Huntington Study Group (HSG) Conference 2024 – Day 1

Read updates from clinical trials and scientific research on Huntington's disease from Day 1 of the 2024 Huntington Study Group conference #HSG2024


By Dr Leora Fox and Dr Sarah Hernandez | **November 12, 2024**

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The Huntington Study Group (HSG) is a clinical research network focused on accelerating treatments for Huntington's disease (HD). This year, the annual conference is being held in Cincinnati, where clinicians, clinical coordinators, social workers, researchers, and pharmaceutical companies are all gathered to share research updates and exchange ideas. HDBuzz is attending the meeting, live tweeting scientific updates as they happen. For those who couldn't catch our live updates, we've compiled our tweets into a summary. Read on to learn what happened on Day 1 of #HSG2024!

Welcome to HSG 2024!

HSG leadership is kicking things off with a series of intros and brief updates about the meeting agenda and the future of the organization. Stay tuned today as well as Friday and Saturday as we share updates on clinical trials and content from sessions on genetic therapy and innovative drug development.

The Huntington Study Group holds an annual conference, taking place in Cincinnati in 2024. This meeting includes two days geared toward researchers, clinicians, and industry that focuses on science and research updates. The third day focuses on Huntington's disease

families, where they get to hear from the experts on research and clinical trial updates.

MyHDStory

The next session involved a few brief updates on clinical trials which are being run by HSG. First, Dr. Karen Andersen from Georgetown and Dr. Alex Dalrymple from the University of Virginia spoke about two research projects under the MyHDStory platform.

MyHDStory is an at-home online study that anyone from an HD family in the USA can participate in. The speakers explained that the study allows people to share their experiences with HD and to participate in upcoming online studies to help improve HD research and care.

KINECT-HD

Next, Drs. Erin Furr-Stimming of the University of Texas at Houston and Dr. Olga Klepitskaya of Neurocrine Biosciences talked about the KINECT-HD study of valbenazine, which was approved earlier in 2024 by the FDA in the USA to treat HDchorea.

KINECT-HD successfully showed that valbenazine can help control unwanted movements. Newer data analysis shows that the biggest side effects, like episodes of sleepiness, happen in the first few weeks of taking the drug, then taper off.

A pro and con debate on huntingtin lowering

For huntingtin lowering

The next session is a keynote involving a bit of debate about the pros and cons of huntingtin-lowering therapies. First, Dr. Blair Leavitt, a clinical HD researcher at the University of British Columbia, will talk about the pros of this approach.

As a refresher, the extra CAGs in the huntingtin gene lead to an extra-long protein. Dr. Leavitt is first presenting evidence from studies of the human gene and protein to show that this expanded form of huntingtin can be harmful. He points to evidence that people with HD who naturally produce less expanded huntingtin protein have delayed onset of HD symptoms.

He also shares data from studies in different animal and cell models showing that it’s safe to lower huntingtin, and often beneficial. The amount of lowering to aim for remains a major question that many laboratory and clinical researchers continue to explore.

Blair also emphasizes that the huntingtin lowering clinical trials of tominersen (Roche), branaplam (Novartis), and Wave drugs were not failures, as researchers continue to learn from them, redesigning drug chemistry, reimagining how therapies are trialed, and incorporating community feedback.

Against huntingtin lowering

Next Dr. Alberto Espay of the University of Cincinnati is speaking to the challenges of huntingtin lowering and the evidence against this approach. He reminds us that huntingtin is found in many, many species, and has multiple functions in different cells and organs, so we need to be careful about removing too much of it.

He states that we are certain that the huntingtin protein *can* function when it is a typical length, but we are not completely sure it *can't* function when it's extra-long. He is urging everyone to consider a gray area where an "abnormal" protein can do both good and harmful things.

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Clumps of huntingtin appear in brain cells over the course of HD, but this is not always directly connected to the loss of brain cells. Plus, huntingtin has hundreds of "dance partners" and not all scientists are convinced that it's a good idea to cut in and break up the dance!

Overall, his argument is that defining extra-long huntingtin as "toxic" might be jumping to conclusions, and we should be careful when deciding when and how much huntingtin-lowering to attempt.

He also suggests that we could consider approaches to increase the amount of "normal" or "wild-type" huntingtin as an alternative to lowering the extra-long or "mutant" kind. The only problem with this suggestion is that this has been tried in mice that model HD and the effects weren't notable, so it wasn't worth advancing toward trials.

Data will advance therapies

This lively session is staged in "debate" format! Dr. Leavitt concedes that huntingtin is very important, but counters Dr. Espay's point that we could try increasing wild-type huntingtin with the point that lots of evidence points to the expanded copy being toxic. Just adding more wild-type protein won't get rid of the toxicity of the expanded copy. However, there is probably a therapeutic window for each huntingtin-lowering drug where the right timing and level of lowering will be essential to figure out.

Dr. Espay urges all the companies and researchers in the room to think about the huntingtin protein and its important role in cells as they continue to innovate in the huntingtin-lowering therapy space.

HD advocate and journalist Charles Sabine, OBE has taken the podium to remind everyone that there remains hope in huntingtin lowering, but that a diversity of research approaches will lead us to a better future for people with HD. A strong conclusion of this interesting debate from Dr. Blair Leavitt: "We will advance therapies based on data!"

Drug delivery

The next session will feature speakers talking about drug discovery. Dr. Mali Jiang from Johns Hopkins is designing novel delivery systems for huntingtin-lowering and other approaches to genetic therapy. Her work in Dr. Lishan Lin's laboratory focuses on a way to re-program liver cells to produce little "bubbles" known as exosomes that can help deliver genetic drugs throughout the bloodstream.

The lab is working on a drug called ER2001 which has already been tested in a very small human trial in China. Dr. Jiang showed data on levels of the drug in the body after it was given through IV injections over the course of a few months.

The ultimate goal is to use this new approach to lower huntingtin. The Lin lab and the company behind this work (ExoRNA Bioscience) are hoping to move forward with larger studies (~30 participants) in China and the US if they are able to find financial support.

PTC-518 has a new name! Votoplam!

Next, Brian Beers from PTC therapeutics is speaking about the PIVOT-HD study of PTC-518, now named votoplam. We wrote earlier this year about the early positive results of this study.

Brian is re-capping the results from people who were on votoplam for up to 12 months. These folks had lower levels of huntingtin in their blood and spinal fluid compared to those who got a placebo (pill with no drug).

This study has enrolled participants across a broad spectrum of early-stage HD symptoms. The side effects reported, like headaches, have been mild, and one update at this conference is that there were no immune system reactions. As we shared in June, PTC is also seeing some early trends in improved function.

Sarah and Leora from HDBuzz live tweeted the event to bring the HD community the latest research and clinical trial updates on Huntington's disease!

Controlling CAG repeats

Up next is a research session on gene editing (altering DNA) and combatting somatic instability (stopping CAG repeat expansion). First Dr. Vanessa Wheeler from Mass General Hospital and Harvard Medical School detailed recent work looking at CAG expansions at the single cell level. This technique has really taken off in the past 10 years and gives researchers TONS of data. Compare looking at the stars with your eyes, or using a powerful telescope. A huge difference!

Vanessa also discussed GWAS data - genetic data that analyzes every single gene in a person. Using these large datasets from lots of people with the gene for HD, scientists can start to determine what genetic information affects age of symptom onset.

This identifies genetic markers (called modifiers) that track with earlier or later age at symptom onset. Getting a better understanding of these genes that modify the course of HD helps identify potential targets for drugs to delay HD symptom onset.

Vanessa and her team are currently looking at modifiers of somatic instability - the perpetual expansion of the CAG repeat in vulnerable brain cells. They're hoping to identify genes that control somatic instability that they can target therapeutically.

Right now they're testing these target genes in mice that model HD. When they use CRISPR to alter levels of these targets they find that they're able to control the amount of somatic instability. So far they've tested 60 different targets. That's a lot of work!

Every modifier gene that controls somatic instability in cells or mice has the potential to become a therapeutic target. They're also testing combinations of targets, which, as you can imagine, gets quite complicated with 60 targets!

Vanessa and her team are also considering how single or combined targets could have different effects in different types of cells. So one modifier that slows or stops somatic instability in support cells in the brain (glia) may have a different effect in neurons.

She also shared details about a specific modifier that they're examining, called LIG1, that seems to reduce somatic expansion in the brains of mice that model HD. We'll be eagerly waiting for more data on this modifier!

Ultimately, Vanessa's goal is to identify genetic modifiers of somatic expansion that will control instability, keep brain cells healthy for longer, slow symptom onset, and give people affected by HD more healthy and happy years.

CRISPR for gene editing

Up next is Dr. Ricardo Mouro Pinto, also from Mass General Hospital and Harvard Medical School. He'll be talking to us about gene editing - the approach of changing the DNA blueprint to investigate and ultimately to treat HD. Exciting!

Ricardo started with a primer on CRISPR - a powerful genetic editing tool that you can think of like molecular scissors. Researchers can identify DNA targets that they want to edit, deploy CRISPR against that DNA letter code, and swap it out with a new sequence. We wrote about the advancements made in medicine for Sickle Cell Disease using CRISPR.

Ricardo's getting into the nitty gritty of how different DNA letters can be swapped out using different techniques. There is so much innovation in this area since the advent of CRISPR technology just 10 short years ago.

Ricardo touches on two major challenges for CRISPR in clinical HD research: delivery and safety. How do we get the drug to the brain, and how do we make sure that the drug is *only* making the DNA changes we want it to?

> **"Every modifier gene that controls somatic instability in cells or mice has the potential to become a therapeutic target. "**

He notes that the NIH (science/medicine funding agency in the USA) has created a new funding initiative to support the advancement of gene editing therapies. Two of the 5 currently funded projects are focused on HD!

One of these projects focuses on trying to chop out extra CAG repeats from within the huntingtin gene, and the other tries to prevent CAG repeats from growing longer, combating somatic instability.

Some people with HD have “interruptions” in their CAG repeats, with a CAA thrown in instead. These folks tend to have later onset of symptoms. One group of NIH-funded collaborators (including Ricardo) is working on techniques to change CAGs to CAAs.

Ricardo refers back to some of those “modifiers” of somatic instability that Vanessa brought up. He is focusing on one called MLH3, exploring complex CRISPR editing techniques to tamp down its levels. In cells, this can slow or stop the growth of CAG repeats. The next step is to test these techniques in mice and in human cells that more closely mimic HD.

We’re likely quite far from human trials of these approaches, but it’s exciting nonetheless to see that this work is gaining traction and funding. The great potential advantage of a gene editing therapy is that it could be administered once with permanent effects.

Current strategies for HD therapeutics

In the next session, companies developing innovative therapies for HD will each give short talks on their most recent updates. HDBuzz’s own Dr. Sarah Hernandez is beginning with a brief overview covering the basics of different approaches and companies in the space.

Sarah is getting into the alphabet soup of huntingtin lowering techniques and delivery methods, like ASOs, RNAi, AAVs, and splice modulators. Several companies will have a chance to talk about their drug development efforts in more detail. She also mentions other therapeutic approaches to HD, like targeting somatic expansion, replacing lost brain cells, and enhancing cell-to-cell communication.

Sarah concludes with an exciting slide showing the many dozens of companies working in the HD space. We’re truly living in the age of clinical trials for HD research!

Alnylam Pharmaceuticals

First up in the innovator’s forum is Dr. Kevin Sloan from Alnylam Pharmaceuticals. They’re using a strategy called RNAi - RNA interference - that adds a bit of genetic code targeting the huntingtin message to lower the protein.

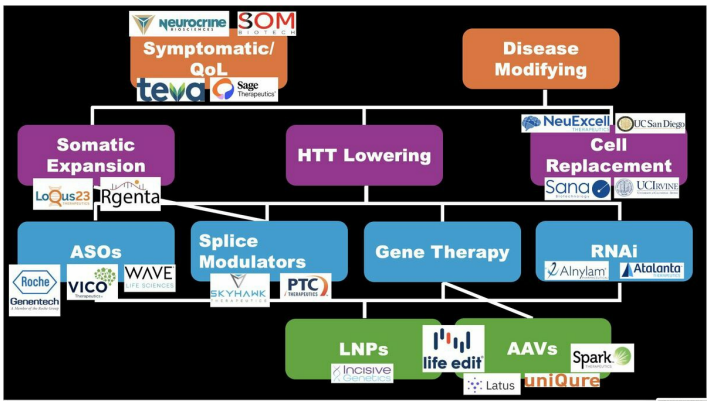
Kevin first covered the details of how RNAi works. One of the major challenges for RNAi-based drugs is delivery. They want to make sure the drug gets to where it needs to go - for HD, that’s all over the brain. Alnylam is also working on other diseases, and Kevin is sharing data from an RNAi drug they have for Alzheimer’s disease that’s moving into a Phase 2 trial.

Now they want to do the same thing for HD. They have an RNAi drug designed for huntingtin called ALN-HTT02. It targets all forms of huntingtin, including short bits prone to clumping. These are called huntingtin exon 1 fragments and they are thought to be toxic to

brain cells.

We've written about these huntingtin exon 1 fragments, also called HTT1a. This tiny little fragment of the huntingtin message seems to code for a protein only made in people with the expanded huntingtin gene.

Alnylam is now testing ALN-HTT02 in monkeys, the step before moving drugs to human clinical trials. Just this week Alnylam announced that they're starting a Phase 1 trial for this drug! This early trial will be initiated in the UK and Canada with recruitment in additional countries planned to follow.



In Sarah's talk, she shared an overview of therapeutic strategies for Huntington's disease, summarized in this slide overlayed with the companies working in these areas.

The primary goal will be safety and tolerability, but they'll also look at how well it targets huntingtin and how levels change in the CSF, the fluid that bathes the brain. They'll use clinical tests to measure symptoms, but would need a larger trial to understand if ALN-HTT02 works to change clinical features of HD. It's always exciting to have new trials announced and we'll be eagerly waiting for new updates from Alnylam!

Rgenta

Up next is Dr. Travis Wager from Rgenta Therapeutics. They are developing small molecules that could be taken as a pill to target somatic instability, the perpetual expansion of the CAG repeat in vulnerable brain cells.

Rgenta are trying to target a gene called PMS1 - not the PMS related to mood swings... Levels of PMS1 are higher in people who show symptoms of HD earlier. Rgenta are trying to decrease its levels in the hopes of delaying the onset of signs and symptoms of HD.

Travis tells us how it's super important to choose the right place on PSM1 to target. So they've spent a lot of time developing small molecules that target PMS1 in the right spot. The best candidates also check other boxes, like getting into the brain when taken as a pill.

Rgenta has been testing their drug in lots of different animal models. They've shown that it's very robust. Lowering PMS1 by 50% stalls instability by 70% - the rate of CAG expansion slows down a whole lot. Exciting!

Travis gave a big shout out to all the researchers in the HD community for being so collaborative and sharing their resources. He said Rgenta wouldn't be where they are today without HD scientists being so collaborative and willing to share.

LifeEdit

Our next speaker is Dr. Logan Brown from LifeEdit Therapeutics, who are advancing gene therapies for HD using CRISPR technology. LifeEdit is working on a CRISPR-based therapy called LETI-101 that selectively lowers expanded huntingtin. They can do this by targeting a genetic signature that differs between a person's two copies of huntingtin.

Not everyone shows this small genetic difference between their two copies of huntingtin. For this reason, LifeEdit estimates that if LETI-101 were to become a drug, it would work for 30% of people with the gene for HD.

The good news about this approach is that because it usesCRISPR for gene editing, it would be a one-and-done approach, so people would only need this treatment once, in theory, to lower huntingtin for the rest of their lives.

So far, they've tested LETI-101 in cells grown in a dish and mice that model HD, and now they're testing it in monkeys. But they're also working to develop a strategy for moving into people, which will require brain surgery.

Sana Biotechnology

Next up is Dr. Joana Osorio from Sana Biotechnology, who are working on cell replacement therapies using stem cells. Sana's technology grew out of experiments showing that support cells in the brain, called glia, contribute to HD disease features in neurons.

With this knowledge, Sana then asked if transplanting non-HD glia cells could improve disease features in mice that model HD. When they did this, they saw improvement in movements and other features of the disease, including increased the lifespan of the mice.

> **"We're truly living in the age of clinical trials for HD research! "**

Scientists at Sana found that when they transplanted non-HD glia into the brains of mice, they "out-competed" the HD glia - they essentially replaced the sick HD glia in the brain! HDBuzz previously covered this work when it was published.

Sana is now working to move these findings into clinical trials, and while they're not quite there yet, they have a plan for getting there. So stay tuned!

Spark Therapeutics

Dr. Juha Savola from Spark Therapeutics is our next speaker in this session, sharing work Spark is doing to advance gene therapies. Spark is best known for their development of a gene therapy for a hereditary form of vision loss (back in 2017). Now they're focusing on HD.

Spark is developing a gene therapy called SPK-10001, which is designed to slow down or

halt progression of HD by lowering huntingtin. Right now they're testing SPK-10001 in monkeys and they're seeing that for up to 12 months, HTT levels remain lower.

In the monkeys, they're testing different doses of SPK-10001 and tracking HTT lowering in different brain areas. This will help them to choose doses to test in people when they move into clinical trials. Juha is sharing details for inclusion and exclusion criteria for the upcoming Phase I/II trial that Spark is planning in people with HD, which will test 2 doses, a low dose and a high dose.

The primary objective of this trial will be safety, but they'll also look at a few clinical metrics to try and get some hints about whether SPK-10001 will work to treat HD symptoms. We'll be eagerly awaiting the recruitment announcement for this trial!

Atalanta Therapeutics

Our last speaker of this session is Dr. Serena Hung from Atalanta Therapeutics, who are working on RNAi-based therapeutics for HD. As Sarah explained earlier in her overview, this is one among several approaches to lower huntingtin.

The advantage of Atalanta's approach is potency. They use a novel technology that helps the drug spread easily to deep regions of the brain. With delivery using a spinal injection, they see that their drug, called ATL-101, is still active out to 6 months in animal models.

Atalanta has shown that in monkeys, they can lower HTT by 75-90% and levels of NfL remain stable. NfL is a marker of brain health that increases as brain cells are damaged and increases as HD progresses. So lots of people keep their eyes on NfL in trials because keeping it level (or even lower!) would be a good thing.

Atalanta is planning to initiate clinical trials for ATL-101 in 2025. We'll keep you posted when we learn any updates about the advancements of this exciting research!

Tune back in tomorrow!

We are off to explore more than 80 research posters presented by HD scientists and clinicians from all over the world. Brief talks will shine a spotlight on brain imaging biomarkers and aspects of the Enroll-HD platform. See you tomorrow for sessions on clinical challenges in HD, biomarkers, trial design, and more.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.
RNA interference A type of gene silencing treatment in which specially designed RNA molecules are used to switch off a gene
therapeutics treatments
CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD
stem cells Cells that can divide into cells of different types
wild-type the opposite of 'mutant'. Wild-type huntingtin, for example, is the 'normal', 'healthy' protein.
exosome Tiny bubble-like particles produced by cells that can transfer chemicals to other cells
neuron Brain cells that store and transmit information
placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't work.
somatic relating to the body
chorea Involuntary, irregular 'fidgety' movements that are common in HD
CRISPR A system for editing DNA in precise ways
ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene
Exons The small fraction of our DNA that is directly used to instruct cells how to make proteins
CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.
HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15
NfL biomarker of brain health
