Hereditary Disease Foundation (HDF) conference 2022 – Day 3

Read updates from clinical trials and scientific research on Huntington's disease from Day 3 of the 2022 HDF Milton Wexler Biennial Symposium #HDF2022




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Pre-clinical work moving toward trials

New tools to lower HTT showing promise in animal models

Welcome back! The first talk we will be tweeting about today is from Anastasia Khvorova, who will be telling us about her teams work on lowering of Huntingtin using technology called RNAi.

HDF pioneered the use of workshops as a way to move HD research forward through collaboration and free exchange of ideas. At #HDF2022, young investigators channel that spirit for lively discussions on their own work as well as outstanding questions in the HD field.

One of the problems in studying drug delivery to the human brain is that animal models, even large ones, all have much smaller brains than us! Mouse and even monkey brains are tiny by comparison, so Anastasia's lab use sheep as they have fairly large brains. In these

sheep brains, the Khvorova lab can measure how drugs are able to spread and work across the different regions of the brain.

Similar to the approach Wave Life Sciences are taking, the drugs Anastasia and her collaborators are testing target small genetic signatures which means they can lower just the toxic form of the huntingtin protein. However, one of the problems about being so specific in which form of huntingtin you are targeting, is that you need more drug to see the same effect.

We've talked a lot about huntingtin protein clumping up in cells, but Anastasia is looking at the huntingtin message - the recipe - forming clumps in the cell's nucleus. She thinks this could contribute to the lengthening of CAG repeats that can cause cells to become sick.

The toxic huntingtin actually comes in a long and short form. The shorter form is thought to be responsible for the toxic clumps that we see in HD models. Anastasia tells us that we have to be careful when looking at these clumps, because they differ between models and people.

Anastasia and her team have identified compounds which are able to reduce the amount of the short form of the toxic huntingtin. They have added this to their toolkit of compounds which change the levels of important targets in HD including total huntingtin, toxic specific and MSH3, a genetic modifier of HD.

Anastasia thinks this toolkit is an excellent portfolio of different options for targeting HD, which may also help us unpick exactly which protein or protein form is important in the disease progression.

Cell replacement treatment options using stem cells

The next talk we'll cover is by Anne Rosser from Cardiff University. As a part of the Stem Cells 4 HD initiative, she'll give an overview of how stem cells are being used to study and potentially treat HD. Stem cells can be used in HD research for various purposes: either as a tool to understand more about HD or, perhaps, as a therapy. Anne's talk focuses on the latter.

The overall goal of using stem cells as a therapy would be to 1) replace cells that have been damaged by disease and 2) release biological factors like chemicals or proteins that might have been lost during disease, to try and keep other cells in the brain healthy.

The cells that researchers have been interested in using for this cell replacement therapy come from "pluripotent stem cells." These can be made from the cell of an adult, like a skin cell or blood cell, and they can be turned into almost any type of cell in the body.

We know from older studies using a different type of stem cell that cells transplanted to the brain do a good job of integrating into their new environment. This would be great news for HD, where they hope that cells added to damaged areas will form connections with other parts of the brain

Anne mentions that there are several HD labs moving this technology forward toward clinical trials. However there are challenges with such an invasive approach, including exactly which cell type to use for transplants and how to create a comparison group.

To deeply consider all of these challenges before moving forward, researchers have created the Stem Cells for HD (SC4HD) group, comprised of stem cell leaders from around the world.

The SC4HD group is standing on the shoulders of giants - learning lots from previous studies that transplanted fetal tissue in the HD brain, changing what didn't work and using what did to move forward logically and safely. To ensure researchers have as much information as possible before moving forward, studies are being done to compare various ways to make striatal neurons, which are the most vulnerable cell type in HD.

There are a lot of variables to consider - controlling between different batches of cells, tracking the cells after they're implanted, and ensuring they turn into the cell type we want once they're in the brain. There's still a lot to work out before we have this technology in humans for HD, but stem cells represent a very powerful source for cell replacement therapies.

It's an action-packed morning, and we'll be back after a break, tweeting briefly about a couple of short talks on impactful topics.

Datablitz: presentations from young investigators

Putting mouse models head-to-head: which is the best?

Sophie St-Cyr was selected to give a short talk related to the advantages and disadvantages of different types of mouse models we use to study HD.

There are dozens of models, grouped in different categories based on how they're created and what HD-like signs and symptoms they have. Sophie compares different behavioral tests in different HD models and across sexes.

As an expert in mouse behavior, she made recommendations to the scientists in the audience about the use of different mouse models and how best to design their behavioral experiments.

At-home collection of samples for NfL detection in blood

Next up is Lauren Byrne from UCL who works on a protein called NfL (neurofilament light), which is released by sick cells and can be used as a biomarker of brain damage in HD. NfL levels go up as HD progresses.

Scientists might also be able to use NfL to track whether a treatment is working, and it is increasingly being measured in clinical trials to check firstly, that there are no safety issues, but secondly, to see if the drug is helping to keep the brain healthier.

Lauren's work has been focused on developing more practical ways to measure NfL levels. Luckily NfL is a very stable protein so Lauren has developed an at-home finger-prick test to collect blood, and then post it back to the lab through the mail for analysis.

She will be running a study called iNfLuence-HD to study NfL levels and improve methods for measurement, and is also heading up the JOIN-HD registry which aims to study juvenile HD patients from all over the world.

That's all from this morning's session. We are breaking for lunch now and will be back with more updates on all this exciting HD research later on this afternoon.

Genes and proteins that modify HD onset

Identifying modifiers by looking at the whole genome

Welcome back! The afternoon session will focus on genetic modifiers of HD, other genes that influence the age that HD symptoms begin. The first talk we'll cover is by William Yang from UCLA, who studies modifiers in mouse models.

What very large sequencing studies have shown us is that many of the modifier genes that change the age of onset in HD have to do with DNA repair. The question is: how can we harness them for HD therapeutics?

Dr. Yang uses mice to study how we might be able to use these modifiers for treatments in HD. His team has created many of the mouse models that have become the standard in the field.

Dr. Yang's lab has compared these different models at different timepoints to understand how HD changes within each model over time. In particular, he has done a deep dive on gene expression changes - how levels of genetic "recipes" go up and down.

Another key feature they examine are clumps of the HTT protein, also known as protein aggregates. This is a unique feature caused by expanded HTT that seems to occur mainly in brain cells called neurons.

The Yang lab has recently created a new mouse model that can be used to study different aspects of HD, like problems with sleep, CAG repeat expansion, and damage to specific brain areas. One of the questions they want to answer with this new model is whether genetic modifiers of HD can influence these features, like changes in gene expression or protein aggregation.

A relatively recently identified feature of HD is somatic instability - expansion of the CAG repeat in certain cells or tissues over time. This happens frequently in neurons and might be contributing to why certain types of cells become sick and die in HD.

Adding or removing certain modifier genes in these HD model mice can cause symptoms and features of HD to improve or worsen. This strengthens the case for targeting these genes with drugs in people.

Dr. Yang's lab has found that altering levels of a specific modifier, FAN1, in HD mice can affect their behaviors, like sleep patterns and ability to walk on a rotating rod. There is also a change in protein aggregation

It seems that just targeting FAN1 alone might not be the answer to HD, but interestingly, when they also target another modifier in these mice, called MSH3, the mice get better in most of the metrics they looked at.

These types of controlled genetic experiments in mice can help to identify and confirm the right targets for drugs that could delay HD onset.

Alfy as a modifier of HD

The next presentation we'll talk about is from Dr. Ai Yamamoto of Columbia University, who works on a protein called Alfy, that is also a genetic modifier of HD.

Large scale human studies found that tiny genetic changes in Alfy can cause the onset of HD symptoms to be much later. Ai's lab created a specialized mouse model to study this rare genetic variation in more depth, and these mice also had delayed onset of symptoms.

Alfy is involved in breaking down clumps of harmful huntingtin protein. In both humans and mice, the Yamamoto lab has found that higher levels of Alfy can have positive effects on symptom onset.

They are now finding that Alfy's role in clearing toxic proteins is highly important in conditions of stress, including in HD and other brain disorders.

The effect of HD on connections between different parts of the brain

This afternoon we've got a very exciting session about BRAINSSSS!! The talks focus on different aspects of brain function, measured with very cool new techniques.

First talk is from Dr. Lynn Raymond, of @UBC. She studies how brain cells called neurons communicate. These communicating cells are the ones that die in HD, so understanding how they start to dysfunction can give us clues about how HD arises.

While the HD gene is expressed in nearly every cell of the body, it's neurons that cause most of the symptoms of HD. And in fact, not all neurons are impacted in the same way. The most impacted include a set of structures within the brain, deeply connected to each other, called the "cortex" and the "striatum".

Dr. Raymond's lab has long studied the details of how these two parts of the brain communicate using mouse models of HD. She sees very clear changes in how the HD mice learn to do new movements, something like the problems that happen in HD patients

Dr. Raymond's lab is using existing new "deep learning" or "artificial intelligence" software tools to analyze the behavior of mice in detail that was not previously possible (@deeplabcut).

To link changes in behavior to changes in brain function, Dr. Raymond uses live, real-time, microscopes that allow tracking of brain activity in HD mice doing specific HD-relevant movements. This is a good example of why we need mice, and other models of HD - there's no way we could record this level of detail of how brain cells talk to each other in humans with HD.

In HD mice, the cortex, an outer bit of the brain critical for our thinking ability, is hyper-excitable. There's a lot more activity accompanying movements in HD mice, compared to controls. So it's as if the brains of the HD mice have to work a bit harder to achieve the goal of the movement. This might be a hint for why some types of movements, and the learning of those movements, are hard for HD patients

That's all from us for today! We'll be back tomorrow afternoon to share a few other talks before the close of the @hdfcures symposium. Tune back in then!

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.
therapeutics treatments
juvenile HD Huntington's disease where symptoms begin before the age of 20.
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
stem cells Cells that can divide into cells of different types
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

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
