Huntington's disease clinical trial round up

Catch up on all the latest Huntington's disease clinical trial news in this one stop shop article covering all of the recent developments in making medicines for Huntington's disease

By Dr Rachel Harding | April 26, 2021 | Edited by Dr Leora Fox

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It seems like the HD community has been inundated with updates from different companies and clinical trials recently. The news is far from complete doom and gloom; although there have been some real disappointments from some of the frontrunner trials, there are also positive updates from many different companies and lots of reasons for us all to stay hopeful. In this clinical trial round up, we hope to provide you with a brief overview of the current status of various potential treatments for Huntington's disease. Next week, the annual CHDI Therapeutics Conference is going virtual, and that means we'll have even more updates for you all, but in the meantime, we hope this piece brings you up to speed on everything that is going on. Let's get started!

Tackling the root of the problem - huntingtin-lowering therapies

We've been talking about huntingtin-lowering therapies for a long time now at HDBuzz including the advanced clinical trials which have been taking place. The basic premise of huntingtin-lowering therapies is that they aim to reduce the amount of the harmful form of the huntingtin protein which is made in the bodies and brains of people who have Huntington's disease. Scientists working on these approaches hope that by reducing the amount of the harmful protein, they might slow or even reverse the course of Huntington's disease. Huntingtin is an essential gene, especially during brain development, which means we must be wary of entirely eliminating it from cells. Therefore, huntingtin-lowering is a careful balancing act of reducing the protein enough to hopefully improve symptoms while leaving enough functional protein present to do its normal jobs in the cell. But what are the different strategies companies are taking to make huntingtin-lowering therapies?

Even when trials don't give us the results we had hoped for, there is still lots we can learn from their findings to help us move forward with finding new medicines for people with HD.

ASOs to lower huntingtin

Researchers have developed molecules called anti-sense oligonucleotides or ASOs which target the genetic message of huntingtin, called mRNA. This message gives our cells the recipe to make the huntingtin protein so if we make the recipe unreadable using an ASO, the levels of the huntingtin protein will go down. One downside of ASOs is that because they are big and bulky molecules that require repeated dosing, they must be given as a spinal injection.

The ***Roche*** clinical candidate ASO, called tominersen, targeted the recipe for both the normal and the harmful forms of the huntingtin protein. Wave Life Sciences also uses an ASO approach but their strategy is a little bit different to Roche. The ASOs that ***Wave*** designed will only target the genetic message of the harmful form of huntingtin because they are engineered to recognise tiny genetic signatures only found in the harmful form of the huntingtin gene. This strategy would leave healthy huntingtin intact, but not everyone has the same genetic signatures, so this means that such drugs, if successful, could not treat all people with HD.

Unfortunately, recent Roche and Wave trials of HD ASOs were not successful. In the case of Wave's PRECISION-HD trials, the ASOs just weren't performing as scientists had hoped: the treatment was safe but simply did not lower huntingtin. However, Wave is developing a third ASO with an improved chemical structure that will be tested in clinical trials in the near future. In the case of Roche, dosing in the GENERATION-HD1 trial was stopped because of a recommendation by an independent committee who can see and access all of the unblinded data. The reasons for this will be revealed in the data to be shared with scientists, clinicians, and families this coming week, through the CHDI conference and discussions with the wider community, and we will definitely keep you updated with any developments.

It is important to remember that trials are not treatments. Trials are some of the biggest and most complex experiments scientists can run and even if they don't pan out as we might hope, they provide a wealth of information and data which can help inform future decisions and design of treatments. Both Wave and Roche have stated that they are committed to

developing treatments for Huntington's disease.

Genetic therapies to lower huntingtin

Although the Roche and Wave trials haven't gone as we might have hoped, there is still broad consensus by many Huntington's researchers that huntingtin lowering might be a potentially promising approach to treating HD. ASOs aren't the only way to reduce the levels of the huntingtin protein and other companies are using different tactics.

The company ***uniQure*** has developed a therapy called AMT-130 which they hope might be a one shot treatment for Huntington's disease. AMT-130 is delivered by a brain surgery and uses a virus to spread the treatment throughout the brain. The treatment targets the genetic messages of both the harmful and normal huntingtin protein, lowering both.

Recently uniQure announced LOTS of important updates about AMT-130. Firstly, they have dosed the first cohort of ten participants in their Phase I/II safety trial in the USA. This happened ahead of schedule despite all of the complications associated with running a trial in the midst of a global pandemic, thanks to the selfless trial participants. They're also planning another small human trial in Europe. They also announced the release of data from experiments in small and large animals, three publications which together show good safety, stability, and spread of AMT-130 throughout the brain.

> **"Despite recent setbacks, the landscape of HD therapeutics is rich with new ideas and approaches. "**

All of this news is very positive for the technical aspects of the AMT-130 approach but we are still waiting for long-term safety data as well as whether AMT-130 therapy helps treat the symptoms of Huntington's disease.

A pill to lower huntingtin

Brain surgery or regular spinal taps are not ideal modes of treatment and would certainly not be broadly accessible to everyone in the world with Huntington's disease. Because ASOs and gene therapies are big and bulky molecules, they cannot get across the blood brain barrier, so they can also only lower huntingtin levels in the central nervous system. For these reasons there is a lot of interest in making small molecules which could be taken as a pill with the aim to lower huntingtin throughout the whole body.

But how do small molecules work to lower the levels of thehuntingtin protein? The small molecule huntingtin-lowering therapies developed to date are not able to interrupt the genetic message in the same way as ASOs or gene therapy approaches. Instead they target the machinery in our cells which cuts, pastes, and prepares genetic messages for the making of proteins - a process called splicing. These small molecules are therefore often referred to by scientists as splice modulators.

Novartis is one company interested in this approach. A drug called branaplam, developed to treat the neurological disorder spinal muscular atrophy (SMA), could be repurposed to treat Huntington's disease. Novartis has received orphan drug status for branaplam to be used in a clinical trial to treat people with Huntington's disease, which should launch this year.

PTC Therapeutics also has a splice modulator called PTC518 which reduces the levels of huntingtin in different animal and lab models of Huntington's disease. A Phase I clinical trial in healthy people is currently underway to investigate the safety of PTC518. Provisional data shared at a recent investor meeting looks promising and indicates this therapy is working as expected, and no dangerous side effects have been identified yet.

New genetic technologies to treat Huntington's disease

We are living in times where great advances in genetic technologies are providing new ways to treat different diseases. The RNA vaccines developed for COVID-19 are just one amazing example but there are companies working on new genetic technologies to treat Huntington's disease too.

Atalanta Therapeutics is working on RNAi therapies for different neurodegenerative diseases, including Huntington's disease. RNAi therapies work in a similar way to ASOs by interfering with a specific genetic message to lower the levels of a specific protein. Atalanta makes a special form of RNAi which has a branched structure which is able to spread well throughout the brain so they think this will be good for treating brain related diseases.

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Locanabio is another company which has also developed new genetic technology which aims to target genetic messages which contain the instructions for cells to make disease causing proteins, such as the harmful form of huntingtin. We are excited to hear more details from both of these companies in the coming months.

Other approaches to treat HD

Some companies are approaching Huntington's disease treatment from very different angles that are based on other aspects of HD biology, rather than the huntingtin protein itself. This diversity of approaches should give us a better chance to find a treatment or multiple treatments which might help the most people.

Annexon Biosciences has a Phase II trial underway for Huntington's patients with their drug called ANX005. This therapy targets part of the immune system called the complement system. People with Huntington's disease seem to have overactive complement systems, leading to nerve cell damage and changes to the connections between brain cells. This therapy aims to correct that by stopping the complement system from switching on too much.

Prilenia is conducting the PROOF-HD trial, a Phase III study of a drug called pridopidine. Recently, scientists have made advances in understanding the potentially protective effect of pridopidine in the brain, through its action on a type of nerve cell called the sigma 1 receptor. Although earlier trials of pridopidine had disappointing results in people with HD, this new trial will treat early manifest patients for much longer in hopes that they may see better outcomes for patients.

Stopping CAG repeat expansion

Building upon a wealth of data from genome-wide association studies, which have provided clues about why HD symptom onset can be so variable, there are companies who are now exploiting new avenues of potential drug discovery to delay age of onset. Although longer CAG numbers are generally associated with earlier signs of disease symptoms, some people who have the exact same CAG number will get sick with HD at very different ages. It turns out that one of the reasons for this variation is found in the DNA code of genes involved in the process of DNA damage repair. We now know that single-letter spelling differences in these genes, which normally have no consequence, can be drivers of earlier symptoms in people with Huntington's disease and are linked to another process called somatic instability which is also important in how HD progresses. ***Triplet Therapeutics*** and ***LoQus23 Therapeutics*** are two companies which are targeting these DNA damage repair processes, with the aim of slowing or halting the progression of HD.

Triplet is currently conducting a study called SHIELD-HD, which does not involve a drug, but aims to track HD progression over time and further explore CAG repeat expansion alongside the development of symptoms. The overarching goal is to determine the best time to treat with the types of therapies that Triplet is developing.

Trials targeting the symptoms of Huntington's disease

Whereas genetic therapies are aimed at altering the course of HD, another important approach is to develop treatments to target symptoms and improve quality of life for people with HD.

Sage Therapeutics is working on tackling some of the cognitive changes that happen to people with Huntington's disease. They are developing and validating tools to measure thinking and planning abilities, specifically reported from the perspective of individuals with HD. This type of evaluation is known as a patient-reported outcome (PRO) and it involves questions answered directly by patients, rather than measurements made by doctors. Sage is also in the process of gearing up to begin a Phase I/II clinical trial to see if their drug, SAGE-718, is beneficial for Huntington's patients in improving their cognitive symptoms.

Observational studies are an important part of the hunt for medicines for treating HD which hope to uncover new aspects of HD biology

Neurocrine Biosciences is working with the Huntington Study Group to conduct a Phase III clinical trial of a drug called valbenazine. The trial is called KINECT-HD and will study valbenazine's effects on the movement symptoms of HD (chorea). Valbenazine is chemically similar to treatments like tetrabenazine (Xenazine) and deutetrabenazine (Austedo), and has already been approved for a disorder called tardive dyskinesia which causes movements of the face and limbs in some people who have been prescribed psychiatric drugs.

Observational and local studies

We have described above the main therapeutic approaches to Huntington's disease that are being developed by pharmaceutical companies in current or future multi-site clinical trials. There are also several large observational studies (not involving a drug), in addition to SHIELD-HD mentioned above, that are of great importance for understanding HD and identifying new aspects of HD biology to focus on for future drug development.

ENROLL-HD is an observational study for HD families that monitors how HD appears and changes in people over time. Through a better understanding of HD, scientists hope they might learn how to make better medicines for HD.

HDClarity is a cerebrospinal fluid collection initiative to facilitate therapeutic development for Huntington's disease. Researchers use the exact same methods to collect spinal fluid from participants all over the world, and these samples provide a window into how the nervous system is affected by HD.

Other academic groups are performing observational research to study HD progression (such as ***PREDICT-HD***) and youth with HD or at-risk for HD (such as Iowa ***ChAnGE-HD***). Many groups are conducting small local trials on tools to study HD such as new imaging methods or questionnaires, surveying families and professionals on communication styles or genetic testing experiences, developing interventions to improve quality of life such as

physical therapy and speech pathology regimens, or testing existing drug combinations or alternative therapies to improve side effects or sleep. This research is on a smaller scale but could yield new ways to improve outcomes and quality of life for people affected by HD.

More updates are imminent - watch this space!

As you can hopefully appreciate, despite recent setbacks, the landscape of HD therapeutics is rich with new ideas and approaches. Even more companies and research groups, not mentioned here, will be presenting exciting science and preclinical data at the CHDI conference, beginning tomorrow. We look forward to bringing you even more updates as we hear from members of industry, academic scientists, and clinicians this week.

Rachel Harding has no conflicts to declare. Leora Fox works at the Huntington's Disease Society of America, which has relationships and non-disclosure agreements with the companies mentioned in this article. For more information about our disclosure policy see our FAQ...

GLOSSARY

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

huntingtin protein The protein produced by the HD gene.

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

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

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

anti-sense the half of the DNA double-helix that is mostly used as a backup, but sometimes produces message molecules

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

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.

manifest after HD diagnosis, or when symptoms are already showing

somatic relating to the body

chorea Involuntary, irregular ‘fidgety’ movements that are common in HD

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

cohort a group of participants in a clinical research study

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

messenger RNA A message molecule, based on DNA, used by cells as the final set of instructions for making a protein.

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

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
