

Huntington Disease Clinical Research Symposium: Working Smarter to Find New Treatments

By Lisa J. Bain – February 2008

The Inaugural Huntington Disease Clinical Research Symposium, held on December 1, 2007 in Boston, Massachusetts, opened with a frank, endearing, and inspiring talk by Katharine (Katie) Moser, a young, healthy woman who learned less than three years ago that she has the gene for Huntington Disease (HD). Moser's comments on the unmet clinical research needs from the perspective of the [pre-manifest](#) population framed the remaining presentations about the wide-ranging efforts currently underway to find new treatments for HD.

Although Katie's childhood was colored by the presence of HD -- her grandfather became symptomatic when she was only four and subsequently died from complications of the disease -- her mother discouraged her from learning more about it, and later discouraged her from getting tested.

But Katie, displaying an independent streak, pursued testing anyway, in part to find an explanation for her mother's erratic and sometimes hostile behavior. "I figured it was better to live life understanding the possibilities than living in denial," she said. And after learning the results of the test, she has broken another one of her mother's rules not to talk about it.

"It's a very lonely disease when nobody will talk about it," she said. "Since testing, I've talked about it a lot," not only to cousins, friends, coworkers, and employers; but also to Amy Harmon, a reporter from the New York Times, National Public Radio, and ABC's "The View". She even optioned the movie rights to her story. Harmon's article "Facing Life with a Lethal Gene," appeared in the Times on March 18, 2007. All of this, said Moser, is to raise awareness about the disease both within the HD community and in the general public. She has also participated in research studies, gotten involved with the Huntington Disease Society of America's (HDSA) National Youth Alliance, and works as an occupational therapist at the Terence Cardinal Cooke Health Care Center in New York City, where she provides care to late-stage HD patients.

In preparation for her talk at the HD Clinical Research Symposium, Moser conducted a brief, non-scientific survey of people with HD to learn about their knowledge and experiences with research studies, as well as their thoughts about what is needed from the research community. The results of this survey suggest a lack of accurate, up-to-date, and accessible information about the goals of studies, who can participate, and how to sign up. In addition, Moser and others reported a lack of follow through after attempting to enroll in a trial. They also suggested a number of areas in which research is needed:

- Juvenile HD
- Psychological, sociological, and cultural aspects of having HD and growing up in an HD family
- Strategies to postpone institutionalization
- Role of nutrition and supplements
- Exercise and stress reduction

- Importance of sleep
- Alternative therapies

Carrying out all of these studies, as well as the drug studies that were the focus of much of the symposium, will of course require more participants, so Moser asked people what motivates them to enroll in clinical trials. In addition to payments and other rewards, an interest in the results, and helping other people with the disease, another important motivator was hearing the results of recent trials.

Some of these issues were addressed in posters presented at the symposium. Abstracts of all the posters will be available in the 2008 volume of *Neurotherapeutics*, the journal of the American Society for Experimental NeuroTherapeutics. Among other topics, posters discussed family participation in HD trials (#15), the decision to forego testing in people at risk for HD (#17), end-of-life care for HD patients ((#22, 23), and quality of life among spouses of people with HD (#26). In addition, with regard to the point about communicating the results of studies to research participants, E. Ray Dorsey from the Huntington Study Group (HSG) reported on a systematic effort that was made to communicate study findings to participants in the TREND-HD trial soon after public release (#35). Participants reported a high degree of satisfaction when they were contacted personally by staff at the trial site or when they participated in a conference call with the researchers.

Karl Kiebertz asked about the best way to communicate results when a trial shows that a treatment was not effective. Moser said that communicating with participants even when the results are negative is important, especially when future studies are planned that leave room for hope. She reminded the audience that better communication and follow-up is also needed when conveying the results of genetic testing.

Preparing for efficient trials when preventive drugs become available – Predict-HD and the HD Toolkit

In preparation for trials of drugs that might slow or prevent disease in pre-manifest individuals, several observational studies have been collecting data to identify early markers of neurodegeneration that might be used to indicate the best time to start treatment and whether a treatment is working. **Kevin Biglan** from the University of Rochester Medical Center presented recent findings from Predict-HD (Neurobiological Predictors of Huntington Disease) study. This international study recently enrolled its 1,000th participant, most of whom have the [expanded HD gene](#) but have not yet begun to manifest symptoms. Using a formula that estimates age of onset based on the person's age and [CAG repeat length](#), the researchers investigated how the baseline total motor score and scores on individual motor tests relate to estimated age of onset and [striatal volume](#) (measured using magnetic resonance imaging, or MRI). They found that the closer an individual was to his or her predicted age of onset, the more likely he or she was to have subtle motor abnormalities and loss of striatal volume. These findings suggest that measurement of subtle motor abnormalities -- in particular bradykinesia (slowness of movements), oculomotor (eye movement) abnormalities, and chorea (involuntary writhing movements) – may be sensitive measures of disease in the pre-manifest period. Continued study of these individuals over several years will be need to see how these measures change over time in order to determine if they could be used to predict disease onset and monitor treatment effects.

Meanwhile **Julie Stout** and colleagues at the Indiana University and Monash University in Australia are conducting a systematic review of the published and unpublished literature to identify the optimal outcome measures to use in clinical trials. Hundreds of measures have been used in the thousands of studies that have been conducted, said Stout, yet until now there had been no systematic analysis of these measures. In the “HD Toolkit Project”, Stout and colleagues have so far reviewed more than 8280 abstracts published since 1993. This is an ongoing study, with new data added as additional studies are conducted.

They rated the tests used in these studies according to well-defined criteria. Only those tests that detected decline in pre-HD subjects over 2-4 years and in more than 30 samples were classified as having “proven sensitivity.” Other possible rankings were: “probable sensitivity,” “promising,” “not recommended,” or “proven insensitivity.” Only 9 measures, all in the cognitive and motor domains, earned the ranking of “proven sensitivity.” While no assessments within the neuropsychological/behavioral or quality of life/functional domains earned the top ranking, Stout said that many measures were ranked “probable sensitivity,” or “promising.” These measures, she said, should be included in upcoming studies in order to gather more data. Stout urged investigators to consider the existing evidence (collected by the HD Toolkit Project) when selecting outcome measures to be used in upcoming studies, and to report findings of their studies with descriptive statistics so they can be included in this meta-analysis as it moves forward.

Many posters also presented data about possible markers of disease progression in pre-manifest subjects. These included positron emission tomography (PET) studies that assess metabolism in the brain (#9,10), biochemical markers that can be measured in plasma or other biological fluids (#11), cognitive and behavioral aspects such as changes in the ability to recognize negative emotions (#18, 19, 29), and smell identification (28).

Emerging clinical candidates from the CHDI pipeline

In parallel to these efforts to determine the best way to evaluate new drugs when they become available, early stage drug development programs are underway to prioritize and optimize candidate compounds that have been identified. CHDI, Inc. is a non-profit organization dedicated to rapidly discovering and developing new drugs using a “virtual” model that combines in-house expertise in drug development with outsourced wet-lab investigations and a number of collaborations with other biotech companies.

Robert Pacifici, Chief Scientific Officer of Drug Discovery and Development at CHDI described six of the programs that are furthest along in the drug development pipeline:

- One program partners with the biotech firm CombinatoRx to comb the existing [pharmacopeia](#) for existing drugs that are safe and well tolerated, and that might be used in combinations with other drugs to achieve a beneficial effect in HD patients. Using a variety of high-throughput assays that look at a number of different mechanisms thought to be important in causing pathology in HD, they have assessed hundreds of combinations across a range of doses. Candidates that appear promising in these tests will next be moved into mouse studies to determine which, if any, should be moved forward into human trials.
- Histone deacetylase (HDAC) inhibitors are already being tested in clinical trials in HD patients. They are thought to counteract [transcriptional dysregulation](#),

- which has been observed in HD tissues and is thought to be an important pathogenic mechanism. Since the currently available HDAC inhibitors may not be ideal, CHDI has been working with partners EnVivo Pharmaceuticals and MethylGene, Inc. to determine which of the many subtypes of HDACs are critical in HD, and then to identify and/or modify candidate compounds so that they inhibit these subtypes. One compound (called “Compound 3”) identified through this collaboration was described in a poster (#25). This compound appears to have desirable HDAC inhibitory properties, low toxicity, can be given orally, and reaches the brain. It is currently undergoing testing in an HD mouse model.
- With collaborator Varinel, Inc., CHDI is evaluating a drug called M30, which was developed for Parkinson’s disease (PD) but targets mechanisms that are also important in HD. M30, which inhibits [monoamine oxidase \(MAO\) A and B](#) and is also a metal chelator, has been shown in some studies to be neuroprotective. In HD mice, the drug improved [rotarod](#) performance and increased survival; and it reduced cytotoxicity in a brain slice assay. CHDI is now trying to improve the pharmacokinetics (e.g., absorption, distribution, metabolism, and excretion) of this compound and is looking across a family of related molecules to decipher which parts of the molecules are responsible for the beneficial effects.
 - Coenzyme Q10 (ubiquinone, also known as CoQ) is a widely available dietary supplement that has shown some beneficial (though not significant) effects in slowing the progression of HD, possibly by reducing oxidative damage. CHDI is now working with Edison Pharmaceuticals, Inc., looking for the “next generation” of CoQ by modifying the naturally occurring substance so that it will have better drug-like properties, such as higher anti-oxidant potency and better solubility. One of the compounds developed thus far has shown good efficacy in a cell-based assay, suggesting that they are on the right track. Other compounds are also being evaluated in a variety of assays. Meanwhile, researchers are planning a trial of ubiquinone in pre-manifest subjects (poster #13).
 - In another collaboration, CHDI is working with the Japanese drug company, Kyowa Hakko Kogyo to evaluate a compound called KW-6002 (Istradefylline), an adenosine A2A receptor antagonist that was also developed as a treatment for PD. Adenosine A2A receptors are involved in [excitotoxicity](#) and neurodegeneration, so they seemed likely to be beneficial in HD. While KW-6002 has shown some promising results in HD mice – improving rotarod performance and some other behaviors – the results in *in vitro* models have been inconsistent, prompting more studies into the compound’s mechanism of action.
 - While most of CHDI’s programs focus on small molecules, they also are working with Isis Pharmaceuticals, Inc. in an effort to discover and develop an antisense drug for HD. An antisense compound would target the mutant huntingtin gene itself, trying to knock down levels of the gene so that less of the mutant protein would be produced. Isis has had success in developing antisense drugs for a variety of other conditions, including the first approved antisense drug, [Vitravene](#), for cytomegalovirus-induced retinitis in AIDS patients. Another drug in their pipeline targets a molecule associated with inherited Amyotrophic Lateral Sclerosis (ALS, also known as Lou Gehrig’s disease). In rats and mice, they have shown some promising results after delivering this drug directly into the

cerebrospinal fluid (CSF) in order to lower the level of mutant protein in the brain. A similar delivery system might be required in HD, however, studies will be needed in a larger animals such as dogs to evaluate distribution of the drug.

Current status of clinical trials:

Two recently completed clinical trials were reported by the HSG. **Steven Hersch**, from Massachusetts General Hospital described the first controlled trial of an HDAC inhibitor, phenylbutyrate, in people in the early symptomatic stage of HD. This trial, dubbed PHEND-HD, was designed to test safety, tolerability, and clinical impact of the drug, and to evaluate the feasibility of assessing several possible plasma biomarkers. For the first four weeks of the study, subjects received either 15 mg. of phenylbutyrate or placebo in a double-blinded fashion. This was followed by a 12 week open-label phase. Results showed that the drug was well tolerated, with only mild adverse effects; however there were only minor effects on HD symptoms. One plasma biomarker – leukocyte histone acetylation -- appeared to change in relation to the drug levels, suggesting that this marker may be useful in assessing the response to treatment with HDAC inhibitors.

E. Ray Dorsey reported results from the TREND-HD study, a trial of ethyl-eicosapentaenoic acid (ethyl-EPA). Ethyl-EPA, an omega-3 fatty acid commonly found in fish oil, is thought to reduce oxidative damage in cells by stabilizing mitochondrial membranes. Mitochondria are the organelles in cells responsible for energy production. A previous study had suggested that ethyl-EPA might improve motor function in people with HD, particularly in those with shorter trinucleotide repeats. In this study, research participants were randomized to receive either ethyl-EPA or placebo for six months. The initial 6-month period was followed by a 6-month open-label trial. Interestingly, at the end of 6 months there was no difference between the two groups; however, after 12 months, those who had initially received ethyl-EPA and therefore had been taking it for a full 12 months had an improved total motor score compared to those who had initially been randomized to placebo and had only taken ethyl-EPA for six months.

Challenges in drug development from the regulatory perspective

The final keynote address was delivered by **Russell Katz**, Director of Neurology Products at the Food and Drug Administration (FDA). Successful development of experimental treatments for any disease involves much more than showing a drug is effective. Safety, adequate manufacturing controls, and information on how the drug is metabolized in the body also must be demonstrated; and these steps, in addition to clinical trials, take considerable time and involve large numbers of study subjects, said Katz. For orphan conditions such as HD, the FDA and Congress have attempted to introduce some flexibility into the approval process. For example, approval requires “substantial evidence” of effectiveness, which had been interpreted as requiring at least two studies that independently showed similar results. However, Congress passed a new law in 1997 that allows the Secretary of Health and Human Services to certify, in exceptional cases, that the “substantial evidence” criterion has been met based on a single well-controlled clinical investigation plus confirmatory evidence that the treatment has produced a beneficial effect. This less stringent standard might be applied, for example, if a single trial showed effectiveness on an important parameter, and if that trial would be difficult to repeat either because not enough appropriate subjects are available or because the affected outcome is of great importance, such as an effect on mortality. Confirmatory

evidence might be something derived from imaging studies or change in a biomarker. Katz noted that this revised standard has yet to be applied in neurology.

The challenges are even greater for a disease like HD, where drugs may be treating symptoms only (without affecting the disease process itself) and where no approved treatments are available for the disease. With no precedent to drug approval for a disease like HD, appropriate outcomes remain unclear. The FDA's response to this dilemma for Alzheimer disease (AD) has been to require a "dual outcome", which means a treatment must show effectiveness on both a measure of cognition and a measure of global functioning. This dual standard for AD has been in effect for 15 years, said Katz, noting that something similar may be required for HD.

The FDA also wants to make sure that the criteria used to assess effectiveness map onto something clinically important at the stage of disease for which the drug is targeted. For example, in evaluating the effectiveness of tetrabenazine as a treatment for chorea (the first ever FDA Advisory Committee for an HD treatment recently unanimously recommended approval), they were concerned that the tools used to measure chorea were picking up clinically meaningful changes. Assessment of some other symptoms, such as dementia and psychiatric problems can be even more problematic since it may be unclear if these symptoms are actually related to HD and if the treatment has an HD-specific effect.

Trials of preventive treatments face even more hurdles. Moreover, it all comes down to labeling. The labeling has to reflect what the treatment does. In this context, said Katz, "prevention is a loaded word. It means that people don't get the disease or don't get symptoms," said Katz. "It's hard to imagine a trial design that would truly support a prevention claim because the period of risk is not finite." In other words, a delay to onset of symptoms is not the same as prevention and does not imply an effect on disease progression. One way to look at the effect of a treatment on progression would be to look at validated surrogate markers. For example, cholesterol level is a validated surrogate marker for heart disease because even though lowering your cholesterol level does not make you feel any better, it has been shown to reduce the risk of heart disease. However, no such validated surrogate marker exists for HD.

Agency rules also allow approval of a drug based on an unvalidated surrogate if it is reasonably likely to predict clinical outcome. But surrogates can fail to predict outcome for a number of reasons. For example, a drug might cause a reaction that is thought to be protective, but in fact does not change the course of the disease. Identification of biomarkers and surrogate markers has thus become a major area of emphasis for the HD drug development community, as evidenced by the presentations and posters at this symposium.

Katz concluded by emphasizing that while typical FDA standards are likely to apply for HD, there is "absolutely room" for negotiating some aspects of the standards such as the number of studies required. "Moving forward is going to require flexibility on all parties, and an understanding of what the rules are and how they can be applied," he said.

GLOSSARY OF TERMS

CAG repeat length – The letters C, A, and G represent three of the nucleotide building blocks – cytosine, adenine, and guanine -- that make up DNA. In people with HD, the huntingtin gene contains a section that has long string of CAGs repeated over and over. The number of CAG repeats is referred to as the CAG repeat length. People with more than 39 CAG repeats will get the disease, but those with fewer than 30 will not.

double-blind clinical trial – a clinical trial in which neither the subject receiving the treatment nor the clinician providing the treatment know whether the subject is receiving the actual drug or a dummy pill (placebo). In other words, both the subject and the clinician are “blind” to the treatment the subject is getting.

excitotoxicity – a process where nerve cells are damaged or killed by the overactivation of receptors for certain neurotransmitters that are toxic at high levels.

expanded HD gene – In people with HD, the huntingtin gene contains a section that has been expanded by a long string of repeats of three nucleotides (DNA building blocks), called cytosine, adenine, and guanine (CAG). Everyone has the huntingtin gene, but only people who have more than 39 CAG repeats will get the disease.

in vitro – Latin for “in glass”. In vitro experiments have been conducted in test tubes rather than in animals or people.

monoamine oxidase (MAO) A and B – monoamine oxidase A and B are enzymes produced in neurons and other cells that play an important role in neurotransmission (nerve cells communicating with one another). MAO inhibitors are used to treat depression and are often used to treat Parkinson’s disease.

open-label clinical trial – a trial that in which both the clinician and the subject know which treatment is being given.

pharmacopeia – the collection of all available drugs.

placebo – a pill or substance made to look like a drug but that actually has no active ingredient. Sometimes the placebo is a sugar pill. In a placebo controlled trial, the placebo is given in a form that looks exactly like the study drug so that participants do not know if they are receiving the real drug or not.

pre-manifest HD – In HD, people who have the expanded HD gene but have not begun to show signs or symptoms are said to be “pre manifest” (before the disease manifests itself).

rotarod – a treadmill device used in mouse and rat studies to evaluate motor coordination and fatigue..

striatal volume – the striatum is the area of the brain that is most severely affected in HD. Because nerve cells in the striatum die as the disease progresses, the volume or size of the striatum decreases. This can be measured using sensitive imaging tests such as magnetic resonance imaging.

transcriptional dysregulation – a disease mechanism in HD where the expression of certain genes is disrupted.

trinucleotide repeats – three nucleotides (DNA building blocks) that are repeated over and over in a gene sequence. In HD the trinucleotide CAG (cytosine, adenine, guanine) is repeated at least 39 times.