First-HD Results Released

Auspex announces promising results from First-HD trial of deuterated tetrabenazine (SD-809)

By: Meredith A. Achey, BM

On December 16, 2014, Auspex Pharmaceuticals announced positive top-line results for the “First Time Use of SD-809 in Huntington Disease” (First-HD) registration trial of SD-809, a deuterated formulation of tetrabenazine (see HD Insights, Vol. 7). The company also released preliminary results of the ongoing open-label “Alternatives for Reducing Chorea in HD” (ARC-HD) study showing that individuals who switched from tetrabenazine to SD-809 maintained chorea control while taking SD-809 (see Table 1 for a summary of the trials). The complete press release is available here.

The primary efficacy endpoint for First-HD was improvement in the total maximal chorea score of the Unified Huntington's Disease Rating Scale. Trial participants who took SD-809 showed an average improvement of 2.5 points (p<0.0001) from baseline to maintenance therapy. In addition, secondary endpoints assessing clinical relevance, including patient global impression of change, clinical global impression of change, and change in the SF-36 physical functioning score (a quality of life measure) showed improvement over placebo (p<0.05), while the Berg Balance test did not show significant improvement (p=0.14). More than 90% of First-HD participants enrolled in the open-label, long-term followup ARC-HD study.

ARC-HD “Switch” was completed in parallel to First-HD, as patients currently taking tetrabenazine for chorea control were switched overnight to SD-809 at approximately half their usual dose of tetrabenazine (see Table 1). After four weeks, the 35 individuals for whom data was available showed an average improvement of 0.8 points (standard error 0.5) in total maximal chorea score. After eight weeks, data for 21 individuals showed an average improvement of 1.9 points (standard error 0.8). The safety profile was similar to that in the First-HD study.

These preliminary results have given the HD community hope for improvement in the treatment of HD. Dr. Samuel A. Frank, principal investigator for First-HD, told HD Insights, “Combined with the excellent adverse event profile seen with the analysis to date, we are far in the process of developing another potential treatment option for patients with HD.”

(continued on Page 2...)
Auspex, cont...

Dr. Francis Walker, Professor of Neurology at Wake Forest University School of Medicine and unaffiliated with the study, told *HD Insights*, “SD-809 may have advantages over tetrabenazine in that it is taken twice instead of four times daily and seems to have a positive effect on function...by preliminary findings, [SD-809] seems to improve upon an existing treatment for HD related chorea.” He cautioned, however, that, “Yet to be reported is the effect of SD-809 on cognition, an area where tetrabenazine has a mild negative effect.”

Dr. Frank highlighted several novel elements of the trial’s design, saying, “This trial... [had] many novel aspects that we may be able [to] apply to other HD trials including capacity assessment in the context of a clinical trial, easy swallowing assessment and direct shipping of study drug to participants...[Additionally], we demonstrated that deuterated compounds penetrate the blood brain barrier, a concept that may be applied to other deuterated compounds used for other neurological conditions.”

Full results of First-HD are expected in 2015, and Arc-HD is scheduled to conclude in mid-2015. Auspex CEO Dr. Pratik Shah indicated that the company will submit a New Drug Application to the FDA by mid-2015 for SD-809 as a treatment for chorea in HD. Auspex continues to evaluate SD-809 in other conditions, including tardive dyskinesia and Tourette syndrome.

**Table 1. SD-809 clinical trials in HD**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Design</th>
<th>Sample Size</th>
<th>Primary Endpoint</th>
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<tr>
<td>First-HD</td>
<td>Randomized, double-blind, placebo controlled 12 week trial of SD-809 vs. placebo</td>
<td>90</td>
<td>Total maximal chorea score</td>
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<tr>
<td>ARC-HD</td>
<td>Open label, long-term safety study of SD-809</td>
<td>116</td>
<td>Overall incidence of adverse events</td>
</tr>
<tr>
<td>ARC-HD Rollover</td>
<td>First-HD participants who have completed First-HD and continue on SD-809 after 1 week washout</td>
<td>80</td>
<td>Overall incidence of adverse events</td>
</tr>
<tr>
<td>ARC-HD Switch</td>
<td>Four week trial to evaluate safety, tolerability and efficacy after switching patients from tetrabenazine to SD-809 at half the dose</td>
<td>36</td>
<td>Overall incidence of adverse events</td>
</tr>
</tbody>
</table>

Source: clinicaltrials.gov


The Huntington Study Group thanks the Fox Family Foundation for their support of HSG 2014

FOX Family Foundation
Meet the Investigator

VITAL SIGNS

NAME: Francesca Cicchetti, PhD

POSITION: Professor and Researcher, Neuroscience Department, Centre de Recherche du CHU de Québec, Faculty of Medicine, Laval University

EDUCATION: BS, McGill University, Montréal, QC; MS and PhD in Neuroscience, Université de Laval, Québec, QC; post-doctoral work with Ole Isacson, MD, Harvard University, Cambridge, MA

HOBBIES: Travel; tango and salsa

Dr. Francesca Cicchetti is a neuroscientist at the University of Laval in Québec, Canada. Her 2014 paper “Mutant huntingtin is present in neuronal grafts in Huntington disease patients,” published in Annals of Neurology, was selected by the HD Insights Editorial Board as one of the most influential papers of the year. Her findings suggest that mutant huntingtin (mHTT) can be transmitted through non-cell-autonomous mechanisms, and potentially implicate the immune system in HD pathology. Her discoveries are already leading to new understanding of HD pathogenesis and have the potential to identify novel targets for early HD therapies. Dr. Cicchetti recently spoke with HD Insights about her past and current research. The following is an edited transcript of the conversation.

HD INSIGHTS: Can you tell us how you first became interested in HD?

CICCHETTI: I was doing a PhD thesis under the supervision of Dr. André Parent, a renowned neuroanatomist based here at Laval University in Québec, and had been assigned a project on tract tracing studies in squirrel monkeys. I became very attached to the animals. I had names for each one of them and fed them bananas in the morning. When it was time to sacrifice them, I simply could not do it, I was just too emotional. I told Dr. Parent that I could not continue the project. At that time, he was also keen to initiate a human brain bank, and asked me if I would be interested in taking on this project instead. So, I began to contact pathologists, and I collected close to 500 human brains. The brain bank is still active today in distributing tissue to various research groups. Through this endeavor, I began studying the human brain: the basal ganglia in normal conditions, and then became interested in pathologies related to striatal dysfunction, such as HD.

HD INSIGHTS: What were your first research experiences with HD?

CICCHETTI: Our initial work focused on the characterization of striatal cell populations, and trying to understand their selective vulnerability. We were particularly interested in subpopulations of interneurons that express calcium-binding proteins. These were the very first papers that we published in the field.

HD INSIGHTS: Your paper in Annals of Neurology suggested for the first time that mHTT might be transmissible from nerve cell to nerve cell. Can you discuss?

CICCHETTI: I believe that this paper is our most important contribution to HD research. We were extremely fortunate, of course, to have access to this unique material, the brains of HD patients who had received fetal striatal transplants as an experimental therapy as an attempt to slow the progression of their disease – a trial that was initiated by Thomas Freeman at the University of South Florida. Our paper demonstrated the presence of the mHTT protein within the grafted tissue a decade post-transplantation. We did not see this in early time points following transplantation. The mutant protein was found within the extracellular matrix of the grafted tissue, not specifically within grafted cells. However, we also saw mHTT aggregates in cells associated with blood vessels as well as in perivascular macrophages within the cerebral tissue of the transplanted HD patients.

When we first submitted the paper reporting this data, it was clear that the reviewers were interested in this finding, but did not quite believe it. We used every technique we could possibly use on human postmortem tissue—immunohistochemistry,
Cicchetti, cont...

CICCHETTI: ...immunofluorescence, confocal and electron microscopy, Western immunoblotting, and infrared spectroscopy, to show that mHTT inclusions were indeed present in the transplanted tissue. This observation, which we were very excited about, raised a whole new set of questions. How did the mutant protein get to the transplanted tissue, which is genetically unrelated to the patient? In the paper, we proposed a series of non–cell-autonomous mechanisms to explain the propagation of mHTT.

HD INSIGHTS: We know that mHTT will be produced within the neurons of individuals with HD. What role would transmission play in the disease and why is that important?

CICCHETTI: This is a very important point. Because of the genetic nature of HD, the mutant protein is expressed ubiquitously, in every cell of the body. The extent to which non–cell-autonomous mechanisms of pathological protein spread may contribute to disease onset and development is unknown, but this observation alone may fundamentally change our understanding of the pathogenesis of HD, and of other neurodegenerative disorders. If non–cell-autonomous mechanisms do indeed play a significant role in disease pathophysiology, developing therapies that are designed to halt the propagation of mHTT will be of significant value.

HD INSIGHTS: I’ll return to the targets in a moment, but I wanted to touch on your mention of other diseases. Dr. Virginia Lee and her colleagues have described trans-synaptic transmission of α-synuclein in PD models. Is there a common theme?

CICCHETTI: Certainly. But besides the transsynaptic transmission of α-synuclein demonstrated in the original publication by Luk et al., Lee’s group also proposed the potential prion-like behavior of α-synuclein. In HD, I do not personally believe that mHTT propagates in a prion-like fashion, that mHTT seeds pathology and changes the conformation of the protein in neighboring cells. However, I do believe in the trans-synaptic propagation of mHTT, something that we are currently working on. But what we are especially keen on is to explore the involvement of the immune system—blood-borne cells in particular—as a vehicle to transport and spread mHTT.

HD INSIGHTS: So you think immune cells may be transporting mHTT?

CICCHETTI: Other groups have already shown that monocytes, for example, express mHTT very early in the disease course. As you pointed out, in HD patients, every cell of the body expresses mHTT, but certain cell types seem to be much more vulnerable to cell death, although the vulnerability of these cell populations is not well understood. So we know that peripheral cells express the mutant protein, and we now have evidence that there is leakage of the blood-brain barrier in HD patients, data that we will shortly submit for publication. Based on this, we believe that the transmigration of peripheral cells to the brain may be facilitated. I do think that that there is a strong possibility that mHTT spreads to the brain via blood-borne cells.

HD INSIGHTS: Which immune cells do you think are involved?

CICCHETTI: Based on current literature, mHTT is detectable in monocytes and T cells, which specifically correlates with burden of disease scores, further suggesting that these populations could be used as biomarkers. Results from PET studies in HD patients also support the idea that microglial activation is an early event in HD pathogenesis. There is strong evidence in favor of an inflammatory or immune-driven response that precedes neurodegeneration in HD.

HD INSIGHTS: Do you think that these immune cells, which are facilitating the propagation of mHTT, are responsible for the spread of mHTT within the brain?

CICCHETTI: I tend to believe so, but I’m not ruling out the possibility that there is a very high expression of mHTT first in the brain, and then we find residues of the protein in the periphery. However, my guess is that it is primarily the other way around, based on the fact that there are early signs of immune dysregulation, including elevated levels of cytokines in HD patients, long before any of the neurological features that are used for diagnosis.

Another avenue of propagation that we are currently exploring is that of exosomes and microvesicles, which can be released from peripheral cells. Their small size would allow them to enter the brain even in the absence of leakage of the blood-brain barrier. What is interesting about these small vesicles is that some of them contain mitochondria, which allows them to travel long distances because they have their own powerhouse. Despite their small size, they are big enough to carry various proteins, and could serve as miniature mHTT cargoes circulating from peripheral blood into the brain.

HD INSIGHTS: Does this also suggest that peripheral markers could serve as biomarkers of HD?

CICCHETTI: Absolutely, and a number of research groups have suggested this. Not only could they serve as biomarkers of HD, but also as markers of treatment efficacy.

HD INSIGHTS: Have we seen any treatments that change these peripheral markers in HD?

(continued on Page 12...)
Research Round-Up

By: Lise Munsie, PhD

In the proteome...

A number of studies suggest a relationship between huntingtin (HTT) and tau protein pathology which has yet to be elucidated. Tau is found predominantly in neurons. In tauopathies such as Alzheimer disease, tau is cleaved and then aggregates. A study by Gratuze and colleagues looks at the phosphorylation state of tau in both the R6/2 and Q175 mouse models of HD.1 Hyperphosphorylation of tau at different positions can be seen in the presence of mutant huntingtin (mHtt). The authors attribute this hyperphosphorylation to a down-regulation of calcineurin phosphatase caused by mHtt. Hyperphosphorylation of tau is not associated with increased cleavage or aggregation.

Two recent publications from the Outeiro group expand these observations. The first examines how mHtt impacts tau localization, molecular interactions and phosphorylation pattern.2 Using biophotonics, they show that mHtt leads not only to altered phosphorylation of tau, but also alters tau’s cellular localization and microtubule stabilizing functions. They describe a new kind of aggregate containing tau and mHtt, and hypothesize that an aberrant interaction with mHtt may leave tau unable to interact with phosphatases. In a second manuscript in Human Molecular Genetics, the group investigates the interaction between HTT and α-synuclein, a protein that aggregates and causes toxicity in Parkinson disease (PD), in a Drosophila model.3 The authors show that co-expression of α-synuclein and mHtt leads to an increase in insoluble aggregates containing both proteins, leading to motor deficits and decreased life span. The co-expression of these proteins synergistically enhances toxicity, accelerating the progression of the disorder. This system may be useful for screening potential drug candidates for both HD and PD.

In the neurons...

A report by Yao and colleagues in Molecular and Cellular Neuroscience describes an unbiased proteomics approach to screen for HTT interactors in synaptosome preparations of brain regions affected in HD.1 A large amount of HTT was found in the synaptosome fraction. HTT was also found to interact with components of the presynaptic cytomatrix: specifically, the Bassoon, Piccolo and Ahnak proteins, components of the cytomatrix at active zone complex. The authors posit that HTT acts as a scaffold, and forms part of the complex that regulates endo- and exocytosis of synaptic vesicles.

Pietropaolo and colleagues report in Neuropharmacology on their investigation of the role of the endocannabinoid system (ECS) in the etiology of HD.2 The ECS modulates brain function in brain regions affected by HD, and has been implicated in HD gene expression. Pietropaolo’s group administered the cannabinoid receptor agonist WIN to R6/1 mice acutely or chronically, then monitored motor and social behavior and neurodegeneration. Chronic administration showed improvements in motor behaviors and decreased degeneration of medium spiny neurons with an increase in inclusions, suggesting a positive influence of aggregates and potential therapeutic benefit of ECS modulation.

A study by the Brouillet group in Human Molecular Genetics examines preferential degeneration of the striatum in HD.3 They look at Crym, an NADPH-dependent P38 cytosolic T3-binding protein that is preferentially expressed in the striatum. The expression of Crym is reduced in full length BACHD and knock-in models of HD, even prior to neurodegeneration. Overexpression of Crym in fragment models of HD also reduces toxicity, suggesting that Crym may be another therapeutic target for HD.

In the clinic...

A recent article by Sussmuth and colleagues published by the PADDINGTON consortium outlines their trial of the safety, tolerability, and deliverability of the SIRT1 inhibitor Selistat for HD patients.4 SIRT1 has been shown to acetylate mHtt, leading to altered transcription. Selistat is a selective SIRT1 inhibitor, as inhibiting SIRT1 has shown therapeutic effects in model organisms. Sussmuth’s group performed a randomized, double blind, placebo-controlled study and found that Selistat is safe and well tolerated in patients with early HD. Importantly, blood plasma contained levels of the drug that have therapeutic effects in model organisms.

Tetrabenazine, currently the only FDA-approved drug for treatment of HD-related chorea, has many adverse effects, including worsening psychological symptoms such as depression. The Haghighi group in Sweden performed a small study evaluating the safety and efficacy of (-)-(R)-OSU6162, a monoaminergic stabilizer that acts on dopaminergic and serotonergic receptors.5 No such psychological adverse effects were associated with the administration of the drug. The researchers noted positive trends in both psychological and motor assessments, suggesting that this class of compound may warrant larger clinical trials in HD.

The PREDICT-HD group published a new study evaluating how measures other than CAG repeat length correlate with age of onset of HD symptoms, to assist in clinical trial design and prognosis.6 There were 4 different measures taken on over 1,000 patients, including imaging, motor, psychiatric, functional, and cognitive measures. The group found several measures that can improve the diagnosis of onset of HD, the strongest being total motor score, putamen volume and the Stroop word test. The results will inform the selection of outcomes for future clinical trials.

1 Yao J, Ong SE, Bajjalieh S. Huntingtin is associated with cytomatrix proteins at the presynaptic terminal. Mol Cell Neurosci. 2014 Nov 4;63C:96-100. doi: 10.1016/j.mcn.2014.10.003. [Epub ahead of print]
Laquinimod is an experimental immunomodulatory drug that has shown promising neuroprotective effects. The exact mechanism by which laquinimod exerts its neuroprotective effects is not fully understood, but it has been proposed that laquinimod reduces leukocyte migration into the central nervous system. The compound has been shown to modify the innate immune system to promote the differentiation of anti-inflammatory/regulatory T cells, activate microglia cells, increase the expression of brain-derived neurotrophic factor, and prevent inflammation-induced excitotoxicity. 

In 2012, a study funded by TEVA Pharmaceutical Industries Ltd. and Active Biotech characterized the impact of laquinimod on CNS-intrinsic inflammation caused by cuprizone-induced demyelination in mice in vivo, and on primary CNS cells in vitro. Results suggest that laquinimod not only prevents cuprizone-induced demyelination but also prevents microglial activation, axonal transections, reactive gliosis, and oligodendroglial apoptoses in wildtype and Rag-1 – deficient mice. Most significantly, laquinimod is believed to inhibit astrocytic NF-κB transcription factor activation, thereby preserving myelin.

TEVA and Active Biotech have investigated laquinimod as a potential oral treatment for a variety of autoimmune and neurodegenerative diseases. Laquinimod was first investigated for the treatment of relapsing-remitting multiple sclerosis (RRMS), an autoimmune disease that causes inflammation-induced demyelination and axonal degeneration of the CNS, resulting in chronic neurological complications and disability. Two of TEVA and Active Biotech’s most recent studies, BRAVO and ALLEGRO, showed that laquinimod decreases the rate of whole-brain atrophy compared to placebo. Results in both studies indicate that oral laquinimod is likely to exert a neuroprotective effect resulting in a reduced amount of irreversible brain tissue damage, which is consistent with possible slowing of disability accumulation in RRMS patients. These evident neuroprotective effects, reduced inflammatory response, and reduction in brain tissue damage shown in the BRAVO and ALLEGRO studies, could prove effective in other autoimmune and neurodegenerative diseases.

TEVA and Active Biotech recently initiated a Phase II randomized, double-blind, placebo-controlled parallel group study (LEGATO-HD) to evaluate the efficacy and safety of laquinimod as a treatment for HD. Laquinimod’s modulation of pathways common to key neurodegenerative disease through the immune cell lineages in the periphery and in the CNS, as well as its evident anti-inflammatory effects, may reduce neuronal death and the harmful inflammatory response seen in HD. The HD trial is in the early phase of recruitment and enrollment. The study is expected to be completed in January 2017.

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The Huntington Study Group thanks the following for their support of HSG 2014:

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Valeant Pharmaceuticals International

Auspex Pharmaceuticals
### Clinical Trials Update

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<th>SPONSOR</th>
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<th>STUDY AGENT</th>
<th>PHASE</th>
<th>PRINCIPAL INVESTIGATOR, CONTACT</th>
<th>DESIGN</th>
<th>TRIAL LENGTH</th>
<th>SITES</th>
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<tr>
<td>Charité University</td>
<td>ETON-Study</td>
<td>Epigallocatechin gallate</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-gallate (EGCG) in changing cognitive function in HD patients</td>
<td>1 year</td>
<td>4 total - Germany</td>
<td>Enrollment complete, study ongoing</td>
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<td>Charité University</td>
<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>
<td>Study complete</td>
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<tr>
<td>Ipsen</td>
<td>NCT02231580</td>
<td>BN82451B</td>
<td>II</td>
<td>Bruno Padrazzi, M.D. <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, the pharmacokinetic and the pharmacodynamic properties of twice daily BN82451B for four weeks in male patients with HD</td>
<td>28 days</td>
<td>1 total - Germany</td>
<td>Currently enrolling</td>
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<tr>
<td>Omeros Corporation</td>
<td>NCT02074410</td>
<td>OM643762</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 OM643762 in subjects with HD</td>
<td>28 days</td>
<td>4 total - United States</td>
<td>Trial suspended</td>
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<td>Prana Biotechnology</td>
<td>REACH2HD</td>
<td>PBT2</td>
<td>II</td>
<td>Ray Dorsey, MD</td>
<td>Randomized double-blind safety and tolerability study of PBT2 of individuals with mild to moderate HD</td>
<td>6 months</td>
<td>20 total - Australia and United States</td>
<td>Results published</td>
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<td>Pfizer</td>
<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>Paris, France</td>
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<td>Pfizer</td>
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<td>PF-0254920</td>
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<td>Pfizer CT.gov Call Center, 800-718-1021</td>
<td>Randomized, double-blind, placebo-controlled proof of concept study of the efficacy and safety of PF-0254920 in HD</td>
<td>26 weeks</td>
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<td>Teva Pharmaceutical Industries</td>
<td>PRIDE-HD</td>
<td>Pridopidine</td>
<td>II</td>
<td>Teva US Medical Information 800-896-5855</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 BID versus placebo for symptomatic treatment in patients with HD</td>
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<td>57 total - worldwide</td>
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<td>Teva Pharmaceutical Industries</td>
<td>OPEN-HART</td>
<td>Pridopidine</td>
<td>II</td>
<td>Karl Kieburutz, 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>22 total - United States and Canada</td>
<td>Enrollment complete, study ongoing</td>
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<td>Teva Pharmaceutical Industries</td>
<td>LEGATO-HD</td>
<td>Laquinimod</td>
<td>II</td>
<td>Teva US Medical Information 800-896-5855</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>
<td>12 months</td>
<td>46 total - worldwide</td>
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<td>Raptor Pharmaceuticals</td>
<td>CYST-HD</td>
<td>Cysteamine bitartrate delayed-release capsules (RP103)</td>
<td>II/III</td>
<td>Christophe Verny, MD</td>
<td>Double-blind, placebo-controlled study to be followed by an open-label extension study</td>
<td>36 months</td>
<td>8 total - France</td>
<td>Study ongoing, preliminary results released</td>
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<td>National Institute of Neurological Disorders and Stroke</td>
<td>2CARE</td>
<td>Coenzyme Q10</td>
<td>III</td>
<td>Merit Cudkowicz, MD, MSc</td>
<td>Randomized double-blind study to see whether coenzyme Q10 is effective in slowing the worsening of symptoms of HD</td>
<td>5 years</td>
<td>48 total - United States, Canada, Australia</td>
<td>Study concluded for futility</td>
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<td>National Center for Complementary and Alternative Medicine</td>
<td>CREST-E</td>
<td>Creatine</td>
<td>III</td>
<td>Steven M Hersch, MD, PhD</td>
<td>Randomized double-blind study to test whether high-dose creatine can slow the progressive functional decline that occurs in adults with early clinical features of HD</td>
<td>3 years</td>
<td>52 total - United States, Canada, Australia, New Zealand</td>
<td>Study concluded for futility</td>
</tr>
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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 Trials, cont...

<table>
<thead>
<tr>
<th>SPONSOR</th>
<th>STUDY NAME/IDENTIFIER</th>
<th>STUDY AGENT</th>
<th>PHASE</th>
<th>PRINCIPAL INVESTIGATOR, CONTACT</th>
<th>DESIGN</th>
<th>TRIAL LENGTH</th>
<th>SITES</th>
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<tr>
<td>Auspex Pharmaceuticals</td>
<td>FIRST-HD</td>
<td>SD-809 Extended Release</td>
<td>III</td>
<td>Samuel Frank, MD Huntington Study Group: 800-487-7671</td>
<td>Randomized double-blind study to determine whether SD-809 ER tablets are effective in the treatment of chorea associated with HD. To be followed by an open-label, long-term safety study</td>
<td>12 weeks</td>
<td>7 total - United States</td>
<td>Study complete, top line results released</td>
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<tr>
<td>Auspex 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>7 total - United States</td>
<td>Enrollment complete, study ongoing</td>
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<td>Assistance Publique - Hôpitaux de Paris</td>
<td>REVHD</td>
<td>Resveratrol</td>
<td>III</td>
<td>Tiffany Monier, MS +33 1 57 27 42 22</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>Not yet recruiting</td>
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<tr>
<td>Assistance Publique - Hôpitaux de Paris</td>
<td>NEUROHD</td>
<td>Olanzapine, Tetrabenazine, and Tiapride</td>
<td>III</td>
<td>Anne-Catherine Bachoud Levi, PhD +33 (0)1 49 81 23 01</td>
<td>Randomized controlled study to compare the beneficial and adverse effects of 3 different neuroleptics in HD</td>
<td>1 year</td>
<td>1 total - France</td>
<td>Currently enrolling</td>
</tr>
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</table>

*To update or add a clinical trial, please e-mail editor@hdinsights.org.*  
*Sources: www.clinicaltrials.gov and apps.who.int/trialsearch/*
Highlights of HSG 2014

The 2014 Huntington Study Group Annual Meeting took place

November 6–8 in Minneapolis, Minnesota

By: Meredith A. Achey, BM

HSG 2014 highlighted "Ideas for the future" of the HSG, exploring education, innovation, and discovery in HD research. The meeting honored outgoing leaders Dr. Ira Shoulson and Dr. Steven Hersch, and welcomed new Chair Dr. Ray Dorsey and Co-chair Dr. Blair Leavitt.

Educational programming catered to both clinicians and researchers. Dr. Martha Nance, Clinical Professor of Neurology at the University of Minnesota, led a panel discussion on genetic testing and reproductive technology. The panel comprised genetic counselor Ms. Michelle Fox from the UCLA HD Center of Excellence; Ms. Debra Lovecky, Director of Program Services and Advocacy for HDSA; and Mr. Matt Bower, a University of Minnesota genetic counselor who also works in a diagnostic molecular genetics laboratory. Panelists brought attendees up to date on the latest genetic testing protocols and sparked a spirited debate.

The meeting included several training sessions for clinical trial teams. Dr. Ralf Reilmann from the George Huntington Institute, Münster, Germany, gave an overview of the quantitative motor (Q-motor) assessment system. Dr. David Craufurd from the University of Manchester, England, led an interactive session titled “Who’s afraid of the Problem Behaviors Assessment?”, describing the development and application of this rating scale. An informative and humorous session led by a panel of HSG coordinators and investigators on the finer points of creating and sustaining a top-notch HD research site followed. Through humorous skits featuring “Dr. P. Eye,” his team of harried coordinators, and auditor “Sawyer Data, FDA,” the panel illustrated the challenges and considerations involved in conducting a "top notch" HD trial.

Several sessions highlighted innovations in HD clinical care and clinical research. The HSG Clinical Trials Update gave members an overview of ongoing and recently concluded clinical trials. Mr. Joe Giuliano, Director of Clinical Operations at CHDI, presented on the opportunities for research available to the HD research community through ENROLL-HD. Ms. Bonnie Hennig, Associate Director of the University of Connecticut Huntington’s Disease Program, led a session titled “What’s hot at your center?”, where Dr. Jean-Marc Burgunder, Chair of the European Huntington’s Disease Network, described the integration of registry studies with clinical care in Europe. Dr. Craufurd described the development of a comprehensive HD care center from his genetic counseling unit in the UK, highlighting their traveling services for HD patients.

Recent scientific discoveries were highlighted throughout the meeting. In the first Insights of the Year panel, Drs. Francesca Cicchetti, X. William Yang, and Chris Tang described their groundbreaking HD research (see HD Insights, Vol. 9). The Innovators’ Forum, with presentations by representatives from Adamas, Intra-Cellular Therapies, Isis, Raptor, and Vaccinex, gave a glimpse into ongoing pharmaceutical research in HD. From new formulations of old compounds, to targeted gene therapeutic approaches and more, these innovators demonstrated the ongoing evolution of the approach to HD therapy.

Caring for young people in the HD community emerged as an important theme. Ms. Chandler Swope spoke about her work as the first HD Youth Organization Youth Worker. She uses counseling and group activities that help youth from HD families to network and share their stories, assisting them in coping with the challenges they face. She spoke of the need for increased involvement of youth in the HD research and clinical care community, in particular for young caregivers. Ms. Kristen Powers, producer of the documentary film Twitch, opened the 8th Annual HD Clinical Research Symposium on the final day of the meeting with a lively keynote presentation about taking a can-do approach to life and HD research, and the necessity of involving youth in the HD community.

Chaired by Drs. Andrew Feigin and Claudia Testa, the 8th Annual HD Clinical Research Symposium further updated members on ongoing research. Dr. Bindhu Paul presented her work on the neuroprotective role of cysteine. Dr. Vicki Wheelock described her team’s work to bring adult mesenchymal stem cells engineered to produce brain-derived neurotrophic factor, to human trials in HD patients. Dr. Diana Rosas described the findings of the PRE-CREST study, highlighting their development of new imaging markers. Dr. Kimberly Quaid described the ethical dilemmas that arise when considering the release of research results to trial participants. Finally, Dr. Dominique Bonneau presented interim results the ongoing CYST-HD trial of cysteamine bitartrate (see HD Insights, Vol. 9).

The meeting concluded with a half-day session for HD community members to learn about ongoing research, and to view Twitch. Led by Dr. Nance, the community events helped remind all HSG attendees of the importance of their ongoing work to find effective treatments for HD.
Cicchetti, cont...

CIÇCHETTI: I do not know of any studies that have specifically monitored the changes in these markers following treatment. However, one study has demonstrated normalization of cytokine levels and moderate motor benefits in animal models of the disease using a bone marrow transplant paradigm and a recent publication in Brain has reported that glucan-encapsulated siRNA can significantly reduce HTT levels in monocytes and macrophages derived from pre-manifest HD patients, which in turn decreases the levels of pro-inflammatory cytokines released by these cells. There were also a number of studies reporting benefits of the anti-inflammatory drug minocycline in animal models of HD, but the treatment did not translate into meaningful improvements in HD patients.

HD INSIGHTS: So we could be looking at mHTT and peripheral monocytes to determine whether new therapies are efficacious in HD?

CIÇCHETTI: If we establish that inflammation or immunity indeed plays a critical role in HD, we could certainly use some of these cell populations to monitor treatment efficacy. But even though inflammation/immunity may be important in driving disease pathology, I suspect the problem is much more complex, and we are likely to need to treat the disease with a combination of approaches.

Gene-silencing therapies using antisense oligonucleotides (ASOs) or RNA interference targeting specific SNPs to lower mHTT seem very promising in animal models of the disease. These methodologies would not target propagation per se but attack the problem upstream of propagation, aiming at the mHTT mRNA before the gene is translated. However, in anticipated clinical trials, ASOs will be delivered through the cerebrospinal fluid and siRNA directly into the brain to target cerebral mHTT, not the expression of mHTT in the periphery. I assume the delivery of ASOs could eventually be considered via the peripheral system to target peripheral cells.

HD INSIGHTS: And you think these peripheral monocytes could be used as an assay of the efficacy of these interventions?

CIÇCHETTI: They could be, or any other blood-borne cells. The monocytes are very few compared to other types of blood cells. We cannot discard other populations as potential biomarkers, nor the microvesicles and exosomes that they can release.

HD INSIGHTS: You mentioned that your research has implications for targets for therapy. Could you elaborate?

CIÇCHETTI: Of the mechanisms that we proposed or suspect underlie mHTT propagation, there are two that we are most eager to investigate. The first is trans-synaptic spread through the corticostriatal pathway, for which there is accumulating evidence both in vitro and in vivo, especially with the latest paper published by Pecho-Vrieseling et al. in Nature Neuroscience. The work of Dr. William Yang showing that modulating the expression of mHTT through the corticostriatal pathway can actually change some characteristics of the pathology, also provides evidence for the importance of this pathway in non–cell-autonomous mechanisms of protein spread. Gene silencing methodologies, either ASOs or siRNAs, applied directly into the brain could block the propagation of the mutant protein.

The second possibility for therapeutic development would be to target circulating immune cells, which we hypothesize carry the mutant protein and can transmigrate into the brain via leaky blood vessels.

Of course, there may be other explanations for the presence of mHTT within genetically unrelated grafted tissue. Explanations could be oxidative stress, inflammation, or poor trophic support. But again, I think that mHTT propagations via the corticostriatal pathway and/or the immune system are the most likely scenarios and therefore the best therapeutic targets.

HD INSIGHTS: Do you see any therapies that are currently under development that could potentially address either one of these possibilities?

CIÇCHETTI: To target the immune system, we could consider vaccines, but this approach has not yielded any benefits in other diseases such as Alzheimer disease, and in fact generates a number of complications. Intrabodies, which are recombinant single-chain antibody fragments, have shown significant effects in reducing the striatal mHTT protein load. ASOs are also showing great promise in animal studies, and could be used to target both cerebral and peripheral mHTT. No matter what the approach, it will be critical to select specific populations of HD patients, before excessive neuropathology has set in. Selecting late-stage patients will prove more difficult because there will be much more aggregated forms of mHTT in such patients, whom will not respond as well to ASOs. We need to silence the gene early, given that the soluble protein is likely to be the toxic form, not the aggregate itself.

HD INSIGHTS: Your paper has created quite a buzz, and was recently recognized as one of the papers of the year by the Editorial Board of HD Insights. Can you tell us who funded the study?

CIÇCHETTI: No one. But since the publication of the manuscript, we have received all the funding we have applied for. Persistence paid off and I am counting my blessings!

(continued on Page 13...)
Cicchetti, cont...

HD INSIGHTS: I assume given its impact that this paper was readily accepted by journals?

CICCHETTI: I can now laugh about it, but publishing this paper was quite a battle. It took close to two-and-a-half years. We first made this observation more than 3 years ago. I went to the microscope and saw the inclusions in the transplant. I remember calling a colleague in Europe and telling him about the observation, and he immediately replied that I needed to publish this paper as soon as possible. But we really, really struggled to get it published. The reviewers were intrigued and interested by the finding, or at least the majority of them, but did not quite believe it, and I think that they were not ready to accept the idea of non–cell-autonomous propagation of pathological proteins in genetic disorders. I have to admit that the first versions of the paper were bold and somewhat speculative, but now the published end product is something of a lobotomized version of what we really wanted to say.

What I was most pleased about when HD Insights contacted me to present this at HSG 2014 was the fact that we finally had a platform to present this work, where people wanted to hear what we had to say. And now that I see the paper of Pecho-Vrieseling et al.—which came out just a couple of months after ours—providing in vitro and in vivo evidence of non–cell autonomous mHTT spread, it is clear that we are now open to discussing these ideas and thinking outside the box.

This has been so rewarding and it has given me so much energy. I was a workaholic before, but now I am unstoppable. I really want to solve this thing. One of the things I have most enjoyed in the last couple of years is that the landscape of research has completely changed. Now we conduct multidisciplinary and multicentric research. Through this project we have teamed up with colleagues who are pure immunologists working on arthritis, for example. And together we are attacking this problem from a completely different perspective. It is a very exciting time.

HD INSIGHTS: What is the most exciting aspect for you?

CICCHETTI: It’s being able to rally colleagues from all disciplines to study this. It’s the collaboration with researchers who are completely outside this field and investigating or trying to apply concepts that they have discovered in their own research—in other words, thinking of the problem differently, in ways we had not thought of before.

I am also a big fan of recycling medicine that is already out there. It takes so long and it is so expensive to do research and development; why not screen compounds that are already available and have a good safety profile, and see if they can have applications for other disorders?

I have been blessed to work with wonderful students and collaborators on the *Annals of Neurology* paper, and to now have them on board, with new collaborators, to pursue this work.

HD INSIGHTS: So when you are not identifying propagation of mHTT, how do you spend your time?

CICCHETTI: I spend a lot of time in the lab. I’m a bit of a nerd and I must say that my staff are completely fed up with me, because even at Christmas parties, I talk about mHTT propagation! But I also love to travel, spend time with my family and practice tango and salsa. I’m going to see my parents in Florida over the holidays.

HD INSIGHTS: Will you take your microscope?

CICCHETTI: No, but I am definitely taking my computer, and working on our next paper reporting blood-brain barrier leakage in HD.

HD INSIGHTS: Dr. Cicchetti, thank you very much for all your time and for your great insights into a new area of HD research that has clearly captured many people’s attention.

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Editor’s Letter

Welcome to the 10th edition of HD Insights, timed for the beginning of CHDI’s 10th Annual HD Therapeutics Conference. We are pleased to continue our mission to promote, disseminate and facilitate research in Huntington disease. We are grateful to the Huntington Study Group (HSG), our sponsors, and our more than 2600 subscribers for their continuing support.

This edition explores several promising areas of current HD research. We discuss the positive results of Auspex Pharmaceuticals’ First-HD trial, which give the HD community hope of a second FDA-approved treatment for HD. We interview Dr. Francesca Cicchetti, whose groundbreaking research was featured in the Insights of the Year competition last fall, and bring you her thoughts on advances in our current understanding of HD and the future of HD research and therapies. Dr. Lise Munsie provides a “round-up” of current basic science and clinical research in HD. Our editorial team examines the use of laquinimod in neurodegenerative disease, which has led to the ongoing LEGATO-HD Phase 2 trial, and brings you the highlights of HSG 2014. Finally, we continue to provide an up-to-date status report on ongoing and recently concluded HD clinical trials.

The HD Insights team continues to rely on the support of firms dedicated to developing novel treatments to support our efforts to reach and educate the international HD research community. If you are interested in becoming a supporter, please contact me at editor@hdinsights.org. We welcome new contributors, suggestions for topics, and ideas about how we can better serve you. If you or someone you know would like to share their ideas with over 2600 HD researchers and clinicians around the world, please contact me at editor@hdinsights.org. Finally, subscription to HD Insights is always free: simply send us an email at subscribe@hdinsights.org.

-- Ray Dorsey, MD
Editor, HD Insights™

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