Hereditary Disease Foundation (HDF) conference 2022 – Day 2

Read updates from clinical trials and scientific research on Huntington's disease from Day 2 of the 2022 HDF Milton Wexler Biennial Symposium #HDF2022

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We're back for day 2 at @hdfcures! This morning's talks will be focused on clinical trial planning and therapeutic updates from clinical studies. The sheer number of talks related to human trials compared to previous years is so encouraging!

Updating metrics for clinical trials

A better system for disease categorization

Key opinion leaders in the field of HD research gather for a photo op during one of the breaks. (L to R: Dr. Leslie M. Thompson, Alice Wexler, Dr. Sarah Tabrizi, Dr. Bev Davidson, Dr. Anne Young)

The first talk of this session is from Jeff Long from the University of Iowa, who will be talking about clinical trial planning using the Huntington's disease Integrated Staging System (HD-ISS). We talked about this last night, and in a recent Buzz article.

Dr. Long is recapping the different stages (0-3) of the HD-ISS, and showing how brain areas, biomarkers, and neurological tests change over the newly defined stages of HD.

Dr. Long also recapped what stages patients were in for various trials. For the tominersen GENERATION-HD trial, and most other trials, patients have been in stage 3. Running trials of people in Stage 1 is likely not feasible right now because of the limited changes observed in this group. It seems stage 2 might be the sweet spot - it's feasible to run clinical trials with people in this stage with current trial outcomes, and they seem to be earlier in disease.

Dr. Long uses statistical models to go through an example of participants required to run a trial, based on what we know about progression in stage 2. It's very important that enough people participate in different arms of trials to provide the study with enough "power". This allows researchers to draw definitive conclusions.

He points out that developing these models to design better trials requires thousands of data points, each of which comes from a different person in an observational HD trial. Without participation in Enroll-HD, PREDICT-HD, TRACK-HD, and other studies, none of this work is possible.

Using computers and robots to understand HD biology

Our next talk is by Dr. Steve Finkbeiner, who will be talking about using artificial intelligence (AI) to look at HD in patients and different animal models. HDBuzz recently wrote about AI and how it can change the game for understanding HD.

Steve attempts to capture the great complexity of the biology of HD by applying mathematical and computer modeling to the many changes observed in cells growing in a dish.

Steve's team also used AI to predict which cells would die and when based only on their shape and some markers. They found their computers were far more accurate than when the same predictions were made by people! The computers also found new ways to predict if cells would live or die based on some of their structural features which scientists hadn't even thought of or discovered yet!

These models can distinguish between healthy and Parkinson's disease cells, and between healthy and Alzheimer's disease tissue, with up to 97% accuracy - something that might be impossible even for a trained pathologist. AI tools like these could be huge game changers for diseases like Parkinson's that have spontaneous cases. But Steve's group is very keen on applying his tools to HD to learn more.

Since AI can see things people can't, Steve wonders if we could harness AI to learn and even plan experiments! His most recent endeavor focuses on "how to make a sick cell healthy" - can his computers develop a model of HD and an effective treatment?

Biomarkers in HD research

Next up is our own Dr. Ed Wild! Ed will be talking about HD biomarkers - things we can measure to get a picture of where a person is in the progression of their HD.

Naturally, Ed started his talk with British pudding...noting that desserts prove themselves when eaten. HD scientists have been searching for an HD biomarker - “making the pudding” - for a long time. Ed detailed a timeline for how long the field has been working on a biomarker for HD. It’s taken about 20 years to get to the point where we’re really at the precipice of reliable biomarkers for HD.

He talked about the challenge of looking at levels of huntingtin in the brain, which must be measured indirectly in spinal fluid or blood. It has thus far been very difficult to distinguish between the expanded and non-expanded forms.

Ed also detailed recent challenges in the field with current trials. While there have been several recent disappointments, they’ve all failed or faced roadblocks for different reasons. The Wave PRECISION trials didn’t “engage the target”, meaning they didn’t lower HTT. The uniQure trial engaged the target, but the low numbers of patients so far make the data variable. And as we recently learned, the higher dose arm of the trial is on pause.

Now Ed is detailing work on NfL - neurofilament light - a biomarker that was touched on during yesterday’s talks. In every test thus far, NfL is turning out to be an excellent biomarker for HD in both CSF and blood. While NfL isn’t currently included in trials as an official biomarker, everything suggests we’re headed in that direction. To help get us there, samples are being collected in many current trials to track NfL levels. Great news for sensitively tracking progression of HD!

Ed also touched on imaging biomarkers, like brain scans, and digital biomarkers, taken from smartwatches and smartphones. These currently have complex results, but are being studied and developed in full force.

To wrap things up, Ed brought back his pudding analogy - he thinks it’s time to eat the pudding, i.e. that we’re ready to start applying all these strategies to clinical trials, and to continue learning as much as we can from existing human samples.

After a short panel discussion, we’re breaking for lunch, but we will be back this afternoon for updates from LOTS of different pharma companies on current HD clinical trials. Stay tuned!

Updates from ongoing clinical trials

The first part of this afternoon’s session will involve short talks about current HD clinical trials.

Triplet Therapeutics – SHIELD-HD natural history study and clinical development of TTX-3360

First, Dr. Irina Antonijevic from Triplet Therapeutics will be talking about the SHIELD-HD trial, a natural history study which is following people with HD to learn more about the expansion of CAG repeats over time.

Triplet's approach is different to many of the other companies making HDtherapeutics. They are not targeting HTT-lowering, but instead a genetic modifier which they believe might slow or delay the onset of symptoms. Before they can test a drug, they are studying people in a two-year observational study called SHIELD-HD, which will help them to develop the most effective ways to measure changes in early HD.

SHIELD-HD is spread across 9 sites in 5 countries with about 70 participants enrolled. They are looking at different biomarkers of disease including brain imaging, CSF analysis, and other measures. About half of participants in SHIELD-HD have completed the trial, and Triplet expects to be able to analyze the early participants' data in the first quarter of 2023.

Triplet have measured the level of a genetic modifier, a protein called MSH3, after treatment with their drug called TTX-3360 and have shown in HD models that the drug appears to be lowering levels of MSH3, as they hoped. Irina also presented data which suggests that MSH3 levels might be higher in patients at more advanced stages of HD, which is important to know about if this is the target of their drug.

uniQure – Trials related to AMT-130

Next up is Ricardo Dolmetsch from uniQure who will be giving us an update on AMT-130, a gene therapy for HD which aims to lower levels of HTT.

AMT-130 is a harmless virus which is injected into a part of the brain called the striatum by brain surgery. From there the special genetic instructions encoded in the virus are incorporated into each cell, so they are able to make the HTT-lowering molecule themselves.

The clinical trial is being run in the US and in Europe and participants in the trial are either receiving a high or a low dose of the drug, and some participants are receiving a sham surgery with no drug. After the surgery, the participants are tracked for 3-5 years to measure lots of different biomarkers and different HD signs and symptoms they might be experiencing, and how these are progressing.

Keep in mind that this is a very small trial (26 people in the US and 15 in Europe) and the major goal is to look at the safety of AMT-130 and whether it can lower huntingtin - looking at its effectiveness for slowing symptoms will come later on.

For the patients who received the low dose of the drug, no serious side effects were observed. However, for those who received the high dose, 3 folks experienced serious side effects. Fortunately, all 3 are no longer hospitalized and 2 have completely recovered, and the other has substantially recovered. This has meant that dosing with the high dose of the drug has been temporarily suspended and the patients in this part of the study will be very carefully monitored moving forward.

Additional announcements about the status of these trial participants, other adverse events associated with the high dose group, and a decision about moving forward, will come later this year, likely around October. Immediately after the participants received the drug, levels of a biomarker called NfL did spike, but seem to be returning to baseline over time, and are not significantly higher than the control group.

Giving the scientists at uniQure hope is the fact that it seems like the levels of the toxic huntingtin protein are decreasing over time after treatment. However, it is early days and the numbers in the trial are still very small. We are hopeful that the high dose group of this trial may resume with new safety measures in place - already 14 out of 16 participants planned for this group have received the surgery.

PTC Therapeutics – Updates for the PIVOT-HD trial testing PTC-518 for HTT lowering

Next up, we have Amy-Lee Bredlau from PTC Therapeutics who will be telling us about their HTT-lowering drug called PTC-518 which is a splicing modulator - it can alter how the huntingtin message is processed, leading to lower levels of huntingtin protein.

PTC have shown that treating HD mice with their drug reduces levels of the huntingtin message molecule in the blood as well as the protein molecule in the brain.

PTC scientists have also shown that the drug is showing promise in people. They found that the more PTC-518 they give to patients, the more the levels of huntingtin are decreased. They also show that the effects of this drug are reversible. The good news is that this means that PTC met their phase I trial objectives in healthy individuals, so this drug has moved forward to the next stage of clinical trial testing.

Now they are running a Phase II study in people with HD. PTC will be looking at safety of the drug in a much larger number of participants (162) and they will also be monitoring how well the drug lowers huntingtin levels in this group. This trial will be giving 2 different doses of the drug and will also have a control placebo group. Depending on how the data from these 2 dose groups looks, there may be an additional dose group later on.

To be recruited in this trial, participants must be 25+ years old and have a CAG number between 42 and 50. However, participants must have perfect scores in clinical metrics called TFC and UHDRS which measure day-to-day function and movement symptoms of HD.

PTC acknowledges that this might be frustrating for patients as the criteria are strict and a bit complicated. However, they hope that by having a very specific patient population in the trial, they will be able to enroll a much larger Phase III trial later on which will be open to a broader range of people with HD.

> **“The sheer number of talks related to human trials compared to previous years is so encouraging! ”**

PTC-518 is an oral huntingtin lowering drug that differs from the Novartis drug branaplam.

Despite the suspension of the branaplam trial, there is hope that PTC-518 could still be successful.

Wave Life Sciences – WVE-003 for selective lowering of expanded HTT in SELECT-HD trial

Next up is Danlin Xu from Wave Life Sciences who will be talking to us about WVE-003, an ASO huntingtin-lowering therapy which specifically targets only the toxic form of the huntingtin protein.

WVE-003 targets a specific genetic signature which is only found in the expanded huntingtin gene, so it could potentially lower just the toxic form of the protein. Not every person with HD has this signature, so if successful this drug would only be able to treat a subset of people with HD.

WVE-003 is an ASO delivered spinally, like Roche's drug tominersen. However, Wave uses a different kind of chemistry to make their ASO's which they believe makes them work better as drugs to target specific genetic messages.

Wave's previous ASOs didn't pan out as we had hoped - they didn't make people any worse but they didn't actually lower huntingtin levels. One problem was that they couldn't test their drugs in HD mouse models previously because existing mice didn't have the right genetic signature. However, Wave now has a mouse model they can test their drugs in.

In this mouse model, they have showed that WVE-003 lowers only the toxic form of the huntingtin protein, not the healthy huntingtin protein. After treatment, they could see this huntingtin lowering effect lasted for at least 12 weeks.

Now Wave are enrolling HD patients into their new trial, SELECT-HD, which is testing WVE-003 in people. It is taking place in Australia, Canada, and Europe. Everyone recruited to the trial needs to have a test to make sure they have the genetic signature that WVE-003 targets.

To make sure their drug is acting as it should and only targeting the toxic form of the huntingtin protein, Wave have developed a special test to measure the levels of just the healthy protein and make sure it is unaffected by the drug. The trial will run with an adaptive design which means that the dose level and frequency may change during the trial based on participant data.

Annexon Biosciences – ANX-005 to treat molecular breakdown between brain cells

Ellen Cahir-MacFarland from Annexon will be talking next to tell us about their complement C1q targeting therapy, ANX-005.

Annexon is targeting a protein called C1q. This is an important protein in a part of the body's immune response, called the complement system. C1q is an interesting target because we know that people with HD experience neuroinflammation, which Annexon believes is caused by complement.

When our bodies are growing, C1q plays an important role in making sure all of our brain circuits are properly formed, by “pruning” improper connections within the growing “tree” that is our nervous system. This process seems to be improperly reactivated in diseases like HD, and C1q activation is linked to neuroinflammation seen in patients.

ANX005 was tested in a clinical trial and it seems to be doing its job targeting the complement system. Annexon also looked at participants’ HD symptoms, and in a subgroup of the participants, it seemed like the progression of symptoms was slowed which is good news. This suggests that there is a sub-population of people with HD who might benefit from treatment with ANX005. Annexon will likely conduct a larger Phase 2 trial to confirm these results.

However, it is important to note that levels of NfL, abiomarker for neurodegeneration, were not improved with drug treatment, so the picture is not entirely clear just yet and more work remains to be done.

SAGE Therapeutics – SAGE-718 for treatment of cognitive symptoms

Now we will hear from Aaron Koenig from SAGE. Their drug called SAGE-718 aims to improve the cognitive symptoms that people with HD experience.

Cognitive symptoms in people with HD can have a really big impact on their quality of life. While it is important that we have drugs which aim to target the root cause of HD, we also need to target symptoms of HD, which might improve patients everyday lives.

A molecule called 24S-HC which targets special nerve cell receptors is reduced in people with HD. SAGE-718 aims to target these same receptors so they might work properly again which SAGE hopes will alleviate cognitive symptoms in people with HD.

In SAGE’s PERSPECTIVE program, they will run 2 studies - one called DIMENSION and the other called SURVEYOR.

DIMENSION is a Phase 2 trial which will test SAGE-718 in people with HD. SAGE will measure how their symptoms change or evolve during the study, particularly cognitive ones. The SURVEYOR study, another Phase 2 trial, will also test SAGE-718, but the study involves additional measures of function in day-to-day life, like ability to go grocery shopping or perform in a driving simulator.

SAGE is using standard HD cognitive tests but have also developed a new measurement called the Hi-DEF scale. This includes measurements on how well participants are able to do day-to-day tasks, including driving, grocery shopping, and so forth.

Prilenia Therapeutics – PROOF-HD trial to test pridopidine

The last talk of this session will come from Michael Hayden from Prilenia, who is also a professor at UBC. He will be talking to us about pridopidine which is being tested in the PROOF-HD clinical trial.

Pridopidine is a drug, taken as a pill, which is thought to target a protein called the sigma-1 receptor. This protein is found in areas of the brain important in HD. More and more data in HD models has confirmed pridopidine's effect on sigma-1.

There are a number of studies which have now been published that show that there seems to be a neuroprotective effect and better nerve cell connections when different HD models and systems are treated with pridopidine.

The PRIDE-HD clinical trial tested pridopidine in people, but it did not meet its clinical endpoints. However, there seemed to be a glimmer of hope when the scientists at Prilenia looked after the fact at a particular measurement called TFC.

Remember, these after-the-fact analyses, known as post hoc analyses, ask questions of the clinical trial data that the trial was not designed to answer, so we must be cautious when interpreting these conclusions.

In this analysis, it seemed that levels of NfL stabilized following pridopdine treatment. Together with the possible improvement in function (TFC), Prilenia set out to run another Phase III trial for this drug called PROOF-HD.

This study is now fully recruited and many participants are now entering the open-label extension, where they can continue to take pridopidine if they choose to. We should get some data updates in the second quarter of 2023 so watch this space for more news on pridopidine.

It's now time for a break so we can all have a much needed cup of coffee! But we will be back with more tweets for you soon as we move to the next session - systems biology approaches to study HD.

Interactions between neurons and other cells in the brain

There will be a few other talks during the afternoon session, but we'll only focus on a talk by Dr. Michelle Gray from the University of Alabama at Birmingham, who will tell us about her work on the interaction between different cell types in the brain.

Michelle and her lab work on astrocytes - a type of brain cell which are thought to be very important in nervous system function and specifically in HD. It seems that in HD, astrocytes behave strangely and they are more likely to die quickly in the HD brain compared to control models and systems.

Michelle's team is able to lower the levels of thehuntingtin protein just in astrocytes in a HD mouse model, and this seems to improve signs and symptoms of HD in these animals. When HTT levels are lowered in these astrocyte cells, there are significant changes in the levels of molecules that brain cells use to communicate, in particular, one called GABA.

Changes in GABA levels suggest that astrocytes might be working differently in this model. Michelle wanted to work out why there were changes in GABA and they found that a group of proteins which have important jobs in transport, are responsible.

Interestingly, we know that GABA signaling is changed in HD mouse models, particularly in cells called medium spiny neurons, which often die early in HD brains. Michelle and her research team wanted to work out if these two findings are linked.

Changes in the levels of GABA can have important implications for how brain cells communicate with one another. Michelle and her collaborators made measurements of electrical impulses in the brains of HD mice and confirmed that this signaling was altered.

She concludes that astrocytes can contribute to imbalances in brain cell signaling in ways that were previously undiscovered.

That wraps up the talks for today. We will be back tomorrow to bring you more exciting updates on the latest and greatest HD research from all of the speakers @hdfcures!

To learn more about the Hereditary Disease Foundation, visit their website. To learn more about the science discussed at #HDF2022, tune into a live webinar on September 15th at noon EST! Register here You can also follow HDF on Facebook, Instagram, and Twitter to ensure you don't miss future webinar updates.

Sarah Hernandez is an employee of the Hereditary Disease Foundation.For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

neuroprotection something that protects brain cells against damage

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

therapeutics treatments

phase III The phase in the development of a new treatment where clinical trials are conducted using many patients, to determine whether the treatment is effective

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.

Receptor a molecule on the surface of a cell that signalling chemicals attach to

splicing the cutting up of RNA messages, to remove non-coding regions and join

together coding regions.

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.

UHDRS A standardized neurological examination that aims to provide a uniform assessment of the clinical features of HD

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

GABA A chemical the brain uses to signal 'slow down' from one brain cell to another

Total Functional Capacity A standardized rating scale for function in HD, used to assess capacity to work, handle finances, perform domestic chores and self-care tasks

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
