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Quickening the pace towards a Huntington's disease gene-silencing clinical trials: pharma giant Roche, Isis enter partnership

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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.

About Me

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Quickening the pace towards a Huntington's disease gene-silencing clinical trial: pharma giant Roche, Isis enter partnership

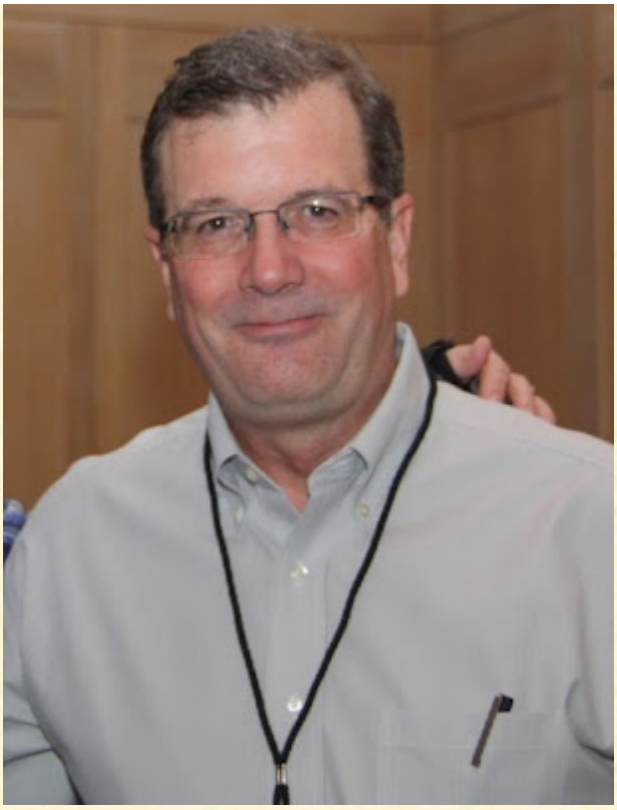
With an infusion of $30 million and access to new technology from the Swiss pharmaceutical giant Roche, Carlsbad, CA-based Isis Pharmaceuticals, Inc., hopes to shorten the timetable for a clinical trial of a potential breakthrough drug for Huntington's disease. It would attack the disease at its genetic roots and could serve as a preventive medicine.

The partnership, announced April 8, puts Isis in a position "to move very aggressively to getting the drug into clinical trials," Frank Bennett, Ph.D., the Isis senior vice president for research, said in a phone interview. "It should accelerate the program."

The deal, which could bring Isis up to $362 million in payments for developing and licensing the drug plus royalties on sales should it prove successful, provides a key piece of the puzzle for the company's HD program. As a dynamic mid-sized company focused on drug discovery but lacking the capital and infrastructure for large-scale clinical trials and drug commercialization, Isis has finally secured the partner necessary for bringing the potential HD drug to market.

"This is the best news," said Don Cleveland, Ph.D., an Isis collaborator who helped envision the treatment of HD with the company's gene-silencing antisense oligonucleotides (ASOs). "Running a clinical trial takes substantial dollars. Isis is a smaller company. Roche is one of the world's largest and most successful pharmaceutical companies."

The partnership gives Isis the "confidence" necessary to move from the early to later stages of the clinical trials, Dr. Bennett said. Roche, with its long experience in central nervous system drugs such as Valium, in use since the early 1960s, will not be "dropping the ball as a partner," he added.



Dr. Frank Bennett (photo by Dr. Ed Wild)

In line with earlier projections, Dr. Bennett stated that Isis still hopes to begin the clinical trial during the first half of 2014.

Shuttling drugs into the brain

The ASOs diminish the production of the huntingtin protein by eliminating huntingtin RNA in brain cells, which are destroyed in HD, producing motor, cognitive, and psychiatric difficulties in affected individuals. (Click here to read more about the efforts to design the drug and bring it to trial.)

Isis and Roche will experiment with the latter's "brain shuttle" technology, which, if successful, would allow greater penetration of the drug into the brain and make it far easier for patients to take.

Isis first aimed to implant a pump in a patient's abdomen and inject the drug directly into the brain. Then it moved to an injection into the cerebral spinal fluid (CSF) through a quarter-sized port implanted near the rib cage, with a catheter running to the area of the spinal cord.

However, as Dr. Bennett explained, with the brain shuttle technique, patients would simply need a subcutaneous injection (under the skin) similar to the kind taken by diabetes patients.

The brain shuttle would "allow us to use systemic dosing," Dr. Bennett explained. (Systemic dosing means the drug enters the bloodstream and is thus more available in the body in comparison with an injection into the CSF.)

"It's much more convenient," he added. "It's a better tolerated therapy. It could capture the symptoms earlier, maybe even prevent the development of the disease."

Glimpsing the Holy Grail?

That convenience also makes it easier to administer the drug to gene-positive asymptomatic individuals, Dr. Bennett noted.

For ethical and scientific reasons, people in this group (including me) have rarely, if ever, participated in HD clinical trials. Basically, scientists haven't yet figured out how to measure how a drug could benefit this group. In addition, its risk-benefit ratio is higher than it is for people with symptoms. Solving these problems, and thus completely preventing HD (as well as other neurological diseases such as Alzheimer's), is what I have called the Holy Grail of the research community.

For the first time, the Isis-Roche partnership suggests how the grail might be found. With reduced risks, participation in trials becomes more attractive, and ethical barriers diminish. In addition, the very entry of asymptomatic people into a trial permits the collection of data about efficacy specific to that group.

However, Dr. Bennett cautioned that this approach would most likely be reserved for second-generation clinical trials. Until the initial trials are completed, it's impossible to venture a guess about the timetable for a second generation.

"As a scientist, you can always make something better, but you have to be careful," he said of the time needed to develop the brain shuttle for ASOs. "For a patient that's suffering from the disease, you don't want to over-engineer and delay getting it to the patient."

Dr. Cleveland pointed out that the brain shuttle approach is new and has yet to be proven as a way to transport drugs into the brain.

"That's precisely why you want to have partners like Roche," he said. "They've been delivering things to the central nervous system for a long time. There's tremendous promise. The challenge will be to bring that promise into real fruition."

Isis and Roche will conduct joint research to discover whether they can attach the ASO to molecules that naturally shuttle other, necessary molecules into the brain across the blood brain barrier, which shields the brain from foreign substances that might cause harm and prevents the ASOs on their own from entering.

Key details and collaborators

"Huntington's is a severely debilitating neurodegenerative disease and a large unmet medical need," Luca Santarelli, Head of Neuroscience and Small Molecules Research at Roche, stated in the press release announcing the partnership. "Treatments are urgently needed, and we believe that the Isis approach in combination with Roche's brain shuttle represents one of the most advanced programs targeting the cause of HD with the aim of slowing down or halting the progression of this disease."

Under the deal, the $30 million investment from Roche will underwrite the project through Phase IIA of the three phases of the first-round clinical trial, with Isis retaining control of the project, Dr. Bennett said. If Phase IIA proves successful, Roche would conduct the more extensive Phase III trial, seek regulatory approval for the drug, and market it.

The agreement also stipulates that over time Isis will reimburse the CHDI Foundation, Inc., the multi-million-dollar non-profit virtual biotech firm that funded and advised the HD research at both Isis and Dr. Cleveland's lab at the Ludwig Institute for Cancer Research at the University of California, San Diego. CHDI will initially receive $1.5 million, with additional reimbursements occurring as Isis receives project milestone

payments from Roche. CHDI will continue to advise Isis and Roche on HD research.

"This is an exciting development for the HD community, and a testament to the excellent work that Isis has done to develop their oligonucleotide therapeutic for HD," said Robi Blumenstein, the president of CHDI Management, Inc., the firm that carries out the goals of the CHDI Foundation. "It's very encouraging that Roche, a pharmaceutical company with a great track record in central nervous system disorders, has now entered into developing treatments for HD. CHDI looks forward to working with both companies to steer this novel approach to the clinic as soon as possible."

Isis, Dr. Cleveland, and CHDI are currently conducting a large experiment to find HD biomarkers (signs of disease) that will enable them to determine the proper dose of the ASO drug and to measure its impact during the clinical trial.

David Corey, Ph.D., of the University of Texas Southwestern also collaborated with Isis on the gene-silencing project.

(Next time: my personal thoughts on the Isis-Roche project as a powerful new sign of hope for the HD community.)

Posted by Gene Veritas at 10:32 PM

Labels: antisense , brain shuttle , cerebral spinal fluid , CHDI Foundation , clinical trials , drug , gene-positive , gene-silencing , Huntington's disease , Isis , Roche , symptoms , treatments

1 comment:

Laurie Bretz said...

Hi Gene- I met you at last HDSA convention in Las Vegas. I have a friend, young brilliant premed student who wants to cure HD. Or at least help. Could you please contact me so we might brainstorm some summer internships for him.
Laurie
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6:10 PM, April 16, 2013

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