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Holding the potential cure in my hand

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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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Holding the potential cure in my hand

After telling yet another audience of scientists about my family's two-decade struggle against Huntington's disease, I held a potential cure for HD in my hand during a visit to Alnylam Pharmaceuticals in Cambridge, MA, on May 17.

For me, it was like holding the most valuable substance in the world. I inherited the HD-causing gene from my mother, who died of the disease in 2006 at the age of 68. At 51, I have now reached the age when HD started destroying my mother's brain, erasing her personality, and leaving her unable to walk, talk, eat, or care for herself in the most basic way.

HD is 100 percent genetic: unless drug hunters get a treatment on the market in the next few years, I *will* get symptoms.

As I held what seemed like a magic compound, held in a small, securely capped plastic container, I smiled. A treatment – and maybe even a cure – now seemed more possible than ever. And Alnylam – along with its partners Medtronic and the CHDI Foundation, Inc., the so-called "cure Huntington's disease initiative – is indeed preparing intensively to start a clinical trial.

A shot of me holding the potential cure (photo by Dr. Mathias Kretschmer of Alnylam).

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

This was a historic moment. As I stood in the lab at the Alnylam (pronounced "al-NIGH-lam") facility, I thought of all the years that our community of affected families and treatment-seeking researchers had waited for scientific breakthroughs.

I, the gene-positive HD person, caught a glimpse of a future filled with hope, even as I recognize that hope depends on further scientific breakthroughs and long odds. In the drug industry, 90 percent of clinical trials fail to produce a treatment.

ALN-HTT: white and flaky

"ALN-HTT" is the name Alnylam has given this candidate drug product, which is a solution containing the drug substance, the term scientists use for the active ingredient in drugs. It stands for "Alnylam" and "huntingtin," the name of both the gene and protein that, when defective, cause HD.

The substance – an "siRNA," or small interfering RNA molecule – is white and flaky.

ALN-HTT in the hands of Dr. Muru Murugaiah, an Alnylam principal scientist, in the company's lab (photo by Gene Veritas)

RNA interference (RNAi) was discovered in 1998 by Craig Mello and Andrew Fire in C. elegans, a species of worm. By interfering with the conversion of the genetic code into specific proteins, RNAi controls helps control the expression of genes and prevents problems from occurring in cells.

For their discovery, in 2006 Mello and Fire won the Nobel Prize in Physiology or Medicine.

At the outset, they and other scientists thought RNAi could not occur in mammals or humans.

Then, in the early 2000s, two teams of German scientists discovered that RNAi did indeed exist in cultured human cells (cells outside the body). In a presentation at the Dana Farber Cancer Institute this past January, Alnylam demonstrated that RNAi also exists in humans.

Gene silencing

This process is also known as "gene silencing." RNAi can turn off practically any gene in the body. The discovery of RNAi virtually coincided with the completion of the Genome Project, which identified every gene in

the human body.

Immediately, scientists embarked on making siRNAs to turn off harmful genes. Drug discovery companies in Europe and the United States sprung up to explore this breathtaking technology, seen by many as the genesis of a new, very large class of drugs for halting all kinds of disease.

Nobel laureate Phil Sharp started Alnylam in 2002. The company took its name from the middle star in the belt of the constellation Orion. “The star has a luminosity that is 250,000 greater than the sun, representative of the potential strength that RNAi therapeutics could bring to bear in human health,” the company states on its website.

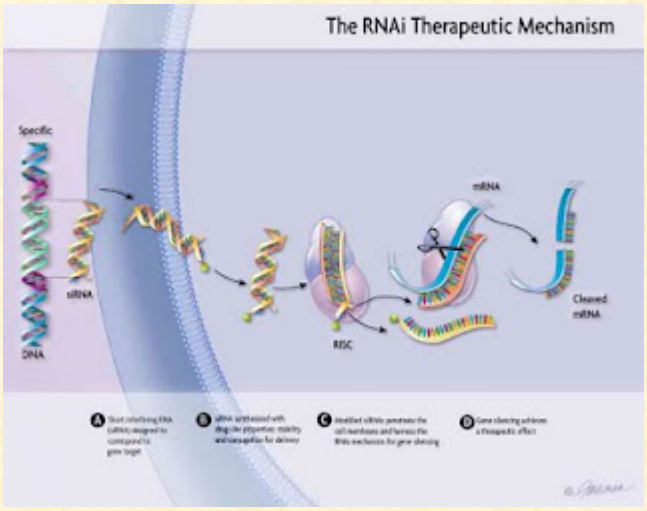
No company has yet put an RNAi drug onto the market, but Alnylam is hoping to be the first. The company has a staff of about 175 and partners with large pharmaceuticals in the search for RNAi remedies. Last year Alnylam ended a five-year partnership with Swiss pharmaceutical giant Novartis, forcing Alnylam to lay off 25 employees, but Novartis continues to pursue drug possibilities using Alnylam experimental treatments. Alnylam has more than $300 million in cash to support its activities.

Alnylam research focuses on a range of diseases and conditions, including liver cancers, respiratory syncytial virus infection (affecting the lungs and breathing passages), ultra-high cholesterol, refractory anemia, and transthyretin-mediated amyloidosis. It also facilitates research on neglected tropical diseases. The company is working on five RNAi products for genetic diseases and aims to have them in advanced stages of clinical development by the end of 2015.

Aiming for a clinical trial

In 2005, Alnylam initiated a major Huntington’s disease research project, aiming not only to address HD but also to develop techniques that might prove useful against other neurological diseases. Because HD is 100 percent genetic, it provides an excellent test for the effectiveness of gene silencing.

Alnylam intends to use ALN-HTT to silence the huntingtin gene so that less huntingtin protein is produced to harm brain cells. If successful, the treatment would save brain cells from dying and slow down and possibly even reverse the course of Huntington’s disease.



Model of how siRNA drugs work: click to enlarge (Alnylam image)

A number of research labs have already demonstrated safety and effectiveness of this approach in transgenic mice that have HD-like symptoms. In preliminary studies, it's also safe in monkeys.

The next step is a big one. Alnylam, Medtronic, and CHDI are preparing to apply in 2012 to the U.S. Food and Drug Administration (FDA) for permission to conduct a Phase I clinical trial of ALN-HTT in humans. Alnylam hopes to start the trial in a small number of HD patients once the application is accepted.

The goal of Phase I studies in general is to demonstrate safety and tolerability – that the drug does not cause adverse impacts. If successful, Alnylam would then proceed to Phases II and III, which would be designed to demonstrate the effectiveness of the drug.

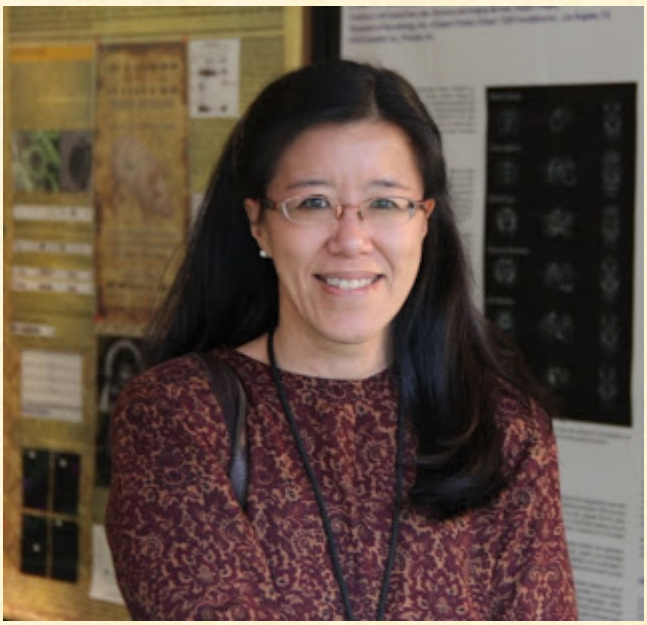
Entering uncharted territory

This is all uncharted territory for the FDA, doctors, researchers, the biotech industry, and investors. Safety for the test subjects is of the utmost importance – but so is the need to find a treatment for those families facing the horrors of HD.

Getting ALN-HTT into the brain is a major scientific and medical challenge. Because of the blood-brain barrier, which protects the brain against foreign substances, many drugs cannot get into the brain. So a drug like ALN-HTT must be injected directly into the brain.

So, for the first time in history, doctors will attempt to treat a brain condition by implanting a device into the skull in order to inject a siRNA drug.

Doctors have already experimented with deep-brain stimulation by implanting electrodes into the brains of patients with Parkinson's, epilepsy, dystonia, depression, and even HD, explained Dinah Sah, Ph.D., the head of the Alnylam HD team and Vice President of Research. The procedure has shown some benefit in Parkinson's, but no known effect yet in HD.



Dr. Dinah Sah, Vice President of Research and the head of the Alnylam HD team (photo by Gene Veritas)

Recently a clinical trial demonstrated improvement in Parkinson's patients who received gene therapy in which a virus was used to transport the genetic message into brain cells.

Physicians have also injected a cell growth stimulant (growth factor) into the brains of Parkinson's patients. This last approach is still under study.

Alnylam has partnered with Medtronic, a leading maker of medicinal pumps, to devise a pump to be placed in the HD patients' abdomens. Doctors will run thin tubing under the skin from the pumps to a nodule at the top of the patients' heads, and from that point a very fine needle will run into the putamen, one of the regions of the brain most devastated by HD.

For all of this to happen, expert doctors in the procedure will conduct an operation on the clinical trial participants. Doctors will then administer ALN-HTT, which will be dissolved in a special solution, by filling the pump and allowing it to send the drug to the brain according to a schedule and in doses to be determined by the researchers.

Other possibilities

This is all just a very brief sketch of the Alnylam project. Soon I will be writing more detailed reports, which will examine how Alnylam and its partners developed ALN-HTT and hope to turn it into a successful drug to treat Huntington's disease. These reports will also consider the many challenges involved in this quest for an siRNA treatment.

Remember, too, that Alnylam is not the only project seeking to control HD at its genetic roots. As I have noted in several articles since 2008, Isis Pharmaceuticals, Inc., of Carlsbad, CA, has devised a similar drug candidate to be applied directly in the brain (click here to read more). And Dr. Jan Nolta's lab at the University of California, Davis, is experimenting with ways to use stem cells to introduce siRNA into the brain. For an overview of HD and gene silencing, see the excellent article by Dr. Jeff Carroll.

Isis and Alnylam operate a joint venture, Regulus Therapeutics, to research microRNAs, an even more recent discovery also involving RNA interference.

HD researchers aren't banking on any one of these initiatives as the sole solution to HD. Although one of them could indeed turn out to be the "cure," most researchers speak of the likely need for an HD "cocktail" of drugs that would stop or at least reduce the many harmful effects on the brain caused by HD.

Seeking patient input

To assist with the HD project, last November Alnylam signed an agreement with CHDI, a multi-million-dollar effort backed by an anonymous donor. CHDI is pumping money into the project and lending its expertise in Huntington's disease.

The crucial CHDI collaboration will reinforce Alnylam's efforts to design a safe Phase I trial.

To that end, Alnylam is also seeking to learn more about the patients and gene-positive people whom it hopes to benefit.

After watching my keynote speech at CHDI's Sixth Annual HD Therapeutics Conference in Palm Springs, CA, on February 7, Dr. Sah invited me to give a similar presentation at the company. My May 17 visit inaugurated a new Alnylam initiative to involve patient advocates in order to put a human face on the conditions they seek to alleviate.

During the Q & A after the speech, attended by about 50 people, Alnylam executives and scientists were anxious to hear my opinion about several aspects of clinical trials.

The desire to function normally

One scientist wanted to know what people affected by HD community would consider to be a successful treatment. Obviously we all want a "cure" that completely eliminates the disease, I responded. But short of that, we need something that would at least allow us to continue to function normally. If someone suffered from chorea (the shaking and trembling caused by HD), a good drug would at least prevent that person from also losing the ability to think and speak.

We also need a drug that would prevent HD from erasing an individual's personality by preventing the behavioral, emotional, and cognitive problems. HD, I said, had stolen my mother's personhood.

One doctor asked: what if we fail and no treatment results from this experiment?

I responded that I recognized that failure is a part of science. You don't know if something will work unless you try it, and if it fails, then you know it's time to proceed to other alternatives.

However, I told the audience that I personally do *not* think about failure. The project *must succeed!* At that, many people nodded enthusiastically, and one of the executives said: "We agree with you!"

At that moment, I felt a special bond with everybody in the room. We were all rededicating ourselves to the quest for the cure – although everybody also recognized that failure remained a distinct possibility.

Avoiding hurdles, gaining speed

Afterwards I met with CEO John Maraganore, Ph.D., President and COO Barry Greene, Dr. Sah, Doug Macdonald, Ph.D., of CHDI, and Jules Greenwald, the development director for the Huntington's Disease Society of America (HDSA). I took the opportunity to interview Maraganore and Greene.

Both stressed the need to prepare an effective Phase I application to the FDA and to convince the agency of the urgency of getting an siRNA treatment to HD patients.

"It's important for us to have a dialogue, which includes patient advocates, with the FDA and other regulatory agencies, so that they appreciate the significant burden that the disease has on patients and their families," Greene said.

"I think they know the disease, but they don't really know the face of the disease," Dr. Maraganore said.

Barry Greene (left), Gene Veritas, John Maraganore, and Dinah Sah

Much of the upcoming discussion with the FDA will revolve around the question of how fast Phase II and Phase III of the trial can go. If the FDA requires an extremely long efficacy study – from seven to ten years – the costs could become prohibitive and scare off funding sources, like investors, Greene explained. For patients and success, "speed really matters," he said.

Another crucial question involves determining "endpoints." In this case, an endpoint would be an observable change in a specific symptom and/or a change in the level of defective protein in the brain cells or some other marker of the drug's effects (biomarkers).

Measuring huntingtin protein levels would likely prove the quickest endpoint, although it's not clear if a lower level of huntingtin in humans will diminish symptoms the way it has in mice.

"We ... want to have a testing approach that doesn't create undue hurdles to the point where you actually make it so difficult to prove that something is maximally safe and maximally effective," said Dr. Maraganore in summarizing the challenges. "So you want to have the right balance.

"The urgency? The need? I think you said it: You have more to lose now than ever," he continued, referring to my race against time as I await a treatment. "That's the level of urgency that needs to be put into this equation in terms of how these medicines are developed. That can only be said by a patient."

Hanging out with the scientists

My day at Alnylam was one of the most intense of my entire life. This article doesn't even scratch the surface of what I experienced.

But Alnylam also planned some relaxation.

I enjoyed hanging out with the scientists at lunch and dinner, and I was impressed by their humanity and openness to new and different perspectives.

I had contemplated removing from my speech a mini-meditation exercise involving a demonstration of deep breathing, and also my discussion of the question of God, HD, and the Jesuit priest-scientist Teilhard de Chardin. But I was glad I didn't. To my great surprise and joy, Sara Nochur, Ph.D., the Vice President for Regulatory Affairs, had read Teilhard's works, and her husband had just completed a book on the topic of the link between science and the transcendental and also knew Teilhard's writings. As we walked back in the rain to the office, Dr. Nochur and I compared notes on meditation and breathing as coping mechanisms.

At dinner Martin Goulet, Ph.D., who handles non-clinical experiments in the Alnylam lab, and I talked about our families. He has a girl about the same age as my HD-free ten-year-old daughter.

Dr. Martin Goulet (right) at work on the Alnylam HD project (photo by Gene Veritas)

Getting out the word on trials and the cause

Over the next few days, I excitedly told other people in the movement that I had held ALN-HTT in my hand. I felt like an apostle spreading news of a religious revelation.

My journey did not end at Alnylam. On May 18 I flew to New York City for meetings with other leaders of the HD movement. That day I visited CHDI headquarters in Manhattan, where communications director Simon Noble, Ph.D., and I discussed at length ways of getting out the word about the need for involvement in upcoming clinical trials.

On May 19, I spent most of the day at HDSA. I gave an informal talk to the staff about my situation and advocacy. I also interviewed CEO Louise Vetter, now in her third year at HDSA. In line with the theme of clinical

trials, we discussed the HDSA Clinical Trial Ambassador program, which will utilize experienced members of the HD community to promote awareness about the trials and answer potential participants' concerns.

On May 20, I traveled to Princeton, NJ, to interview scientists from CHDI's clinical trials division.

The visit began with an informal brainstorming session at the home of Maria Beconi, Ph.D., the director for drug metabolism and pharmacokinetics (how drugs are absorbed, distributed, and excreted from the body).

After we consumed pizza, soft drinks, brownies, and cupcakes, Maria introduced me. I thanked the team for its commitment to HD research and explained that I was tracking the social history of the HD movement and the work of the scientists towards treatments and a cure.

I'll be writing more about this issue and the CHDI unit in a future article.

In New York I met up twice with my friend and "HD alter ego," Norman Oder, who edits this blog. We caught up on each other's lives, and we discussed strategies for broadening the message of the HD cause.

Alnylam: passionate about HD

In 2008, when I first studied the Isis HD project, I fantasized about wearing a drug-injecting pump on my head. That was a somewhat inaccurate fantasy, because the pump would not be located on the head itself, but in the abdomen. Isis plans to use this kind of system. But even if it *were* located on the head, I would gladly use it – or any other device in any other location, for that matter.

Likewise, I would happily accept the implantation of an ALN-HTT pump in my abdomen. My need to avoid HD far outweighs any potential inconvenience caused by such devices.

I came away from Alnylam energized by its scientists' seriousness, intelligence, practicality, and commitment to stopping HD. "We are very passionate about this disease and finding a cure for it," Dr. Maraganore told me at the end of our interview.

Dr. John Maraganore (Alnylam photo)

Dr. Maraganore told me that Alnylam will likely call on me again, as well as other patient advocates, to offer advice on the design of the clinical trial and to put a human face on the disease for the FDA.

Holding the cure is not enough

During the Q &A after my speech and the interview with Maraganore and Greene, I had an uneasy sensation in my gut. Alnylam's scientists wanted not only to learn about my personal struggle against HD: they also wanted me to become involved in the strategizing for a clinical trial. I suddenly felt myself taking on a new, challenging, and immense responsibility in my HD advocacy. Though I have no training in science, I need to increase my knowledge of HD, the research for treatments, and the clinical trial process.

Dr. Maraganore observed that, as a result of Alnylam's new collaboration with CHDI, the company was "smarter about what we need to do" to get ALN-HTT into trials. "By being smarter, we're going to be faster," he added.

I, too, felt a bit smarter after meeting the Alnylam team. And I need to get even smarter as we all move together towards this potentially historic treatment.

Holding the potential cure in my hands is just the beginning. I must do my part to help get that cure into our patients and ultimately into me.

(Note: because Alnylam invited me to speak and visit its facility, the company paid for my round-trip airfare to the East Coast, my hotel in Cambridge, and meals related to the visit. I maintained the right to express my opinion in this and other articles on the HD project.)

Posted by Gene Veritas at 7:32 PM

Labels: ALN-HTT , Alnylam , CHDI , clinical trial , cure , gene silencing , gene-positive , genetic , Genome Project , huntingtin , Huntington's , Isis , mother , RNAi , siRNA , Teilhard , treatment

8 comments:

Unknown said...
This is amazing! I'm with you all the way.--Lauren Holder
6:20 AM, May 26, 2011

EJ said...
Thank you for updating us with this important information and giving hope for the HD community. E.J. Garner
10:54 PM, May 26, 2011

june Brown said...
Such amazing story, how proud you must be to have a possiable cure for HD your hands.
11:54 PM, May 26, 2011

Dinah Sah said...
Thank you, Ken, for your memorable visit to Alnylam - it was very impactful for us as well.
With best wishes,
-Dinah
3:21 PM, May 27, 2011

Tara Ziemann said...
I read and re-read and re-read and smile. I pray to God that this is it. Thank you so much for sharing.
5:34 PM, May 27, 2011

Caroline said...
Thank you so much for laying out the science and the current state of the research so clearly! Excellent post and as always, may God be with you and bless your work.
7:50 AM, May 28, 2011

Anonymous said...
Gene
My father was recently diagnosed with HD. Do you have an email address where I could as you a few question?
Aimee
You can email me at skrumshz (at) gmail (dot) com.
11:08 AM, May 28, 2011

Hellen said...
This is so interesting and exciting. I can actually feel some hope again.
Thank you for sharing
Helen from Sweden
2:32 PM, May 28, 2011

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