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‘Drug hunters’ bring hope to Huntington’s families

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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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About Me

GENE VERITAS

MONDAY, FEBRUARY 21, 2011

'Drug hunters' bring hope to Huntington's families

Scientists and pharmaceutical companies are making steady progress in the search for treatments for Huntington's disease, increasing the hope that this generation of HD-affected families will finally get long-awaited relief from its devastating, ultimately deadly symptoms.

This was the message of the Sixth Annual HD Therapeutics Conference, sponsored by the CHDI Foundation, Inc., from February 7-10, 2011, at the Parker Palm Springs hotel in Palm Springs, California.

After delivering the keynote address to about 250 prominent scientists, physicians, pharmaceutical representatives, and supporters of the HD cause on the evening of February 7, I spent the next three days observing scientists speak on the latest advances in HD research and their plans for finding treatments.

This was a conference of "drug hunters," the people in the trenches of university, corporate, government, and foundation labs who are working as quickly as possible to develop a myriad of ways to stop HD.

Informally known as the "cure Huntington's disease initiative," CHDI invited researchers to outline progress in four main areas, which I describe below after the following overview interview with Robert Pacifici, Ph.D., CHDI's chief scientific officer.

Overview video and summaries

Click "play" on the video below to see my interview with Dr. Pacifici. In addition to outlining the main points of the conference, Dr. Pacifici urged the HD community to participate in trials that will assist scientists in their quest for treatments.

You can also read a daily summary of the conference at the excellent new science website http://www.hdbuzz.net/.

View my complete profile

HD Links

Huntington's Disease Society of America
International Huntington Association
Huntington's Disease Drug Works
Huntington's Disease Lighthouse
Hereditary Disease Foundation
Huntington's Disease Advocacy Center
Thomas Cellini Huntington's Foundation
HDSA Orange County (CA) Affiliate
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HD Blogs and Individuals

Chris Furbee: Huntingtons Dance
Angela F.: Surviving Huntington's?
Heather's Huntington's Disease Page

Gene Veritas interviews CHDI chief researcher Robert Pacifici

from **Gene Veritas**

17:18

Gene Veritas interviews CHDI chief researcher Robert Pacifici from Gene Veritas on Vimeo.

Area 1: Decreasing huntingtin

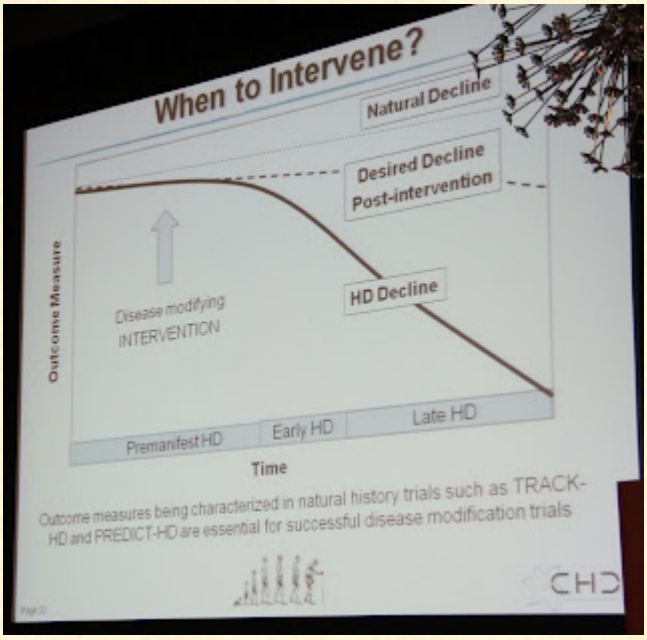
The first and most promising area involves the attempt to attack HD at its genetic roots. This approach is called "lowering huntingtin," the protein produced in our cells by the huntingtin gene. HD people have a mutated gene, and that mutation produces a faulty huntingtin protein, which compromises the health of brain cells.

As a result, they have two kinds of this protein. There is the "good," or normal, huntingtin, which is produced by the gene inherited from the non-HD parent. And there is "bad," or abnormal or defective huntingtin, which is produced by the gene from the parent with HD.

"In my six years at CHDI, we've seen (potential drug) targets come and go," said Douglas Macdonald, Ph.D., CHDI's director of drug discovery. "Only one has continued: huntingtin."

Above, Dr. Macdonald addresses the conference. Below, a slide from his presentation pointing out the need to lower huntingtin before symptoms

begin (photos by Gene Veritas).



CHDI's current budget stands at approximately $100 million, a substantial sum compared to the amounts available just a decade ago in the world of HD research. CHDI intends to spend about half of the drug development portion of its budget in the area of huntingtin lowering. This approach appears to come closest to the idea of a "cure," although most scientists believe that HD will be merely controlled like diabetes or high cholesterol, and then only with a cocktail of drugs.

On this front CHDI has partnered with a number of firms and labs: Isis Pharmaceuticals, Inc. (click here to read more); Alnylam Pharmaceuticals; Evotec; Dr. Neil Aronin of the University of Massachusetts School of Medicine; Dr. Paul Patterson of the California Institute of Technology; Dr. Edvard Smith of the Karolinska Institutet in Stockholm, Sweden; and Dr. Robert M. Friedlander of the University of Pittsburgh School of Medicine. Novartis, one of the world's largest pharmaceutical companies, is also engaged in this area of research.

Both Isis and Alnylam are very close to applying for permission from the Food and Drug Administration to begin human clinical trials with their potential drugs.

Challenges

While potentially very effective for those with HD, lowering huntingtin also poses several huge challenges for scientists, Dr. Macdonald pointed out.

What should be targeted, good or bad huntingtin or both? How much should the protein be lowered? What part of the brain should be treated? And at what stage of the disease should a drug be given to a patient or non-symptomatic, gene-positive individual such as myself?

After all, the huntingtin protein is needed for the development of the cell. Even defective huntingtin does some good, Dr. Macdonald explained.

Unfortunately, so far the potential drugs for lowering huntingtin do not distinguish between the good and the bad, so reducing the bad decreases the good by the same percentage. (I'll be writing soon on how Isis is attempting to find a way to keep the good while lowering the bad.)

In an interview, world-renowned HD specialist Dr. Michael Hayden, of the University of British Columbia, told me that beyond decreasing the defective huntingtin, another solution would be to increase the supply of the good.

Huntingtin's job

For a long time, scientists had no idea about the function of huntingtin. In the last few years, however, they have made a number of discoveries.

Huntingtin is like the spider at the middle of a web of cellular functions, explained Scott Zeitlin, Ph.D., of the University of Virginia School of Medicine. If you reduce its capabilities, you reduce the strands in the web, in other words, the things the cell can do. And if you remove it, you sever the strands, that is, you completely turn off important processes.

Dr. Scott Zeitlin explains the functions of the huntingtin protein (photo by Gene Veritas).

In his presentation, Dr. Zeitlin identified six major functions for huntingtin, including the transport of materials inside the cell, the decoding of genes, and regulating metabolism. On the whole, huntingtin helps keep the cell stable (protein homeostasis).

It also helps keep the brain as a whole stable.

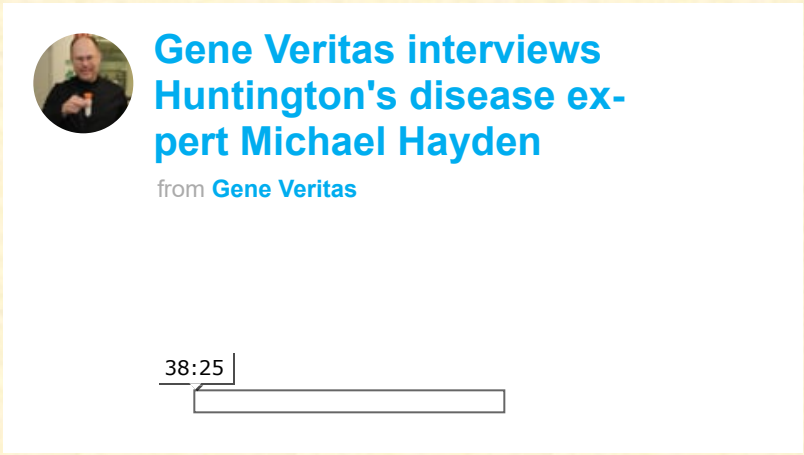
Dr. Zeitlin also pointed out that huntingtin is important in the development of an embryo. Too little huntingtin in a mouse embryo, for example, causes the animal to be born deformed.

Other views on lowering huntingtin

Providing the example of protein regulation in another disease, Dr. Karen Chen of the Spinal Muscular Atrophy (SMA) Foundation demonstrated how an Isis compound has improved the health of mice afflicted with SMA. Adjusting huntingtin could work similarly in HD, she suggested.

In his presentation, Dr. Andreas Weiss of the Novartis Institute for Biomedical Research discussed the methods and technologies used to track the presence of normal and abnormal huntingtin in cells and brains. Data from these observations will help in the design and dosing of treatments – including, once again, the question of how much to lower huntingtin.

(For an informed outlook on lowering huntingtin and controlling HD, watch my interview with Dr. Hayden in the video below. Dr. Hayden's lab collaborates with Isis on attempts to lower huntingtin. In this interview Dr. Hayden also recounts his journey from working as a young doctor in South Africa to conducting research in North America, and he discusses the increased number of HD patients and the deep discrimination faced by HD-affected families everywhere. For additional background on Dr. Hayden, read this article.)



Gene Veritas interviews Huntington's disease expert Michael Hayden from Gene Veritas on Vimeo.

Area 2: saving brain cells

The second main area for researchers involves the problem of dysfunctional brain cells and how to save them early enough to prevent the disease from advancing.

This portion of the conference focused on such key problems as synaptic dysfunction, the misfiring the synapses, where the signals between brain cells are carried. The deficit in brain cell activity was also examined. Researchers also addressed the problem of "excitatory cell death", in which dying cells release chemicals that, in turn, overstimulate and cause damage to other cells.

Dr. Michael Orth of the University of Ulm, Germany, discussed transcranial magnetic stimulation (sending of weak electrical currents into the brain), a method he has used to measure brain activity in pre-symptomatic, gene-positive individuals like me. He observed abnormal activity in the motor cortex portion of the brain, the area responsible for movement. Chorea, or the shaking and trembling of the body, is one of the primary symptoms of HD.

Dr. Vahri Beaumont of CHDI outlined the organization's programs for combating synaptic dysfunction, which is primarily the problem of miscommunication between neurons. She noted that such dysfunction can occur as early as two decades before a person has noticeable symptoms. A couple of compounds currently used in clinical trials for other diseases could be beneficial for HD patients, she suggested.

Along these lines, Dr. Pacifici noted that large pharmaceutical companies have shown great interest in this area of brain health and have developed many compounds. These compounds can be "repurposed" quickly and moved into HD trials in the near future.

Area 3: bioenergetics and HD

The third group of presentations focused on a well-known problem caused by HD: an individual's extremely high usage of energy, which causes patients to lose weight. Scientists are examining the causes of this problem at the cellular level and seeking remedies.

This characteristic of HD has led patients and asymptomatic gene-positive individuals to take supplements such as coenzyme Q-10, creatine, and trehalose. These might increase cellular energy. These substances are under study by HD researchers.

This session of the conference included discussion of dysfunction in the mitochondria, the powerhouses of the cell, and possible drug targets.

Dr. Pacifici that scientists are seeking to understand the specific causes of the energy deficit in HD and match them up with possible drug molecules.

Area 4: fertilizers for the brain

The final portion of the conference focused on "neurotrophic factors" (growth factors), which help maintain brain cells and the brain's functions.

In Dr. Pacifici's words, neurotrophic factors are like "fertilizers" for the brain. With HD, there is a shortage of certain molecules – the fertilizer – which must be put back into the brain to make it grow new cells and stay healthy.

Dr. João Siffert of Ceregene described his company's implementation of a Phase II human clinical trial for CERE-120, a drug that is intended to increase the growth factor neurturin in the brains of Parkinson's disease patients. Ceregene is conducting pre-clinical research on CERE-120 for use in HD.

The protein BDNF

One of the most frequently mentioned growth factors in HD research is BDNF, a protein known as brain-derived neurotrophic factor. As stated by Dr. Jordi Alberch of the University of Barcelona, BDNF is a potent protector of neurons in the striatum, one of the areas of the brain most affected in HD. The level of BDNF decreases in HD patients.

In his presentation on brain receptors that link up with BDNF, Dr. Moses Chao of the New York University School of Medicine noted that the lack of

the substance is a cause of the neuropsychiatric symptoms of HD (such as depression).

Dr. Moses Chao speaks on BDNF (photo by Gene Veritas).

BDNF, he observed, contributes to a number of important activities in the brain, including the development of the cytoskeleton (the skeleton of the cell) and the ability of the synapses to adjust their strength. BDNF also helps cells survive.

As Dr. Chao pointed out, scientists first thought it might be possible to inject BDNF directly into the brain to help patients. However, in their experiments they encountered difficulties in delivering the BDNF, and it proved to be very "sticky," meaning that it did not move easily in the brain. There were also negative side effects.

More recently, Dr. Chao explained, scientists have sought ways to bypass these problems. That research has focused on the BDNF receptors, molecules in the brain that link to BDNF so that it can carry out its tasks. Scientists are also examining substances that can bind to the receptors and act as a substitute for BDNF.

Evidence has also shown for quite some time that certain chronic antidepressants increase BDNF levels.

Scientists have long known that exercise stimulates the production of BDNF. Therefore, Dr. Allan Tobin of CHDI has conducted a workshop to investigate the use of molecules that could mimic the effect of exercise on the brain and therefore increase BDNF levels.

In his presentation, Dr. Alex Kiselyov of CHDI reviewed several "paths" that might be followed in solving the BDNF deficit problem.

Visiting the poster session

As with most scientific conferences, the CHDI event included an area where scientists could present posters summarizing their research.

The collection of posters was like an ultra-advanced science fair. Authors gave short oral presentations to other scientists circulating through the area, and a panel of three judges chose the three top posters. After hearing formal presentations, the conference participants selected a winner.

(In the video below you can watch the scientists as they examine and discuss the posters.)

Huntington's disease drug hunters view posters at 2011 research conference

from **Gene Veritas**

01:25

Huntington's disease drug hunters view posters at 2011 research conference from Gene Veritas on Vimeo.

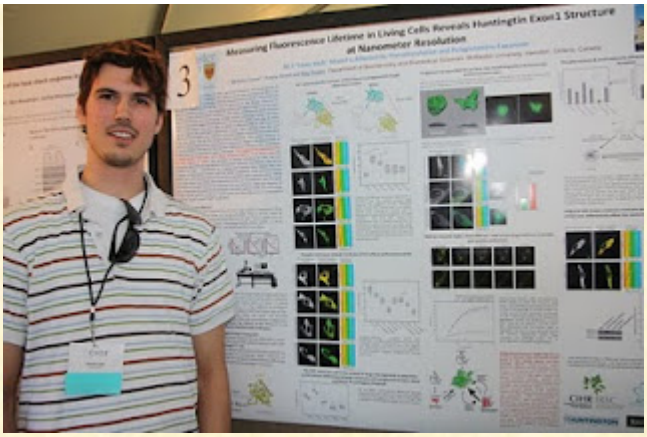
This year's winner was a poster by Dr. Ray Truant of McMaster University in Hamilton, Ontario, and his graduate students Nicholas Caron and Randy Atwal. It was titled "Measuring Flourescence Lifetime in Living Cells Reveals Huntingtin Exon1 Structure at Nanometer Resolution." It was subtitled "N17 'Loop-back' Model is Affected by Phosphorylation and Polyglutamine Expansion."

As explained to me by Caron, the experiment involved the use of an extremely powerful laser microscope to examine the real time workings of live mouse cells. They observed actual protein-to-protein interactions.

The normal huntingtin protein has a kind of hinge, but the abnormal protein becomes too long and too rigid and thus makes this hinge less flexible.

The team concluded that they can use this technique to screen for small molecules that can influence the disease process within the cells. The goal is to find ways to reduce toxicity within cells.

Their research builds on the 2009 discovery of a "molecular switch" that might be used to stop part of the disease process in Huntington's.



Ph.D. student Nick Caron (above) with the winning poster, and Dr. Ray Truant (below) explaining the team's project to the conference participants (photos by Gene Veritas).

Another piece of the puzzle

The featured speaker of the conference was the eminent neuroscientist Dr. Solomon H. Snyder of the University of Johns Hopkins Medical School.

Dr. Snyder provided a look back at the last five decades of discoveries about the brain, its receptors, and the many important kinds of drugs resulting from this research.

In 2009, he and other scientists in his lab reported a key new finding about HD involving a protein called Rhes. Located only in the striatum, Rhes binds to the huntingtin protein. When it binds with abnormal huntingtin, it causes cell death.

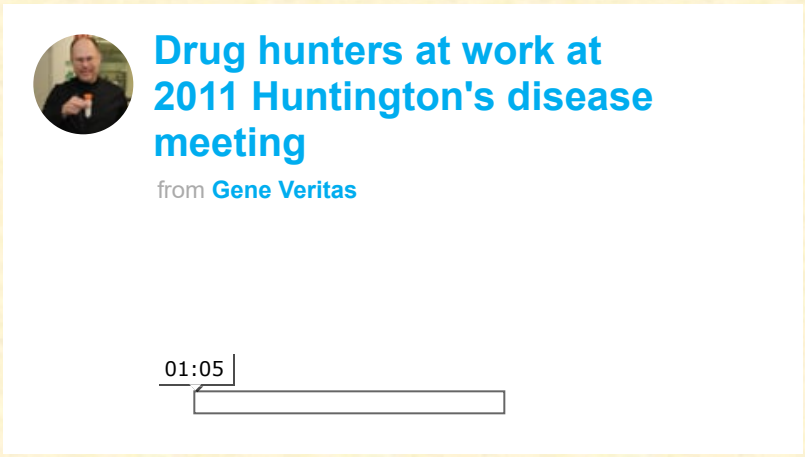
As Dr. Synder stated, the limited presence of Rhes in the striatum could help explain why that area of the brain suffers more damage than others.

Researchers are now looking for ways to stop the harmful effects of Rhes. Dr. Snyder stated that a Rhes drug might be safe, because its use would be required only in the brain, not all over the body.

CHDI's key role

In the final session of the conference, Dr. Pacifici and two lead CHDI researchers summarized CHDI's work in developing completely new compounds that might be able to treat other problems that occur in HD-afflicted brains. Dr. Ignacio Muñoz-Sanjuan, the vice president for biology, and Dr. Celia Dominguez, the vice president for chemistry, detailed the efforts to prepare two of these compounds for testing in animals.

(Watch the video below for a part of Dr. Muñoz-Sanjuan's talk and to get a view of the scientists at work in the main conference room.)



Drug hunters at work at 2011 Huntington's disease meeting from Gene Veritas on Vimeo.

The development of these and other CHDI compounds reveals how the organization has assumed an ever more important leadership role in the search for treatments and a cure. As a virtual biotech company, CHDI not only contracts with other firms and labs to carry out research and testing, but pioneers in new areas. CHDI is determined to explore as many remedies as possible.

At this conference CHDI's importance was further reflected by the record number of attendees and posters. In fact, this year the organizers needed to add a couple of extra rows of seats to accommodate attendees.

"At any time, CHDI is working full-speed on about ten different drug development projects," noted Dr. Jeff Carroll (click here to read more), an HD researcher and, like me, gene-positive for the disease. "For a sense of scale, that's more programs than most large pharmaceutical companies have in all areas of brain research, including much more common diseases like Alzheimer's or Parkinson's disease. CHDI is changing the pace and scope of HD drug development."

Reasons for optimism

Dr. Pacifici concluded that HD families can "have hope."

"There are an incredible number of shots on goal," he said. "We're doing this as quickly and as rationally as possible, and I think that there's really good reason to be optimistic that within the next period of time we're going to start seeing the creation of new chemical entities, new drugs that were specifically designed with Huntington's in mind."

"I can see that we're getting to the final stretch. It's been a long marathon,"

said Dr. Hayden. "And I'm optimistic. I've been in this field for 34 years. We did the first predictive test 25 years ago in Vancouver in 1986. So we've watched the whole development.

"So for me the opportunity to work with many of these companies, keep them focused on the issues, and help to provide the reagents and resources to get this done is just an incredible privilege and an exciting time.

"We know that for families listening to this, every day counts."

Posted by Gene Veritas at 1:11 PM

Labels: Alnylam , brain , CHDI , chorea , coenzyme Q-10 , creatine , cure , gene , gene-positive , genetic , huntingtin , Huntington's , Isis , symptoms , synapse , synaptic dysfunction , treatment , trehalose

3 comments:

Angela_F said...

A great account of what seems like a very exciting and successful conference.

Thanks so much Gene for providing this update. It's so good to know the sheer amount of progress being made.

xx

7:13 AM, February 23, 2011

Anonymous said...

Wow, thank you for a great synopsis of this event! How exciting it is for HD families and scientists in this area of study. How do I thank each person involved? My heart is overflowing with optimism for my family and especially my young children that there may be a treatment in the near future! THANK YOU!!

11:12 AM, February 23, 2011

Abbie Mattix said...

My Grandpa two uncles had Hd..may Dad was just diagnosed two months ago...It's very scary for me. Thank you for posting this...

9:02 AM, August 02, 2011

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