Hereditary Disease Foundation (HDF) conference 2024 – Day 1

Read updates from clinical trials and scientific research on Huntington's disease from Day 1 of the 2024 HDF Milton Wexler Biennial Symposium #HDF2024

 

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The HDBuzz team was back in Boston this year to livetweet updates from the Milton Wexler Biennial Symposium hosted by the Hereditary Disease Foundation (HDF), the first of which was held in 1998! This is a 4-day event that brings together almost 300 world leaders in Huntington's disease (HD) research to share their current data, generate new ideas, and get us closer to a treatment for HD.

"I'm glad you're sitting down for this"

Our first talk is by Fyodor Urnov, who will give us an update on editing the brain with CRISPR for therapeutics. Interesting! Dr. Urnov starts by reminding us how far things have come in brain research in the last few years, stating that he can give us a "healthy dose of optimism".

The HDF has long had a mission to support and promote young investigators within the field. Ahead of the conference, young investigators within the field were gathered to share their research, discuss outstanding questions in the field, and form collaborations to move the needle toward a therapeutic.

He started by showing us a timeline of data that has led to medicines for editing DNA. It's been an explosion over the past few decades! All culminating in the development of a regulatory approved drug, for blood-based diseases. HDBuzz wrote about that drug, called Casgevy, recently.

Fyodor will tell us about drivers of CRISPR progress, the revolutionary gene editing technology, and how they build on each other. Let's go!

Fyodor works with Jennifer Doudna, one of the inventors of CRISPR. Who better to have on team HD to help us develop medicines!? He very excitingly is showing data about a company he works with, Intellia Therapeutics, and how they're moving forward with CRISPR -based treatments for other brain diseases with over 700 participants. Unthinkable just a few years ago!

And all of this has spurred from a scientific discovery that was made only 12 years ago for which Jennifer was awarded a Nobel prize. Quite amazing! Fyodor keeps stating, "I'm glad you're sitting down for this" as he tells us about more stellar science that is knocking our socks off.

CRISPR is being used for other diseases, but what is learned from these diseases can be streamlined to be used for HD. This will take efforts from many companies, which they plan to “daisy-chain” into a platform of CRISPR cures, bringing everyone’s expertise together.

Fyodor is sharing a platform that could be a game changer for genetic diseases. He talks about a world where children that have a gene that can be edited could potentially have a cure in 4 years for $25-70 million dollars. Currently a dream which may soon become reality.

Now he moves on to the good stuff -therapeutics for Huntington’s disease! He’s sharing his research working to correct the expanded version of huntingtin (HTT), the molecule that causes HD. As the CRISPR technology quickly improves, so do the options for HD. There are lots of different flavors of CRISPR, so we have all sorts of tools in the toolbox to work out the best path forward to potentially make a HD gene therapy.

Foydor makes a bold prediction that there will be a CRISPR-based drug for cholesterol within 3 years. This will provide a regulatory track record for CRISPR-based drugs, making the path clearer for diseases like HD. Fyodor is telling us about the successes of CRISPR approaches in other diseases, since information from these clinical trials will help inform therapeutic strategies for HD.

For HD, Fyodor and his team is planning to use CRISPR to change the way the HTT gene is put together - something called splicing. They’ll specifically do this to target only the expanded, disease-causing copy of HTT.

Like an approach from a super villain movie, they’ll use something called a “poisonexon”. Sinister sounding... All this means is that they’ll splice in a piece of genetic code that causes the expanded HTT copy to get sent to the cellular trash bin.

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So far they’ve only done this in cells in a dish, but this approach seems quite promising. Using this technique, they can reduce the amount of the expanded HTT copy by ~70%. Impressive in the world of molecular biology!

Another challenge for HD gene therapies is getting the CRISPR drug into the brain, no mean feat. Instead of a harmless virus usually used to deliver these types of drugs to the brain, tiny carrier molecules called lipid nanoparticles seem to do the trick, at least in mice and cells grown in a dish.

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A light at the end of the tunnel?

Our second and last talk for tonight is from the one and only Ed Wild, co-founder of HDBuzz. He'll be sharing an exciting update on clinical trials in the HD space.

Ed starts by reminding us about the state of play the last time we gathered for this meeting in 2022 - we had just had a slew of sad and disappointing news about many HD clinical trials which HDBuzz readers will remember well.

Ed reminds us that everyone's journey with HD starts with bad news, but we must get back up and come together to generate good news. Recently we've had a deluge of very much needed good news from many HD drug hunting companies that he will review for us now.

The first company and drug Ed talks about is tominersen from Roche. They've worked hard to comb through the data from the GENERATION-HD1 trial to determine if there is a way forward for this drug.

They're currently moving forward with GENERATION-HD2, a Phase 2 trial to test tominersen in younger people with less pronounced symptoms of HD and a lower dose of the drug. Testing drugs in early HD was previously challenging, as it's challenging to determine if the drug is working in someone who doesn't have clear symptoms. This is now possible because expert HD scientists and doctors got together to work out a new staging system for HD to figure out what they could measure in younger people.

The fact that companies are shifting to testing drugs at earlier stages does not mean that it's too late for people who have developed symptoms. Something that works to prevent or slow HD will likely also work in people at later stages.

Ed Wild shared an exciting overview of the HD clinical space, which has had a windfall of great news in 2024. He also had some thoughts to share on the new look of the hotel where the conference is held.

You can learn more about the Roche GENERATION-HD2 trial from a recent HDBuzz article.

Ed then moved into talking about the recent good news from PTC Therapeutics, which was recently covered by HDBuzz. PTC Therapeutics are testing their HTT lowering drug PTC-518, which is a small molecule that is taken as a pill. PTC-518 lowers HTT levels in a dose-dependent manner i.e. the more drug you take, the more lowering that happens.

A new piece of data we learned from their recent update was that HTT lowering does not inevitably lead to high NfL levels, indicating damage to neurons. While this sounds obvious, we actually didn't know this until recently.

Previous trials testing HTT lowering had all shown a spike in NfL levels - a molecule that rises when brain cells are damaged. So scientists thought this was causing things like brain swelling because of the drug or brain surgery, but no one actually knew. Until now! People who were given PTC-518 had flat levels of NfL, suggesting that HTT lowering itself wasn't the cause of a transient rise in NfL levels in previous clinical trials. Good news!

We also learned that this type of drug, called a splice modulator, appears to be safe in treating HD. This is the same type of therapeutic as the Novartis drug branaplam that was halted, so this is also very welcome good news.

PTC also showed that people taking PTC-518 had HD symptoms that seemed to advance more slowly, perhaps suggesting that the drug is doing what we hope. However, this is a small trial, so we have to take this information with a pinch of salt. Excitingly, PTC are making moves toward a Phase 3 trial for PTC-518.

Next Ed shared an update from Wave Life Sciences, which we also recently covered. Wave are testing a HTT lowering strategy that specifically targets the expanded copy of HTT. This leaves the unexpanded copy alone, left to work in the body and brain, to perform its normal functions. Again, it seems that WVE-003 seems to be doing just this!

Ed suggests we should keep tabs on the NfL data from this study, as the data does show somewhat of a spike for a few folks. Ed thinks that HD researchers need to put their heads together to figure this out before we test this drug in more people.

When things are all going in the right direction, they're easy to interpret. But already confusing things can confound our interpretation. So proceeding cautiously is best.

Ed is now providing an update from the uniQure trial, which you can read more about here. This trial is testing yet another HTT lowering strategy; this one involving a single dose of a drug delivered by a harmless virus via brain surgery. With this kind of approach, things must move very slowly to ensure safety at every step of the way.

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uniQure's drug, AMT-130, caused an initial spike in NfL. This was expected since any brain surgery will at least temporarily harm some brain cells. However, it looks like NfL goes down back to baseline, and possibly drops below baseline - we'll see if this trend holds!

While uniQure also shared data suggesting AMT-130 slowed disease progression, again, it's important to note that this is a small number of people. So results here also have to be interpreted with caution. However, any movement of the needle is welcome news in our books!

Up next is an update on Skyhawk Therapeutics, who recently released data from their Phase 1 trial testing a HTT lowering drug, called SKY0515, that can be taken as a pill.

While they didn't release much data with this update, they did show that they're able to lower HTT in a dose dependent manner. So the drug does what they want! They're now moving on to a third arm of the study that will test SKY0515 in people with HD.

Ed shared a quick update about Prilenia. Ed noted that pridopidine failed to meet its primary or secondary endpoints of their recent trial testing this drug. Despite this setback, you may have seen some news stories about how Prilenia plan to move things forward.

Ultimately, Prilenia sliced and diced the data after the trial was over to try and gain some insight. These aren't conclusive since the study wasn't designed to test this. Under this extremely distorted lens, Prilenia think that neuroleptics might affect how the drug works.

Neuroleptics are antipsychotic medications often prescribed to people with HD to manage psychiatric symptoms, like depression, that are sometimes associated with HD. This is a key part of treatment for many people with HD.

Ed is somewhat worried about the confusion generated around neuroleptics. Before we make decisions about which drugs people with HD should be taking, he believes we should be informed by clinical trial data.

Anyone who has been prescribed neuroleptics by their neurologist should not go off their medication without first speaking with their medical team. A blinded clinical trial would need to first be run to make any conclusions about how neuroleptics affect the severity of HD.

Ed then went into a long-winded explanation about the stars in London - apparently he's gotten into astrophotography.... In a way that only Ed can, a moderately self-congratulatory departure was used to wrap and liken HD drugs to the stars in our sights.

That's all for Day 1. The HDBuzz team will be back for Day 2 with some hot off the presses HD science updates!

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

GLOSSARY

secondary endpoints Additional questions asked in a clinical trial that help scientists look at treated patients as broadly as they can to determine the effects of a drug

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

therapeutics treatments

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

CRISPR A system for editing DNA in precise ways

Exons The small fraction of our DNA that is directly used to instruct cells how to make proteins

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
