3-2-2020

CHDI head scientist Pacifici: 'hang on in the learning roller coaster ride of Huntington's disease clinical trials'

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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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MONDAY, MARCH 02, 2020

CHDI head scientist Pacifici: 'hang on in the learning roller coaster ride of Huntington's disease clinical trials'

With historic clinical trials now aiming for the first effective treatments for Huntington's disease, affected individuals and their families need to clearly understand the news about these efforts and their implications.

That critical recommendation was offered by Robert Pacifici, Ph.D., the chief scientific officer of the nonprofit HD-treatment-seeking CHDI Foundation, Inc., during an interview on the last day of the organization's 15th Annual HD Therapeutics Conference, held February 24-27 in Palm Springs, CA.

"Getting to this stage – which we've all so been hoping for – is still a bit of a roller coaster ride," Dr. Pacifici told me. "You have to be able stay in our seats and weather the ups and downs. I think we're well-poised for some great news, as some of these trials hopefully report out. Even a whisper of efficacy would be just amazing."

However, there will also be "disappointments, where, despite our best attempts, some of the things that showed so much promise didn't end up meeting their endpoints," he cautioned. "But it's going to be a learning roller coaster. So hang in there. Don't lose hope."

The HD-affected (and their caregivers) should keep informed about the trials by consulting their physicians, attending meetings of patient organizations such as the Huntington's Disease Society of America (HDSA), and keeping abreast of developments in such sources as HDBuzz.net and this blog, Dr. Pacifici advised.

Become knowledgeable, he urged, "so that you are not disproportionately spooked or elated when these bits of information come out."

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Featured conference speaker Christopher Austin, M.D., the director of the National Center for Advancing Translational Sciences/National Institutes of Health, presents part of the Drug Discovery, Development and Deployment Map the research and pharmaceutical community must navigate in today's complex and challenging scientific world (photo by Gene Veritas, aka Kenneth P. Serbin).

'Genuinely interested' in treating HD

Dr. Pacifici began the interview noting the excitement generated by the conference and within the HD field, with a record 380 participants, overflow seating, and more than 100 people turned away. However, CHDI's goal ultimate goal is not to host well-attended conferences, but to stop HD, he emphasized.

"There are that many people who are genuinely interested in presenting the results and learning about the incredible developments that are unfolding in Huntington's disease drug discovery and development," he said of the response to the conference.

Dr. Pacifici also noted the very high quality of the presentations, in comparison with the early years of the event.

"We're batting 1,000 this time – every single talk very relevant," he observed.

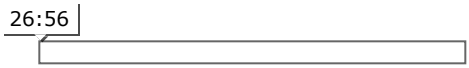
Considered science fiction a decade ago, the new technologies applied in HD research are transforming the field and allowing for a more thorough analysis of cells in the quest to understand the disease, he added.

Dr. Pacifici cited the example of whole-genome sequencing on individual brain cells, which permits the reading of the DNA sequence of "every single gene in there, and doing that thousands of times."

You can watch my interview with Dr. Pacifici in the video below. For my video album of the conference, please click here (and check back in the coming days as I add videos).

Hang on in the 'learning roller coaster ride' of Huntington's disease clinical trials

from **Gene Veritas**



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New understanding of the protein

Dr. Pacifici also discussed new research into the huntingtin protein presented at the conference. Such research suggests that the protein might have a key role in maintaining the integrity of the huntingtin gene and also in the way the gene expands over time (known as somatic expansion), which researchers now see as a key driver of the disease (click here to read more).

With this potential new finding, a single drug might be developed to counteract the mutant protein by both reducing its quantity and preventing it from causing somatic expansion, he speculated.

He pointed in particular to the presentation by Jeffrey Carroll, Ph.D.

A possible key biomarker

Dr. Pacifici also commented on the discussion around phosphodiesterase-10 (PDE-10). A PDE inhibitor was seen as a potential "Viagra for the brain" but ultimately showed no improvement in a clinical trial run by the drug giant Pfizer.

However, PDE-10 might still play a role for the HD community as a biomarker (sign of disease and/or effect of a treatment), Dr. Pacifici said.

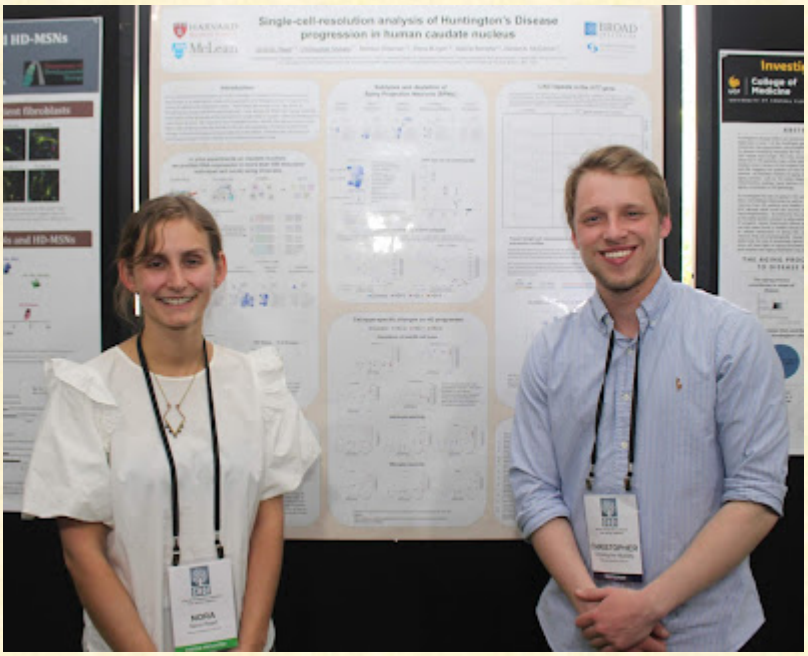
"It is pretty uniquely expressed in the neurons that we know are affected by Huntington's disease, the medium spiny neurons," he explained.

If PDE-10 decreases in HD because the gene is shut down or cells die or some combination of both, and "if you had a molecule that bound to PDE10 and sent out a signal, then you could know how much PDE10 was in that brain, and if it was declining, that would mean that the disease was progressing." Similarly, with an effective therapy, "you would see PDE10 levels going up," Dr. Pacifici added.

The U.S. Food and Drug Administration is unlikely to approve a drug based solely on evidence from a biomarker, because it needs to see actual clinical benefits in patients, Dr. Pacifici said. However, the biomarker could give a drug maker the "confidence" that the "intervention is doing its job biologically and now it's worth waiting for the clinically meaning outcome."

(The presentation by Steven A. McCarroll, Ph.D., of the Harvard Medical School, included discussion of the role of PDE-10.)

Above, Dr. Steven McCarroll answers a question from the audience after his presentation on single-cell analysis of HD biology. Below, McCarroll lab researchers Nora Reed (left) and Christopher Mullally with the lab's poster on single-cell analysis, which took second prize in the poster competition (photos by Gene Veritas).



The terrifying truth about drug development

Dr. Pacifici reflected on the in-depth talk by the conference's featured speaker, Christopher Austin, M.D., the director of the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health. NCATS, founded in 2011, aims to speed the development of treatments and cures.

I asked Dr. Pacifici to comment on the phrase that struck me from Dr. Austin's presentation: "The hard work that nobody else wants to do."

Scientific research is "unsexy" and "difficult to understand," but Dr. Austin challenged the field to forge ahead, I observed.

"He painted a pretty bleak picture of how we're sadly finding diminishing returns on our investment," Dr. Pacifici said regarding drug investigation in general. "In other words, he kind of flipped around Moore's law. Instead of things getting better and faster, the more money we spend, the fewer treatments we see coming out, especially for the harder neurological diseases."

Dr. Austin presented to the audience what he called a "truly terrifying fact": "The number of new drugs approved per billion dollars spent, inflation-adjusted, has gone down by half every nine years, since 1950."

You can learn why this is so – and its very serious implications for HD – by watching Dr. Austin's presentation by clicking here.

The HD field hopes to be the exception and the model

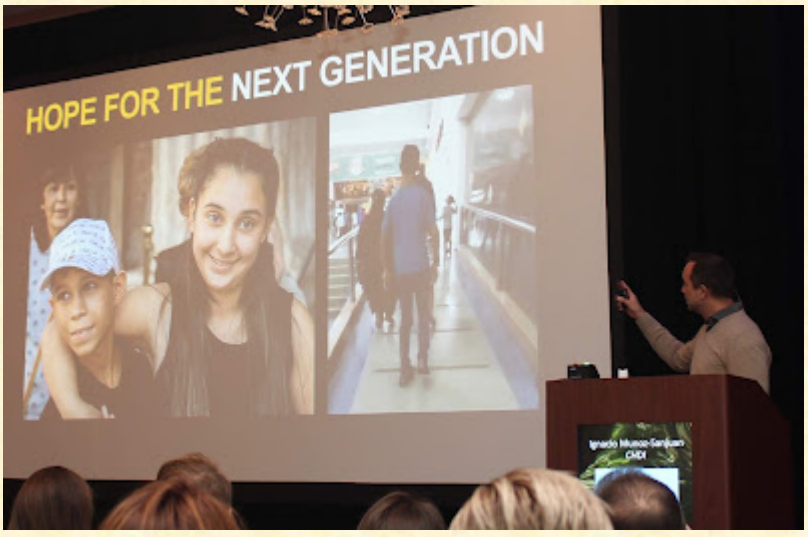
Dr. Pacifici pointed to the difficult and complex challenges involved in drug discovery, as illustrated by Dr. Austin.

Everybody wants to be the "star" that "made the compound that turned out to be the cure," Dr. Pacifici said. But imagine: the compound is there, but no patients are available to do the clinical trial. Or patients participate, but researchers lacked the "outcome measures to see whether people were actually getting better." Or, antibodies and assays needed to measure the samples derived from patients weren't there.

Those things are the not-so "sexy" but need to get done, he said.

The HD field will need to overcome the inertia of diminishing returns, Dr. Austin emphasized. Deeply familiar with HD science, he believes that HD as a monogenetic disease has the potential to do so and could serve as the model for treating other, more common neurological disorders.

Dr. Pacifici agreed. He praised the HD research and biotech community not only for its commitment to make sure that key elements of the drug-hunting process are "proactively put in place," but the "selflessness with which they are shared, so that those don't represent competitive advantages for one company or another. I think everybody has come to the realization that this is a really hard problem. It's no use competing with each other. We're going to have to help each other."



At the start of his talk on huntingtin-lowering strategies, Ignacio Muñoz-Sanjuán, Ph.D., a CHDI scientist and the co-founder of Factor-H, reminded the audience of

the goal of the HD cause: to help individuals like Anyervi (in cap) and Brenda, two youths from South America with juvenile HD (photo by Gene Veritas).

Posted by Gene Veritas at 11:06 PM

Labels: biomarkers , CHDI Foundation , Christopher Austin , clinical trials , HD Therapeutics Conference , huntingtin , Huntington's disease , Jeff Carroll , PDE-10 , Robert Pacifici , Steven McCarroll , treatments

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