Beyond huntingtin lowering: out-of-the-box approaches for the treatment of HD

The HD pipeline is rich and varied. Let's talk about some out-of-the-box approaches for developing drugs for HD that don't involve huntingtin lowering.

By Kelly Andrew | November 24, 2023 | Edited by Dr Leora Fox and Dr Rachel Harding
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In recent years, HD research headlines have trended toward huntingtin lowering: experimental therapies that target the root genetic cause of HD. But there are also several drugs in development to treat HD that do not aim to lower huntingtin. Some of these are aimed at managing individual symptoms of HD, like managing involuntary movements, or improving cognition. Others take more preventative approaches, like preserving the health of brain cells or slowing down the expansion of CAG repeats in the huntingtin gene.

Beyond huntingtin lowering

HD is caused by an expansion in one section of the huntingtin gene, so cells produce an extra-long form of the huntingtin protein. Expanded huntingtin proteins are believed to be toxic, especially to the brain cells responsible for control of mood, movement, and memory. Naturally, this has made lowering the amount of expanded huntingtin in the brain and body a major priority of efforts to treat HD.

All of our metaphorical HD research eggs are not just in one basket...

Despite trial failures that have rocked the HD community in recent years, huntingtin-lowering remains a viable approach to treat HD, and dozens of companies and academic labs are working to make this an accessible reality. However, all of our metaphorical HD research eggs are not just in this one basket.

As novel science weaves a broader understanding of HD biology, potential new avenues of treating the disease are coming into focus, and there are dozens of companies and academic labs working to develop these strategies into accessible realities, too. In this article, we'll explore some of these approaches to treating HD.

Targeting cholesterol

Cholesterol is a type of fat molecule found throughout the body. You're probably familiar with its roles in heart health or hormone production, but you may not know it is especially important for the health of connections between cells in the brain. Maintaining optimal levels of cholesterol in the brain is tricky; cholesterol molecules are large, and it is difficult for them to pass freely between the brain and the blood that circulates through the rest of the body. A special enzyme, CYP46A1, helps eliminate excess amounts of cholesterol in the brain, but it can stop working properly in Huntington's disease.

Asklepios BioPharmaceutical (AskBio) is developing an experimental gene therapy that targets this enzyme. AskBio's drug, AB-1001, is delivered directly to brain tissues in a single dose on each side of the brain with an MRI-guided brain surgery. AB-1001 tells the body to produce more CYP46A1 to help restore a better balance of cholesterol in the brain.

AskBio hopes that repairing this cholesterol pathway will support the overall health of neurons, and could also help the brain lower its own levels of mutanthuntingtin protein without affecting levels of healthy huntingtin. Currently, this drug is being studied in a small group of people with HD in a Phase I/II trial in France that began at the end of 2022. While there is no news yet as to the drug's safety or efficacy, the results of this safety study will determine whether a larger trial will take place.

Preserving connections between brain cells

Synapses are the connections between brain cells that allow them to communicate. Sometimes these connections stop working as well as they should, and a part of the immune system, called complement, gets rid of them. This process, called synaptic pruning, is especially important in early phases of brain development, but occurs throughout a person's life.

It's a bit like trimming back an overgrowing shrub in a garden that might block sunlight or monopolize nutrients from surrounding plants. A complement protein called C1q attaches itself to declining synapses, causing them to be cleared, to make sure healthy synapses can continue to do their job effectively.

In HD, C1q proteins become overactive and can tell the rest of the complement system to begin breaking down healthy brain cells instead of damaged ones. If C1q protein levels could be managed, it might help preserve healthy synapses for longer to support the brain's

resiliency against the onset of HD. The company Annexon has been developing an experimental therapy to block C1q and calm over-activity in the complement system.

ANX-005 is an antibody therapy that is delivered with an IV; in 2022, a Phase II trial was completed to check its safety and efficacy in people with HD. The study didn't have a placebo group to compare the effects of ANX-005 to the natural progression of HD, so the results are a bit difficult to interpret. However, the findings indicate that HD symptoms were stabilized in some participants, particularly those who started out with a more active complement system. Annexon is planning for a larger, placebo-controlled Phase II/III study to begin in 2024.

> **"A major goal of HD research is to find options to slow or stop the disease in its tracks. Another important objective is to help people with HD maintain independence and quality of life for longer by managing symptoms. "**

Slowing somatic expansion

DNA is constantly being pulled apart and put back together again to be used as a blueprint to make message molecules, called RNA, which in turn encode proteins. Our cells perform these tasks nearly 2 trillion times per day—they literally have it down to a science. This also means that there are plenty of opportunities for mistakes. Our bodies plan for this, and have machinery to detect and fix errors: DNA mismatch repair proteins.

Certain stretches of DNA pose an extra challenge for these auto-correct proteins. In people with HD, DNA mismatch repair proteins are more prone to slip on the extra CAG repeats in the huntingtin gene, like a needle might get caught on a scratch in a record. Sometimes this results in even more CAG repeats– especially in the cells of the striatum, the part of the brain that controls movement and mood.

This tendency for the expanded stretch of the huntingtin gene to grow over time is called somatic instability. While some cells are more prone to CAG repeat expansion over time, like in the brain or liver, this phenomenon is less likely to occur in other types of cells, like those in our blood. This means that the results of a person's genetic blood test wouldn't be changed over time by somatic instability.

Some scientists think that as CAG repeats in huntingtin gene grow longer, the resulting huntingtin proteins become even more dysfunctional and toxic. Scientists are still understanding what this means, but it is believed that somatic expansion contributes to the death of brain cells in HD, making it a key therapeutic target to treat the disease.

LoQus23 and Pfizer are researching drugs to slow or stop somatic expansion in the mutated stretch of the huntingtin gene with the goal of slowing or stopping the progression of HD. While still in early stages of development, they are targeting some of the proteins involved

in DNA mismatch repair to accomplish these aims, and many more companies and academic researchers have an interest in pursuing HD treatments related to somatic instability.

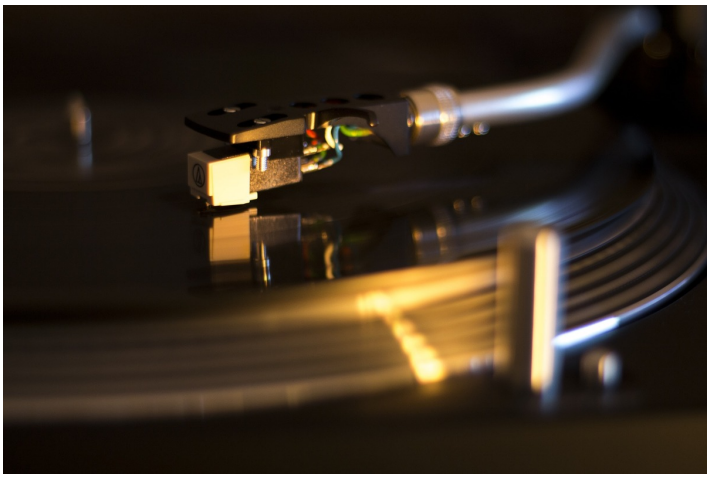
Managing movements

A major goal of HD research is to find options to slow or stop the disease in its tracks. Another important objective is to help people with HD maintain independence and quality of life for longer by managing symptoms of the disease. One approach to this is reducing the involuntary movements that are common in people with HD, chorea. These movements may not be bothersome for some, but others may find chorea disruptive to day-to-day activities or safety.

There are currently three drugs available for treating HD chorea. Each is taken by mouth and employs similar drug chemistry to manage involuntary movements. Xenazine (tetrabenazine), Austedo (deutetrabenazine), and INGREZZA (valbenazine) all limit the activity of VMAT2 proteins. These proteins act as transport vehicles for the chemical messages that are passed between brain cells, especially dopamine. Dopamine plays a role in movement, and managing its levels in the brain can help minimize chorea.

While these three drugs are similar, and there are additional drugs that doctors may prescribe for movements alongside other HD symptoms, having options to manage chorea is a good thing. One drug may be preferable over others for a variety of reasons, including cost, dosage, and frequency. HDBuzz recently wrote about the FDA approval of INGREZZA in the United States in August 2023, as well as the other chorea-management medications currently available for people with HD. You can read more about that here.

Improving function



DNA mismatch repair proteins are more prone to slip on the extra CAG repeats in the huntingtin gene, like a needle might get caught on a scratch in a record.

Image credit: Webster2703

Early signs of HD often include slight disruptions in someone's ability to perform day-to-day activities, such as handling their finances, remembering directions, and managing household chores. HD clinicians often use a rating scale to measure "Total Functional Capacity" (TFC), which encompasses many aspects of someone's capacity to live and function independently. Maintaining TFC for longer could improve quality of life for people by preserving their independence.

Prilenia has been testing a drug to support total functional capacity in people with HD. Pridopidine, which is taken by mouth, has been studied in humans for more than a decade, but no large trial has met its goals of slowing the progression of HD. Pridopidine activates a protein called the sigma-1-receptor, which helps brain cells survive under stress.

The latest study of pridopidine, PROOF-HD, wrapped earlier this year, but the results are somewhat unclear. Pridopidine has a good safety profile, but was not found to effectively improve total functional capacity or movement symptoms in people with HD. The drug may have been helpful for the first year in some participants, those who were not taking certain medications that alter dopamine. Prilenia is continuing to analyze the data, and to conduct additional research to interpret these results.

Improving cognition

NDMA receptors are critical for tasks like combining and linking memories, multitasking, and effective decision making—functions that all fall under the umbrella of cognition. Sage Therapeutics is also hoping that their drug will improve early changes in these thinking abilities for people with HD. Their drug, SAGE-718, is designed to increase activity of NMDA receptors to preserve cognition in people with HD.

A small, early clinical trial showed some promising results in people with HD. Sage is now studying the drug's safety, efficacy, and effects on cognitive performance in a series of Phase II trials called the PERSPECTIVE program. Two of these trials are currently recruiting participants in North America; while similar, they have different goals.

The DIMENSION study investigates the safety and efficacy of SAGE-718. The SURVEYOR study also assesses safety and efficacy, and evaluates the drug's effects on tasks of daily living. The study protocol includes virtual reality simulations of things like cooking a meal, using transportation, shopping, or managing money, as well as an optional driving simulation.

Looking forward

Huntingtin-lowering therapies have dominated the HD-research landscape, but this is one among many approaches to treating HD. New paths to treat HD are being uncovered and explored all the time. This is one reason why observational research studies like Enroll-HD

are so important; the greater our understanding of HD biology, the better our understanding of how to treat it, and the more drug targets are revealed to fight the disease and manage its symptoms.

While all cases of HD result from a single gene, this doesn't mean that every person's symptoms will progress in the same way. In an ideal world, there would be multiple strategies available to treat and slow HD that could be attuned to an individual's symptoms and genetics. More tools in the toolbox is a good thing, and the treatment strategies described in this article are only a handful of the possibilities currently in the HD research pipeline from a few of many companies working to bring options to HD families.

Kelly Andrew and Leora Fox work at the Huntington's Disease Society of America, which has relationships with all of the companies mentioned in 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

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

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

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

efficacy A measure of whether a treatment works or not

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

neuron Brain cells that store and transmit information

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't work.

hormone Chemical messengers, produced by glands and released into the blood, that alter how other parts of the body behave

somatic relating to the body

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

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

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