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Designing the best drug possible to defeat 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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Designing the best drug possible to defeat Huntington's disease

With an eye on starting a clinical trial possibly as early as 2014, a scientific team in San Diego is painstakingly working to design the best drug possible to defeat Huntington's disease.

For the past seven years, Don Cleveland, Ph.D., of the Ludwig Institute for Cancer Research at the University of California San Diego (UCSD) and Frank Bennett, Ph.D., the senior vice president for research at Isis Pharmaceuticals, Inc., have envisioned treating HD with a revolutionary gene-silencing technology that, if successful, would attack the disease at its genetic roots and perhaps even partially reverse symptoms.

Since late 2007, the UCSD and Isis teams have partnered with the CHDI Foundation, Inc., the multi-million-dollar non-profit biomedical organization dedicated to finding HD treatments. Together they aim to develop what Dr. Bennett has described as a "laser-guided missile" to prevent the damage to brain cells caused by the mutant huntingtin gene carried by HD patients.

Dr. Cleveland and Isis senior scientist Holly Kordasiewicz, Ph.D., were honored as the 2012 Researchers of the Year by the San Diego Chapter of the Huntington's Disease Society of America (HDSA-San Diego) last night before some 500 attendees at the chapter's twelfth annual Celebration of Hope Gala.

Isis employs a cutting-edge technology known as antisense oligonucleotides, or ASOs. DNA, the building block of life, runs our cells by telling them which proteins to make. It does so by sending messages with another molecule called messenger RNA.

As encoded by DNA, RNA has a very specific template, somewhat akin to a unique electrical outlet into which a plug can fit. RNA is known as a sense molecule, and Isis manufactures specific ASOs, artificial strands of DNA, to act as antisense molecules, the plugs that control the RNA. (Click here and here to read previous reports on the project.)

The ASOs accomplish two goals. First, they destroy the huntingtin RNA and thus prevent the production of the huntingtin protein. Second, eliminating the RNA removes it as a potential cause of other problems in the cell.

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

Above, some of the Isis HD team members: (left to right) Michael Oestergaard, Punit Seth, Bethany Fitzsimmons, Curt Mazur, Amy Blackley, Eric Swayze, Holly Kordasiewicz, Frank Bennett, and Marco Giorgetti (photo by Gene Veritas) (click on image to enlarge). Below, Gene Veritas inside the Isis facility in Carlsbad, CA (photo by Amy Blackley, Isis).

Fine-tuning, tailoring, and twiddling

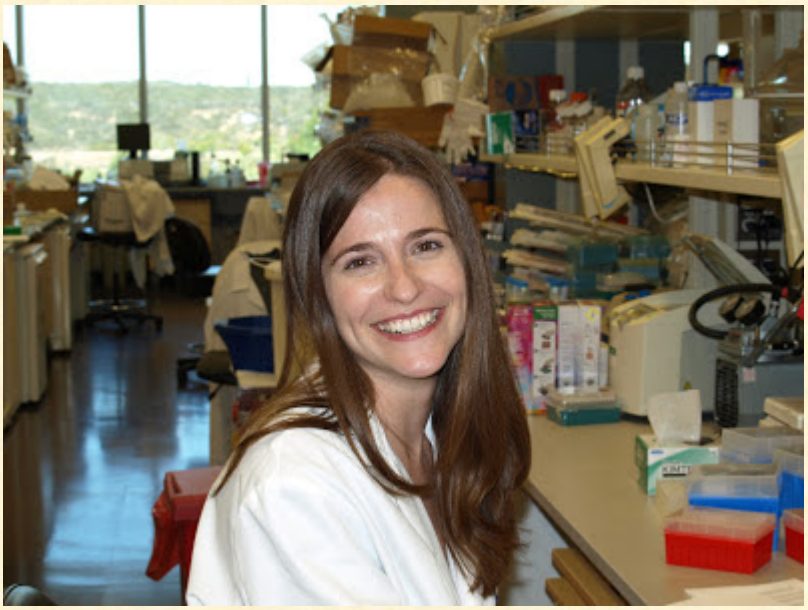
Isis had originally hoped to begin a clinical trial as early as late 2010, but has delayed the project in order to perform highly important fine-tuning on several fronts.

As previously described by Dr. Bennett, Isis is searching among the many "flavors" of ASOs it makes in order to find the best match for treating HD. From an original pool of thousands, Isis has narrowed down the candidate ASOs to just five, Bennett said in a recent interview.

Isis, CHDI, and other researchers have also made significant advances on two other key research questions. First, how much of the huntingtin protein should the drug remove? So far, the scientific consensus seems to have settled on 50 percent lowering (also known as knock-down) as the current target. However, this question will ultimately be resolved through the clinical trials.

The second, related question is trickier but could ultimately open the door to an even better drug. Because HD patients have both mutant and normal huntingtin proteins in their brain cells, should the drug lower both or just the mutant? In the early going, the ASOs did not distinguish between the "good" and "bad" proteins. However, Isis has now developed a way to knock down just the bad.

At least in theory, knock-down of just the bad is the safer approach for patients, although the project's experiments have also surprisingly demonstrated that knock-down of both is not harmful, explained Dr. Kordasiewicz, the former head of the HD project in Dr. Cleveland's UCSD lab.



Dr. Holly Kordasiewicz in the lab at Isis (photo by Curt Mazur of Isis)

"The decision still hasn't been made," she said, referring to the choice between the two types of ASOs. "It's hedging your bets. Everything's on the table. The chemists are doing amazing things. It would be irresponsible of us not to consider all of the options before making our final decision."

"You never know, once you get into a human, what's going to work," she added. "So having everything ready to go, so you don't have to wait three more years to develop the next thing, if one doesn't work, you try the next."

Using second-generation ASO technology, the Isis chemists found ways to increase both the selectivity (the ability to bind to the mutant RNA as opposed to the normal one) and the potency of the potential HD drug.

"It improves potency quite a bit," said Punit Seth, an Isis senior research fellow in medicinal chemistry, in describing one of the key chemical innovations. "You can get anywhere from three-fold to ten-fold improvement, which then translates to lower costs in drugs and administering less [of the] drug to the patients."

Dr. Cleveland added that these improvements would also produce a drug with potentially fewer side effects.

Eric Swayze, Ph.D., Isis's vice president for medicinal chemistry, summed up the fine-tuning as "tailoring" and "twiddling with the number of different building blocks" that go into the ASO.

"It turns out to make a huge difference, which we didn't really expect," he observed.

Dr. Eric Swayze explains the function of the Isis ASOs (photo by Gene Veritas).

Patient-friendly delivery

Isis has also strived to simplify the delivery of the drug. Originally, the company planned to direct the drug into the brain using a device implanted in the abdomen and connected to a catheter running under the skin to the skull.

Now, however, the researchers aim to introduce the ASO directly into the cerebral spinal fluid (CSF, the fluid that bathes the brain) by injecting it through a quarter-sized port implanted near the rib cage, with the catheter running to the area of the spinal cord.

This method is "more convenient to the patient and longer-term more commercially attractive," Dr. Bennett observed.

Gene Veritas (left) with Dr. Bennett at a CHDI conference in February

Dr. Bennett noted that Isis gained valuable experience in drug delivery through a trial of its ASO drug for spinal-muscular atrophy, a childhood neurological disease. Isis also has conducted a Phase I ASO clinical trial for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

With the improved delivery method, instead of continuous infusion of the drug, patients will probably need only occasional injections, each one

lasting only a few minutes, Dr. Bennett added.

"There's a long history of safety and efficacy using this method," he said.

Furthermore, the Isis approach avoids the potentially more risky delivery methods used in two other HD gene-silencing approaches: the use of a virus, or an operation on the skull to introduce the drugs into the brain.

Getting into the brain

To improve the efficacy and safety of the ASOs, Isis and CHDI have been testing them in mice and non-human primates.

One of the key mouse testing sites is Dr. Cleveland's lab at UCSD, where an HD team led first by Dr. Kordasiewicz and, after her departure to Isis, by Clotilde Lagier-Tourenne, M.D., Ph.D.

In conjunction with experiments in other labs, the Cleveland HD team has demonstrated surprisingly good results.

One major hurdle to treating the brain is the blood-brain barrier, which shields the brain from foreign substances that might cause harm. The barrier makes it difficult to get drugs into the brain.

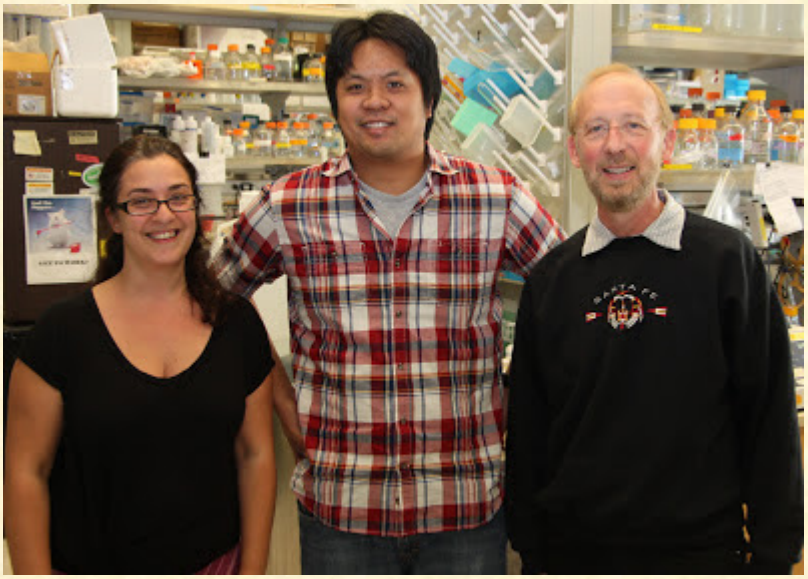
Significantly, an article recently published in the journal *Neuron*, with Dr. Kordasiewicz as the lead author, suggested that the ASOs delivered via the CSF reach a wide area of the non-human primate brains, including the regions known as the cortex and the striatum, two areas critically damaged in HD.

As Dr. Cleveland explained, a decade ago scientists viewed neurological diseases as the result of problems in a particular kind of neuron (brain cell). Since then, they have developed a radically different view: the various kinds of cells are linked together in a system – including connections between the cortex and the striatum.

"It's actually a disease not just of individual neurons but of the whole system, a neuron and the cells surrounding it," Dr. Cleveland said of HD. "It's such a simple message. It's a little surprising that it took so long to realize it. Neurons don't live by themselves. They require their partners, and the partners develop damage that drives and spreads disease. So, in Huntington's disease it's now clear that there's a partnership between striatal neurons that send projections into the cortex and vice versa."

Above, Dr. Cleveland in his office at the Ludwig Institute for Cancer Research on the UCSD campus. Below, Dr. Cleveland with lab scientists

Jon Artates (middle) and Jihane Boubaker (photos by Gene Veritas).



A 'Huntington's holiday'

The most stunning test results involved the amelioration of symptoms.

"Because we are hitting the cortex to such a high level, my prediction would be that we will have a very strong effect on things like cognition and mood and anxiety," said Dr. Kordasiewicz of the ASOs' ability to restore brain functions lost in HD. Chorea, the shaking and trembling that occurs in HD, also could be ameliorated, she added.

By reducing the level of mutant huntingtin protein in the mouse brains, the ASOs reversed the HD-like symptoms.

"It was better than we could have imagined. In the sickest animals, we stopped further brain loss," said Dr. Cleveland "In other mice, a single treatment led to partial reversal of symptoms. And what's more, the improvements lasted more than six months after a single treatment. And even then, the disease process did not start back up. It was amazing."

Dr. Cleveland observed that, unlike other kinds of substances the ASOs are made of DNA that isn't rapidly degraded by enzymes the way many other drugs are affected.

"Once they get intracellular, they're intracellular acting to catalyze the destruction of the target RNA for, not just hours, not just days, not just weeks, but actually months," he continued. Just a single injection of the ASO leads to a month of huntingtin RNA suppression in mice. A two-week infusion brings four months of suppression.

The scientists refer to the as yet unexplained symptom-free period after the ASO treatment is gone as a "Huntington's holiday."

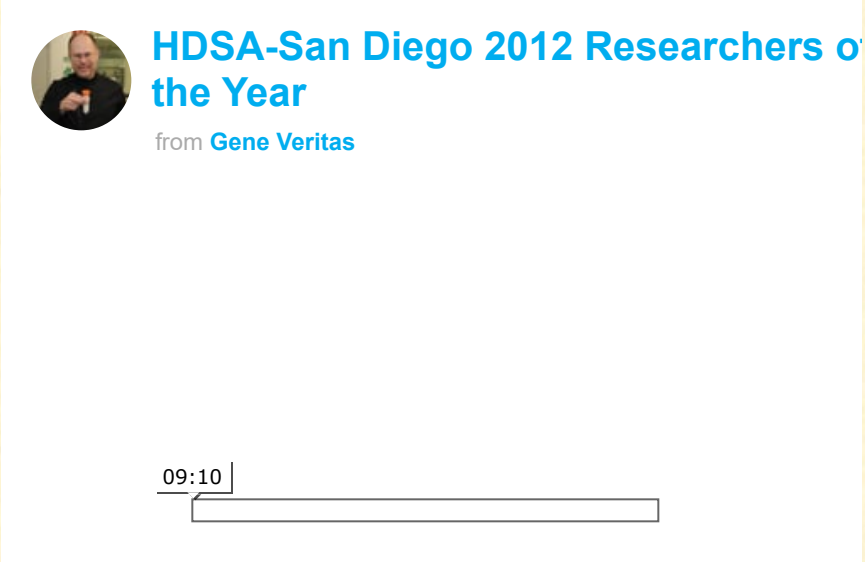
Dr. Cleveland speculated that "since it takes 30-40 years for HD symptoms to develop. If you could introduce a Huntington's holiday, maybe you could reset the pathogenic process so that it might take a considerable time to build back up."

As he and others have observed, success with this approach means people might need to take an ASO HD drug only a few times per year.

As a preventive remedy, a future generation of ASOs might even be prescribed early in life for individuals like me who have tested positive for

HD but remain asymptomatic, Dr. Cleveland added.

Watch Drs. Cleveland and Kordasiewicz receive their HDSA-San Diego awards and speak about the promise of their work for an HD treatment in the video below.



HDSA-San Diego 2012 Researchers of Year from Gene Veritas on Vimeo.

Measuring the impact in people

In the final run-up to the proposed clinical trial, the Isis-UCSD-CHDI team and its collaborators are seeking the answer to two more crucial questions: how can the efficacy of the ASO be measured when humans participate in trials? And what is the proper size and frequency of the dose?

The impact of the ASOs on mice and non-human primate brains is fairly easily measured. However, the scenario is different for humans, who cannot be manipulated, sampled, or subjected to the other kinds of experiments done with animal models.

To answer these questions, the scientists are seeking to develop "biomarkers" for the ASO effects.

As Dr. Cleveland explained, the researchers are hoping to find "signatures" in the cerebral spinal fluid of the trial participants that would indicate the impact of the ASO. Those signatures could be related to both to alterations in genes and the secretion of proteins.

"It's a very big experiment," Dr. Cleveland said. "We need a partner like CHDI with deep pockets to do this. It's an expensive experiment, but we absolutely have to do it. Can we find biomarkers? I'm an optimist. We'll know the answer over the next six months."

If successful, this experiment will help the scientists determine the amount of drug to give to the patients and provide specific measures of drug impact.

The pharmaceutical firm Novartis has found a way to measure the huntingtin protein in the bloodstream and is seeking to do so in the CSF. The Isis-UCSD-CHDI project also has at its disposal the valuable data from long-term natural history studies of HD patients (TRACK-HD), and it will also probably rely on brain imaging of the trial participants.

Light in the tunnel

In 2013, Isis hopes to select the final ASO drug candidate to move into pre-clinical testing. If that testing is successful, then the company will need another 12-18 months to obtain approval from the Food and Drug Administration to initiate the Phase I human trial.

Planning for Phase I will involve not only the ASO researchers, but toxicologists (who check for safety), pharmacokineticists (who measure the penetration and exit of the drug), and clinicians (who work with and care for the trial participants).

"They're already starting to engage in the project, because they can see the light at the end of the tunnel," said Dr. Bennett. "They're becoming involved in thinking through the strategy of how we're going to develop this drug."

Dr. Bennett emphasized that Phase I effort's main purpose is to measure safety and tolerability – not drug efficacy – although the researchers will also take note of the effects. If Phase I is successful, efficacy comes into play in the potential Phase II and III trials.

"We're committed to try to do our best to bring that drug forward," said Dr. Bennett, who noted that the Isis HD team has worked many nights and weekends to speed the project. "There's still a lot of caveats in there. The best-laid plans sometimes run into roadblocks. But we are very enthusiastic. We're in this to help patients."

"For patients and their families, I know it's too slow, but I don't think it could be done any faster," concluded Dr. Cleveland. "I think everyone's working absolutely flat out."

Bringing hope to the HD community: Dr. Cleveland at the Gala with advocate Amy Anderson, wife of Craig Anderson, a former pilot afflicted with HD (photo by Gene Veritas)

Posted by Gene Veritas at 4:08 AM

Labels: ASO , asymptomatic , chorea , clinical trial , cortex , DNA , drug , gene-silencing , genetic , Huntington's , Isis , Lou Gehrig's , neurological , neuron , oligonucleotide , protein , RNA , striatum , symptoms

1 comment:

dawn kelly said...

Lord plz let this work. My grandmother died from HD. My mom is real bad with it. I have young cousins with the gene and me and my little sister have a 50/50 chance of getting HD
God bless you all who are working to help so many HD infected families

7:30 PM, April 17, 2013

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