

GPR52: Exploring a new way to lower huntingtin

A Chinese research team developed a new way to lower huntingtin protein indirectly, by targeting a protein called GPR52. The molecules they designed were protective in cells and in mice with HD.

By Dr Rachel Harding February 11, 2021 Edited by Dr Leora Fox

Scientists have found new leads for how to reduce the levels of the Huntington's disease (HD) protein by targeting a protein called GPR52. A team of researchers working in Shanghai, China developed small drug-like molecules which lower huntingtin protein levels in HD tissue culture models and in HD mouse models. Treatment with their molecules was also shown to improve the HD mouse symptoms.

New avenues for huntingtin lowering

Huntingtin-lowering therapies are heralded by many researchers and clinicians as a very promising avenue for treatment of HD. People with HD have a longer or expanded CAG number in their HD gene, *huntingtin*. This means that throughout the body and brain they make a different, longer form of the huntingtin protein. This expanded protein is thought to be responsible for many of the symptoms we observe in people with HD.



GPR52 is part of a family of proteins called G-protein coupled receptors that sit on top of cells and receive messages, like a satellite dish.

The idea of huntingtin-lowering therapies is that if you reduce expanded huntingtin, you might also get rid of its toxic effects. There is evidence in lab HD models that huntingtin-lowering can slow or improve HD symptoms, but we await the results of ongoing clinical trials before we can be sure that the same effect will be observed in patients.

As many HDBuzz readers probably know, there are already lots of different companies and academics working on huntingtin-lowering either in the lab or the clinic. We have profiled many of these companies recently and you can read the latest updates on how their therapies are progressing in [this article](#) and [this article](#). Many companies at the front of the field such as Wave, uniQure and Roche are using genetic approaches such as gene therapy or antisense oligonucleotides, which are very large molecules. They must be administered directly into the brain or spinal cord in order to reach the nerve cells in our brains that are most affected by HD. Other companies are working to find “small molecules” which might also lower huntingtin levels. The hope is that small molecule huntingtin-lowering therapies could be taken as a pill, making them more accessible to patients.

What has GPR52 got to do with huntingtin lowering?

GPR52 is part of a family of proteins called G-protein coupled receptors that sit on top of cells and receive messages, similar to a satellite dish. These types of receptors are commonly targeted by FDA-approved drugs. This gives scientists optimism that using new medicines to target members of this receptor family, like GPR52, could be safe and effective.

GPR52 was first identified by scientists as a protein of interest for HD in a genetic screen. A genetic screen can be thought of as a scavenger hunt, where scientists look at different genes one-by-one to see how they might, in this case, change signs of HD. Scientists then used genetic tricks in the lab to delete the GPR52 gene or to lower the levels of GPR52 protein, and this helped to improve signs of HD in cells and flies. A team of researchers in Shanghai, China, recently took this one step further and tried reducing the levels of GPR52 in mice. In this recently published research, they show that reducing GPR52 reduces the levels of huntingtin, indicating that GPR52 would be a good candidate to target with small molecules for huntingtin-lowering therapies.

Targeting GPR52 with small molecules lowers huntingtin and improves symptoms in HD lab models

The scientists describe the development of small molecules which stick on very tightly to GPR52 but not other proteins in our cells. These type of properties of a small molecule suggest that down the road this potential therapy could be very specific and avoid other

unwanted effects. The best or lead molecule identified in this study, called Comp-43, was then used in a variety of different experiments to test how well it worked for huntingtin-lowering and reducing signs of HD-related damage and improving behaviour.



Mice treated with Comp-43 had improved symptoms when tested on laboratory tasks that measure their movement and coordination.

Image credit: [Derek Traynor](#)

They first showed that Comp-43 could reduce huntingtin levels and preserve the health of mouse nerve cells in a dish. Following this exciting result, the scientists went on to test Comp-43 in HD mice. Critically, Comp-43 could cross the blood brain barrier in mouse models and lower huntingtin levels in some brain regions. This suggests that if Comp-43 was developed into a medicine in the future, people with HD might take it as a pill. Mice treated with Comp-43 had improved symptoms when tested on laboratory tasks that measure their movement and coordination, like a log-rolling exercise called the Rotarod or their ability to cross a balance beam. They also showed that mice treated with Comp-43 had more and healthier brain cells.

So, what's next for GPR52 in HD research?

All of the data available in the literature to date indicates that GPR52 is a very promising drug target for huntingtin-lowering therapies but there are still many hurdles to cross before we are treating patients with GPR52 targeting molecules. Many therapies work well treating HD in cells in a lab dish or in different animal models of HD but don't necessarily go the distance in safely treating people with HD.

It is not yet apparent what additional effects targeting GPR52 might have, beyond changing huntingtin levels and HD symptoms. GPR52 has important jobs to do in our nervous system and may play a role in dopamine signalling, chemical messages that affect mood, movement, and motivation. Sustained targeting on GPR52 by this type of huntingtin-lowering therapy might have side effects which we just haven't yet observed in the shorter treatment experiments completed to date.

It should also be noted that targeting GPR52 lowers the levels of both normal and expanded huntingtin. We know that targeting both forms of the protein with other therapies such as Roche's tominersen, which is also non-selective, is safe in the trials completed to date, but targeting expanded huntingtin while preserving normal huntingtin is still the goal for many researchers.

Nonetheless, small molecule targeting of GPR52 represents an exciting new way to lower huntingtin levels and we expect to see answers to many of these outstanding questions in future studies.

Dr. Leora Fox works at the Huntington's Disease Society of America. HDSA has relationships and nondisclosure agreements with pharmaceutical companies such as Roche, which is mentioned in this article. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

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

huntingtin protein The protein produced by the HD gene.

dopamine A signaling chemical (neurotransmitter) involved in movement control, mood and motivation

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

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