Updates from the EHDN Meeting 2021

Last month, HDBuzz attended the online European Huntington's Disease Network (EHDN) meeting. Read our summary of all the latest clinical trial updates.

By Dr Rachel Harding | October 28, 2021 | Edited by Dr Jeff Carroll

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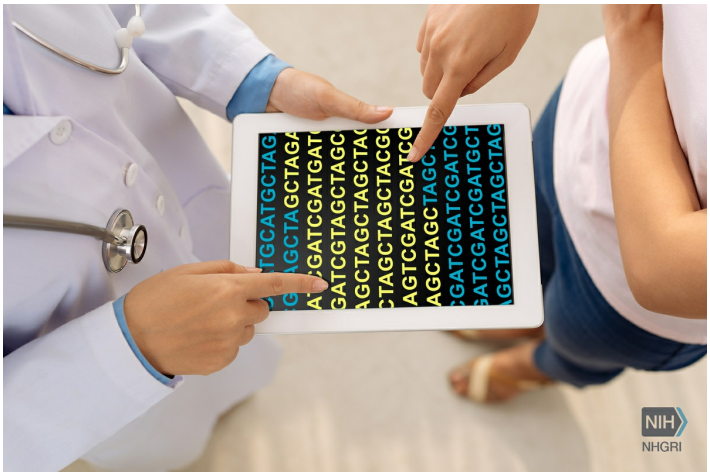
Last month, the Huntington's disease (HD) research community, patients and other stakeholders met online at the European Huntington's disease network (EHDN) conference. Despite the ongoing global pandemic, there is a tremendous amount of work underway in labs and clinics around the world as researchers continue to better understand HD and how we might best treat it. Although 2021 has been a year of disappointing news in some respects for the HD patient community, there are lots of reasons to be hopeful as we learn from past clinical trials and use that information to inform new ideas for medicines which we are now beginning to test in the lab and the clinic. Here, we give an overview of the clinical trial updates.

Scott Schobel from **Roche** gave an update on the huntingtin-lowering drug tominersen and the GENERATION-HD1 clinical trial. The decision to halt dosing in this trial was made earlier this year following advice from the Independent Data Monitoring Committee (iDMC), a neutral organisation whose job it is to review the data at set time points throughout the trial. Following this announcement, more than 40,000 samples needed to be shipped from all around world to designated labs for analysis. The samples need to be analysed using predefined procedures and in relatively few batches to ensure the data obtained from the samples is of the highest quality. Having good quality data from the trial should help scientists better analyse exactly what happened. This is a huge logistical operation, but analysis of the data is now underway and Roche hope to begin sharing some of their findings by the end of this year with the full analysis being released early next year. This might seem slow and frustrating, but Roche want to avoid releasing partial information which might lead to misinformation or unrealistic expectations which would be extremely unfair to the HD patient community. Many open questions remain; does the stage of HD a patient is at play a role in how well tominersen might work? Was too much drug administered in the trial? Which factors about a patient predict response to drug? Hopefully we will have answers to these questions soon. If you want to know more about the halting of GENERATION-HD1, we recently wrote a detailed Q and A with Roche about the halting of this trial and next steps for Roche on HDBuzz.

Maurice Zauderer from **Vaccinex** gave an update about pepinemab which was investigated

in the SIGNAL trial. Pepinemab is an antibody therapy which specifically targets a protein in our bodies call SEMA4D. SEMA4D has an important job in inflammation, a response that is critical to how our immune system deals with infections and some diseases. Last year, we reported that unfortunately pepinemab did not improve symptoms in HD patients and that the trial did not meet its primary end points – clinical goals decided upon before the trial begins. However, since last year's announcement, scientists involved in the trial have been re-analysing the data to see if they might eke out some additional information on the usefulness of pepinemab. In this "post-hoc" analysis, it seems that pepinemab might be beneficial in early-stage HD patients for improving certain behaviours such as apathy. However, it is important to remember that this Is not what the trial was designed to work out so these findings should be treated with caution.



Even though the COVID-19 pandemic has disrupted so much of our lives, scientists and clinicians have still been extremely busy with their research. At EHDN we heard lots of updates and discussion about the different Huntington's disease clinical programs underway or about to start

Image credit: Darryl Leja, NHGRI

Vissia Viglietta from **Wave Life Sciences** gave an update on the latest trial they are working on which will test WVE-003 in a trial called SELECT-HD. Wave's approach is to selectively lower the toxic form of the huntingtin protein whilst preserving the healthy huntingtin protein. This rationale is based on lots of data which shows that normal huntingtin protein is very important for brain function, especially in the context of different stresses. Wave can achieve this selectivity by targeting a specific signature in the DNA code which is only found in the toxic huntingtin gene. Although Wave's previous clinical trials had disappointing results, they are optimistic that this new drug will perform better as they have changed the chemical decorations on the drug which should make it more potent, last longer in the body and spread more easily to the regions of the brain it needs to be. They have been doing lots of work in the lab, testing this latest version of their drug in cells in a dish, mice, and monkeys, all of which have had encouraging results.

David Cooper from **Uniqure** gave an update on their gene therapy approach to treating HD, currently underway in trials called HD-GeneTRX-1 and HD-GeneTRX-2. Uniqure's drug, called AMT-130, is a one-shot treatment delivered by brain surgery. AMT-130 provides your body the recipe to make the therapy which will lower the levels of the huntingtin protein. Uniqure have been busy with lots of proof-of-concept experiments in different HD models. They have tested AMT-130 in cells in a dish, HD mice and rats, as well as bigger animals like monkeys. Uniqure have also tested their drug in HD pigs where they have tested long-term effects of treatment – an important experiment as this treatment is an irreversible procedure. To date, Uniqure's data suggest that the drug is safe long-term in these animal models. The HD-GeneTRX-1 trial aims to test safety of AMT-130 in humans, how long the drug stays in the body as well as how AMT-130 affects different markers of HD progression. The trial will enroll 26 early-stage HD patients at 12 different HD study centres in the US and will run for 1 year with follow up for a further 5 years. Because the drug is delivered by brain surgery, the brain anatomy of each potential participate is evaluated to ensure they are good candidates for the trial. A similar study, HD-GeneTRX-2, will run in Europe with 15 participants across 3 different sites.

Irina Antonijevic from **Triplet Therapeutics** gave an update on their drug TTX-3360. Triplet's approach to treating HD is to lower the levels of a key DNA repair protein identified in HD patients. In previous studies, scientists have searched for genetic traits that influence the age at which someone with the HD mutation first experiences symptoms. We have known for a long time now that patients with the same CAG number can have symptoms start at very different ages so scientists suspected other genes might be "modifying" the age of onset. Triplet's target gene, MSH3, was identified as one of these "modifying" genes. Triplet's drug will lower the levels of MSH3, with the aim of delaying onset of disease symptoms on HD patients. Lowering the levels of MSH3 is safe in mouse and monkey models so Triplet are hopeful that the drug will also be safe in humans. Getting the drug into the right parts of the human brain is challenging so Triplet have decided to opt for a novel delivery approach for their drug, compared to other ASO drugs tested in HD so far. This approach will allow an implanted catheter to deliver Triplet's drug to the deep brain structures we think are important for HD symptoms. Triplet hope to start their clinical trial for TTX-3360 next year so watch this space!

Michael Hayden from **Prilenia** gave an update on their drug, pridopidine. Pridopidine works by targeting a protein called the signal-1 receptor (S1R) which has been shown to improve signs of HD in different models in the lab. An advantage of pridopidine is that it may be taken as a pill – not surgery or spinal tap. However, the previous PRIDE-HD clinical trial which tested pridopidine in HD patients did not improve patient movement symptoms. There were some glimmers of hope however that some symptoms of HD, also referred to as total functional capacity (TFC), might be improved following pridopidine treatment so now Prilenia is running PROOF-HD. This study will test more people (480 participants) for much longer to see if this feature of HD is improved.

Beth Borowsky from **Novartis** gave an update on their drug, branaplam. Branaplam can switch different genes on or off and has been shown to lower huntingtin levels. Branaplam can be taken as a pill so it places significantly less burden on patients than spinal tap or brain surgery approaches to huntingtin lowering and will also treat the whole body, not just brain and nerve cells. Novartis have shown branaplam works well in the brains of HD mouse models to lower the levels of HTT. Novartis also have a lot of data from SMA patients treated with branaplam which shows that the drug is safe and well tolerated as well as also lowering the levels of HTT in the blood of these patients. However, SMA patients are children, so Novartis is conducting a "first-in-adult" clinical trial, treating 32 healthy adults with branaplam to check safety and work out an appropriate dose of the drug to give to adults. This study informed design of a Phase IIb trial where branaplam will be tested in early-stage HD patients. Recruitment for this trial will begin at the end of 2021 in sites across Europe and North America.

8 different drug discovery companies presented at EHDN on their approaches to treat Huntington's disease. Maybe one day, one of these drugs might be a new medicine to treat people with HD.

Brian Pfister from **PTC Therapeutics** gave an update on their drug, PTC518 HD. PTC518 is another drug which may be taken as a pill to lower the levels of the huntingtin protein recipe molecule, like branaplam. PTC have shown that their drug lowers the levels of huntingtin in both the blood and brain of HD mouse models. PTC518 is able to lower huntingtin across lots of different brain regions in these mice which indicates the drug spreads well. In studies with monkeys, PTC have shown that their drug is able to cross the blood-brain barrier, again, demonstrating that PTC518 should be able to reach the important regions of the brain after being taken as a pill. There is currently an early stage trial underway for PTC518 testing safety of this drug in healthy participants. Importantly, data from this clinical trial shows that the more drug given to participants, the more the levels of the huntingtin are lowered by. Unlike gene therapy approaches, PTC's huntingtin lowering is reversible so if you stop treatment, huntingtin levels should bounce back to normal. Later this year, PTC518 will enter a Phase II clinical trial so hopefully we will have some more news for you soon.

It's exciting to see so many companies continue to work on a diverse range of approaches

to treat the route cause and symptoms of HD. We look forward to reporting on more updates soon as many of these trials get underway and start reporting their findings.

Jeff Carroll is on the Scientific Advisory Board of Triplet Therapeutics. He has conducted sponsored research with Triplet Therapeutics and Wave Life Sciences. No one from Wave or Triplet had any input to this article. For more information about our disclosure policy see our FAQ...

GLOSSARY

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

blood-brain barrier A natural barrier, made from reinforcements to blood vessels, that prevents many chemicals from getting into the brain from the bloodstream

huntingtin protein The protein produced by the HD gene.

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

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

therapeutics treatments

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

ASOs A type of gene silencing treatment in which specially designed DNA 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
