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‘It’s really getting real’: payoffs in the effort to treat Huntington's disease

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At Risk for Huntington's Disease

HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.

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'It's really getting real': payoffs in the effort to treat Huntington's disease

The path to treating Huntington's disease – a potential major breakthrough in the history of science and medicine – is becoming clearer.

That was the takeaway message from the Ninth Annual HD Therapeutics Conference, organized by the CHDI Foundation, Inc. and held February 24-27 at the Parker hotel in Palm Springs, CA. Spending tens of millions of dollars annually, CHDI is a non-profit, virtual biotech founded solely to discover HD treatments. Some 300 participants from academia, the pharmaceutical industry, and biotech firms took part, as well as a number of patient advocates, including Olympic rowing medalist Sarah Winckless, who delivered the keynote address.

"The tagline would have to be 'it's really getting real,'" said Robert Pacifici, Ph.D., the chief scientific officer for CHDI Management, Inc., in an interview with me at the conference. "What I'm seeing at this conference already is the culmination of very large, very long-term efforts – things that have taken years and thousands of person hours, patients', caregivers', researchers', and physicians' – finally coming together in ways that are really conclusive and really helpful."

All that work has involved numerous questions about the disease and potential ways to treat it, Dr. Pacifici explained.

"All of those things sadly have an incredibly high attrition rate," he observed. "The fact that we're getting answers is the thing that makes me the most excited. Sadly, sometimes we don't like the answer. Sometimes the answer is: 'That doesn't work.' But that's still very useful for researchers."

Winnowing out the useless approaches allows researchers to "refocus our resources on something that we feel has a better chance of bearing fruit," Dr. Pacifici said.

Sitting one evening with a group of CHDI researchers, I expressed the natural concern of the HD community – a concern sometimes tinged with impatience and frustration: could the rapidly expanding knowledge about HD result in an endless search for treatments fueled by questions that simply produce new questions rather than treatments?

They answered with an emphatic *no*. Echoing Dr. Pacifici, they said that real solutions were in the works.

The conference did seem more coherent in comparison with the previous three I had attended. Indeed, as one senior CHDI advisor observed in response to my observation, Huntington's researchers now have an understandable "story to tell" about the disease and the research.

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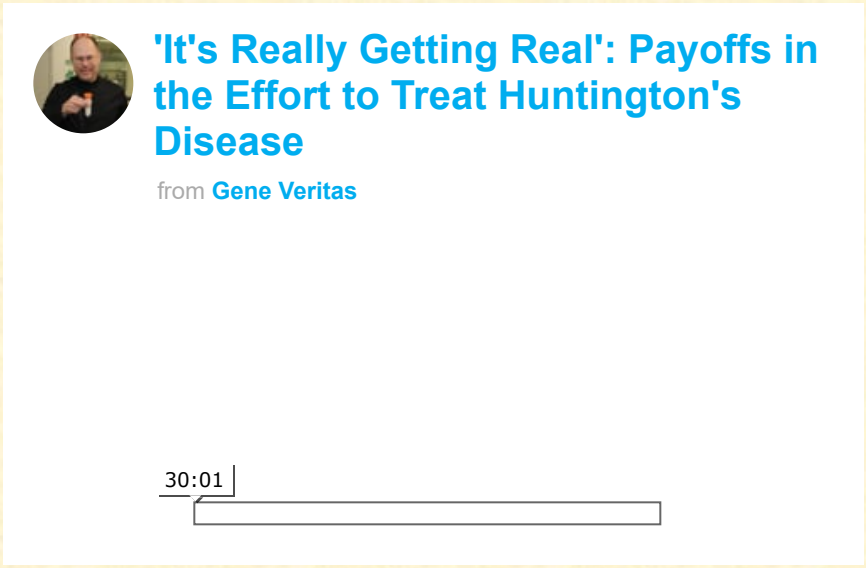
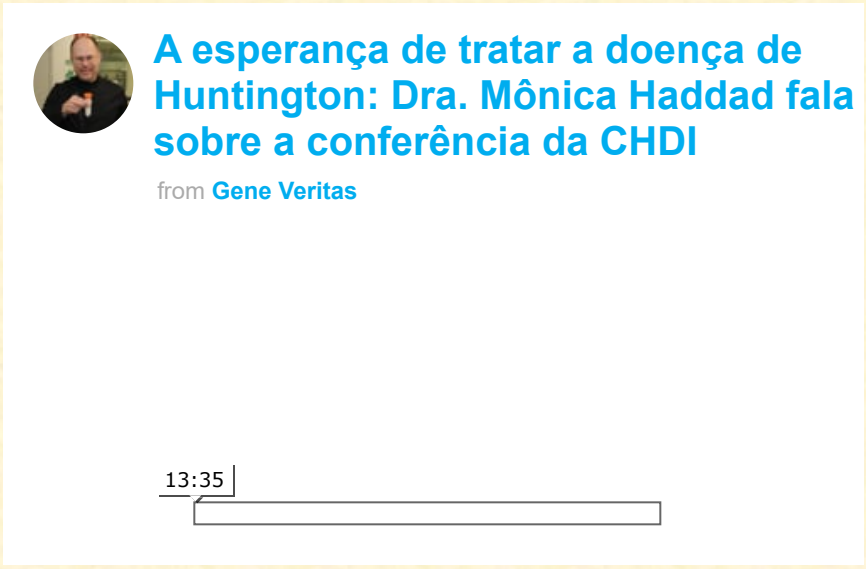
You can watch my interview with Dr. Pacifici in the video below. Just below the Pacifici interview, Portuguese speakers can watch my interview about the conference with Dr. Mônica Haddad of Brazil.



'It's Really Getting Real': Payoffs in the Effort to Treat Huntington's Disease from Gene Veritas on Vimeo.



A esperança de tratar a doença de Huntington: Dra. Mônica Haddad fala sobre a conferência da CHDI from Gene Veritas on Vimeo.

Confirming the shots on goal

Just three days before the conference, CHDI and Genzyme Corporation announced an agreement to jointly develop a "novel gene-silencing therapeutic for Huntington's disease" using an adeno-associated virus, which does not cause disease, as a delivery system.

The venture expands CHDI and other research projects' portfolio of potential treatments for HD, several of which are in the early stages of clinical trials or aim to begin trials soon.

In Dr. Pacifici's words, the growing number of drug targets means there are more "shots on goal" in the quest for treatments.

CHDI is concentrating on "validating" (confirming) the targets to assure that as many potential remedies as possible have a chance of becoming effective, safe treatments, Dr. Pacifici explained.

"It's important for any drug discovery organization, because when you select a target, that's what underpins the rest of the (drug discovery) activity," he said.

No organization has yet discovered how to validate targets "exactly," he said. However, CHDI is especially working hard to insure that a "particular target is really tethered" to the HD disease process and not some other disease or process, he added.

"While nobody has the magic bullet there, it was really impressive to see the variety of approaches that were taken," Dr. Pacifici said of the talks on target validation.

These included X. William Yang's report on his latest research with transgenic HD mice, Ernest Fraenkel's study of the impact of the mutant huntingtin gene at the molecular level, and CHDI scientist Jim Rosinski's efforts to unify and interpret the totality of biological data on HD by employing a systems biology approach.

You can watch an excerpt from Dr. Fraenkel's presentation, Dr. Rosinski's full presentation, and most of the other talks by viewing my 2014 CHDI video album.

Finding a modifier gene, delaying onset

Jim Gusella, Ph.D., one of the lead discoverers of the HD gene in 1993, described the work of a large international team to find a so-called modifier gene, which might act as a trigger for the disease and affect the rate of progression.

Such a gene could also become the target of a treatment, Dr. Pacifici explained.

"Imagine coming up with a drug that can delay your age of onset by 30 years," he said, referring to the wide variability in age of onset for people with the same degree of mutation. "That would be fabulous."

The Gusella team's search for the modifier gene points to "a couple of specific sites on human chromosomes," Dr. Pacifici said. In contrast with the numerous studies done in mice and other organisms, this project "was generated with human data. So we don't have to worry about the predictive value of those studies."

Dr. Pacifici described the 20-year quest for the modifier gene as "a great example of how the community pulls together and the generosity of the families affects the progress of research. Without your blood, without your DNA sequences, without your permission, there's no way these types of studies could be done."

The team analyzed DNA from more than 4,000 HD gene carriers and affected individuals. The study also required the ongoing commitment of participants to allow researchers to track their symptoms.

"We need to make the correlation as to when the motoric age of onset (the start of involuntary movements) occurred," Dr. Pacifici explained. "That's invaluable and incredibly appreciated. Hopefully now people can understand why participation in trials like this leads to such exciting discoveries."

New potential therapies

A session on "novel therapeutic approaches" focused on potential remedies different from the traditional concept of oral medication.

Jan Vesper, M.D., presented the promising results of his pilot trial using deep brain stimulation, which involves the placement in the brain of metal capsules covered with electrodes. Long-time HD specialist Gill Bates, Ph.D., discussed her new research on the muscle deterioration involved in HD mice and the potential use of a myostatin inhibitor to remedy the problem as well as perhaps ameliorate the involuntary movements typically suffered by patients. Beth Stevens, Ph.D., explained the importance of restoring proper function of microglia (cells performing as the immune system of the nervous system) in pruning synapses, the connections between brain cells.

'A horrible, lifelong case of jet lag'

Changes in people's behavior could provide another way to ameliorate HD, Dr. Pacifici noted.

Along those lines, Christopher Colwell, Ph.D., presented critical new research on the circadian rhythm – our sleep clocks – and how its disrupted function in HD might worsen symptoms.

"Think of Huntington's almost as a horrible, lifelong case of jet lag," Dr. Pacifici said in describing the implications of Colwell's and others' work in this area. "By entraining (synchronizing) the clocks in your mind and the clocks in your various organs to stay in sync with each other – by using things like when you eat, when you go to sleep, when you exercise, what kind of light you're exposed to – you could compensate for some of the mechanisms that go awry in Huntington's disease. That type of regimen could be a therapy, or an add-on to a therapy, rather than something as traditional as a pill."

Dr. Colwell's engaging talk provided a wealth of ideas about the circadian rhythm and keeping it healthy. You can watch his presentation in the video below.

Circadian disruptions in Huntington's disease: mechanisms and possible treatment options

from Gene Veritas

37:54

Circadian disruptions in Huntington's disease: mechanisms and possible treatment options from Gene Veritas on Vimeo.

Alpar Lazar, Ph.D., Stephen Morairty, Ph.D., and Tom Warner, Ph.D., provided additional evidence about the importance of the sleep cycle.

Assuring the drug does its job

In the session on "huntingtin lowering biomarkers," several presenters described cutting-edge techniques for measuring the efficacy of potential therapies designed to attack HD at its genetic roots and reduce the effects of the mutant huntingtin protein. Those projects include the above-mentioned CHDI-Genzyme venture and the Isis-Roche-CHDI partnership.

"What you'd like to do is make sure that after you administer one of those drugs, that the drug has done its job," Dr. Pacifici explained. "We don't want to wait for five years to measure hundreds of people only to find out that the drug never did its primary job, which was to lower huntingtin levels."

Along with an expert task force, CHDI has developed a series of ways to determine huntingtin-lowering efficacy in humans within a period of weeks, he said.

"Because we want to know what's going on in the human brain, and we can't go in there and take a little chunk of brain out every couple of weeks, we have to figure out a way of non-invasively making those measurements," Dr. Pacifici continued.

The techniques include quantitative EEG (a kind of brain mapping), magnetic resonances pectroscopy, assessment of dysfunction in the mitochondria (the powerhouses of the cell), and measurement of huntingtin in bodily fluids such as cerebral spinal fluid.

Scientists are developing ways to measure other types of potential HD remedies such as phosphodiesterase inhibitors (aka "Viagra for the brain").

As the HD field moves towards clinical trials, CHDI has increasingly emphasized the need for the exchange of information between scientists in the lab and physicians and others focused on patients and clinical trials, Dr. Pacifici commented. Such teamwork will enhance the possibility of finding treatments, he said.

Supporting Enroll-HD

The conference also featured several activities promoting Enroll-HD.

First announced in 2010 and officially launched in 2012, the CHDI-sponsored Enroll-HD is building a worldwide registry of HD patients, HD gene carriers, untested at-risk individuals, family members, and volunteers. It aims to facilitate scientific understanding of HD, identify potential participants in clinical trials, and therefore speed the process of finding therapies.

In a pre-conference meeting of Enroll-HD physicians and administrators on February 23, participants focused on ways to use the project to improve patient care. On February 24, Enroll-HD's international steering committee met to discuss administrative matters.

On February 25, the CHDI conference featured a practical lunchtime session that provided an update on program details like the number of participants.

A 'matchmaker' facilitating clinical trials

In order to deepen understanding of Huntington's, Enroll-HD looks at individual and family histories of HD "over a long period of time," Joe Giuliano, CHDI's director of clinical operations and the chief Enroll-HD administrator, said in an interview on February 24.

"The vision for Enroll-HD is to provide a clinical research platform that can be used by the community of HD researchers around the world to do

clinical studies, and it can be used by pharmaceutical sponsors to do clinical trials," Giuliano explained. "It's an enabling tool to help answer important questions about Huntington's disease using clinical research."

Giuliano described the program's three levels: the international administration, the wide range of sites based in local communities (run by physicians and other health workers), and the HD families.

"It starts with families," Giuliano said. "Enroll-HD is really a study for all the family to participate in.

"Enroll-HD is a great opportunity for us to come together as a global research community. The clinical trials that are going to lead ultimately to new therapies for Huntington's disease are going to be conducted in global clinical trials.... The more people we can get in Enroll-HD, the more powerful the study can become, for example, for recruiting for clinical trials. Enroll-HD can help identify participants ... who are eligible for clinical trials."

This potential makes Enroll-HD "very attractive" for pharmaceutical companies to collaborate with the program, Giuliano said.

Enroll-HD is a "matchmaker" putting together researchers, patients, drug companies, and others, he continued.

Anybody in the HD community can participate, including unaffected relatives of HD people. "By joining Enroll-HD, you're being very proactive in a lot of different ways," he said. "You're providing the possibility that you may be eligible for a future clinical trial."

The larger the pool of potential participants, the faster trials can take place, he concluded.

You can watch my interview with Giuliano in the video below.

For other coverage of the conference, visit www.HDBuzz.net.

Coming soon: a detailed report and more videos on Enroll-HD.

What is Enroll-HD? An interview with Joe Giuliano

from **Gene Veritas**

22:49

What is Enroll-HD? An interview with Joe Giuliano from Gene Veritas on Vimeo.

Posted by Gene Veritas at 10:49 PM

Labels: biotech , brain , CHDI , circadian rhythm , drug target , Enroll-HD , gene silencing , Huntington's disease , modifier gene , muscle , patient , pharmaceutical ,

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