Huntington's Disease Therapeutics Conference 2025 - Day 1

HDBuzz reported live updates on Bluesky from the 2025 HD Therapeutics Conference. Read on for coverage of Day 1. #CHDI2025

 

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Hello from Palm Springs! The HDBuzz team are here and ready to report on all of the exciting science that we are going to hear over the next 3 days from HD experts who have travelled from all over the world to be at CHDI's 20th Annual Huntington's Disease Therapeutics Conference. Get ready to follow along for some exciting Huntington's disease research over the next 3 days!

Clinical Trial Updates

Our first set of talks are updates from pharma companies that have ongoing clinical trials.

Team HDBuzz front and center, excited to bring you live updates from CHDI's 20th Annual Huntington's Disease Therapeutics Conference!

Image credit: Jeff Carroll

PTC Therapeutics - PIVOT-HD Testing Votoplam

Up first is Amy-Lee Breadlau from PTC Therapeutics with an update on votoplam, formerly PTC-518. Votoplam is a HTT-lowering drug that's taken as a pill. The idea is that by lowering the disease-causing protein, signs and symptoms of HD will be reduced.

Amy-Lee started by sharing the fantastic news that PTC has an exciting new collaboration with Novartis, a massive drug developer. PTC will complete the ongoing PIVOT-HD trial, but Novartis will be in charge of all future clinical trials, like their planned Phase 3.

So far, people in the PIVOT-HD trial have been taking votoplam for 12 months. They were really interested in knowing if people who have been on the drug this long have positive changes in biomarkers - biological metrics that track with HD progression. The most reliable biomarker we have right now is neurofilament light, or NfL. We know that levels of NfL increase as HD progresses. Excitingly, Amy shows that levels of NfL remain steady for people who have been on votoplam for 12 months.

She's now showing super exciting data that suggest there is improvement in clinical measures in people who have been on the drug for 1 year. At the end of the day, *this* is exactly what we want! A drug that improves clinical signs of HD is a drug that's working against HD!

The final results from PIVOT-HD are expected to be released this summer. We'll certainly keep you updated as we learn more!

Roche - GENERATION-HD2 Testing Tominersen

Up next is Peter McColgan from Roche who is sharing an update on their Huntington's disease portfolio. Their largest trial has been GENERATION-HD1 for their HTT-lowering drug tominersen. While that trial wasn't successful, it provided the data for their ongoing GENERATION-HD2 trial that is testing tominersen in a more specific group of people living with HD.

The big news that Peter is sharing today is that GENERATION-HD2 is fully enrolled. They're active in 15 countries at 70 sites and they're hoping to complete the trial by late 2026. Throughout the duration of the study, an independent safety committee will regularly review the data to determine if they should continue, modify, or stop the study.

Roche has a collaboration with the HD Regulatory Science Consortium to share data from their previous studies, the natural history data and data from the GENERATION-HD1 trial from people who weren't on the drug. This type of data allows researchers to understand how HD normally progresses as people live their day-to-day lives and age. This valuable information will be open to researchers, and will help us design better trials.

Roche also has a collaboration with CHDI to better understand the biomarker NfL. Their goal is to understand if NfL is more than a biomarker and could be used as a diagnostic test for HD. Using NfL as a diagnostic test could help give us information about where people are in the progression of disease. This could help tailor future drugs and help customize care plans based on disease stage.

> **"To everyone who participates in these observational studies - THANK YOU! YOU are truly changing the face of HD research! With your contribution, HD**

> **scientists are learning more about this disease every day, getting answers to questions that will get us to a treatment. ”**

They’re using multiple datasets, from Enroll-HD, HD-Clarity, Track-HD, and Track-On, to see how NfL changes over time. Collectively, these datasets give them samples from almost 7,000 people living with HD!

We can’t overstate how important these datasets are to the HD scientific community. So to everyone who participates in these observational studies - THANK YOU! YOU are truly changing the face of HD research! With your contribution, HD scientists are learning more about this disease every day, getting answers to questions that will get us to a treatment. If you’re interested in learning more or contributing to HD research, you can visit the Enroll-HD website.

Wave Life Sciences - SELECT-HD Testing WVE-003

Up next is an update from Wave Life Sciences on their HTT-lowering drug WVE-003 being tested in their trial SELECT-HD. This drug is unique because it specifically targets the expanded copy of HTT that causes HD. There are advantages for specifically targeting the expanded copy of HTT.

Wave also thinks that targeting the expanded copy will have an influence onsomatic instability, the perpetual expansion of the CAG repeat within the HTT gene. While this would be super cool, we don’t yet have data to show that WVE-003 can actually impact somatic instability.

Wave did show that there’s a slowing of brain atrophy for people who are taking WVE-003. They hope to use this measure in future clinical trials as a readout of clinical outcomes.

However, we’ll have to interpret any data around brain atrophy carefully in context with biomarkers. Looking at brain atrophy alone can’t really tell us if HD is improving because other things could be at play here, like brain swelling. If a drug is causing inflammation of the brain, that could look like the brain is shrinking less, but doesn’t necessarily mean a drug having a positive effect.

But if there are biomarkers also suggesting that the drug is improving biological measures of HD, that would be a fantastic thing! We’ll have to interpret any data around brain atrophy carefully as we learn more and as WVE-003 progresses through the clinical trial pipeline. Wave is hoping to move forward with a Phase 2/3 study by the end of this year. We’ll keep you updated as we learn more!

UniQure - Testing AMT-130

Our last speaker in this session is David Margolin from uniQure sharing an update on AMT-130, a HTT-lowering gene therapy delivered via brain surgery. His focus today is on their recent alignment with the FDA on a path to accelerated approval for AMT-130.

AMT-130 is a drug delivered by brain surgery which lowers both the regular and toxic forms

of huntingtin. Their drug hits right at the start of the huntingtin message molecule which means they also expect the toxic fragment form of huntingtin to be lowered too.

This conference always kicks off with the perspective from HD family members. This year we are hearing from Amanda Staveley and Mehrdad Ghodoussi. Amanda shared her amazing story of all her achievements and her HD journey. We were excited to learn that they're active readers of HDBuzz! Hi Amanda and Mehrdad!

UniQure have applied to the FDA for RMAT - Regenerative Medicine Advanced Therapy Designation. This application was successful! This is important because it reduces the time it could take AMT-130 to get to market by *several years*. Obviously, this is very important for all HD families! UniQure continue to be in discussions with the FDA about exactly what data they will need for their drug to be approved on an accelerated time frame.

UniQure are planning to use natural history data to work out how well their drug is working. This means they will be comparing folks in their study against what is expected on average for people with HD who are the same age and so forth, but who didn't receive the drug. This is a bit different to having a placebo control which is what companies typically use.

One of the big things that the FDA agreed on with uniQure is the use of cUHDRS as a metric for how well their drug is working. cUHDRS is a combo of lots of different measures about all kinds of signs and symptoms of HD. It is thought to be better than just using one measure as each has various caveats. However, when used in combination, these caveats can be weeded out and we can work out pretty quickly if the drug is REALLY working.

Further, the FDA also agreed to consider levels ofNfL in spinal fluid as supportive evidence that AMT-130 is working. NfL typically goes up over time in people with HD. So, NfL levels going down or holding steady is good news for brain health for people with HD.

The fantastic news is that we now have agreement between the FDA and HD drug hunting companies about exactly what metrics and measures will be expected to show a drug is working well enough and is safe enough for the FDA to approve a drug.

Connecting The Dots: HTT Biology From The Lab To The Clinic

Our next session focuses on what we are learning in the lab about HD biology to inform clinical trials.

Longzhi Tan: Genetic Architecture

First up is Longzhi Tan from Stanford University, sharing his work on the architecture of genetic material and how HD influences its shape and where that genetic material sits in the cell. Genetic architecture sounds super cool! But what exactly is it?

We have a lot of genetic material that makes all of us unique, and where it sits within the cell matters. The DNA inside each cell of our body is 2 metres long!! To fit inside each tiny cell, it must fold and compress to be squeezed in. Tan is interested in studying exactly how the DNA is organised in cells and where each gene might be found.

Quite surprisingly, Tan can determine different types of cells just by where the DNA is sitting inside the cell. How DNA is organised and where it sits in the cell changes throughout life.

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Now he’s looking at how HD affects the architecture of genetic material in mice that model the disease. He’s showing the crowd the very first 3D map of what the genetic material looks like in cells from HD mice. HD causes drastic changes, specifically in cells that are vulnerable in HD. Tan shares that he thinks these changes are leading to a loss in cell “identity” - genes that make certain cell types what they are.

Tan is also looking at how genes that control somatic instability might affect genetic architecture. Specifically, he looked at the modifier gene Msh3. When Msh3 levels are lowered in HD mice, it seems to correct the genetic architecture changes caused by HD. Very snazzy!

The take home message here is that targeting Msh3 in different HD models could be good for restoring many of the hallmarks of HD back to normal. This type of really detailed analysis is supportive that Msh3 is a good target for scientists to be working on to try and make new medicines.

Kejia Wu: Computer-Designed Proteins

Up next is Kejia Wu from University of Washington, in Seattle. She's a recent PhD graduate from the lab of David Baker, 2024 Nobel Prize recipient. Her research tries to design new types of proteins to do specific jobs. This work uses all kinds of specialist deep-learning and AI-guided tools to try and think up new designs.

Kejia is interested in targeting floppy bits of protein molecules. Turns out these floppy regions are really important for all kinds of biology but were traditionally thought to be "undruggable". She hopes to target these floppy regions with newly designed proteins that her AI-guided computer methods hallucinate.

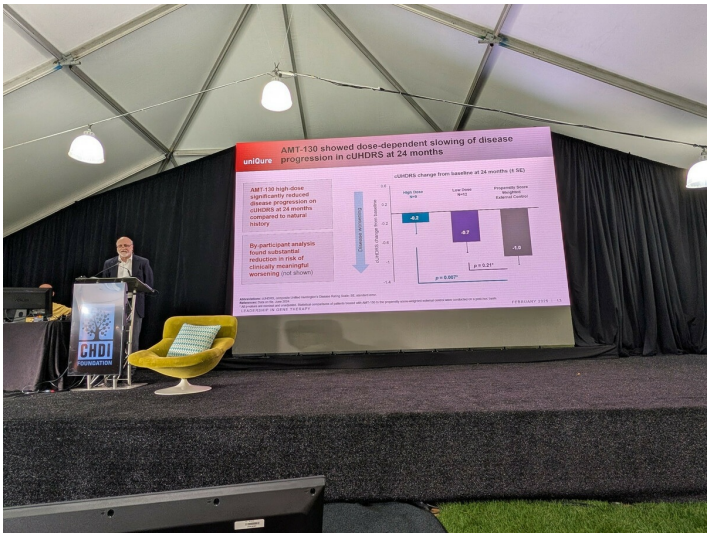
The huntingtin protein has lots of these floppy regions which HD scientists have shown to be important for how the protein knows where to go in the cell and which proteins to hang out with. Kejia is applying her technology to huntingtin to try and design new proteins which target the long string of glutamines found at the start of the disease-causing protein. There is a similar string of glutamines in regular huntingtin protein, but it is a lot shorter. However, the difference is subtle, so finding something selective is tough!

The HD community is lucky to have so many technology experts like Kejia and Tan interested in working on understanding HD and helping us find new ways we might design medicines for the future!

Gill Bates: Toxic Fragment HTT1a

Our next speaker is Gill Bates from University College London. Gill's group are focussed on a type of huntingtin protein called HTT1a. This is a small fragment of the huntingtin protein which forms toxic clumps in cells.

Gill's team are looking at how much of the HTT1a form is made in different models of HD. It turns out that the longer the repeat length of the HD mutation, the more HTT1a is made. At the same time, the levels of the full-length form of huntingtin go down.



David Margolin from uniQure shared the exciting clinical improvements AMT-130 seems to be having, seemingly reducing disease progression in a dose-dependent manner.

Next Gill's team looked to see if there were changes in how much protein was forming toxic

clumps. They believe that HTT1a could be the catalyst which kicks off huntingtin protein clumping. To try and figure this out they used a special mouse model of HD which is not able to make HTT1a. These mice have many fewer clumps than regular HD mice, and these clumps form more slowly.

These protein clumps, aka aggregates, are thought to be toxic to cells in many different ways. One of the most studied ways is how clumps in the nuclei of cells, where the genetic material is stored, can impact which genes are switched on or off. Gill and her team looked at how clumps in the nucleus tracked with these genetic changes. The more clumps they saw, the more genetic changes they saw.

HD scientists are still trying to figure out exactly how much each type ofhuntingtin protein is responsible for causing disease in HD. Gill and colleagues are using genetic tools which target just one type of the huntingtin protein to tease out what is happening.

Looking at aggregate levels and which genes are switched on and off, they found that lowering the amounts of HTT1a and the expanded huntingtin had the biggest effect, however they didn't see a large effect for lowering other types of huntingtin in the mouse models they used. This matters for the field as we have all sorts of huntingtin lowering therapies in the clinic which each work slightly differently and each lower different forms of huntingtin protein that exist in the cell. We don't yet know which is going to work out best in people so the more we understand at this detailed molecular level, the better.

Gill is working with the Khvorova lab in the US to design new tools to lower levels of HTT1a. They are developing siRNAs which target huntingtin message molecules and reduce levels of HTT1a protein. More tools for our HD toolbox!

Won-Seok Lee: Influence of Protein Clumps on Somatic Instability

Next up is Won-Seok Lee from the McCarroll lab at Harvard Medical School. Recently, the McCarroll lab published a paper showing that vulnerable cells in HD have somatic expansion - where the CAG number increases a lot in specific cells.

In HD mouse models which have enormous CAG repeats, we see lots ofaggregates. In people, only a few cells end up with these huge CAG repeats and we see relatively fewer aggregates. However we don't know if the cells with the aggregates are the ones with the long CAG numbers.

The McCarroll team wanted to figure this out! They sorted post mortem human brain samples to find the cells with the aggregates. They then figured out that the types of brain cells which have the aggregates are spiny projection neurons - the cells most impacted by HD - which were also the cells that had very long CAG numbers.

Next they looked to see how genes were switched on and off in these cells and saw that these cells had rather wonky genetic signatures, with genes switched on which should have been off and vice versa. This is big news as it links somatic instability with aggregate

formation in human tissue samples AND with messed up gene regulation, a hallmark feature of HD.

Next, they tried to figure out which type of huntingtin protein was found in the aggregates and it looked like it was mainly the fragment HTT1a we heard about earlier from Gill. Together, this work is helping us understand how each form of huntingtin is contributing to disease, which is critical for making sure we are targeting the right version with therapeutics.

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Spark Therapeutics: Non-Clinical Testing of SPK-10001

The final talk of this session is from Liz Ramsburg from Spark Therapeutics. Spark is a gene therapy company with a big focus on HD. Spark are making gene therapies which lower huntingtin levels. The therapy is packaged into a harmless virus which can then infect cells to deliver the machinery which lowers huntingtin.

The best way that Spark found to deliver their drug was by direct brain injection. Although this sounds like quite a scary approach, the drug generally worked well in animal models they tested when delivered this way. Spark are working to improve their surgery procedure to reduce side effects.

Their drug, SPK-10001, seems to spread well through the brain and levels of huntingtin go down in a dose dependent way i.e. the more drug you give, the more you reduce the levels of huntingtin. Spark followed the animals for a year after they received the drug and things looked generally fine in terms of side effects, changes to brain structures, etc. NfL levels also seemed to stabilise in a reasonable timeframe. This suggests the drug is pretty well tolerated - good news! We look forward to learning more about Spark's progress developing SPK-10001. Liz says she hopes they will be in the clinic soon!

Somatic Instability & Mismatch Repair

Dorothy Erie: Seeing Molecules With An Atomic Record Player

First up this afternoon is Dorothy Erie who studies proteins involved in DNA damage response. Her lab team uses a technology called atomic force microscopy, or AFM, to find out about how proteins stick together. AFM works a bit like a record player, with a needle that drags over the surface, and reveals the topology or nooks and crooks of a sample. AFM works at the molecular level and so instead of the needle helping play the music of a record, it gives us information about whatever is on the surface, in this case, proteins.

As many of you may remember, DNA damage response is a hot topic in HD, as many of the genetic modifiers encode DNA damage repair protein. Understanding how these molecular

machines work could help us unpick their role in HD.

Using AFM, Dorothy and her team can see all of the different shapes which these proteins can make. They move around a lot which she likens to dancing the macarena!

Brinda Prasad: Targeting Modifiers

Next up is Brinda Prasad from the CHDI foundation. She will be talking to us about different approaches to therapeutically target a specific DNA repair complex, called MutSBeta. This is a hot drug target in HD being pursued by lots of researchers in academia and different companies.

The Parker Hotel in Palm Springs, CA is a fantastic place to spend the week learning about cutting edge Huntington's disease research - under the big tent, surrounded by palm trees, in the shadow of Mount San Jacinto.

MutSBeta is actually made up of two different proteins called MSH2 and MSH3. You may remember MSH3, as this is one of the genes which was identified as a genetic modifier of HD. Scientists think if we can switch it off or reduce the levels of MSH3, we might delay onset of HD.

There are lots of different ways that scientists have thought up to target MutSBeta. MutSBeta works with other DNA repair machines, so Brinda and colleagues made special circular blocking molecules which stop it from sticking together with these partners.

Next, Brinda and colleagues looked into switching off the activity of MutSBeta with small molecules. They have a whole suite of different experiments to test these molecules to see how well they are working and develop them to have desirable drug-like properties. This MutSBeta inhibitor program is going well and they are hoping to start testing some of their lead molecules in animal models of HD later on this year.

Another program in this area at CHDI is making chemicals which knock MutSBeta off of DNA. These particular tools stick irreversibly to MutSBeta and stop it from doing its normal job - working directly on the DNA strand to repair damage.

CHDI are making all of the tools and experimental systems available for the research community to help scientists around the world pursue this critical drug target and accelerate progress. That's what we like to see!

Britt Adamson: Editing The Genetic Code

Next up is Britt Adamson from Princeton University. She is also studying DNA damage response in HD, focussing on mismatch repair proteins. These molecular machines are thought to be responsible for somatic instability and so shutting them off is one way some scientists think we might treat HD.

Her lab uses genome editing tools to study mismatch repair proteins. They deliberately introduce errors into the genome and then figure out which proteins are important for their repair and what types of edits they each prefer. They tested a TON of different edits in cells which are lacking different mismatch repair proteins to try and map who is doing what - very cool and a great resource for the field!

Britt's team have developed this methodology into a cool new platform to test small molecule inhibitors of MutSBeta. They can rapidly assess how well the inhibitors work as well as how specific they are for MutSBeta over other mismatch repair proteins. Technology developments like this will really help drive drug discovery in this area and ensure drug hunting scientists are only progressing the very best molecules which are on target and selective for MutSBeta.

X. William Yang: Genetic Modifiers Drive CAG Expansion and Disease

Next, we will hear from X. William Yang, from UCLA. William's team uses mouse models to study HD. Today, we'll hear about his work on, you've guessed it, mismatch repair proteins!

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William is reminding us about the impactful large human genetic studies that identified other genes besides huntingtin that can affect when symptoms start to appear. Mismatch repair genes were identified thanks to you, the HD community, signing up for natural history studies!

William and his team are studying these genes in different mouse models of HD. His team are world experts in mouse genetics! While mice are not the same as humans, there are some similarities as to which brain regions are affected in HD in these models compared to humans. This allows them to ask questions about the role of mismatch repair in disease progression in these models.

A key finding of this study is that totally removing MSH3 seems to help restore many of the molecular signatures of HD, in the mouse model they used. Genes which were incorrectly switched on or off in HD mice were returned to regular levels when they got rid of MSH3.

This is good news for folks working to develop drugs that target MSH3, as it suggests that many features of HD could be corrected by this type of therapeutic.

Not surprising given its role in DNA repair, removing MSH3 also helped to reducesomatic instability. Other features were also corrected, such as the protein clumps that tend to build up in the mouse brain, as well as some of the behaviours associated with HD mouse models. William reminds us that mouse models are useful tools to study HD but this is a human disease, we must validate findings in people and human-based models too.

Anastasia Khvorova: Two Targets, One Drug

The final talk of the day is from Anastasia Khvorova from the University of Massachusetts. Anastasia's team are working to develop RNAi-based therapies that target both mismatch repair proteins AND huntingtin protein levels at the same time.

Anastasia's group has expanded their repertoire of RNAi tools to reduce a whole panel of mismatch repair proteins in a mouse model of HD. This helps us understand which proteins will make the best targets. At this stage of the day, you might have guessed which was most important.... If you guessed MSH3, you would be correct!

Next they looked to see what happened to the levels of different mismatch repair proteins when you knock down MSH3 or other proteins in their panel. This way, they hope to map out which proteins hang out together or rely on each other in the cell.

To look into this further, Anastasia's group looked at knocking down MSH3, thehuntingtin protein itself, or both at the same time, in a mouse model of HD. The mice seemed to have better behavioural signs and symptoms of HD in all cases. The combination treatment seemed to edge out MSH3 or huntingtin knock down treatment alone in terms of reducing levels of the toxic protein clumps and some other molecular readouts.

This work is still ongoing so we look forward to learning more from Anastasia and colleagues when they have more data to share with everyone.

That's all for Day 1 of the 20th Annual Huntington's DiseaseTherapeutics Conference! Stay tuned for Day 2!

Sarah Hernandez is an employee of the Hereditary Disease Foundation, who has provided financial support to researchers who have work described in this article or are on the Scientific Advisory Board. Tam Maiuri works for the Huntington's Disease Society of America, which has relationships with many of the companies who attended this meeting or were mentioned in articles related to this conference. For more information about our disclosure policy see our FAQ...

GLOSSARY

NfL biomarker of brain health

huntingtin protein The protein produced by the HD gene.

Genome Editing The use of zinc-finger nucleases to make changes in DNA. 'Genome' is a word for all the DNA we each have.

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

inflammation Activation of the immune system, thought to be involved in the HD disease process

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

aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

nucleus A part of the cell containing genes (DNA)

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

genome the name given to all the genes that contain the complete instructions for making a person or other organism

RNA interference A type of gene silencing treatment in which specially designed RNA molecules are used to switch off a gene

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15