Antisense Oligonucleotides Enter Clinical Trials
Meet the team behind IONIS-HTT_{Rx}, the antisense oligonucleotide therapy with the potential to transform HD treatment

Ionis Pharmaceuticals' HTT_{Rx} development team, from left to right: Roger Lane, Curt Mazur, Holly Kordasiewicz, Erika Paz, Kristin Balogh, Anne Smith, Tom Zanardi, Dan Norris, Eric Swayze, Tiffany Baumann, Kristina Bowyer, Gene Hung, Jose Mendoza, Frank Bennett (Not pictured: Gina Mc Mullen, Ed Wancewicz). Read more about IONIS-HTT_{Rx}, in our interview with Drs. Lane, Kordasiewicz, Smith, and Bennett, and learn about Ionis' partnership with Roche Pharmaceuticals from Dr. Scott Schoel, beginning on page 10.

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Editor’s Letter
Welcome to the thirteenth edition of HD Insights, timed for release at the beginning of the 11th Annual CHDI HD Therapeutics Conference. We are pleased to continue our mission to promote, disseminate, and facilitate research in HD, and grateful to our subscribers, our editorial board, and our sponsors for their generous support of the periodical.

For our first edition of 2016, HD Insights introduces a new layout and a renewed emphasis on bringing you the latest in preclinical and clinical HD research. We profile Ionis Pharmaceuticals’ antisense oligonucleotide IONIS-HTTRx, currently in a Phase I/IIa trial. We interview the team of scientists and physicians responsible for the drug’s development, and explore Ionis’ partnership with Roche Pharmaceuticals in an interview with Dr. Scott Schobel. We highlight a selection of highly cited original research articles from 2014, including new insights into the role of astrocytes in HD pathophysiology, a mutation commonly responsible for HD phenocopy syndromes, and the importance of autophagosome abnormalities in HD. Dr. Alpar Lazar describes his work with Dr. Roger Barker, characterizing the emergence of sleep disturbances in prodromal HD patients. Our colleagues at the Journal of Huntington’s Disease continue to advance HD research through excellent scholarship. We selected one article from their recent edition and invited the authors to share their work on the new Genetic Modifiers of Motor Onset Age database. Dr. Lise Munsie reprises her Research Round-Up, and joins our editorial team as a scientific content reviewer. Then, for those who were unable to attend HSG 2015, Shoulson Scholar Mr. George McNally summarizes the highlights of that meeting. Finally, we continue to provide an up-to-date status report on HD clinical trials and the development of novel therapies in the pipeline.

HD Insights relies on the support of those firms dedicated to advancing HD therapeutics to continue to bring you the latest on HD research. If you would like to become a supporter, or to submit an article, comment, or suggestion, please send us an email at editor@hdinsights.org. For a free electronic subscription, please send an email to subscribe@hdinsights.org. Thank you for your continued support.

-- Ray Dorsey, Editor in Chief

HD Insights™

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HD Insights™
Thanks Teva for its generous support

Teva CNS is committed to continued research and development of its product portfolio and to the development of medicines aimed at meeting the specific needs of the patient communities it serves. Teva’s legacy in CNS is grounded in its commitment to ongoing collaboration with academia, medical institutions and patient advocacy groups to find innovative solutions for patients who live with chronic and debilitating diseases.
Highly Cited HD Research

In this edition of HD Insights, we take a look at some of the most impactful HD research articles of 2014. We searched Thomson Reuters’ “Web of Science” service in December 2015 and identified five papers as the most highly cited original research articles on HD published in 2014. Reviews and book chapters were excluded, as well as articles pertaining only tangentially to HD. We contacted the corresponding authors and requested articles on their work, and received the following responses. These pieces highlight several ongoing areas of exploration in clinical and basic science research in HD, and suggest new frontiers for clinical practice and potential therapeutic targets.

Astrocytes in HD

By: Baljit S. Khakh, PhD and Michael V. Sofroniew, MD, PhD

Original Article: Astrocyte Kir4.1 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice (cited 45 times as of 2/8/2016)

Understanding the mechanisms that lead to neurological and psychiatric disorders remains a major goal of neuroscience. Considerable advances have been made in understanding the roles of neurons in brain function and disease. In contrast, astrocytes, which represent about half the cells in the human brain, have been less thoroughly investigated. Recent studies show that astrocytes are essential for the normal activity of neural circuits, but the possibility that astrocyte dysfunction may contribute to, or perhaps even drive disease mechanisms, remains incompletely explored. Broad analyses show that recent neuroscience drug development based on our improved understanding of neurons has resulted in many failures, suggesting that investigating astrocytes in diseases such as HD may be beneficial.

Evidence suggests that astrocytes may be involved in HD. Brains from HD patients and from mouse models of HD show accumulation of mutant huntingtin protein (mHTT) in striatal astrocytes, which contributes to age-dependent HD-like pathology (see Figure, part a). However, it remains unknown whether and how astrocytes contribute to HD pathology or disease mechanisms. We therefore used HD mouse models R6/2 and Q175 to assess astrocyte contributions to HD pathophysiology. We found that concomitant with the onset of HD symptoms, significantly more astrocytes had mHTT inclusions and significant reductions in important functional proteins (including the potassium channel Kir4.1) without major phenotypic changes associated with astrocyte reactivity. These findings suggest that mHTT is associated with early disruption of the expression of important astrocyte functional proteins that alters astrocyte function (see Figure, part b) without triggering astrogliosis. Congruent with other studies of mouse models and human HD, we found progressively increasing astrogliosis at later disease stages that exhibit overt neurodegeneration.

Based on past studies, the loss of Kir4.1 currents in striatal astrocytes predicts reduced spatial K+ buffering, which, in the simplest interpretation, would lead to higher ambient K+ levels. We found that the extracellular K+ concentration was doubled in R6/2 mice, prompting us to explore the impact of increased K+ on the properties of striatal medium spiny neurons (MSNs).

Figure: Striatal astrocytes from R6/2 HD-model mice display nuclear mHTT inclusions and lower membrane conductances.

a. Representative immunofluorescence images showing that GFAP, S100, GS and Aldh1L1-labeled astrocytes (green) contain nuclear mHTT inclusions. Nuclei were labeled blue with DAPI, and mHTT is shown in white.

b. Representative traces of whole-cell voltage-clamp recordings from striatal astrocytes from WT and R6/2 mice at P60. The current waveforms show the response to a step depolarization, revealing clear differences in membrane conductance between WT and R6/2 astrocytes.
Highly cited: Astrocytes, cont…

To our surprise, we found that exposing wild-type mice to equivalent increases in K\(^+\) reproduced the elevated excitability features of MSNs described in a variety of HD mouse models. We then delivered Kir4.1-GFP channels to striatal astrocytes in HD-model mice by using adeno-associated viruses, and found that one motor symptom (stride length and width) was attenuated by this approach. We also found that MSN membrane properties were partly recovered by astrocyte expression of Kir4.1-GFP in R6/2 mice, strongly supporting the notion that some HD-like phenotypes derive from neuronal dysfunction that itself derives, in part, from astrocyte disturbances.

To date, research efforts have been focused almost exclusively on identifying neuronal cell-autonomous mechanisms to account for changes in MSN properties in HD models. Our findings provide evidence that key aspects of altered MSN excitability in HD are secondary to disturbance of astrocyte maintenance of extracellular K\(^+\). The precise cellular functions of HTT are not known, and it is not clear how mHTT impacts Kir4.1. Interestingly, transcriptome profiling of astrocyte responses to inflammatory mediators revealed HTT at the center of one of the top three most significantly altered gene networks. This intriguing finding warrants further exploration.

Overall, our findings show that aspects of altered neuronal excitability associated with HD may be secondary to changes in astrocyte function, thereby revealing striatal astrocytes as potential therapeutic targets for drug development. Interestingly, astrocytes display a distinctly different library of molecules compared to neurons. Further studies are warranted to determine whether astrocyte-specific molecular processes and pathways can be exploited to produce desirable effects, either directly or indirectly, on neural circuits in brain disease.

This study was supported by the CHDI Foundation (BSK, MVS) and partly by the NIH (NS060677, MH104069 to BSK).

C9orf72 expansions and HD phenocopies

By: Carolin A. M. Koriath, MD, Davina J. Hensman Moss, BA, MBBS, Sarah J. Tabrizi, MBChB, PhD

Original Article: C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies (cited 28 times as of 2/8/2016)

HD is the most common genetically determined neurodegenerative disease. This autosomal dominant condition, caused by a CAG repeat expansion in the huntingtin gene, is typically defined by a triad of movement, cognitive, and psychiatric symptoms. However, while chorea is common and usually accompanied by cognitive decline, patients can also suffer from akinetic-rigid syndromes, dystonia, ataxia, as well as solely cognitive or psychiatric symptoms, which can complicate clinical diagnosis.

Approximately 1% of those with suspected HD do not carry the CAG expansion in the huntingtin gene. These patients suffer from so-called HD phenocopy syndromes; differential diagnoses include HD-like syndromes (HDL), 1, 2, and 3, spino-cerebellar atrophy 17, and dentatorubral-pallidolusyan atrophy. An intronic hexanucleotide repeat expansion in the C9orf72 gene was first described in 2011 as the most frequent cause of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). The expansion has since been identified in additional syndromes, such as cerebellar ataxia.

In our study, 514 patients, who had been referred for HD testing by an experienced specialist and tested negative for the HTT CAG expansion, were examined for the C9orf72 expansion to establish whether it should be included in the routine genetic assessment for this patient cohort. Ten patients (1.95%, 95% confidence interval) were found to carry the C9orf72 GGGGCC repeat expansion, as well as the associated risk allele (rs3849942 A), either homo- or heterozygously. The size of the expansion did not differ significantly from other C9orf72-mediated syndromes or between those with and without chorea/dystonia. At almost 2%, this is the most frequently identified cause of HD phenocopy syndromes in a United Kingdom cohort. While 70% of the C9orf72 positive cases had a family history of neurodegenerative disease, 30% did not, leaving sporadic cases a possibility. Furthermore, while the reported age of onset of C9orf72-caused disease is approximately 57 years of age, in this cohort it was 42.7 years, broadening not only the phenotype, but also the demographic in which this diagnosis should be considered.

True HD and HD phenocopy syndromes can present with a spectrum of cognitive, psychiatric, and movement symptoms, and without an obvious family history. C9orf72-caused disease can also present with a very heterogeneous range of symptoms from FTLD/ALS to parkinsonism. We therefore propose that genetic testing for C9orf72 should be included in the clinical algorithm for the HD phenocopy work-up, following the test for the HTT expansion, and preceding the test for spino-cerebellar ataxia 17.
Autophagosomes in HD

By: Yvette C. Wong, PhD and Erika L. F. Holzbaur, PhD

Original Article: The regulation of autophagosome dynamics by huntingtin and HAP1 is disrupted by expression of mutant huntingtin, leading to defective cargo degradation, (cited 30 times as of 2/8/2016)

Autophagy is an essential cellular pathway for degrading defective organelles and aggregated proteins, mediated by the formation of an autophagosome around its cargo and subsequent cargo degradation via lysosomal fusion. In neurons, autophagosomes form constitutively at the axon tip and undergo robust retrograde axonal transport towards the cell body, during which they mature and gradually acidify via fusion with lysosomes along the axon. This retrograde transport is regulated by the retrograde motor protein dynein, but additional motor adaptors regulating autophagosome dynamics and maturation along the axon also are necessary to maintain this pathway.

Autophagy has previously been implicated in HD, as both soluble and aggregated mutant huntingtin (polyQ-Htt) are predominantly degraded via the autophagy pathway.
Highly cited: Autophagosome, cont…

Huntingtin (Htt) and its adaptor protein huntingtin-associated protein-1 (HAP1) can act to scaffold motor proteins and regulate vesicular microtubule-based dynamics, as Htt binds dynein and HAP1 binds both the anterograde motor protein kinesin and the retrograde motor adaptor dynactin. We identified Htt and HAP1 as novel regulators of autophagosome axonal transport. Using live cell imaging of primary neurons from GFP-LC3 transgenic mice, we found that depleting either Htt or HAP1 in neurons resulted in decreased retrograde motility of autophagosomes and increased the stationary population of autophagosomes along the axon. In addition, Htt and HAP1 copurified and colocalized with neuronal autophagosomes along the axon. Interestingly, expression of Htt unable to bind dynein or HAP1 similarly disrupted autophagosome transport, suggesting that Htt forms a complex with both HAP1 and dynein to mediate the regulation of processive autophagosome transport in neurons.

We next examined whether autophagosome axonal transport might be disrupted by polyQ-Htt in HD and contribute to autophagy-related defects. We found that expression of polyQ-Htt in either primary neurons or striatal cells from HD homozygous knock-in mice was sufficient to disrupt the axonal transport of autophagosomes, leading to more stationary autophagosomes. Interestingly, we found that both wild-type and polyQ-Htt preferentially interacted with the neuronal-specific dynein isoform (DIC1A), rather than the ubiquitously expressed dynein isoform (DIC2C), suggesting that dynein-based transport of autophagosomes may be selectively impaired in neurons and contribute to the neuronal-selective degeneration observed in HD.

Finally, we investigated whether misregulation of autophagosome axonal transport might disrupt either upstream or downstream steps in the autophagy pathway. We found that Htt was not required for constitutive autophagosome formation at the axon tip, nor for cargo loading of ubiquitinated proteins or mitochondria into these constitutively-formed autophagosomes. However, defective autophagosome transport observed in both Htt-depleted neurons and polyQ-Htt-expressing neurons led to inefficient downstream degradation of autophagic cargo, such as engulfed mitochondrial fragments. Together, these results suggest that misregulation of the active transport of autophagosomes along the axon in HD may contribute to inefficient autophagosome maturation and cargo degradation, potentially due to inhibition of autophagosome-lysosome fusion along the axon (see Figure). The resulting defective clearance of cargo, including polyQ-Htt oligomers and aggregates, and dysfunctional mitochondria might further contribute to their neuronal accumulation, thus accelerating the progression towards cellular death in HD.

Our lab has subsequently shown that JNK-interacting protein-1 (JIP-1) also regulates autophagosome axonal transport, suggesting that autophagosome dynamics in neurons may be tightly regulated by several protein adaptors. We have also recently identified optineurin, a huntingtin interacting protein, as a novel autophagy receptor for damaged mitochondria in mitophagy. The latter observation is of particular interest given the link between mitochondrial dysfunction and HD pathogenesis, as well as the proposal that Htt functions as a scaffold for selective macroautophagy. Together, these observations suggest that further study of the mechanisms that regulate autophagosome dynamics in neurons will advance our understanding of how this essential degradative pathway is disrupted in HD.

Figure: Model of Htt’s regulation of autophagosome axonal transport in neurons.

Htt and HAP1 normally regulate the motor activity of microtubule motors dynein, dynactin, and kinesin on autophagosomes, via Htt’s interactions with HAP1 and neuronal-specific dynein isoforms, to drive the robust retrograde transport of autophagosomes back to the cell body in neurons along microtubules (MT). Retrograde autophagosome transport is necessary for efficient fusion with lysosomes along the axon for degradation of autophagic cargo, such as mitochondria. In HD, pathogenic polyQ-Htt disrupts the Htt/HAP1 motor protein complex on autophagosomes, via altered polyQ-Htt/HAP1 association. This misregulation of motors leads to bidirectional/stationary autophagosome dynamics in HD neurons, thereby disrupting the retrograde transport of autophagosomes necessary for efficient degradation of dysfunctional mitochondria and polyQ-Htt. 

\(^3\)Wong YC, Holzbaur EL. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc Natl Acad Sci U S A. 2014;111(42):E4439-4448.
Research Round-Up

By: Lise Munsie, PhD

In the lab...

The Ranum laboratory published their discovery of Repeat Associated Non-ATG (RAN) translation in HD in Neuron. This was the first demonstration of RAN translation in a disease where the causative triplet repeat expansion occurs in the coding region. They showed that poly-Ala, poly-Cys, poly-Leu and poly-Ser proteins are translated in neurons that express huntingtin (Htt) mini-genes with disease-causing CAG expansion lengths. Accumulation of these proteins increases with expansion size. They found RAN-translation proteins in brain regions affected by disease in post-mortem HD brain tissue, with abundance and protein specificity correlating with disease severity.

Bowles and colleagues used the immortalized striatal cell line derived from Q111 mice to examine phosphorylation of Htt by stimulating the epidermal growth factor (EGF) pathway. They found alterations in MEK and AKT phosphorylation of wild-type compared to mutant Htt (mHtt) after EGF stimulation, leading to altered nuclear localization and altered transcription of a subset of genes. Inhibiting these kinases in the presence of EGF affects Htt localization, especially in the mutant cell line. The authors hypothesize it may be possible to attenuate these changes using MEK and AKT inhibitors. Kinase inhibitors may correct Htt localization, attenuating pathology associated with altered transcription.

Whether over-expression or activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) is neuroprotective or toxic in HD remains controversial. Using nematode models and murine striatal neuron models, a recent report showed that AMPK over-expression has positive outcomes in models.3 Using fluorescence resonance energy transfer (FRET) techniques, Vázquez-Manrique and colleagues showed a decrease in soluble mHtt (FRET) techniques, Vázquez-Manrique and colleagues showed a decrease in soluble mHtt expression has positive outcomes in models. Their findings suggest that AMPK activation, may be useful as a treatment for aspects of HD pathology, correlating with disease severity.

Finding heterozygous polymorphisms that exist in cis with the mHtt allele is essential to development of allele-specific silencing therapies. A recent report in Molecular Therapy prioritized target selection by examining diverse HD patient populations across Canada, France, Sweden, and Italy.3 The group defined three target haplotypes, A1, A2, and A3, that could be targeted by allele-specific antisense oligonucleotides (ASOs) to treat the 80% of patients who have one of these haplotypes. The group demonstrated that ASOs against polymorphisms in the A1 haplotypes selectively inhibit mHtt in a potent and specific manner.


In the pipeline...

Using an unbiased screen for huntingtin (HTT)-interacting transcription factors, the La Spada group identified peroxisome proliferator-activated receptor delta (PPAR-δ) as a novel HTT interactor.1 An alteration in PPAR-δ transactivation in a polyglutamine-dependent manner leads to mitochondrial dysfunction, enhancing cell death. When injected into the central nervous system of mice, a dominant-negative PPAR construct produced motor dysfunction, neurodegeneration, and mitochondrial abnormalities consistent with HD. Pharmacologically inducing PPAR-δ activity ameliorated HD-induced dysfunction and cell death in mouse and stem cell striatal cell models. The authors propose that KD3010, a compound which enhances PPAR-δ activation, may be useful as a treatment for aspects of HD pathology.

The Messer laboratory performed studies examining the safety of active vaccination as a treatment for HD in mice.2 They assessed the safety and immunogenicity of 11 immunization protocols, including different combinations of peptide, protein and DNA vaccines. They found that a combination of three non-overlapping Htt exon-1 peptides resulted in the greatest immunogenicity, but also led to transcriptional dysregulation of immune-related genes. This treatment strategy may necessitate adjuvant therapies aimed at restoring immune controls.

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1Ocicer AS, Pineda VV, Tsunemi T, et al. PPAR-[delta] is repressed in Huntington’s disease, is required for normal neuronal function and can be targeted therapeutically. Nat Med. 2015 Dec 7; doi: 10.1038/nm.4003. [Epub ahead of print].
2Ramsingh AI, Manley K, Rong Y, et al. Pharmacologically inducing PPAR-δ compound which enhances PPAR-δ transactivation in a polyglutamine-dependent manner leads to mitochondrial dysfunction, enhancing cell death. When injected into the central nervous system of mice, a dominant-negative PPAR construct produced motor dysfunction, neurodegeneration, and mitochondrial abnormalities consistent with HD. Pharmacologically inducing PPAR-δ activity ameliorated HD-induced dysfunction and cell death in mouse and stem cell striatal cell models. The authors propose that KD3010, a compound which enhances PPAR-δ activation, may be useful as a treatment for aspects of HD pathology.
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In stem cells...

The Ellerby group created isogenic induced pluripotent stem cell (iPSC) lines from HD patients’ cells.1 In a recent Stem Cell report, the group performed transcriptome analysis on the HD and the isogenic lines. They found a 10-fold increase in differentially expressed genes in the HD line compared to the isogenic line after differentiation to neural stem cells, compared to differentially expressed genes prior to differentiation.

The group showed that transforming growth factor (TGF-β) and netrin-1 signaling pathways are differentially regulated at the neural stem cell stage, and can be modulated to rescue HD-related phenotypes in both the in vitro stem cell model and an in vivo mouse model.

Another recent report utilized iPSCs derived from the YAC128 mouse model, an adult-onset HD patient, and a juvenile-onset HD patient, to investigate pathways involved in HD pathogenesis.2 Multiple signaling pathways were altered in these lines, including the MAPK/ERK pathways, and p53 signaling. Other pathways (such as TGF-β) were not affected in the undifferentiated cells. This paper indicates that some, but not all, pathways are affected early and, possibly, peripherally in HD.

Stimulation of the A2A adenosine receptor (A2A,R) in cell culture models of HD has positive anti-apoptotic outcomes. A paper published in Human Molecular Genetics used iPSCs derived from HD and control patients differentiated into DARPP32 GABAergic neurons, and examined how stimulating A2A,R differentially effects the two cell lines.3 Treating the cells with hydrogen peroxide introduced oxidative stress and caused double-stranded DNA breaks, with more double-stranded breaks in the HD-derived neurons. A2A,R agonists ameliorated this phenotype in the differentiated neurons through PKA activation. The authors suggest the use of this platform for drug screening.

2Szalachie WJ, Switowski PM, Krzyzowski WJ, et al. Huntington disease iPSCs show early molecular changes in intracellular pathways are affected early and, possibly, peripherally in HD.
# Clinical Trials Status Report

<table>
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<th>SPONSOR</th>
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<th>PHASE</th>
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<td>SRX246</td>
<td>I/II</td>
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<td>Randomized, placebo-controlled, double-blind, 12 week, 3-arm dose escalation study of SRX246 in individuals with irritability and early symptomatic HD</td>
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<td>NCT02263430</td>
<td>Pins Stimulator System</td>
<td>I</td>
<td>Jia Fumin, PhD 010-59361265 <a href="mailto:pins_medical@163.com">pins_medical@163.com</a></td>
<td>Randomized, double-blind, parallel-group, sham-controlled trial of Globus Pallidus Deep Brain Stimulation in individuals with HD</td>
<td>1 year</td>
<td>Beijing, China</td>
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<td>Charité University</td>
<td>ETON-Study</td>
<td>Epigallocatechin galate</td>
<td>II</td>
<td>Josef Priller, MD +49 (0)30 450 617209</td>
<td>Randomized, double-blind study testing the efficacy and tolerability of (2)-epigallocatechin-3-galate (EGCG) in changing cognitive function in HD patients</td>
<td>1 year</td>
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<td>Action-HD</td>
<td>Bupropion</td>
<td>II</td>
<td>Josef Priller, MD +49 (0)30 450 617209</td>
<td>Randomized, double-blind study testing the efficacy and tolerability of bupropion in changing apathy in patients with HD</td>
<td>10 weeks</td>
<td>3 total - Germany</td>
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<td>Heinrich-Heine University</td>
<td>HD-DBS</td>
<td>ACTIVA® PC neuro-stimulator (Model 37601)</td>
<td>II</td>
<td>Susanne Harnisch +49 6421 2866555 <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>
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<td>TRIHEP3</td>
<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>BN82451B</td>
<td>II</td>
<td>Bruno Padrazzi, MD <a href="mailto:clinical.trials@ipsen.com">clinical.trials@ipsen.com</a></td>
<td>Dose escalation, proof-of-concept study to investigate the safety and tolerability and the pharmacokinetic and the pharmacodynamic properties of twice daily BN82451B for four weeks in male patients with HD</td>
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<td>Omeros Corporation</td>
<td>NCT02074410</td>
<td>OMS643762</td>
<td>II</td>
<td>Albert Yu, MD 206-676-5000</td>
<td>Randomized, double-blind, placebo-controlled, sequential cohort study to evaluate safety and efficacy of OMS643762 in subjects with HD</td>
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<td>NCT01806896</td>
<td>PF-0254920</td>
<td>II</td>
<td>Pfizer CT.gov Call Center, 800-718-1021</td>
<td>Randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and brain cortico-striatal function of 2 doses of PF-0254920 in individuals with early HD</td>
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<td>PF-0254920</td>
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<td>Randomized, double-blind, placebo-controlled proof of concept study of the efficacy and safety of PF-0254920 in HD</td>
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<td>Teva Pharmaceutical Industries</td>
<td>PRIDE-HD</td>
<td>Pridopidine</td>
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<td>Katie Blatt, Teva 610-727-3297</td>
<td>Randomized, double-blind, placebo-controlled study of safety and efficacy of pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg BD versus placebo for symptomatic treatment in patients with HD</td>
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<td>Pridopidine</td>
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<td>Open-label, single-group assignment study to assess the long-term safety of 45 mg of pridopidine in HD participants</td>
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<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, 1.0 and 1.5 mg/day) in HD</td>
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To update or add a clinical trial, please e-mail editor@hdinsights.org. Sources: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [apps.who.int/trialsearch](http://apps.who.int/trialsearch/)
Clinical Trials, cont...

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<td>VX15/2503</td>
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<td>Robert Fekete, MD (914) 594-4293 <a href="mailto:robert_fekete@nymc.edu">robert_fekete@nymc.edu</a></td>
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To update or add a clinical trial, please e-mail editor@hdinsights.org. Sources: www.clinicaltrials.gov and apps.who.int/trialsearch

Clinical Development of HD Therapeutics as of January 2016
Ionis Pharmaceuticals has been developing antisense-based therapies for a variety of conditions since 1989. The company has developed an antisense oligonucleotide (ASO) that targets huntingtin messenger RNA. In July 2015, they began a first-in-man, Phase I/IIa trial on IONIS-HTTRx in early manifest HD patients to evaluate the safety, tolerability, and pharmacokinetics of intrathecal administration of the drug. HD Insights sat down with four of the individuals involved in the development of HTTRx to find out more. The following is an edited transcript of the conversation.

HD INSIGHTS: Dr. Kordasiewicz, tell us about the rationale for ASOs in HD and what you learned in animal models.

HOLLY KORDASIEWICZ: It is pretty straightforward. The idea is to go after the source of the disease, which we know is mutant huntingtin protein (mHTT). We can use ASOs to selectively lower huntingtin RNA, which reduces the total amount of huntingtin protein (HTT), including mHTT. By lowering mHTT in patients with HD, we can hopefully stop the course of the disease.

With the work that we have done in animal models, we lower mHTT using ASOs, and some aspects of the animal disease—which are similar to what we see in HD patients—are reversed, and the animals begin to do better in a number of different ways.

These animal studies have been a collaborative effort with the group here at Ionis, Dr. Don Cleveland’s laboratory at UCSD, CHDI and also Genzyme, particularly Dr. Lisa Stanek, who was responsible for the work done in the YAC128 mice. We have looked at the R6/2 mouse, the YAC128 mouse, as well as the BACHD mouse. All of those mice express either fragments or the whole human mutant Huntington gene (mHTT).

HD INSIGHTS: How did you deliver the drug in the mouse models and how might that differ in humans?

KORDASIEWICZ: In human patients we deliver the drug intrathecally, directly into the cerebrospinal fluid (CSF), so that the drug can access the full brain. It is very difficult to do intrathecal delivery in mice because they are so small, so we use intraventricular delivery instead. We go into the mouse right lateral ventricle, which is just a little bit of a larger space so it is easier for us to access.

HD INSIGHTS: Two of the concerns with this approach are the potential need to give repeated injections and the possible need for allele selectivity. Could you comment on those concerns?

KORDASIEWICZ: When we started this approach, we did not realize how long ASOs and their effects last once you introduce them into the brain. About two weeks after we deliver the drug, we have maximum RNA reductions, and then those levels start to come back to normal. In mice, it takes about 12 to 16 weeks for levels to return to normal after a single injection, so in the human Phase I study we are trying monthly dosing. Eventually we could be looking at less frequent dosing, based on the characteristics of the drug.

ROGER LANE: The monthly dosing in the initial Phase I study is just to get concentrations up during the three-month dosing period.

KORDASIEWICZ: We spent a lot of time looking at allele selectivity. We did a collaboration, initiated by Dr. Frank Bennett, with Dr. Michael Hayden’s group to look at allele-selective approaches. The chemists here also worked with Dr. David Corey’s group at UT Southwestern, looking at using different antisense mechanisms to achieve allele selectivity. The work that I did in the mouse models examined the consequences of lowering only mutant human HTT, or both mutant human HTT and wild-type mouse Htt. In the mice, we found that we did not attenuate our benefits by lowering both the mutant human and the wild-type mouse protein; it was very similar to lowering just mutant human huntingtin alone. Because of that, we have gone forward with the non-allele-selective approach, but we have spent a lot of time working to find potential allele-selective approaches.

HD INSIGHTS: Did any safety issues emerge in your animal models?
Meet the Company, cont...

KORDASIEWICZ: We looked at a number of endpoints and we followed animals for a year after dosing. We did not see any safety issues either in the wild-type mice or non-human primates resulting from lowering wild-type huntingtin.

HD INSIGHTS: Dr. Smith and Dr. Lane, what led you to determine that the drug was ready for study in humans?

LANE: Well, if you have a very good mechanistic rationale for a drug, support from good animal models of the disease, confidence that it can distribute to its target tissues and engage its target, and you have a means of measuring that target engagement, then you have a rational basis for a clinical development program.

HD INSIGHTS: Can you tell us about your Phase I/IIa clinical study?

ANNE SMITH: We can discuss it in general, but since it is ongoing, we will not discuss any data that is accruing. It is a small study, intending to enroll about 36 patients at sites in Canada, the UK, and Germany. We began dosing midyear, and the study is going well. Our sites are run by investigators at institutions who have been involved in helping us shape this program for many years. They are thought leaders in the area.

LANE: It is a multiple ascending dose study where patients are being treated with four intrathecal injections over a three-month period, then followed up for four months after that.

SMITH: Drug development is a long process. This is the first trial in humans, so we have planned several stops along the way where we have an independent group look at safety and help guide us if any changes are needed. So far, the study is proceeding according to plan.

HD INSIGHTS: From your clinicaltrials.gov listing, it seems that you are focusing on individuals with early manifest HD. Can you explain your rationale for that, and discuss the decision not to look at individuals with, for example, prodromal HD?

SMITH: Yes, we are indeed limiting participation in the study to early manifest patients. In later manifest HD patients, we had concerns about ability to consent. In prodromal patients, it would be a different sort of clinical development program. It is an area that we are very interested in going into, but if you are looking at patients who do not yet have motor symptoms, it changes the clinical endpoints that you would use in that study.

C. FRANK BENNETT: In this population, we felt the risk-benefit ratio was appropriate. We were concerned about enrolling individuals too early in the course of the disease in a first-in-man study. Without any experience with the drug in humans, we felt that the risk was too high for those patients. We identified individuals with early manifest HD as the ideal patient population.

HD INSIGHTS: What clinical endpoints are you looking at in this study?

SMITH: This first study is a safety and tolerability study, so the primary endpoints are a battery of safety endpoints. We are looking at a number of exploratory markers of disease in hopes of seeing a signal, but this is a short study in a small number of patients and it is certainly not designed, nor powered, to detect any changes in those types of endpoints.

LANE: We have a secondary endpoint to make sure that we are achieving the concentrations of ASO in the CSF that we are expecting, and then we are looking at target engagement – whether we reduce mHTT in the CSF. We have a variety of other markers we are using to look at whether we are having a biological effect on the disease, including other CSF markers, EEG, neuroimaging, etc. We have some clinical measures, which we do not expect to be impacted in such a short-term study, but which we want to monitor for any deterioration. There is just a tiny chance that they could show something positive as well.

SMITH: These markers may also be useful in planning later studies if we see any small changes in this preliminary study.

HD INSIGHTS: I believe this will be the first clinical trial that investigates CSF markers. You mentioned that you are looking at mHTT in CSF. Can you talk about the reliability of CSF markers in HD and what you expect to find in the study?

SMITH: Well, there are challenges in being first. Assays for mHTT levels have been explored in several publications, and it is such a clear, obvious marker for our product and we are optimistic that we will be able to see changes with that marker. The other CSF markers we are using, such as neurofilament light chain and synaptic health markers, are definitely exploratory. Being first, we do not know what happens to these markers when you have modified the disease, so ask us when the study is over!

HD INSIGHTS: TRACK-HD and other studies have looked at brain volumetric MRI over time and found it has potential as a biomarker in HD. Are you looking at volumetric MRI or other outcome measures?

SMITH: We are looking at volumetric MRI, yes. TRACK-HD and other studies have given us beautiful natural history data that has helped a lot with our program and designing our study. Again, it is a short study, so we do not expect to see positive changes. We will use these markers primarily to assess whether there is deterioration in the trial participants.
Meet the Company, cont...

HD INSIGHTS: For clinical assessments, you are using the HD Cognitive Assessment Battery (HD-CAB) developed by Dr. Julie Stout and colleagues. Are there other clinical measures that you are looking at, such as the Q-motor?

SMITH: The HD-CAB is our primary cognitive measure and again, being early, there really is not longitudinal data in that one either, so it will be interesting to see how that performs longitudinally. We do not have the Q-motor in the study.

HD INSIGHTS: When do you expect the initial results of the study to be available?

SMITH: We are on pace to meet the timeline we initially set, with a primary completion date of March 2017, and a study completion date of September 2017.

HD INSIGHTS: What has been the response of the HD community to the study? Have they been receptive? Was education required?

SMITH: We have wonderful support from our principal investigators. My understanding through them is that there has been a lot of interest in participating in the study, including “cold calls” from patients they know, to them and to us. Enrolling this study is probably not going to be a challenge because the community is very well educated about what is available to them now and what is coming. There is a lot of excitement around this product.

HD INSIGHTS: Are there other topics or questions that you would like to address related to your efforts?

BENNETT: Just that although our initial study is being done in Canada, the UK and Germany, subsequent studies would probably involve patients from more countries, including the USA. We are doing everything we can to accelerate the development, making sure that we are staying on track. And that if the drug is successful, we will start further studies as expeditiously as we can.

SMITH: I just want to remind people that it is a lengthy process and it is going to be a long timeline. There is a lot of anxiety in the community because people feel that they are missing something, even though its development has just barely started. Making sure we maintain realistic expectations is important.

HD INSIGHTS: What are your plans for future development should the initial studies go well?

BENNETT: We do not have very firm, locked-in plans, but the thought is that the next studies would test longer-term exposures with a larger group of patients, really Phase II studies.

LANE: The next studies may involve patients at earlier stages of HD. In addition, with this approach we can start thinking of prevention. At the moment, HD is diagnosed at the stage of clinical manifestations of brain pathology, but patients have had brain pathology developing for a long time before this stage. With genetic testing and the inevitability of the disease once the pathology has started, we have the prospect of going back to earlier points, when patients are not yet exhibiting symptoms, and treating them to prevent or delay the development of the disease. That may be some way in the future.

HD INSIGHTS: Thank you all for your efforts.

C. Frank Bennett, PhD: Dr. Bennett is the Senior Vice President of Research at Ionis Pharmaceuticals. He contributed his thoughts on the earlier stages of IONIS-HTTRx’s development to HD Insights, Vol. 3, and has continued to oversee this and other ASO programs at Ionis since that time.

Holly Kordasiewicz, PhD: Dr. Kordasiewicz is the Director of Neurological Drug Discovery at Ionis Pharmaceuticals, where she has worked since 2011 after completing her postdoctoral fellowship in the lab of Dr. Don Cleveland. She focuses on the preclinical development of novel drug candidates, investigating compounds in animal models and then characterizing the compounds prior to clinical development.

Roger Lane, MD, MPH: Dr. Lane is the Vice President for Clinical Development at Ionis Pharmaceuticals, a position he has held since January 2014. He leads clinical development efforts in the neurological therapeutic area at Ionis.

Anne Smith, PhD: Dr. Smith is the Director of Clinical Development at Ionis Pharmaceuticals, and serves as the Project Team Leader for IONIS-HTTRx.


**MEET THE COMPOUND: IONIS-HTT<sub>Rx</sub>**

By: Priya Hays, PhD

MANUFACTURER: Ionis Pharmaceuticals

MOLECULAR STRUCTURE: DNA-based antisense oligonucleotide targeting huntingtin messenger RNA

MECHANISM OF ACTION: ASOs bind messenger RNA to prevent translation and promote degradation by various cellular mechanisms.

_Figure:_ “Schematic illustration of the three main approaches to lowering huntingtin expression. Zinc finger protein therapeutics aim to reduce transcription of the huntingtin gene. Translational repression can be attempted at the pre-mRNA level using DNA-based antisense oligonucleotides (ASOs) or on mature mRNA using short interfering RNA (siRNA) compounds. Different cellular mechanisms degrade the bound mRNA.”

Due to the inadequate identification of extensive direct quotations, this article has been withdrawn by the editors as of May 4, 2016.

This summer, Ionis Pharmaceuticals (formerly Isis Pharmaceuticals), in collaboration with the CHDI Foundation and Roche Pharmaceuticals, began a Phase I trial of the antisense oligonucleotide (ASO) IONIS-HTT<sub>Rx</sub> in Canada and Europe. The trial, named “Safety, tolerability, pharmacokinetics, and pharmacodynamics of IONIS-HTT<sub>Rx</sub> in patients with early manifest Huntington’s disease,” uses a randomized, placebo-controlled, double-blind design to evaluate the safety and tolerability of ascending doses of IONIS-HTT<sub>Rx</sub>. Both the active drug and placebo are administered intrathecally at four-week intervals over a 13-week treatment period. If successful in this and subsequent trials, the compound could become the first disease-modifying drug for HD on the market.

Gene silencing therapies for HD have long been a promising avenue of exploration. Nucleotide-based gene silencing methods have advanced considerably in recent years, and IONIS-HTT<sub>Rx</sub> is the first tested in human HD patients. By attacking HD near its genetic roots, the drug could potentially reduce, partly reverse, or even prevent the symptoms of HD. Numerous successes have been reported in rodent models, first with RNA-based compounds, and more recently with ASOs. ASOs are synthetic, modified nucleotide agents designed to bind to a chosen sequence in mRNA using Watson-Crick complementarity. Once bound, several cellular mRNA disposal mechanisms remove the mRNA, repressing gene expression by reducing translation and protein expression. ASO-bound mRNA is degraded by RNase H prior to splicing and nuclear export (see Figure).

Most trials in animal models have focused on nonselective silencing of both wild-type and mutant HTT alleles, though research into allele-selective approaches has also been undertaken. Directly infused into the brain parenchyma or ventricles of HD-model mice, ASOs appear to significantly reduce mRNA expression and total HTT levels. This has been associated with both slowing of the phenotypic progression of HD, and substantial improvement in some manifestations that have clinically significant counterparts in human HD.

The effect of lowering wild-type HTT in humans remains unknown. Though the function of wild-type HTT is not understood, knocking out the gene is lethal to embryos in murine models, and conditional HTT knockout has been reported to produce neurodegeneration. However, using ASOs to knockdown 75% of total huntingtin in BACHD mice produced no detectable behavioral or motor deficits (though subtler effects may not be detectable in murine studies). The benefits of lowering the pathogenic mHTT protein may significantly outweigh the potential side effects of lowering the wild-type protein.

HD INSIGHTS: Can you tell us how Roche became interested in Ionis Pharmaceuticals?

SCHOBEL: Roche’s strategy of innovation is to follow the science and disease areas in which we believe we can make the greatest difference in peoples’ lives. We consider our collaboration with Ionis Pharmaceuticals in HD to be true to this strategy. The particular thing that attracted us is that Ionis has generated a huntingtin antisense oligonucleotide (ASO). This is a second-generation antisense therapy—the first to enter clinical development—designed to reduce the production of all forms of HTT, including mHTT. The life-transforming potential of this ASO made it a very attractive opportunity for us.

HD INSIGHTS: HTTRx recently began a clinical trial with a Phase I study in individuals with early HD. Can you tell us about that?

SCHOBEL: First, I should say that Ionis is running the trial. They are in charge of development until the end of Phase I. In the Phase I trial, we are seeking to better understand the ASO. The two key parameters we are interested in are that it is safe and well tolerated, and whether its expected huntingtin-lowering action is proven through the lowering of protein levels in participants’ cerebrospinal fluid (CSF).

HD INSIGHTS: Can you tell us about measuring HTT levels in the CSF? The assay has not been widely used, and has never been used in a clinical trial.

SCHOBEL: What is known is coming out of the collaboration with CHDI and the labs of Dr. Ed Wild and Dr. Amber Southwell. They have shown in clinic that one can measure mHTT in the CSF, which is a very exciting development. These assays appear to be ready for prime time. The other exciting aspect of the assays is that they track disease stage, and associate with clinical severity, at least in cross-section. We want to learn more about how those assays perform longitudinally in terms of their test-retest reliability. A forthcoming study – the HDClarity study – will hopefully elucidate that. In the Phase I study of HTTRx, we are looking to see whether HTTRx can change the levels of mHTT and total HTT in the CSF from baseline. That would be a very exciting first-in-human clinical accomplishment.
Meet the Partner, cont...

SCHOBEL: The final thing to say is that published preclinical results from Amber Southwell’s work have shown the proof of principle that lower levels of mHTT in the CSF reflect lowering of mHTT in the brain. That link has now been empirically established in rodent models, and is a light for us to follow into the clinic.

HD INSIGHTS: The Phase I study is investigating whether monthly intrathecal infusions are safe, well-tolerated, and lower both total HTT and mHTT levels in the CSF. Are there any other major outcomes of interest?

SCHOBEL: Those are the key outcomes. Any other positive outcomes we might observe in Phase I would be a pleasing upside. The treatment duration is probably insufficient to result in disease modification. The sample size is also very small, so I think that any effects we might see on motor or cognitive functioning, or an overall sense of well-being, for example, would be pleasing, but not what we really expect.

HD INSIGHTS: Can you tell us about your plans beyond Phase I?

SCHOBEL: We are now in an option-planning period. First of all, we are learning from our partner’s considerable efforts and prior knowledge from having developed the ASO to date, and taken the lead on Phase I. From there, we are looking together towards the future of the program, what an integrated program may look like, as well as clinical development options.

I consider this to be a process. We are engaging in collaborative discussions with stakeholders and therapeutic experts. We are also actively engaged in a disease-modeling effort to help us better design clinical efficacy trials. This has been made possible in part through generous sharing of datasets from academic investigators, including Dr. Sarah Tabrizi of University College, London, and Dr. Jane Paulsen of the University of Iowa.

HD INSIGHTS: Are there plans to start a subsequent clinical trial?

SCHOBEL: The partnership is structured such that at the end of Phase I we have an option to opt-in for full development. We are planning for success now and in the future, but of course we are waiting for the Phase I data to formally trigger planning of later trials. We are mapping it out right now.

HD INSIGHTS: You recently came to Roche from academia. Can you tell us what brought you here?

SCHOBEL: I came to Roche from academia because I became convinced that investigating first-in-class or first-in-man drug candidates would be a very good way to make a big difference in patients’ lives. I can happily report that my expectations have been met in every way in that regard. I have found that at Roche I can do every bit of the science, and work with these fantastically exciting novel molecular entities to try to help to make a difference. That is what brought me, and that is what I am doing, so it is a happy report. I am in charge of clinical development plans for the program on the Roche side. That involves everything involved in planning clinical efficacy studies, by integrating what we think the preclinical package is telling us with the early clinical experiments, then planning the efficacy studies.

HD INSIGHTS: What would you view as a success for this partnership? Where would you like the partnership to be? And where would you like this ASO to be?

SCHOBEL: Well, everybody’s hope and expectation is that we could see a safe, well-tolerated ASO administered intrathecally that could lower mHTT in the CNS, as measured by levels in CSF. That would set us up to conduct efficacy studies to see whether this will translate into a safe and well-tolerated therapy that makes a difference in peoples’ lives. However, even short of that, the fact that we are in the clinical field with a huntingtin-lowering therapy is an important aspect of this program. We hope for the best for this particular therapy, but we should consider it a first shot on goal for this type of therapy in this field. We anticipate that the field will deliver on other promising methods of lowering mHTT over the next five to ten years. We are very excited for this program and hope for the best, but it is really just the beginning of what we hope will be a whole next-generation wave of therapies that can impact patients’ lives by limiting disease progression, which is really our ultimate goal.

HD INSIGHTS: Thank you very much.

Sleep disturbances are among the earliest non-motor symptoms in HD

By: Alpar S. Lazar, PhD and Roger A. Barker, MRCP, PhD, FMedSci

We spend approximately one-third of our lives asleep. Sleep quality is central to brain health, and problems with sleep are commonly seen in most neurodegenerative disorders, including HD. Several studies convincingly show abnormal sleep quality in manifest HD patients, and indicate that this happens early in the course of the disease. Exactly what the first sleep problems are in HD, and whether they emerge in the premanifest stage, when other non-motor symptoms including cognitive abnormalities are already present, is unknown. Patients with HD have metabolic alterations characterized by weight loss and increased energy expenditure, which may also relate to sleep problems, given that both are controlled by similar CNS structures, such as the hypothalamus.

We therefore aimed to investigate whether sleep problems are found in premanifest patients, and if so, to characterize these problems, and evaluate whether they are associated with cognitive and/or metabolic deficits. We designed a comprehensive cognitive, sleep, and metabolic study, performed both in the field and in the laboratory, with 38 individuals with premanifest HD and 36 age- and sex-matched controls. This consisted of two weeks of actigraphy at home, allowing assessment of habitual rest-activity rhythmicity using a small, wrist-worn movement sensor; two nights of sleep study (polysomnography) and multiple sleep latency tests in the laboratory, allowing objective assessment of sleep quality, brain electric activity (EEG) and daytime sleepiness; and a body composition assessment using dual energy X-ray absorptiometry scanning. Energy expenditure was measured over 10 days at home using doubly labelled water (DLW), and for 36 hours in the laboratory by indirect calorimetry (IC). DLW is water containing a stable isotope which is administered to the patients and its elimination tracked by daily urine samples to enable estimation of metabolic rate. IC determines metabolic rate based on oxygen consumption and carbon dioxide production during rest and exercise performed in an isolated respiratory chamber. We also performed detailed cognitive and clinical assessments.

We found that premanifest HD gene carriers had more disrupted sleep, characterized by a fragmented sleep profile, meaning more time spent awake during the night (see Figure); increased objective daytime sleepiness; and alterations in sleep-dependent brain activity as measured by EEG, with a clear association with increasing disease burden. In addition, the development of these abnormalities coincided with the development of cognitive, affective, and subtle motor deficits, and preceded any metabolic alterations. In spite of the presence of these objectively measured sleep deficits, premanifest HD gene carriers did not complain of poorer sleep quality compared to controls, which fits with an earlier study we had done in a small group of early manifest patients who also denied any sleep problems, despite objective measures to the contrary. This suggests that subjective measures of sleep quality are not necessarily helpful for research or clinical use in HD.

Figure: Representative sleep profiles of a premanifest participant and an age- and sex-matched control showing more awakenings and time spent awake during the sleep period with less REM sleep, and an overall more fragmented sleep profile in the premanifest participant.

(continued on Page 20...
Genetic factors that modify clinical onset of HD

By: Jong-Min Lee, PhD on behalf of the Genetic Modifiers of Huntington’s Disease (GeM-HD)

HD is due to a dominantly inherited CAG trinucleotide repeat expansion in the HTT gene that is both necessary and sufficient to cause clinical manifestations. The size of the expanded CAG repeat largely determines the rate of the pathogenic process that leads to clinical symptoms of HD. However, the size of the expansion does not perfectly predict individual age at onset of clinical disease, suggesting the existence of genetic and possibly environmental disease modifiers that interact with HTT-driven disease pathogenesis to alter the timing of clinical symptoms of HD.

In order to identify human genetic factors capable of delaying or hastening age at onset of motor signs, the GeM-HD Consortium capitalized on the power of genome-wide association (GWA) analysis by using naturally occurring single-nucleotide polymorphisms (SNPs) in the DNA as genetic markers. DNA samples were collected from 4,082 HD patients to determine genome-wide SNP genotypes and, from corresponding clinical information, the difference between observed and CAG-predicted age at onset (i.e. residual age at onset) was calculated. Subsequent statistical analysis aimed at identifying genetic variations correlated with residual age at onset revealed two genome-wide significant regions representing three independent modifier effects. A region on chromosome 15 harbors two independent modifier association signals in the HD population: one that hastens age at onset by approximately 6 years, and the other that delays it by approximately 1.4 years. A region on chromosome 8 carries a modification signal that delays onset by approximately 1.6 years. In addition, near-significant signals at MLH1, a gene on chromosome 3 involved in DNA repair, and analyses that capture signal from SNPs by pathway rather than individual gene, suggest a potential role for DNA mismatch repair/maintenance processes in modifying disease pathogenesis before onset.²

These findings demonstrate that HD can be modified prior to clinical disease onset, supporting the potential of genetic modifier pathways as therapeutic targets. Many additional genetic modifiers may still remain undetected in this 4,082-person GWA study due to sample size and to the magnitude of individual modifier effects. Observations that HTT participates in a wide variety of cellular functions support the likelihood that there may be numerous genetic modifiers of HD.

We created a user-friendly website called Genetic Modifiers of Motor Onset Age (GeM MOA), accessible through Huntington’s Disease in High Definition, to disseminate the full set of GWA results and to facilitate alternative genetic-based approaches to HD modifiers.² Registered users can view association results by searching a gene symbol, a SNP name, or a region of interest. We strongly advise that the data be interpreted with care; for example, as most SNP signals represent indirect association, the location of the SNP does not necessarily implicate the nearest gene. Conversely, the absence of even suggestive p-values near a gene may not dictate a lack of potential for it to modify HD, as this may instead reflect a lack of naturally occurring variations that impact the gene’s function. Nevertheless, the discovery of significant genetic modifiers of HD provides the proof of principle that disease modification in HD is possible. The GeM MOA website is designed to accelerate the search for targets for development of therapeutic interventions, validated in humans, that are effective before the emergence of clinical disease.

HD Insights™
Thanks Raptor and Lundbeck for their ongoing support
Highlights of HSG 2015

The Huntington Study Group held their 22nd Annual Meeting and the 9th Annual Clinical Research Symposium October 21–24, in Tampa Bay, FL.

By: George McNally, BMedSc

HSG 2015 provided a platform for the world’s leading HD experts, clinicians, scientists, and the HD community to discuss the most promising and latest innovations in HD research. Chaired by Dr. Ray Dorsey and co-chaired by Dr. Blair Leavitt, this year’s annual meeting focused on building the future of the HSG, and featured keynote presentations, educational courses, and interactive working group sessions over three days, designed to facilitate further exploration of potential life-changing treatments. The 9th Annual HD Clinical Research Symposium took place in the morning of the final day, followed by a family-oriented educational program for members of the HD community.

The first open session of the meeting was a panel session titled “The FDA is coming: Now what?” HSG Site investigators were invited to share their experiences, and provided key lessons on how to survive a fateful visit from the FDA. A similar forum led by veteran Project Managers Elise Kayson and Jody Goldstein asked study PIs from First-HD, SIGNAL-HD and PRIDE-HD to discuss the anticipated and unanticipated challenges they encountered throughout their clinical trials. Working group sessions covering care, education, behavior, and rehabilitation aspects of HD were available to all attendees, enabling both expert and junior researchers to discuss recent developments in their specific fields of interest.

Dr. Ray Dorsey discussed the recent progress of the HSG and provided an insight into the directions the group wishes to pursue in the next five years. He emphasized the value of bringing the HD community together annually, highlighted by incorporating the ENROLL-HD North American Meeting into the first day of proceedings. He acknowledged the success of the Phase III trial for SD-809, which concluded that the compound not only improved chorea symptoms, but also total motor score, functional, and quality of life measures. Dr. Dorsey also highlighted new online initiatives that allow patients, families, and researchers to communicate more freely and easily, including the updated HSG Link website, and recent ventures into social media (Twitter and Facebook).

Dr. Ira Shoulson, founder of the HSG in 1994, and Chair of the HSG Executive Committee 2008–2014, welcomed new HSG scholarship recipients at the inaugural HSG breakfast, which encouraged mentorship, and provided networking opportunities, while also inviting new members to share their thoughts for the future of HSG with the committee.

Dr. Michael Hayden presented the keynote presentation, “Ripples of hope: Prospects for the future in HD.” He talked about Teva Pharmaceutical Industries’ success in developing new treatments, particularly dutetrabenazine (SD-809), and the importance of considering the commonality of pathways across neurodegenerative disorders to help drive future HD research. He provided hope to families, stating that HD can become a treatable disease comparable to the management of multiple sclerosis or HIV.

Also noteworthy was the “Novel outreach methods” session, in which Dr. Kevin Biglan, Ms. Chandler Swope, and Ms. Katie Jackson described their respective work developing telemedicine, “youth-friendly” promotional material, and Help 4 HD, a multimedia communication platform.

Prof. David Corey, Dr. Lisa Stanek and Prof. Sarah Tabrizi covered the exciting new therapeutic area of gene silencing, introducing attendees to the basic cellular mechanisms, as well as the potential benefits and risks.

Chaired by Dr. Biglan, the 9th Annual HD Clinical Research Symposium opened with an inspiring presentation by Dr. Erika Bjorklund, speaking from her own experiences about how to deal with a diagnosis of HD in the family. Dr. Kyle Fink described the prospect of using mesenchymal stem cells as a potential therapy. Dr. Claudia Testa presented on the recent success of Teva’s SD-809 in the First-HD trial. The keynote address on gene silencing by Dr. Juan Sanchez-Ramos echoed a recurring theme from the conference, expressing optimism that together, the HD community will be able to find a way to stop the progression of this disease.
Sleep disturbances, cont...

These new sleep results in patients are in line with reports from transgenic rodent models of HD that report gradually worsening sleep quality from a very early stage, and together raise many interesting questions. What causes these early sleep disturbances? What is their significance in the early cognitive deficits and the onset and progression of the disease? These questions remain to be investigated. Finally, it remains to be established whether therapeutic sleep quality improvement could help premanifest and manifest patients with HD to reduce the cognitive symptoms or even slow down the disease process, as suggested by earlier studies performed in transgenic animal models of HD,\textsuperscript{17,18}

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