Oral drug may change the story for huntingtin lowering

Researchers with PTC Therapeutics recently published exciting new findings - a promising new huntingtin lowering drug that can be taken as a pill. Will this change how we move forward with huntingtin lowering?


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Huntingtin lowering has gained lots of attention in HD research, and for good reason. It was the first potential treatment designed to directly target the cause of HD – the huntingtin protein. But there are limitations to current huntingtin lowering approaches: they require delivery to the spinal fluid or brain surgery for delivery, can show limited distribution within the brain, and don't cross the blood-brain barrier (which is why they require a lumbar puncture or brain surgery). They also don't reduce huntingtin outside of the brain in "peripheral" tissue.

Scientists from PTC Therapeutics recently published their work in the prestigious journal Nature Communications describing a series of drug molecules that lower huntingtin which can be taken orally, and show distribution throughout the brain and body. These are results that would have sounded like science fiction even 5 years ago. But in a post-2020 world, wonders never cease! So let's dive into what their data show and what it means for huntingtin lowering.

Needle in a haystack

PTC started by screening a huge library of molecules – around 300,000 different ones! They tested each of these molecules on cells derived from HD patients. This is a promising first pass for identifying molecules of interest because it screens molecules for effects they'll have in cells from humans. Often times, drugs don't work the way scientists thought they would if studies are only done in animal models before being tested in people. First looking in human cells suggests the drug molecules will have the intended effect in the only organism we're most interested in – people.

Finding HTT-C2 was like finding a needle in a haystack. HTT-C2 is not only able to lower huntingtin, but it can also be taken as a pill and crosses the blood-brain barrier – traits that make this drug seem almost too good to be true.

Changing the message

From those 300,000 molecules, PTC's scientists narrowed in on two promising molecules that were able to lower huntingtin in human cells. Both molecules are "splice modulators", meaning that they can lowers huntingtin levels by changing the way the message that produces the huntingtin protein is read. The scientists at PTC went on to analyse these molecules in different experiments, and also looked at a very similar molecule they called HTT-C2.

You can think of each gene like a story book. When the sequence for the gene, or story, is over, the final part reads "The End" to signal to the cell that the sequence for that gene is complete. These splicing modulators work by moving the last page up, so the story reads "The End" before the end of the sequence. Because the story no longer makes sense, the cell destroys that message and doesn't make the associated protein. Just like you would toss a book that made no sense with a premature ending and read, "Once upon a time, The End".

Selective targeting of huntingtin

One drawback of splicing modulator drugs like those PTC identified, over other approaches that are specifically designed to only target the huntingtin sequence, are “off-target effects”. Drugs like HTT-C2 can also change where “The End” is placed in other genes. But the good news is that HTT-C2 seems to primarily affect huntingtin over other genes at low doses. When experiments were done to examine all the genes in treated cells, widespread effects weren’t observed even at dose levels far higher than would ever be used. This suggests that HTT-C2 is surprisingly able to discriminate between just the huntingtin gene, despite the potential to alter levels of other genes.

Effects are adjustable and reversible

But all the previous experiments were done on cells in a dish. What happens when you give HTT-C2 to an entire organism? Does it have the same effect? Can it lower huntingtin in the brain? To answer those questions, PTC’s researchers turned to mouse models of HD.

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Mice were fed HTT-C2 every day. Yes, you read that correctly – the mice were given this drug orally. This is a huge difference from previous huntingtin lowering therapeutics! For those who have followed the huntingtin lowering field, previous therapeutics have required either lumbar puncture or brain surgery, neither of which are ideal. This new type of approach, that accomplishes huntingtin lowering with a pill, could be a game changer for patients who have been hesitant about more invasive treatments.

Encouragingly, the more HTT-C2 the mice were given, the more huntingtin was lowered. This is great news because it suggests HTT-C2 dosage can be actively adjusted to change how much huntingtin is lowered. We don’t yet know how much total huntingtin should be lowered in people to produce beneficial effects without being harmful, so this is a massive safety advantage – if huntingtin isn’t lowered enough, more drug can be given, and if huntingtin is lowered too much, the dose can be reduced.

Another exciting finding is that the effects of HTT-C2 were quickly reversible. Just 10 days after treatment stopped, huntingtin levels returned to that which was observed prior to treatment. This is another major safety advantage – the “washout” of this drug is very fast, meaning the time it takes for the drug to leave a patient’s system will be relatively quick. If a negative consequence is observed after HTT-C2 is given, the effects can be quickly reversed. However, 10 days is the washout timeline in mice and this will likely be different in people.

Reduces huntingtin in the brain and body

HTT-C2 treatment targets both the expanded and unexpanded copies of huntingtin, unlike current ASO-based approaches by Wave Life Sciences that will only target the expanded copy. Because the unexpanded huntingtin copy is still needed to carry out its normal jobs inside cells, it's important to track how much of both copies are being lowered.

Splice modulators change the genetic story – they move the ending up so it no longer makes sense to the cell. The same way we would throw away a book that said "The End" half way through, the cell degrades the genetic message that no longer makes sense.

When researchers looked at the brains of HD mice dosed withHTT-C2, they saw about 50% reduction of both expanded and unexpanded huntingtin throughout the whole brain. This included in regions most sensitive to HD, which suggests HTT-C2 is having an effect in the areas where it's needed most.

Huntingtin is expressed in all cell types of the body, not just the brain. So while we know about the effects of HD in the brain because changes there control the most apparent parts of the disease like mood changes and chorea, there are also effects in other tissues like the heart and muscles. Because of this, it may also be beneficial to lower huntingtin in all tissues, not just the brain.

When the authors assessed how much HTT-C2 lowered huntingtin in tissue outside of the brain, they found it was actually much higher than in the brain – it was lowered over 90%! While research suggests a 50% reduction would be tolerated, 90% is likely too much.

For safety reasons, the researchers at PTC further tweaked the drug by changing the chemical structure – resulting in another a drug they called HTT-D3. When given to mice, HTT-D3 showed huntingtin lowering in both the brain and body to equal levels of around 50%.

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What's next for splice modulators in HD?

Splice modulators are an exciting new approach for huntingtin lowering. Encouragingly, a similar drug called risdiplam has already been granted FDA approval and is currently being used to treat another neurodegenerative disease, spinal muscular atrophy. This strengthens the possibility that something similar can be used to treat HD.

While HTT-D3 was used as a proof-of-concept drug in this paper, PTC Therapeutics is moving forward with a different drug discovered using their pipeline. This drug is called PTC-518. The Phase 1 safety trial for PTC-518 in non-HD individuals is ongoing, but interim results suggest the trial is going well. So far, the drug has been well tolerated with no adverse events. Huntingtin is being engaged by the drug and expression is being reduced in a dose-dependent manner, similar to what was observed in mouse models. Their Phase 2 trial in HD patients is planned to start by the end of 2022.

Splice modulators, like HTT-D3 from this paper and PTC-518 from PTC's drug discovery program, seem to check all the boxes – they lower huntingtin both inside and outside of the brain, they can be taken orally, they bypasses the blood-brain barrier, and they're selective for huntingtin. In a year of tough news for HD research, it almost seems too good to be true. But right now the data looks very promising and the HD community is eager for some promising news.

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

GLOSSARY

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.

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

therapeutics treatments

splicing the cutting up of RNA messages, to remove non-coding regions and join together coding regions.

chorea Involuntary, irregular 'fidgety' movements that are common in HD

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