4-25-2013

A key new ally in the search for Huntington's disease treatments

Kenneth P. Serbin
University of San Diego

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.

Blog Archive

- ► 2021 (12)
- ► 2020 (16)
- ► 2019 (19)
- ► 2018 (16)
- ► 2017 (14)
- ► 2016 (13)
- ► 2015 (24)
- ► 2014 (24)
- ▼ 2013 (30)
  - ► December (3)
  - ► November (3)
  - ► October (3)
  - ► September (3)
  - ► August (2)
  - ► July (1)
  - ► June (1)
  - ► May (3)
  - ▼ April (4)
    - A key new ally in the search for Huntington's dise...
    - Feeling the hope
    - Quickening the pace towards a Huntington's disease...
    - Brazil's big place on the Huntington's disease map
  - ► March (2)
  - ► February (3)
  - ► January (2)
- ► 2012 (26)
- ► 2011 (33)
- ► 2010 (26)
- ► 2009 (21)
- ► 2008 (7)
- ► 2007 (7)
- ► 2006 (4)
- ► 2005 (17)

About Me

THURSDAY, APRIL 25, 2013

A key new ally in the search for Huntington's disease treatments

With the new partnership between Roche and Isis Pharmaceuticals, Inc., reported here on April 11, the search for Huntington's disease treatments has gained an accomplished and ambitious ally in the person of Luca Santarelli, M.D., Ph.D.

Dr. Santarelli, the 44-year-old head of neuroscience and small molecule research at Roche's world headquarters in Basel, Switzerland, will oversee the Roche-Isis effort to bring Isis's proposed gene-therapy drug to a long-awaited crucial clinical trial, tentatively scheduled to start in the first half of 2014.

A native of Italy, Dr. Santarelli in the early 2000s made an astounding discovery about Prozac-type antidepressants while conducting postdoctoral research at Columbia University in New York City: these drugs actually led to neurogenesis, the birth of new neurons in the brains of adults.

With these findings, Dr. Santarelli joined Nobel laureate Dr. Eric Kandel, Dr. Rene Hen of Columbia, and Dr. Fred Gage of the Salk Institute for Biological Studies in San Diego to found a company, Brain Cells, Inc., that focused on the development of novel antidepressants for stimulating neurogenesis.

In 2005, Dr. Santarelli joined Roche. He quickly rose in the company ranks and now oversees efforts to design drugs for brain disorders and related conditions, including schizophrenia, depression, Alzheimer's disease, multiple sclerosis, spinal muscular atrophy, and neurodevelopmental disorders such as autism and Down syndrome.

Nature's Trojan horses

Now, turning their attention to HD, Santarelli and Roche researchers will collaborate with Isis to speed progress towards the clinical trial, infusing $30 million into the project.

They also will seek ways to make the potential Isis drug easier for trial participants and eventual patients to absorb. Instead of Isis's potentially riskier and certainly less comfortable method of implanting a quarter-sized port near the rib cage connected to a catheter running to the area of the spinal cord, Roche aims to create a drug that patients could take through an intravenous or subcutaneous (under the skin) injection. (It's still too early to tell where in the body patients would receive such a potential subcutaneous injection.)

To design this kind of drug, Roche will use a so-called "brain shuttle," a new approach to transporting drugs past the highly impermeable blood-brain barrier, which protects the brain from foreign objects.

The blood-brain barrier also makes it difficult for so-called large molecule drugs to enter the organ and thus has presented researchers with a major hurdle to treating brain disorders and diseases.

Dr. Santarelli, in a phone interview on April 22, was asked to explain the brain shuttle in everyday terms.

"It works by hijacking a biological system that is normally used to shuttle proteins into the brain," he told me. "It uses cellular receptors outside the blood brain barrier and uses them as Trojan horses to take in a cargo."

Dr. Luca Santarelli (photo courtesy of Roche)

The cargo could include an antisense oligonucleotide, or ASO, the specially designed piece of artificial DNA made by Isis that, in mice experiments, has reduced the amount of the harmful huntingtin protein in brain cells and produced a "Huntington's holiday," a disappearance of the symptoms.

"A cargo can be an ASO," Dr. Santarelli continued. "It could also be a peptide or an antibody. Receptors are on the outside (of the blood-brain barrier), but they also move to the inside. They are built by nature to allow certain large molecules (to move in)."

Explaining the concept

No brain shuttle drug yet exists. I was eager to know exactly what kind of shuttle Roche might have in mind and how it could work with the ASOs.

However, because of the trade secrets involved in private drug research, Dr. Santarelli declined to comment.

Nevertheless, he emphasized that the brain shuttles are "built by nature to allow the transfer of large proteins inside the brain." Different shuttles have different capacities, he added, and they work in a "controlled fashion."

"The concept of proteins that shuttle large molecules has been known for a while," he said, referring to the decade-plus research on the phenomenon.

Dr. Santarelli cited the example of the shuttle known as transferrin.

"We know that transferrin works in this way," he said. "Transferrin is a protein that carries around iron in the bloodstream. Iron doesn't go around freely. It's absorbed and transferred around to the organs. It (transferrin) binds with iron – iron gets released into the brain."

Advantages of the brain shuttle

By carrying an ASO into the brain in this revolutionary manner and avoiding the discomfort of a lumbar (lower-back) puncture or other long-term invasive approach, the brain shuttle approach helps drug discovery in two key ways.

First, it allows researchers to include people in clinical trials who previously were not eligible – namely, people genetically at risk for a disease but without symptoms. In terms of ethics and comfort, it is difficult to justify their participation because of the risk posed by invasive procedures.

With the brain shuttle, however, discomfort is reduced. So is the ethical barrier, because the injury risk diminishes.

Secondly, by including presymptomatic people in drug studies, researchers can measure how a drug affects a patient *before* the disease develops, thus providing clues about how to stop the disease from ever occurring.

Only a few years ago, this kind of approach to neurological drug research seemed futuristic. The lack of opportunities to participate in clinical trials and the absence of a strategy to prevent the disease in asymptomatic people have proved especially frustrating for the HD community, where people like me await in great fear the onset of a disease foretold by genetics.

A unique Alzheimer's trial: intervening early

With Isis, Dr. Santarelli and Roche are working to raise the hope of preventing asymptomatic gene carriers from ever experiencing onset.

Roche is especially well-positioned because, as Dr. Santarelli pointed out, it focuses on both drug development *and* disease diagnostics.

Roche's "strategic objective" is to intervene "as early as possible" in the course of the disease, he emphasized.

"As an organization, we've done this in Alzheimer's," he explained.

In developing its proposed Alzheimer's drug, now under study in a clinical trial involving 800 patients, Roche has taken the unique step of including individuals who have not yet developed dementia, but have merely mild cognitive impairment, Dr. Santarelli said. (Click here for further background.)

In the trial Roche is using molecular testing to diagnose and select trial subjects at risk for Alzheimer's. This is done by performing a lumbar puncture to obtain a sample of cerebral spinal fluid (CSF) to check the presence of amyloid, the substance that forms plaques in the brain of Alzheimer's patients and is considered one of the causes of the disease.

If successful, the Roche drug will not only clear plaques from the brains of the Alzheimer's patients but also delay (or stop) the progression of the disease, Dr. Santarelli said.

The diagnostic technique used in the trial to measure CSF amyloid is experimental and has yet to reach the market, Dr. Santarelli noted.

He stressed that the Roche approach involves both the more traditional *clinical* (observational) measurement of the patients' symptoms and, with this new measurement technique, a *molecular* measurement.

Roche's "culture of combining diagnostics and therapeutics" will definitely provide useful for the development of HD drugs, Dr. Santarelli observed.

A number of other HD research efforts also focus on the search for molecular measurements.

Patient involvement

Because of the highly experimental nature of the brain shuttle and the newness of Roche's neurological diagnostics, Dr. Santarelli could not forecast when these approaches will bear fruit in HD research.

"We have to go through all the experimentation," he said of the partnership with Isis.

Whatever the timeline, Roche will depend on collaboration with the HD community, as it has with advocates for other diseases.

"You guys are playing an extremely important role for lowering barriers to making progress in this area," he said. "I feel personally honored that I can make a contribution in this area."

Posted by Gene Veritas at 1:18 PM

Labels: Alzheimer's , antisense , blood-brain barrier , brain , brain shuttle , clinical trial , Huntington's disease , Isis , Luca Santarelli , lumbar puncture , neurogenesis , neuroscience , oligonucleotide , Roche , treatments

2 comments:

Anonymous said...

I just found your blog. I've been following the news about Isis and Roche. I've followed the news about gene silencing, RNAi therapies, ASO's, and many other treatments. I've been poked and prodded in clinical trials, all while having hope. But, I've never felt so much hope until reading your blog. My hope is not false. We are so close to a cure. There are so many amazing things happening right now in brain research and it's so very encouraging! Thank you for your words. I look forward to reading more posts from you!

9:15 AM, May 08, 2013

Mark said...

This is great news and offers an unlimited arsenal of hope to me. My significant other is currently displaying symptoms of this malicious disease and will soon be tested. Both of us are completely scared of the possibility she will be positive for it. She is growing more melancholy everyday about it I see her and it rips my heart apart. I hope whoever is above grants these gentlemen with the best possible results of their partner ship. Thank you for this post. Thank you for this hope.

2:09 PM, May 24, 2013

Post a Comment

Newer Post Home Older Post

Subscribe to: Post Comments (Atom)