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‘The first at-bat is never a grand slam’: how Huntington's disease drug research has matured with the Roche and Wave setbacks

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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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'The first at-bat is never a grand slam': how Huntington's disease drug research has matured with the Roche and Wave setbacks

Despite the disappointing clinical trial results reported last week by Roche and Wave Life Sciences, Huntington's disease drug researchers see an upside: they are using the data collected to achieve new insights, offering renewed hope of effective treatments.

The news of these setbacks produced one of the most heartbreaking moments of the last several decades for the HD community and researchers.

"That kind of news, I hope it's okay to say: it sucks!" said Robert Pacifici, Ph.D., the chief scientific officer for CHDI Foundation, Inc., of the Roche and Wave trial data. "All of us who hold out so much hope and recognize that there are so many families who so desperately are waiting for much needed relief and therapies – it knocks the wind out of you."

The companies made their first formal scientific presentations of their data at the start of the CHDI-sponsored 16th Annual HD Therapeutics Conference, held virtually from April 27-29. A nonprofit virtual biotech, CHDI focuses solely on developing Huntington's therapies.

Roche confirmed that its drug tominersen failed to alleviate symptoms in its Phase 3 clinical trial; patients receiving the highest of two possible doses may have done even slightly worse than those on placebo. Two early-stage Wave trials failed to meet the goal of reducing the amount of mutant huntingtin protein in the

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trial participants – an objective already achieved by Roche in an earlier tominersen trial. (Click here to read more.)

Dr. Pacifici offered his assessment of the Roche and Wave data and the state of HD drug research in a wide-ranging, 46-minute Zoom interview with me after the close of the event.

Dr. Robert Pacifici moderates panel discussion of huntingtin-lowering clinical trial results with Dr. Vissia Viglietta of Wave Life Sciences and Dr. Scott Schobel of Roche (screenshot by Gene Veritas, aka Kenneth P. Serbin)

Gaining perspective

"My reaction though, now that I've come back down to earth, is really not one of surprise," Dr. Pacifici said. "Drug discovery, as we've discussed many times, is a really tough business. The probability of success on any given endeavor is incredibly low."

Dr. Pacifici used a baseball metaphor to explain: "How often does the first batter get up to the plate and hit a grand slam home run? A grand slam, never, because you need to load up the bases with three people. Even a home run is incredibly rare."

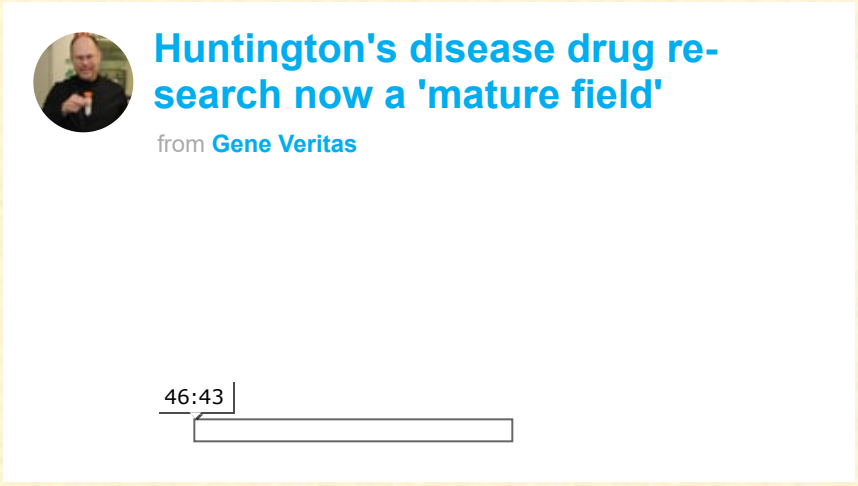
The "name of the game" in discovering effective treatments is to carry out as many trials as necessary, "doing it well, failing, but making it a good failure that we can learn from so that subsequent efforts have a much higher chance of success," Dr. Pacifici explained. "And we continue to snowball and build on that so that we can learn the things to do better, the things that we can do differently, or the things that we should stop doing altogether because we now have confirmed that those are not viable lines of investigation."

The accumulation of experience through research and clinical trials, including the crucial participation of patient volunteers, has produced "an incredibly positive thing," Dr. Pacifici observed.

"Look at how the field has matured," he said. In the past, scientists would have kept a trial running for three years, waiting for patient improvement, only to discover that "the drug really didn't even have a chance of working" because it hadn't done what it was "tasked with doing, which is lowering huntingtin levels."

Now the process is moving "faster" and is "better informed," Dr. Pacifici said.

Watch the entirety of my interview with Dr. Pacifici in the video below.



Huntington's disease drug research now a 'mature field' from Gene Veritas on Vimeo.

Huntingtin lowering still in the running

Dr. Pacifici commented on the critical topic of lowering (reducing) the mutant huntingtin protein, the first strategy aimed at HD's genetic cause. Scientists believe that the mutant protein is a main driver of the disease. In mouse studies, lowering that protein led to a disappearance of symptoms, and, beginning with the Roche trial, researchers have sought to achieve similar results in humans. Thus, until now, lowering mutant huntingtin has been seen as the potentially most promising path to a treatment.

Both Roche and Wave used a type of drug known as an antisense oligonucleotide (ASO), an artificial strand of DNA. Other firms and labs are also investigating ASOs.

"When two of those things don't move forward simultaneously, it's perfectly reasonable to ask the question, 'Well, is this one of those times where we've learned that this approach is not going to work?'" Dr. Pacifici asked. "I can say unequivocally that that's not yet the case. There are just too many things that factor into how a drug needs to do its job that remain unanswered."

He said that possible key factors affecting the outcomes of the Roche and Wave trials include the stage of disease of the participants, the concentration of the drug tested, and the proper distribution of the drug within the brain. The particular characteristics of the drugs selected could have also impacted the outcome, he added.

Another possible explanation involves the design of the trials, the techniques for measuring patient response, and biomarkers (signs of disease and a drug's effects).

In addition, even though Roche's tominersen reduced the level of mutant huntingtin protein in trial volunteers' cerebrospinal fluid, researchers still do not know whether the samples of protein actually came from the brain and, if so, cells relevant to HD, Dr. Pacifici cautioned. Scientists also lack other critical details about those samples; for example, they could be fragments, he said.

Crucially, the "interim analysis" of the Roche data at the Therapeutics conference did not demonstrate whether lowering huntingtin can help people feel, function, or survive better, Dr. Pacifici observed.

Even a "whisper of efficacy" would have validated the huntingtin-lowering approach and "prepared the path for subsequent trials with gusto and confidence," he continued, adding, however, that "the opposite is not true. We still have great hopes that this is a viable mechanism of action."

Wave plans to start a trial of a third ASO later this year. Roche has also stated that it will continue to explore drugs for HD.

Exploring other avenues

Because the effectiveness of huntingtin-lowering remains an open question for the field, Dr. Pacifici renewed his call to redouble and diversify drug-hunting efforts.

Dr. Pacifici noted that other potential huntingtin-lowering approaches are in the works using non-ASO compounds, while others propose different methods of delivery, including a pill. In the Roche and Wave trials, participants received the drug via spinal tap.

"If we were in a fantasy world of the 20th new treatment for Huntington's coming, you would worry about things like convenience: 'I'd like to have a pill instead of an injection,'" Dr. Pacifici said. "'I'd like to have a pill I can take once a day. I'd like to have a small pill that's easy to swallow.'"

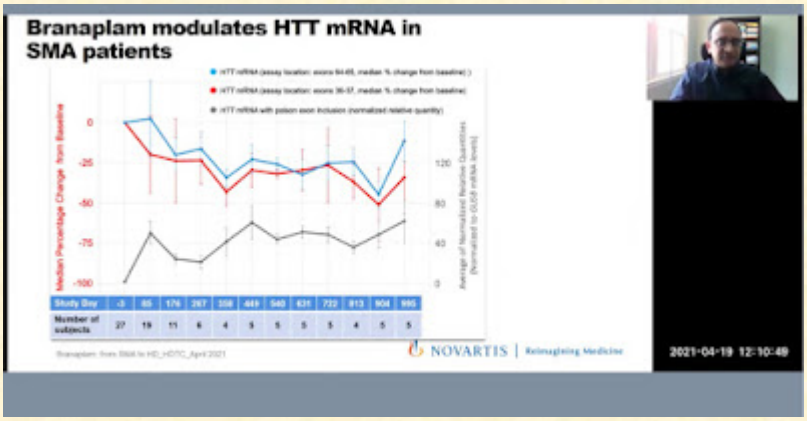
However, Dr. Pacifici observed, "we're not at that stage yet." Even so, "very critical advantages" exist in exploring different modes of delivery, he said.

Indeed, another possibility emerged at the conference. A scientist from pharmaceutical giant Novartis presented research on its drug branaplam, a pill used to treat spinal muscular atrophy (SMA), which causes severe muscle weakness in children. Novartis researchers discovered that Branaplam also reduced the amount of the huntingtin protein in a study of SMA patients. Novartis plans a trial of branaplam in HD patients, with details expected in the coming weeks and over the summer (click here to read more).

Like other so-called small-molecule drugs, branaplam becomes distributed very evenly across the whole body, including the brain, whereas a drug like an ASO tends to concentrate where it is administered, Dr. Pacifici explained. He added that small-molecule drugs can be dosed "creatively" – for example, weekly instead of

daily – to maximize the "beneficial effect" and allow the person a rest from the drug.

(I will explore the quest to develop this type of HD drug in a future article.)



Dr. Rajeev Sivasankaran of Novartis presents data demonstrating the effect of the drug branaplam on huntingtin RNA in a study of spinal muscular atrophy patients (screenshot by Gene Veritas).

Sharing knowledge rises all boats

Dr. Pacifici emphasized that success in the fight against HD ultimately depends on the sharing of scientific information – even negative research results that private companies are loathe to reveal to protect their egos and their stock prices.

He cited the presentation by featured speaker Aled Edwards, Ph.D., the founder and CEO of the Structural Genomix Consortium, which practices and advocates for open sharing of scientific information, particularly as it applies to protein science, chemical biology and drug discovery. Dr. Edwards spoke on "HD drug discovery in the public domain – a model for CHDI."

"I think the HD field will benefit by everybody realizing how difficult this problem is," Dr. Pacifici concluded. "It's not giving up a competitive advantage by being transparent about what happened. It's sharing data. That knowledge rises all boats. Everybody needs to know about these things."

Sharing of data and other knowledge has also been one of CHDI's trademarks as a nonprofit. Dr. Pacifici pointed to specifics:

knowledge about the disease, potential treatments, biomarkers, and clinical outcome measures (the techniques for measuring patient response).

With such sharing, he asserted, everybody will have an increased chance of success.

Refusing to do so will "doom us to the same failure we see in other neurodegenerative fields that have outspent us and been at this a lot longer than we have."

Posted by Gene Veritas at 4:31 PM

Labels: Aled Edwards , ASO , branaplam , CHDI , clinical trials , HD Therapeutics Conference , huntingtin lowering , huntingtin protein , Huntington's disease , Novartis , Robert Pacifici , Roche , tominersen , Wave Life Sciences

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