficacy and safety of Laquinimod (0.5 or 1.0 mg/day) in HD</td>
<td>12 months</td>
<td>52 total - worldwide</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>University of Auckland</td>
<td>VCAS-HD</td>
<td>Varenicline</td>
<td>II</td>
<td>Ailsa McGregor, PhD +61 3 479 4235 <a href="mailto:ailsa.mcgregor@otaog.ac.nz">ailsa.mcgregor@otaog.ac.nz</a></td>
<td>Randomized, double-blind, placebo-controlled trial of varenicline using the standard dosing regimen for smoking cessation in patients with HD</td>
<td>16 weeks</td>
<td>1 total - New Zealand</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Vaccinex Inc.</td>
<td>SIGNAL</td>
<td>VX15/2503</td>
<td>II</td>
<td>Andrew Feigin, MD, Huntington Study Group: 800-487-7671</td>
<td>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</td>
<td>12-21 months</td>
<td>19 total - United States</td>
<td>Expanding by invitation, study ongoing</td>
</tr>
<tr>
<td>Hôpitaux de Paris</td>
<td>REVHD</td>
<td>Resveratrol</td>
<td>III</td>
<td>Fanny Mochel, MD, PhD <a href="mailto:fanny.mochel@upmc.fr">fanny.mochel@upmc.fr</a></td>
<td>Randomized, placebo-controlled study to evaluate the therapeutic potential of Resveratrol on caudate volume in HD patients, using volumetric MRI</td>
<td>1 year</td>
<td>1 total - France</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Teva Pharmaceuticals</td>
<td>ARC-HD</td>
<td>SD-809 Extended Release</td>
<td>III</td>
<td>Samuel Frank, MD Huntington Study Group: 800-487-7671</td>
<td>Open-label, long-term safety study of SD-809 ER</td>
<td>58 weeks</td>
<td>40 total - United States</td>
<td>Study ongoing</td>
</tr>
</tbody>
</table>

To update or add a clinical trial, please e-mail editor@hdinsights.org. Sources: www.clinicaltrials.gov and apps.who.int/trialsearch/
As of September 2017

Disease-modifying therapies

- Cellavita HD (Azidus Brasil)
- SRX246 (Azevan)
- Laquiniqmod (Teva)
- Pridopidine (Teva)
- VX15/2503 (Vaccinex)

Preclinical | Phase 1 | Phase 2 | Phase 3 | To patients

Neuroprotective compounds

- Resveratrol
- Triheptanoin oil

Preclinical | Phase 1 | Phase 2 | Phase 3 | To patients

Symptomatic treatments

- Varenicline
- Deutetrabenazine (Teva)
- Tetrabenazine

Preclinical | Phase 1 | Phase 2 | Phase 3 | To patients

Gene-targeting therapies

- AAV-miRNA (uniQure)
- AAV-RNAi (Voyager/Genzyme)
- AAV-shRNA (Spark Therapeutics)
- WVE-120101 (WAVE Life Sciences)
- WVE-120102 (WAVE Life Sciences)
- IONIS-HTTRx (Ionis)

Preclinical | Phase 1 | Phase 2 | Phase 3 | To patients

Sources: www.clinicaltrials.gov, HDSA's Therapies in Pipeline, and company/developer websites
To add or correct a therapy in development, please email editor@hdinsights.org.
HIDDEN NO MORE
POPE FRANCIS LENDS HOPE TO HD SUFFERERS
Today we are here because we want to say to ourselves and all the world: ‘Hidden no more!’ ‘Ocultá nunca más!’ ‘Mai più nascosta!’

Those were the words of Pope Francis, the current pope of the Roman Catholic Church, as he addressed an audience of 2,000, including 150 HD sufferers, on May 18 at the Vatican. The event was sponsored by HDdennomore (pronounced ‘Hidden No More’), a global coalition of patient advocates dedicated to raising awareness of HD and ending the stigma and shame around the disease.

According to Charles Sabine, a journalist who helped to organize the event and a gene carrier for HD, Pope Francis was the first world leader to formally recognize the disease and to meet with patients.

“In centuries gone by, people thought it must be some sort of curse, or witchcraft, or that someone had offended the gods,” Sabine told a reporter at *The Guardian*. “In the early 20th century the eugenics movement in America suggested sterilising people with the disease. The Nazis took it a step further and put them in gas chambers. The culmination of all this, not surprisingly, especially in more remote parts of the world, is a massive stigma attached to the disease that means many people who are affected by it do not admit it.”

Families from 23 countries attended the event, including several from Venezuela, Colombia, and Argentina who received financial assistance from Sabine’s organization HDdennomore. At the event, HDdennomore aired a poignant video it had created to document the backgrounds of some of the families, many of which live in extreme poverty. Pope Francis spent close to an hour greeting and hugging the patients who attended the event.

“It was spectacular,” Nancy Wexler, the Higgins Professor of Neuropsychology at Columbia University, is quoted as saying in The Guardian article. “It meant so much to hear him say the words ‘Huntington disease,’ to say that he understood the problems, that it was a genetic disease and that it is nobody’s fault.”

Sabine and his co-organizers hope the pope’s endorsement will make it easier to get recognition for the disease from other world leaders, and will lead to increased funding for research.

"We hope this event will help to end the stigma attached to HD and open new doors to finding a cure.”

— Charles Sabine

Read the article in *The Guardian*

Watch highlights of the event, including HDdennomore’s video
MEET THE TECHNOLOGY

CRISPR/Cas9
MEET THE TECHNOLOGY: CRISPR/Cas9

Dr. Xiao-Jiang Li, Distinguished Professor of Human Genetics at the Emory University School of Medicine, discusses the use of the gene-editing technique CRISPR/Cas9 to remove from the genome the mutation that causes HD. Li’s own research using CRISPR/Cas9 shows great promise in mouse models of HD.

Cas9, to see whether that could inactivate the expression of mutant human huntingtin (mHTT) in adult mice. Is that correct?

LI: Yes. Because the mouse model was generated by inserting the human CAG repeat expansion into the mouse gene, mutant huntingtin is expressed at the endogenous level, but it carries the much larger CAG repeat expansion than the wild type allele, just like in a human patient. To correct the gene mutation in the neuronal cells in the brain, we use an adenoviral vector to deliver the CRISPR/Cas9.

How do you deliver the adenovirus into the mouse?

LI: We do a stereotactic brain injection. We can deliver the adenoviral vector specifically into the striatum because we know the striatum is the most affected area in the brain of HD patients. And in that particular HD mouse model, researchers have already found that the expression of the large CAG repeat in the mouse Htt gene in the striatum can cause mice to acquire a deficit in motor function. So, once we do the injection, we can look at motor function to see if there is any improvement of phenotype.

What did you find?

LI: We found an improvement in motor function. This is a very good sign to indicate that removing mutant huntingtin expression in this mouse model leads to improvement of phenotype.

Dr. Xiao-Jiang Li
Distinguished Professor of Human Genetics,
Emory University School of Medicine

HD INSIGHTS: You introduced the human mutant huntingtin gene (mHTT) into mice and then used an adenovirus to deliver CRISPR/Cas9, to see whether that could inactivate the expression of mutant human huntingtin (mHTT) in adult mice. Is that correct?

LI: Yes. Because the mouse model was generated by inserting the human CAG repeat expansion into the mouse gene, mutant huntingtin is expressed at the endogenous level, but it carries the much larger CAG repeat expansion than the wild type allele, just like in a human patient. To correct the gene mutation in the neuronal cells in the brain, we use an adenoviral vector to deliver the CRISPR/Cas9.

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LI: We found an improvement in motor function. This is a very good sign to indicate that removing mutant huntingtin expression in this mouse model leads to improvement of phenotype.

Continued, Page 24
**HD INSIGHTS:** You point out in your paper that there is concern that this non-allele-specific approach will also decrease normal wild-type expression of huntingtin. Did you find any side effects in your study?

**LI:** Early studies showed that if you deplete Htt expression in mice, they die at the embryological stage. So, Htt is very critical for neuronal survival. Our study has found that Htt is important for early development of the CNS, but when mice become adults, we can suppress Htt, and not see any obvious neurodegeneration. We found that when we inactivate normal or wild-type alleles, we do not see obvious neurodegeneration. We do not see any side effects, at least for a few months. We can use CRISPR/Cas9 to inactivate mHTT expression in this mouse model, and achieve therapeutic benefits.

**HD INSIGHTS:** Given the promising results of your study, what are the next steps?

**LI:** The immediate issue we must address is the long-term effect of CRISPR/Cas9 and the biosafety of this technology. Studies using the HD mouse model just observe the mice for several months. I think we need to do long-term observation to see if there are any side effects from removing huntingtin expression in adult brain tissue. We also need to identify a less invasive way to deliver CRISPR/Cas9 into the brain, because that remains a challenge.

Also, we use viral vectors, and we must be concerned about the toxicity of viral vector expression. The challenge is: can we find another safe way to deliver non-viral CRISPR/Cas9 into the brain?

In addition, the human brain is much larger than the mouse brain. For mice, we only inject the brain with a small amount of viral vector. In human brains, maybe we will have to do more injections, but will that result in toxicity due to the viral vectors? These are the kinds of biosafety issues we will address in the future.

Finally, we must do trials on non-human primates before we can do human clinical trials.

**HD INSIGHTS:** As you know, clinical trials are underway for gene-silencing techniques using antisense oligonucleotides and RNA silencing techniques. Where does CRISPR/Cas9 genetic therapy stand in relationship to those interventions?

**LI:** They are all different approaches, but CRISP/Cas9 has certain advantages. It can permanently remove or correct the mutation in the genome so that we need not continuously inhibit the expression of a mutant gene. Other methods would probably require repeated administrations.

**HD INSIGHTS:** Can you predict when we might see CRISPR/Cas9 gene-editing therapies in human clinical trials?

**LI:** I do not know how many years it will be. The field is moving so fast. I think we will see more and more reports of the use of this new technology.

**HD INSIGHTS:** When you are not investigating gene-editing techniques aimed at HD disease, how do you spend your time outside the lab?

**LI:** I spend most of my time in my lab or work. I work on different projects, of which HD is one. I also work in China on CRISPR/Cas9, and to generate non-human primate models.

**HD INSIGHTS:** Professor Li, congratulations on the great finding, and many thanks for your contributions to the field.
Each year, we recognize the most influential papers in HD research in three categories: basic science, clinical research, and biomarkers and imaging. The winners of the 2015-2016 competition nominated 15 articles for consideration in the 2016-2017 competition. Ten authors provided summaries, included in this edition, and the remaining five are cited. The HD Insights Editorial Board and prior winners then voted to select the three most influential papers, one from each category. The authors of the winning papers will present their research in a panel discussion at the HSG Annual Meeting in Colorado, on November 2, 2017. Congratulations to all the nominees and winners!
MUTANT HUNTINGTIN ACCELERATES IMPAIRED CELLULAR PHENOTYPES

Most influential paper (Basic science)

By Fatima Gasset-Rosa, PhD

The onset of neurodegenerative disorders such as HD is strongly influenced by aging. Hallmarks of aged cells include compromised nuclear envelope integrity; impaired nucleocytoplasmic transport; and accumulation of DNA double-strand breaks.

We show that mHTT markedly accelerates all these cellular phenotypes in a dose- and age-dependent manner in the cortex and striatum of mice. Huntingtin-linked polyglutamine initially accumulates in nuclei, leading to disruption of nuclear envelope architecture; partial sequestration of factors essential for nucleocytoplasmic transport (Gle1 and RanGAP1); and intranuclear accumulation of mRNA. In aged mice, accumulation of RanGAP1, together with polyglutamine, is shifted to perinuclear and cytoplasmic areas.

Consistent with findings in mice, marked alterations in nuclear envelope morphology, abnormal localization of RanGAP1, and nuclear accumulation of mRNA were found in the cortex of HD patients. Overall, our findings identify polyglutamine-dependent inhibition of nucleocytoplasmic transport and alteration of nuclear integrity as a central component of HD.

In this study, we identified a genetic modifier of HD progression, thereby opening up avenues for potential therapeutic development. By using the extensive phenotypic information available from the TRACK-HD studies, we defined a novel multi-dimensional progression score in HD (n = 216). A parallel progression score using 1,773 previously genotyped subjects from the EHDN REGISTRY study was then developed.

Despite use of less phenotypic information to generate the REGISTRY progression score, the TRACK and REGISTRY progression scores were significantly correlated (r = 0.674). These two progression scores were used in genome-wide association studies to look for genetic variants associated with disease progression. Meta-analysis of progression in TRACK-HD and REGISTRY gave a genome-wide significant signal (p = 1.12 x 10^-10) on chromosome 5, spanning 3 genes: MSH3, DHFR, and MTRNR2L2. The lead SNP in TRACK-HD (rs557874766) is genome-wide significant in the meta-analysis (p = 1.58 x 10^-8), and encodes an amino acid change (Pro67Ala) in MSH3.

Such a strong association in a small sample implies that the progression measure is a sensitive reflection of disease burden, that the effect size is large, or likely both. As knockout of Msh3 reduces somatic expansion in HD mouse models, this highlights somatic expansion as a potential pathogenic modulator.

No blood biomarker candidate studied to date has shown robust association with HD progression, onset and clinical severity. In the TRACK-HD cohort, we investigated neurofilament light protein (NfL) in blood as a potential prognostic marker of neurodegeneration in HD patients.

We found that mean concentrations of NfL in plasma at baseline were significantly higher in HTT mutation carriers than in controls, and the difference increased with disease stage (Fig. A). There was a striking CAG-dependent genetic dose-response relationship of plasma NfL level at a given age (Fig. B). Premanifest individuals with higher levels of NfL at baseline were more likely to progress to manifest HD during the period of study. Baseline levels of plasma NfL were strongly associated with subsequent cognitive decline and brain atrophy, independent of age and CAG, suggesting that plasma NfL may have predictive value above that of other predictors of HD progression. In a separate cohort, we showed that CSF and plasma levels of NfL were highly correlated, indicating that plasma levels have a CNS-derived origin. We conclude that plasma NfL is a promising potential biomarker of neurodegeneration in HD.

HD ACCELERATES EPIGENETIC AGING OF BRAIN AND BLOOD TISSUE
Nominee (Basic science)
By Steve Horvath, PhD, ScD

The patient’s age at HD motoric onset is strongly related to the number of CAG trinucleotide repeats in the huntingtin gene, suggesting that biological tissue age plays an important role in disease etiology. Recently, a DNA methylation-based biomarker of tissue age has been advanced as an epigenetic clock, which is arguably the most accurate molecular biomarker of aging.

Using large-scale human brain and blood data sets, we have found that HD is associated with an accelerated epigenetic age of blood and brain tissue. Further, HD has a genome-wide significant effect on the DNA methylation levels of many CpGs, but the effect appears to be tissue-specific. Overall, our results demonstrate that HD is associated with accelerated epigenetic age and has profound effects on DNA methylation levels. Future research in mouse models and in longitudinal human cohort studies will help elucidate cause and effect relationships.


CRISPR/CAS9 PERMANENTLY INACTIVATES HD MUTATION
Nominee (Basic science)
By Jong-Min Lee, PhD

All cases of HD are due to expansion of the CAG trinucleotide repeat in the first exon of HTT. However, expanded and normal CAG repeats sit on very diverse HTT haplotype backbones that carry numerous genetic variations. Some variants create or eliminate the CRISPR/Cas9 protospacer adjacent motif (PAM) site, which is required for Cas9 endonuclease. Such PAM-altering SNPs (PASs) provide opportunities for distinguishing the mutant allele from the normal allele in allele-specific CRISPR/Cas9 targeting.
To identify mutant allele-specific CRISPR/Cas9 targets in a given HD subject, PAM sites generated by SNPs were mapped to HTT haplotypes, and two haplotypes were compared. Then, CRISPR/Cas9 strategies can be designed based on mutant allele-specific CRISPR/Cas9 PAM sites for a given HD subject. For example, a CRISPR/Cas9 strategy simultaneously using gRNA1 and gRNA2, chosen based on PAM sites on the mutant allele, is predicted to excise the promotor region, transcription start site, and CAG repeat from the mutant allele, leading to prevention of the production of mHTT. Our allele-specific strategy does not target the CAG expansion mutation, but rather the haplotype harboring the mutation. Therefore, other CAG repeat-containing genes will not be influenced, making our strategy safe for therapeutic applications.

_A CRISPR/Cas9 strategy simultaneously using gRNA1 and gRNA2, chosen based on PAM sites on the mutant allele, is predicted to excise the promotor region, transcription start site, and CAG repeat from the mutant allele, leading to prevention of the production of mutant HTT._

_Courtesy: Jong-Min Lee_

INSIGHTS OF THE YEAR

NUCLEAR PORE COMPLEX IS DISRUPTED BY mHTT
Nominee (Basic science)
By Jonathan Grima, PhD

HD is caused by an expanded CAG repeat in the huntingtin gene (HTT). The mechanisms by which mHTT causes disease are unclear. Nucleocytoplasmic transport – the trafficking of macromolecules between the nucleus and cytoplasm – is tightly regulated by nuclear pore complexes (NPCs) made up of nucleoporins (NUPs). Previous studies offered clues that mHTT may disrupt nucleocytoplasmic transport, and a mutation of an NUP can cause HD-like pathology. Therefore, we evaluated the NPC and nucleocytoplasmic transport in multiple models of HD, including mouse and fly models, neurons transfected with mHTT, HD iPSC-derived neurons, and human HD brain regions.

These studies revealed severe mislocalization and aggregation of NUPs and defective nucleocytoplasmic transport. HD repeat – associated non-ATG (RAN) translation proteins also disrupted nucleocytoplasmic transport. Additionally, overexpression of NUPs and treatment with drugs that prevent aberrant NUP biology also mitigated this transport defect and neurotoxicity, providing future novel therapy targets.

Nuclear transport protein RanGAP1 (red) clumps up with mutant huntingtin protein (green) in neurons.

Courtesy: Jonathan Grima

INSIGHTS OF THE YEAR

AN ENHANCED MOUSE MODEL OF HD
Nominee (Basic science)
By Amber Southwell, PhD

Considering the vast majority of Huntington disease (HD) patients are heterozygous, heterozygous HD mice are highly relevant for research. The zQ175 Knock-in (KI) model of HD arose as a natural expansion from Q140 KI mice, and, unlike its predecessor, exhibited substantial HD-like phenotypes when heterozygous. In an effort to increase severity of disease, we backcrossed zQ175 mice to FVB (Q175F), a strain particularly susceptible to mutant huntingtin (HTT)-induced neurodegeneration.

Interestingly, this introduced sudden, early death by fatal seizures. Seizures are not a feature of adult onset HD, but they are seen in FVB mice. The Q175 KI exacerbated these seizures from mild to fatal. HTT protects against FVB seizures, and the neomycin (neo) cassette used to generate the Q140 KI can reduce gene expression. Thus, we deleted the neo cassette generating Q175FDN mice. Q175FDN mice have about two-fold more KI Htt than Q175F mice and do not have fatal seizures, demonstrating that HD KI mice with an intact neo cassette can model HTT deficiency rather than HD. Q175FDN mice also display reduced survival, but death is preceded by an extended decline of body weight, gait, and activity. Moreover, Q175FDN mice display robust, early onset HD-like phenotypes, several of which are truly dominant, making them a superior preclinical model.


A LONGITUDINAL ANALYSIS OF THE INTERMEDIATE ALLELES CARRIERS’ CLINICAL MANIFESTATIONS IN HD
Nominee (Clinical research)
By Esther Cubo, MD, PhD

After the characterization of the gene mutation, a distinct category of HD genes named intermediate alleles (IAs) has been recognized. IAs have been consensually defined as those with a CAG repeat size between 27 and 35, a range just below the disease threshold of 36 repeats. It has been shown that IAs confer genetic instability, and might broaden into the disease range within one generation through the paternal line and, exceptionally, the maternal line. The prevalence of IAs varies between 1.5–5.8% in both the general population and HD families, showing no significant differences between them, and with similar haplotype distributions.

Continued, page 33
Although IAs are not considered to be associated with the HD phenotype, there has been emerging evidence that some individuals with IAs might develop HD-like clinical and neuropathological manifestations. Our study was designed to establish the clinical manifestations of IA carriers for a prospective European HD registry.

We assessed a cohort of participants at risk with <36 CAG repeats of the HTT gene. Outcome measures were the UHDRS motor, cognitive, and behavior domains; total functional capacity (TFC); and quality of life (SF-36). This cohort was subdivided into IA carriers (27–35 CAG) and controls (<27 CAG), and younger versus older participants. We have analyzed and compared the clinical manifestations in elderly versus young patients, and IAs versus non-expanded controls in terms of UHDRS scores, and by subdividing the UHDRS into chorea, bradykinesia, dystonia, and gait domains. In addition, we analyzed the association of several environmental factors, treatments, and sociodemographics with clinical manifestations.

In this study, 12,190 participants of the European HD registry – 657 (5.38%) with <36 CAG repeats, 76 IAs (11.56%), and 581 controls (88.44%) – were included. After correcting for multiple comparisons, at baseline, IA participants were similar to controls in terms of age, quality of life, TFC, total UHDRS motor, behavior and cognitive scores, use of antidopaminergic drugs, body mass index, education background, tobacco and alcohol exposure, residence, and marital and working status.

However, older participants with IAs had higher chorea scores compared to controls (p = 0.001). Linear regression analysis showed that aging was the most contributing factor to increased UHDRS motor scores (p = 0.002). On the other hand, one-year follow-up data analysis showed that IA carrier participants had greater cognitive decline compared to controls (p = 0.002).

The results of this study highlight the need for longitudinal data of IA clinical manifestations, which are classically underrepresented in observational registries. Based on these results and prior observations of IA-associated late-onset HD, the allele ranges might warrant further adjustment so that the category of reduced penetrance extends to include shorter expansion lengths stretching into the IA range. These results have important implications for clinical practice and genetic counseling for those individuals who are IA carriers.

INSIGHTS OF THE YEAR

THE CREST-E STUDY FOR HD

Nominee (Clinical research)

By Steven Hersch, MD, PhD

Our manuscript is the primary report for the CREST-E study (Creatine Safety, Tolerability and Efficacy), which was sponsored by the NIH and the FDA, and conducted by the Huntington Study Group in North America and Australasia. Creatine was previously demonstrated to be neuroprotective in animal models, and to slow progressive brain atrophy in presymptomatic HD patients. CREST-E was designed to assess the efficacy of high-dose creatine (up to 40 grams daily) in early symptomatic HD patients for slowing progressive functional decline.

The study opened for enrollment in 2009, and included more than 550 subjects by the time clinical activity ended in 2014 following a preplanned interim analysis that suggested that the study was very unlikely to show overall benefit of creatine. Lack of benefit was confirmed in the primary analysis, although preplanned secondary analyses raised the possibility of unexpected differential effects in males and females.

The legacy of CREST-E includes the unique clinical experience with high-dose and long-term creatine administration; a large safety database for a widely used supplement; longitudinal outcomes data for early HD that will be applicable to future clinical trials; identification of possible interactions between gender, HD, and creatine; and extensive biological and neuroimaging biomarker data that continue to be analyzed.


SYMPTOM HETEROGENEITY CORRELATES WITH NEURONAL DEGENERATION

Nominee (Biomarkers and imaging)

By Nasim Mehrabi, PhD

This study completed the overview of cortical cell degeneration in HD by specifically focusing on loss of inhibitory interneurons in three functionally distinct areas of the human brain (primary sensory cortex, superior frontal cortex, and superior parietal cortex) in HD patients compared to neurologically normal individuals. Based on their predominant symptom, the HD patients were grouped into three different symptom groups (‘motor’, ‘mood’, and ‘mixed’). The results of this study demonstrated a heterogeneous loss of interneurons in these cortical areas, which correlated with the variable symptom profiles of the HD cases. For example, we observed a significant loss of interneurons in the primary sensory cortex of the ‘motor’ cases, but not in the ‘mood’ cases. We are now extending our research on differential cell loss in HD to other parts of the ‘motor circuitry’, such as the thalamus and cerebellum.


Continued, page 36
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