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The first dose is hope: moving towards treatments for 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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With its incurable genetic attack on the brain, Huntington's disease wreaks havoc on its victims and their families, leaving them helpless, bereft of hope. I felt powerless as I watched my own HD-stricken mother become a mere shadow of herself and then worried about my own onset after testing positive for HD in 1999.

However, we have reason for hope. After many years of quiet but steady progress, drug makers are beginning to harvest significant results in the quest for treatments.

Since my mother's death in 2006, I have seen scientists move from *cautious optimism* to *optimism* and now to *genuine optimism*.

At the 7th Annual HD Therapeutics Conference last week in Palm Springs, CA, I observed how many of the world's leading HD researchers are preparing for clinical trials of remedies that could prolong and improve the lives of patients – and prevent me from becoming symptomatic. Notably, this year's conference included many pharmaceutical companies: Alnylam, Isis, Medtronic, Novartis, Pfizer, Sangamo BioSciences, and Vertex.

As I participated in the conference, I felt hope come alive for the HD community.

Scientists pushing forward

I witnessed hope in the scientists' confident smiles, animated conversations, and enthusiastic handshakes – including that of Dr. Robert Pacifici, the chief scientific officer of CHDI Management, Inc., the multi-million-dollar HD treatment initiative and the organizer of the conference.

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
HD Free with PGD!
Stanford HOPES
Earth Source CoQ10, Inc.

HD Blogs and Individuals

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

Dr. Robert Pacifici (left) and Gene Veritas

"There are now eight things with the potential to reach the clinic in a two-year time horizon and a bunch more behind that," Dr. Pacifici told me in an interview.

I also encountered optimism in Dr. Jim Gusella, whose research team found the general location of the HD gene (the marker) in 1983 and, in 1993, cloned it, making possible a simple, 100-percent accurate genetic test for the disease.

In many ways, his historic work laid the foundation for today's advances. His current work includes the search for modifier genes – genes that, in addition to the HD gene, might affect the onset of the disease.

But scientists require an engaged HD community. In an interview, Dr. Gusella told me that patient participation is "incredibly important" in the drive for treatments.

"You cannot study a human disease without studying the people who have the human disease," he explained. "You can't test a drug unless you have people to test it on to see whether it does anything. The more they can participate, the better, whether it's just giving a blood sample or going in and having neurologic exams to look at progression of disease or participating in a clinical trial."

And, Dr. Gusella added, the community must maintain hope.

Dr. Jim Gusella (left) and Gene Veritas

Lowering huntingtin

Above all, I saw hope personified in the conference's two dozen presentations and nearly 100 posters – all of them focused on the goal of understanding HD more deeply and/or developing treatments.

As I strived to process the vast information of this highly compressed 72-hour event, I felt exhilarated at the prospects of being freed from the threat of HD.

I paid special attention to the sessions on "lowering huntingtin," a variety of strategies for reducing the amount of defective protein in brain cells. These strategies seek to block HD at its genetic roots, thus ameliorating or preventing symptoms.

I've followed one of these initiatives, a collaboration between CHDI and Isis Pharmaceuticals, Inc., since early 2008 (click here to read more).

I was thrilled to watch Dr. Frank Bennett, the Isis senior vice president of research, present an update . This year or next, Isis likely will apply to the federal Food and Drug Administration for a Phase I clinical trial to test the safety of its "antisense" technology, a class of substances known as "oligonucleotides," or "oligos," which would interrupt the production of defective proteins.

Isis, CHDI, and academic collaborators such as the HD lab of Dr. Michael Hayden at the University of British Columbia achieved an important breakthrough by discovering a way to lower defective huntingtin proteins while allowing normal huntingtin to carry on its vital tasks in the brain cells.

Isis has demonstrated the feasibility and safety of lowering huntingtin in mice, rats, and non-human primates.

Significantly, the Isis oligos have helped alleviate symptoms in HD mice.

An excellent scenario

Sitting cross-legged on the floor in front of the podium, I snapped photos of Dr. Bennett's slides and listened intently to each word.

It was like having a front-row seat at a grand theatrical production – but one that was about *me* and the hundreds of thousands of people around the world affected by HD as patients or gene-positive people awaiting onset.

Dr. Frank Bennett (right) and Gene Veritas (photo by Dr. Ed Wild)

We wait as the actors, these scientific heroes, unravel the plot towards effective treatments.

"CHDI like a dream – couldn't have imagined a better scenario," I wrote in my notes. "Incredible vision with gene silencing."

(Later this year I plan to pay my fourth visit to the Isis labs in Carlsbad, CA, to prepare a detailed update on the project.)

Inspiring connections

As we depend on the scientists literally to save us from HD, they also depend on the HD community for inspiration.

In remarks to the audience, Dr. Ladislav Mrzljak, CHDI's director of neuropharmacology, recalled my 2011 CHDI keynote speech. Dr. Mrzljak told me personally that my speech had inspired him as he assumed his new role at CHDI after eleven years at the pharmaceutical giant AstraZeneca.

After one speaker noted that a researcher at my alma mater, Yale, had received a CHDI grant, I asked Dr. Mrzljak for details. Not only did Dr. Mrzljak personally know the researcher; he himself had spent the 1990s at

Yale studying with world-famous cognitive neuroscientist Patricia Goldman-Rakic.

Dr. Mrzljak presented evidence that a CHDI-designed compound (CHDI-246) produced positive effects as measured in brain samples taken from HD mice. Research on CHDI-246 continues.

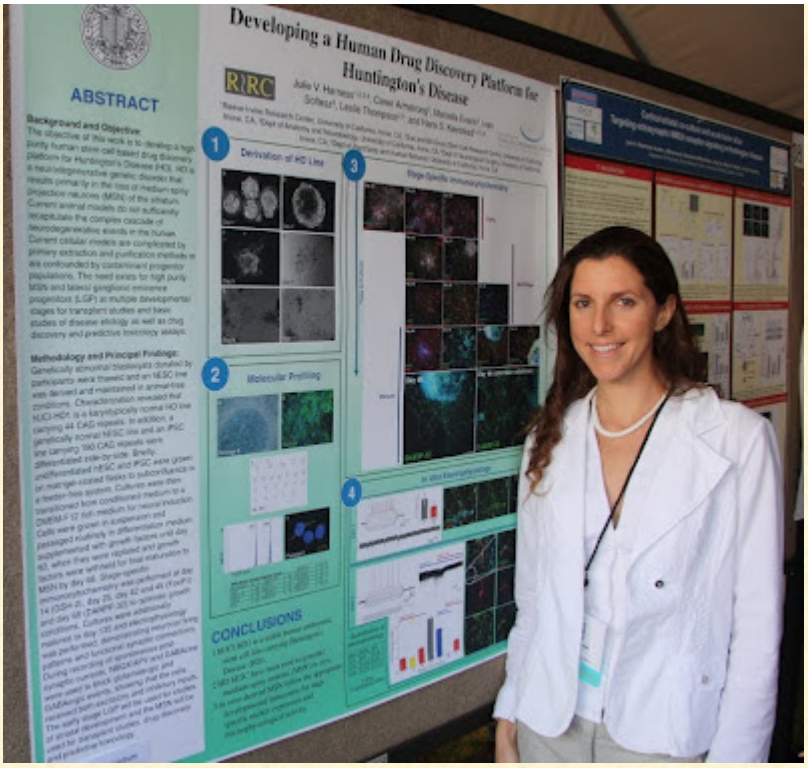
Dr. Ladislav Mrzljak (photo by Gene Veritas)

In addition to scientific veterans, this year's conference included many young poster presenters. I met Julie Harness, a Ph.D. student specializing in HD stem-cell research at the University of California, Irvine (UCI).

Using both normal and HD-affected embryonic stem cells derived from discarded blastocysts from couples who opted for pre-implantation genetic diagnosis, Harness seeks to understand the causes of HD and perhaps develop an approach to treatment, including drug discovery. (Click here for more on California's HD stem-cell-research. In a future article I will explore UCI's HD research in depth.)

Harness told me that she felt inspired to present a poster this year after seeing photos of posters from last year sent by another UCI graduate student who had attended the 2011 meeting. Perhaps I took those photos – because I have included poster photos in this blog and since 2010 have supplied CHDI with a CD containing photos of all posters.

Julie is also a reader of this blog.



Julie Harness and her poster on a stem-cell drug-discovery platform for HD (photo by Gene Veritas)

Coming down to the wire

Despite the positive outlook, participating in the conference also magnified my fears of onset. My mother's symptoms apparently began in her late 40s. At 52, I count each day without the classic symptoms – chorea (shaking), cognitive loss, and mood disorders – as a bonus.

I wondered: will the clinical trials prove successful, and will the medicines come in time to save me? If I become ill, will they help me recover?

As I watched Dr. Sarah Tabrizi's slides demonstrating significant changes in the brain before classic onset, my heart sank. She stated that these changes begin as early as 20 years before predicted onset.

I glanced over at Jeff Carroll, a recently minted Ph.D. who is emerging as a leader in HD research. His poster – a study of HD mice and cell metabolism that suggests another potential approach to treatment – won first prize. Dr. Carroll, 34, is also gene-positive for HD and, like me, places great hope in the Isis project. His research has contributed to that project.

Dr. Jeff Carroll ponders Dr. Bennett's Isis update (photo by Gene Veritas).

"We're fried!" I thought to myself as I viewed images of the brain shrinking.

To my relief, Dr. Tabrizi pointed out that, despite significant changes in the brain, "premanifest" individuals maintain an almost normal level of cognitive abilities.

"Despite striking brain changes, premanifest HD gene carriers did not deteriorate significantly over 24 months in cognition or motor function tasks," she said in reference to the TRACK-HD study that she headed. "I think that tells us that the brain is functionally plastic and is compensating. And the good news is that there may be a lot to rescue."

"We gene positive are really coming down to the wire!" I wrote in my notes. "Can we hold on??? If I get sick, can I recover with meds? Evidence in mouse trials suggests: yes!"

The first dose

I shook many hands at the CHDI meeting – perhaps even the hands of those who will produce the first effective treatment to stop HD symptoms.

After the conference, we have all returned to the HD trenches.

The scientists must now turn hope into actual treatments.

I must continue my work as an advocate for the Huntington's Disease Society of America (HDSA).

My task is to carry the message of hope of a treatment to everybody I encounter in the HD community, either in person or online.

Indeed, this must become the priority of HDSA and advocates everywhere.

In an HD treatment, the first dose is hope.

Gene Veritas and CHDI's newly launched logo. Dr. Simon Noble, CHDI's director of scientific communications, explained to the audience that the new logo symbolizes CHDI as a "drug development organization" seeking "effective treatments" as its first goal. The tree represents the biology and chemistry involved in HD and HD research, clinical developments, neurons, biological pathways, and the hereditary nature of HD. The logo's muted color reflects the "somber nature" of CHDI's mission. While the initials "CHDI" once referred to "cure Huntington's disease initiative," the foundation emphasizes that the initials no longer signify that phrase. "We can worry about curing down the line, however you want to define curing," Dr. Noble stated. (photo by Lev Blumenstein)

(In a future article I will examine the research progress reported at the CHDI conference.)

Posted by Gene Veritas at 10:33 PM

Labels: brain , CHDI , chorea , clinical trials , cognitive , gene , gene silencing , gene-positive , genetic , genetic test , hope , huntingtin , Huntington's , Isis , Michael Hayden , oligonucleotide , onset , stem cell

4 comments:

Thumper! said...
Thank you for giving us all hope for the future
4:43 AM, March 08, 2012

Anonymous said...
Thank you so much for keeping us all updated on everything you do! I can not thank you enough. It is so appreciated. I've literally read every one of your blogs and look so forward to the next ones.
7:00 AM, March 08, 2012

owen said...
Thanks my friend.. my mother is dying from hd and i dont want to check uf im infected but bow im worried for my 4 year old sin i donr want him to go through what i go through every day waching my mother dying slowly it hurts and we all knOW..
BUT YOU GAVE ME HOPE TODAY THANK U AND KEEP UP THE GOOD WORK.
GOD BLESS
4:27 PM, March 11, 2012

Malcolm P Garris said...
How can my wife be included in an upcoming trial.My son does not have HD and my daughter(37) has not been tested.
9:24 AM, March 29, 2012

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