University of San Diego
Digital USD

At Risk for Huntington's Disease | Department of History

10-15-2020

# Triplet Therapeutics aims to transform the approach to treating Huntington's disease, similar disorders

Kenneth P. Serbin
*University of San Diego*

Follow this and additional works at: https://digital.sandiego.edu/huntingtons

 Part of the Nervous System Diseases Commons

## Digital USD Citation

Serbin, Kenneth P., "Triplet Therapeutics aims to transform the approach to treating Huntington's disease, similar disorders" (2020). *At Risk for Huntington's Disease*. 293.
https://digital.sandiego.edu/huntingtons/293

This Blog Post is brought to you for free and open access by the Department of History at Digital USD. It has been accepted for inclusion in At Risk for Huntington's Disease by an authorized administrator of Digital USD. For more information, please contact digital@sandiego.edu.

More Create Blog Sign In

# 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)
  - ► December (1)
  - ► November (3)
  - ▼ October (1)
    - Triplet Therapeutics aims to transform the approac...
  - ► August (1)
  - ► July (1)
  - ► May (1)
  - ► April (1)
  - ► March (3)
  - ► February (3)
  - ► January (1)
- ► 2019 (19)
- ► 2018 (16)
- ► 2017 (14)
- ► 2016 (13)
- ► 2015 (24)
- ► 2014 (24)
- ► 2013 (30)
- ► 2012 (26)
- ► 2011 (33)
- ► 2010 (26)
- ► 2009 (21)
- ► 2008 (7)
- ► 2007 (7)
- ► 2006 (4)
- ► 2005 (17)

## About Me

GENE VERITAS

View my complete profile

## HD Links

Huntington's Disease Society of America
International Huntington Association
Huntington's Disease Drug Works


THURSDAY, OCTOBER 15, 2020

## Triplet Therapeutics aims to transform the approach to treating Huntington's disease, similar disorders

Huntington's disease causes complex symptoms and attacks the brain – the most difficult organ to access with drugs. Thus, current remedies only help manage symptoms. They do not stop the disorder from progressing and, ultimately, causing death.

Now, building on groundbreaking research into the genetic roots of HD, Triplet Therapeutics, Inc., is taking a bolder stance: restoring the idea of transformative treatment onto the agenda by directly attacking the disease's underlying causes.

Founded in late 2018, Cambridge, MA-based Triplet aims to start a clinical trial in the second half of 2021 for a potential drug, for now called TTX-3360, targeted at stopping the mutant huntingtin gene's tendency for continued expansion with age. That expansion compromises brain cells and triggers disease. Using the same mechanism, Triplet hopes to develop transformative treatments for many of the more than 50 other so-called repeat expansion disorders (REDs). For REDs of the central nervous system, it would use the same drug as for Huntington's.

The DNA that comprises the mutations of many REDs – as with Huntington's – occurs in triplets of the letters of the genetic alphabet. This helped inspire Triplet's name. But other repeats, from 3-12 letters long, have also been described. Also as in HD, the DNA in other repeat expansion disorders grows longer and thus may cause disease.

"There's a lot of the genome that we actually don't know about, and a lot of putative genes there that, frankly, we don't know functionally what they do," Triplet founder and CEO Nessan Bermingham, Ph.D., said in a January interview on the podcast BioBoss. "So, I think of the opportunities in our industry as we think about treating disease is very much going in and trying to actually understand and segment these regions of the genome to understand how targeting them may actually prevent or treat or cure disease."

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

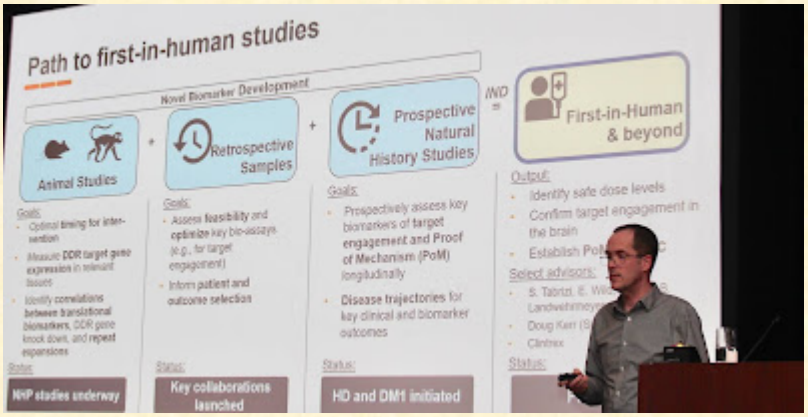
The efforts for treatments have taken "significant steps forward," Dr. Bermingham observed.

Triplet secured $59 million in initial financing and investment. The company's scientific advisory board includes key researchers in the fight against Huntington's such as Harvard University geneticist James Gusella, Ph.D., the leader of the team that discovered the huntingtin gene in 1993, and Sarah Tabrizi, FRCP, Ph.D., a professor at University College London and one of the chief medical collaborators in the development of the historic Phase 1/2a HD gene-silencing clinical trial run by Ionis Pharmaceuticals, Inc., followed by an in-progress Phase 3 trial run by Roche (discussed below).

Triplet has also consulted with CHDI Foundation, Inc., the nonprofit virtual biotech dedicated solely to developing HD therapies (drugs and/or other treatments) and sponsor of the 15th Annual HD Therapeutics Conference in February. Produced by former NBC-TV foreign correspondent and global Huntington's advocate Charles Sabine, this year's conference highlights video featured Triplet and its senior vice president for research, Brian Bettencourt, Ph.D. Dr. Bettencourt was the lead scientist in the design of TTX-3360.

As I wrote nine years ago, preventing onset in premanifest (presymptomatic) gene HD gene expansion carriers like me has been the "Holy Grail" not only for Huntington's, but other neurological disorders, given that brain damage starts many years before visible symptoms occur.

"To hear what has been up and coming in the past five years and to hear what Triplet Therapeutics has been doing is so exciting for somebody like me who is premanifest and who has kids, one who is at risk," said leading advocate Lauren Holder, 34, during her July 22 interview of Irina Antonijevic, M.D., Ph.D., Triplet's chief medical officer, on the Help4HD Live podcast.




*Above, Brian Bettencourt, Ph.D., Triplet's senior vice president for research, explains a slide illustrating the firm's pathway to a potential HD drug at the 15th Annual HD Therapeutics Conference (photo by Gene Veritas, aka Kenneth P. Serbin). Below, Nessan Bermingham, Ph.D., Triplet founder and CEO (Triplet photo).*

**Leveraging trailblazing insights of HD genetics**

As a December 2019 news release stated, Triplet is "leveraging insights of human genetics to target the underlying cause" of REDs.

Those insights from genetic data collected over decades in more than 9,000 people affected by HD have changed standard thinking about Huntington's genetics. This type of broad-ranging study is known as GWAS, genome-wide association study.

"My company, Triplet Therapeutics, was quite literally founded based on the information that came out of the Huntington's GWAS," Dr. Bettencourt said in his interview with Sabine. "The GWAS provided us a really, really rich list of good gene targets for drugs." These genes modify the age of onset and progression of HD.

"The research in HD has really driven the research in this entire field," Dr. Antonijevic told me in an interview via Zoom on October 4. From 2009-2010, she served as CHDI medical director. Later, she worked for Wave Life Sciences, which is conducting an HD clinical trial with a drug similar to the one developed by Roche for its historic clinical trial.

Dr. Antonijevic pointed to the "trailblazing" work of Harvard University HD genetics researchers Dr. Gusella, Marcy MacDonald, Ph.D., and Jong-Min Lee, Ph.D. With others, they demonstrated why people with the same repeat length in the huntingtin gene can experience widely different ages of onset (click here to read more).

This might very well explain why HD struck my mother in her late 40s, turned her into a debilitated, mere shadow of herself by her late 50s, and

took her life at 68, while I, with the same degree of mutation, have reached 60 essentially healthy, without motor onset, and able to function normally.

**Somatic expansion: a driver of disease**

The disease-causing expansion of the relevant portion of the huntingtin gene is the trinucleotide repeat CAG, letters in DNA alphabet. The expansion over an individual's lifetime is known as somatic expansion or somatic instability. The breakthrough in HD genetics has revealed that so-called modifier genes linked to the speeding or slowing of somatic expansion can hasten or delay the age of HD onset by just a few years or by as many as 40.

Most of the modifiers contribute to the maintenance and repair of DNA, which, in general, helps cells remain healthy. Scientists call this process the DNA damage response (DDR) pathway.

"We tend to think of DNA as a fixed blueprint, an overarching plan for the biological bricks and bridges that constitute our cells, organs, and bodies," a recent HDBuzz article explained of somatic instability. "But like any good plan, DNA is actually dynamic and adaptable."

**Roche/Ionis achievement a 'stimulus' to other companies**

Like Roche's historic, in-progress Phase 3 gene-silencing clinical trial (GENERATION HD1), the Triplet program will use an antisense oligonucleotide (ASO), a synthetic modified single strand of DNA that can alter production of certain proteins.

In its Phase 1/2a trial, the Roche ASO successfully reduced the amount of mutant huntingtin protein in participants' cerebrospinal fluid (CSF), obtained from lumbar punctures (spinal taps). The CSF bathes the brain. Roche researchers are looking hard for biomarkers (signs of disease and a drug's effectiveness) in the CSF. Triplet and other research programs are also studying CSF.

Roche and its partner Ionis, which designed the drug candidate Tominersen over nearly a decade, did the scientific heavy lifting required to develop the first HD ASO and administer it safely to clinical trial volunteers using lumbar punctures.

To date, Roche has not reported any serious adverse effects after the many lumbar punctures done on the hundreds of volunteers in its clinical trial program. The company expects to complete GENERATION HD1 and start analyzing data in 2022.

"The demonstration in a clinical study that a drug can lower mutant huntingtin levels was a critical development for the field," Ignacio Muñoz-Sanjuán, Ph.D., the CHDI vice president for translational biology, told Sabine in the HD Therapeutics Conference highlights video. "It really

provides stimulus to many other companies to use similar approaches and similar methodologies to try to establish treatments that really benefit the life of patients."

Ionis has also been studying the control of somatic expansion as an additional Huntington's therapy. Researcher Jeff Carroll, Ph.D., presented on this topic at the HD Therapeutics Conference. In July he co-published a paper on this subject with a team of researchers, including two Ionis scientists. The research demonstrates that lowering the huntingtin protein with an ASO in mice and human neurons in a lab (but not yet in a clinical trial) decreases somatic expansion and may also decrease the size of the expansions.

"We remain committed to finding effective treatments for Huntington's disease and are investigating multiple targets beyond lowering of huntingtin in our drug discovery group and with academic collaborators," Frank Bennett, Ph.D., Ionis executive vice president and chief scientific officer, wrote me in an October 12 e-mail.

**Taking the foot off the disease accelerator**

Dr. Antonijevic indicated that Triplet has leveraged publicly available knowledge gained from the Roche/Ionis program and others to plan Triplet's development program.

"I think it is great to see that there is trial activity," she said. "Ultimately the more trials with different approaches there are, the better the chance that there will be a treatment for the patient."

*Dr. Irina Antonijevic (Triplet photo)*

However, Dr. Antonijevic pointed out a key difference between Triplet's approach and Tominersen: lowering the amount of the mutant huntingtin

protein does "nothing" to block the harmful expansion of the huntingtin gene, because it does not "touch the DNA."

As with all ASOs, the Triplet approach blocks the action of RNA. However, Triplet's drug will act "upstream" of the mutant, disease-causing gene itself by targeting another gene that promotes huntingtin's somatic expansion, Dr. Antonijevic explained.

"This is why we say it's upstream: it affects the huntingtin gene at the DNA level," she observed. "This is where we think it matters. The continuously increasing toxicity of the mutant gene is stopped, because the expansion at the DNA level is stopped."

At the HD Therapeutics Conference, Dr. Bettencourt drew a contrast between the huntingtin lowering done by the Ionis/Roche ASO and Triplet's targeting of somatic expansion. Huntingtin lowering is like "putting a brake on the process," he said. As a result, the drug is "not dealing with the constant foot on the gas, whereby the DNA repeat is continuing to expand." Triplet is different: "our therapies quite simply seek to remove that foot on the gas," with the DNA no longer expanding, he said.

*Dr. Brian Bettencourt (Triplet photo)*

**Drug candidate now ready**

Triplet announced the selection of its ASO drug candidate, TTX-3360, in July. "TTX" stands for Triplet; 3360 is the number of the molecule.

Triplet very quickly developed its ASO because of "luck and expertise combined," Dr. Antonijevic told me, explaining that TTX-3360 has been tested in animals, including non-human primates (monkeys). "We are excited to move it forward."

To help select candidate compounds, Dr. Bettencourt stated at the Therapeutics Conference that Triplet relied on computational screening, experiments in animals, and tests in cells derived from HD patients. The company has also used siRNAs, small interfering RNA molecules, to test potential drug targets.

In its studies in non-human primates, one of Triplet's test drugs was safe, well-tolerated, and had significant "knockdown" (reduction, a desired positive effect) on the targeted gene, Dr. Bettencourt added.

Dr. Antonijevic stated that TTX-3360 will target a modifier gene, but did not reveal which one. The modifier gene itself is "not pathologic," she added. However, by reducing this gene's expression as a protein that acts on the huntingtin gene, Triplet hopes the deleterious expansion of the huntingtin gene will slow or stop.

Triplet has not yet announced how it will deliver TTX-3360 in in the Phase 1/2 trial.

"Ultimately what we think is most important is that we get the drug to those areas in the brain that are important to target when treating an individual with Huntington's disease, and we will let the science drive what the right delivery is," she said.

**SHIELD HD: preparing for a clinical trial**

Before Triplet can launch a study of its drug aiming to cure HD, it wants to understand in greater detail how the disease progresses. It also wants to confirm existing biomarkers and measure new ones to help track the effectiveness of its drug.

Under Dr. Antonijevic's leadership, last May Triplet initiated SHIELD HD, a critical, two-year "natural history study" of approximately 60 HD gene expansion carriers to help prepare the Phase 1/2 clinical trial of TTX-3360 that the firm hopes to launch in the second half of 2021. Triplet is recruiting volunteers in Canada, France, Germany, the United Kingdom, and the U.S.

"SHIELD HD" aligns with some of the letters in the study's longer scientific name, "but ultimately it reflects that we think of our approach as a protection from the disease," she told me.

A natural history study involves no "intervention or treatment," she added. "We are studying the disease as it would normally progress, using clinical [observation] and biomarkers. So, it is really the natural course of the disease."

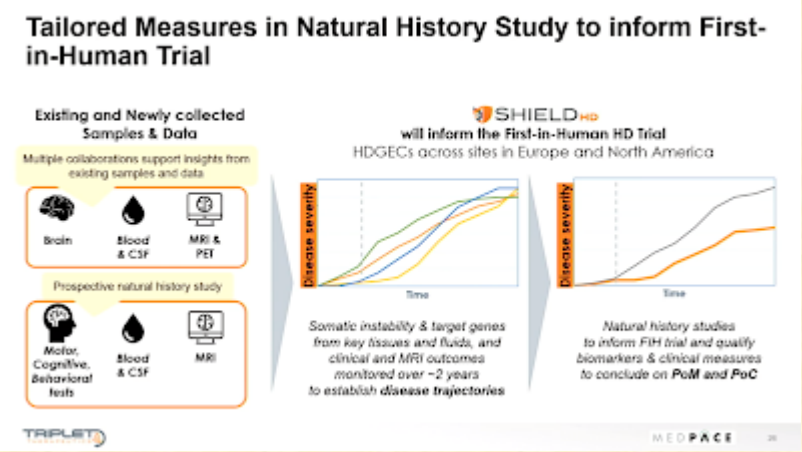
As part of the study, Triplet scientists are analyzing volunteers' CSF, MRI brain scans, blood, and data from cognitive tests, including HD-CAB, a

refined "cognitive assessment battery" developed with input from the U.S. Food and Drug Administration and researchers predominantly for premanifest individuals, Dr. Antonijevic said in the Help4HD Live interview.

"It is really a performance test," Dr. Antonijevic told advocate Holder. "This is something that does not require the physician or the investigator to assess a patient, but it is the individual who performs the test."

The cognitive tests provide a "snapshot in time" of the individual's decline because of HD and measures change over time, Dr. Antonijevic continued. "It's really more objective than, for instance, a rating scale." (Physicians use rating scales to determine a person's level of HD.)

The study is also measuring DDR gene expression and the brain protein neurofilament light chain, the latter a marker of disease progression. SHIELD HD participants are also evaluated by a physician. Increasing somatic expansion in HD models was associated with elevations of neurofilament light chain, Dr. Bettencourt noted in his conference talk.




*A slide from Dr. Bettencourt's presentation explaining SHIELD HD (screenshot by Gene Veritas)*

**Participants before official onset**

Because of Triplet's ultimate goal to prevent onset of symptoms, SHIELD HD is enrolling volunteers who have not yet experienced motor onset – the involuntary movements and problems with gait that form the classic criteria for diagnosing HD but have been called into question over the past few decades.

As Dr. Antonijevic told advocate Holder, studies of postmortem HD brains demonstrate that somatic expansion occurs many years before motor onset.

"There are a number of symptoms that are measurable, trackable, and predictable long before motor symptom onset," Dr. Bettencourt noted at

the Therapeutics Conference. He described the three groups of individuals under study in SHIELD HD as "prodromal," "peri-manifest," and "manifest."

Prodromal refers to a period of years before motor onset, during which gene carriers have already shown some cognitive and emotional symptoms. Within the prodromal period, peri-manifest signifies the start of so-called "soft" motor symptoms. Manifest individuals have an official diagnosis of HD.

(For an in-depth discussion of premanifest and early-HD stages, click here.)

Aiming to improve clinical trial design, researchers continue to refine definitions of onset and disease progression. For instance, IBM has produced a model of the disease with nine stages instead of the traditional three. The traditional stages are *after* motor onset and do not include the first two of early-stage categories indicated above.

**SHIELD HD volunteers can do Phase 1/2 trial**

Significantly, eligible SHIELD HD participants can later participate in the TTX-3360 Phase 1/2 trial, Dr. Antonijevic explained to Holder. This will enable the clinical trial investigators to compare an individual's performance in SHIELD HD, with no drug, to a period on treatment.

"This can be statistically a very powerful tool to measure the effect of a therapy," Dr. Antonijevic observed.

Triplet projects the trial as a Phase 1/2 so that it can test for the crucial safety and tolerability typical of a Phase 1 but also perform measurements that could "tell us a little bit more about the mechanism of our drug," Dr. Antonijevic told me. "We'll be looking at the totality of data from this Phase 1/2 study to inform the subsequent study."

**Helping hundreds of thousands of patients**

Triplet's leadership has emphasized how the company's search for an HD drug might work for other REDs, the repeat expansion disorders. These include myotonic dystrophy type 1, fragile X syndrome, familial amyotrophic lateral sclerosis (ALS), and spinocerebellar ataxias as well as dentatorubral-pallidoluysian atrophy.

Large-scale genetic studies such as the Huntington's GWAS "have revolutionized the way we identify the underlying genetic drivers of repeat expansion disorders," CEO Bermingham stated in the news release about SHIELD HD. "Our targeted approach is based on results from these studies with our internal research providing insight into the central role the DDR mechanism plays in these diseases. Our approach has the

potential to address a broad range of repeat disorders addressing unmet medical needs for hundreds of thousands of patients."

As Bermingham stated in the BioBoss podcast, the potential now exists to treat large numbers of diseases with the same drug.

According to Dr. Antonijevic, the number of REDs is actually increasing: scientists are discovering new disease genes, and a growing number of existing disease genes are now known to undergo somatic instability. She believes that ranking them by number of affected people is not helpful, in part because for each diseased person there can be many more asymptomatic gene carriers.

For example, there are an estimated 41,000 HD-affected individuals in the U.S., and more than 200,000 at risk for having inherited the gene. Some 140,000 people in the U.S. suffer from myotonic dystrophy type 1, and, Dr. Antonijevic noted, additional people are at risk. Myotonic dystrophy type 1 symptoms include skeletal muscle weakness and myotonia (difficulty relaxing muscles after use), cardiac dysfunction, respiratory dysfunction, excessive daytime sleepiness, cataracts, and other abnormalities.

The focus on a one-drug-for-all approach distinguishes Triplet from other companies that have developed ASOs against a specific disease gene, she added.

Previously, scientists have sought a way to address energy loss in HD-affected brain cells and other disorders such as epilepsy as a possible path to a common drug to correct the problems in bioenergetics (click here and here to read more), but without success so far.

To further its strategy, on August 18 Triplet announced that it would take part in a large international natural history study of myotonic dystrophy type 1 aimed at deepening understanding of the disorder and developing therapies.

**Rescuing neurons – and people**

Despite the COVID-19 pandemic, SHIELD HD – the natural history study – is "definitely on schedule," Antonijevic told me. Dr. Bettencourt said that Triplet plans to provide a report on its research, including SHIELD HD, at the 2021 HD Therapeutics Conference.

Triplet's plan for a Phase 1/2 trial of TTX-3360 in 2021 is exciting news for the HD community and beyond – not just for individuals with diseases caused by repeat expansion disorders, but for the hundreds of thousands of asymptomatic gene carriers (like me) fearful of their futures.

As Dr. Antonijevic said to Holder, "We think that, by intervening early, we could rescue more neurons and have ultimately hopefully a greater therapeutic benefit."

The Triplet drug development program became possible because of the decades of research by scientists around the globe – and the participation of thousands of HD families in research studies.

A growing number of companies are competing to develop HD therapies. However, thanks to CHDI's nonprofit role, academic researchers, and the overall ethos of the HD cause, researchers have collaborated in remarkable ways.

The HD community can take great comfort and pride in the hope that its efforts can potentially benefit so many other rare and neurological disease communities.

More than ever, #CureHD can become a dream fulfilled.

*(Disclosure: I hold a symbolic amount of Ionis shares.)*

Posted by Gene Veritas at 12:17 AM

Labels: antisense oligonucleotide , DNA , HD gene carrier , huntingin , Huntington's disease , Ionis , repeat expansion disorder , Roche , SHIELD HD , somatic expansion , treatments , Triplet Therapeutics , TTX-3360

## No comments:

Post a Comment

Newer Post Home Older Post

Subscribe to: Post Comments (Atom)