A spoonful of branaplam helps the huntingtin go down

Branaplam was originally designed to treat spinal muscular atrophy, but a new paper outlines how it could hold promise for treating Huntington's. This oral drug lowers huntingtin protein and will now be tested in a study called VIBRANT-HD.

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Scientists at Novartis and The Children's Hospital of Philadelphia have recently published a paper detailing how the drug branaplam, originally developed for the neurological disease spinal muscular atrophy (SMA), could be repurposed to treat Huntington's disease. Branaplam can lower levels of the huntingtin protein and is now being tested in the clinic in a phase IIb study, VIBRANT-HD.

Huntingtin-lowering therapies are being pursued by lots of companies

Despite setbacks with some recent clinical trials, many experts in the field agree that huntingtin-lowering remains an attractive strategy for treating HD. Every person with HD has an expansion in their huntingtin gene which means they will make an expanded form of the huntingtin protein. This expanded form of the protein seems to be toxic and is thought to cause to the signs and symptoms of HD. If we can reduce the amount of this toxic form of the protein, researchers hope we might slow or stop the progression of HD.

Lots of companies are working on huntingtin-lowering therapies, racing to see if their drug will help slow or halt symptoms for people with HD

Lots of companies are testing huntingtin-lowering drugs in the clinic, including Roche, Wave Life Sciences, and uniQure, all of whom are using slightly different approaches to target the genetic message which is made into the huntingtin protein. The drugs they have developed cannot easily spread through the body, so they are given to patients through spinal tap or direct injection into the brain. While this means the drug can get to the parts of the body most badly affected by HD, these procedures are demanding for patients and very expensive. These are also not treatment options which could be trivially rolled out to the global community of people with HD due to healthcare access issues and prohibitive costs.

Repurposing an SMA drug to try to treat HD

What scientists call “small molecule therapies” are an attractive option to treat diseases affecting the brain. This type of drug can often be formulated so it can be taken orally as a pill or syrup, which is much easier for patients, and these drugs have a better likelihood of crossing from the bloodstream into the brain so patients can avoid onerous procedures. For a long time, it was a pipedream for many folks in the HD community that a small molecule huntingtin-lowering therapy could ever be made and then, two independent companies did just that! Very similar drugs developed by both Novartis and PTC Therapeutics can lower huntingtin – we recently wrote about a paper which describes the PTC drug on HDBuzz. Now we have more details about the Novartis drug, called branaplam.

Branaplam targets machinery in our cells which processes genetic messages, called splicing machinery. Each genetic message can be thought of like a story book, and when the story is over, the final part of the message reads the genetic equivalent of “the End” to tell the cell that the sequence for that message is complete. Drugs like branaplam rejig the pages of the story book so “The End” is read before it makes sense. When this happens, the cell will destroys the message and won’t make the associated protein, similar to how you might get rid of a book that had a premature ending which made no sense.

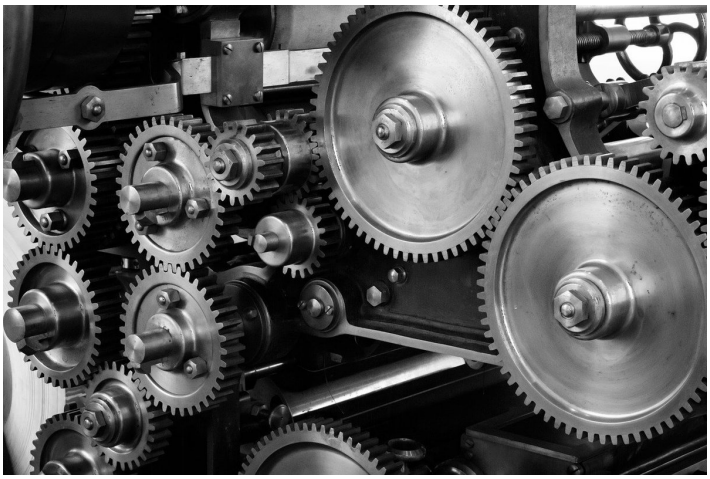
> **“For a long time, it was a pipedream for many folks in the HD community that a small molecule huntingtin-lowering therapy could ever be made and then, two independent companies did just that! ”**

Branaplam was originally developed for a fatal childhood disorder called SMA because it also changes the levels of a protein called SMN2, which underlies that disease. Scientists at Novartis discovered that branaplam also changed the levels of the huntingtin protein so switched gears to test if branaplam would be a good treatment for people with HD and have now published their findings which we’ll digest for you here.

Working out how branaplam lowers levels of the huntingtin protein

First, the research team treated cells in a dish with branaplam and looked at how the genetic messages in the cells were affected. They found that a signature in the huntingtin genetic message, which is normally chopped out by the splicing machinery, called a pseudoexon, was kept in the message molecule in branaplam treated cells. The scientists went on to show that this reduced the amount of the huntingtin genetic message because keeping in the pseudoexon genetic code, targets the huntingtin message to the trash bin of the cell. When the branaplam treated cells were no longer treated with the drug, this effect was reversed, and the levels of the huntingtin message bounced back to normal.

Whilst changes to the huntingtin message are a good sign, what we are really interested in is the levels of the huntingtin protein. The team measured huntingtin protein levels when different amounts of branaplam was dosed in cells in a dish and showed that the more drug was given, the more the level of huntingtin protein was lowered. The team next tested if this finding held true for cells in a dish derived from people with HD i.e. folks who have the Huntington's disease mutation. They showed that the levels of huntingtin message and protein were also reduced by branaplam in these cells too.



Branaplam targets machinery in our cells which processes genetic messages, called splicing machinery

Insights from branaplam in HD animal models and SMA patients

Next, the scientists went on to see how branaplam performed in a mouse model of HD. Mice were given different oral doses of branaplam and then the levels of the huntingtin message were measured in different areas of the brain. In four different brain regions, they showed that the level of the huntingtin message including the pseudoexon was increased the more drug that was administered. This was matched by a decrease in the levels of the huntingtin protein. The scientists found that if mice were no longer treated with branaplam, the effect was reversed and huntingtin levels bounced back.

Lowering the levels of huntingtin is all well and good, but what the research team really wanted to know is if this improved symptoms in the HD mouse model. Next, they tested the motor skills of the HD mice who had been treated with branaplam and compared them to HD mice which hadn't be treated as well as regular lab mice. The scientists suggest that the branaplam treated mice are more like the regular mice but the presented data is fairly limited.

The team finally looked at the levels of the huntingtin message in blood from branaplam treated SMA infant patients. Patients in the open-label extension of the SMA branaplam trial received weekly doses of branaplam for over 2 years. After over 900 days, a sustained decrease in the levels of the huntingtin message in these blood samples could still be seen, showing ~40% decrease at this timepoint in the study. The Novartis team believes this indicates that the drug was having the desired effect over a long period of time in people.

> **"The next step for branaplam is a phase IIb study called VIBRANT-HD; this will be the first time branaplam is tested in adults with HD "**

What's next for branaplam?

We recently heard from scientists at Novartis at the recent CHDI therapeutics meeting who gave us updates on their branaplam program. Dr Beth Borowsky gave us details of a now completed phase I study, where the drug was tested for the first time in adults to figure out a safe amount and frequency of dosing. As branaplam was originally developed to treat SMA in infants, figuring out a safe dose for adult patients is an important first step.

The next step for branaplam is a phase IIb study called VIBRANT-HD. This will be the first time branaplam is tested in adults with HD and this study will work out what dose of the drug needs to be administered to lower huntingtin. Branaplam will be given as an oral liquid, like cough medicine, that people in the trial will drink once a week. Different patients will be given different doses of branaplam so Novartis can work out what dose will work best for a second phase of the trial. Lots of different clinical measurements will be collected from participants in the trial, including levels of various biomarkers, like huntingtin and neurofilament. Recruitment for this trial is underway and hopefully we'll hear updates on how the trial is proceeding soon.

The authors have no conflicts to declare For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.
therapeutics treatments
splicing the cutting up of RNA messages, to remove non-coding regions and join together coding regions.