From gene to treatments

The gene that causes Huntington’s disease (HD) was discovered in 1993. Since then, enormous progress has been made in laboratories throughout the world in understanding how the gene, and the abnormal protein it produces — huntingtin — cause brain cells to malfunction and die, causing the symptoms of HD.

Treatments that slow down the disease in humans are still several years away, but the progress that has been made is very promising. The HD research community has expanded and organised dramatically, and there is much more funding available for HD research than there used to be. We believe a cure is possible, and we are united in working towards it.

Hope for disease-slowing treatments

In the past few years, our increased understanding of how the HD gene causes disease has led to laboratory studies of HD animal models, in which experimental treatments have been shown to slow down the damage caused by HD — and even reverse it.

Many possible treatments for HD are being developed. They are at different stages of development — some are very early in laboratory models of HD, while others have already been tested in HD patients.

This leaflet explains the latest and most promising approaches to the development of treatments for HD.

Improvement in a model of HD

If the HD gene is “switched off” in a mouse model of HD — even after clinical signs develop — improvement can be seen in brain cells and clinical signs. This gives us reason to believe that, if we can introduce successful treatments in humans, patients may improve clinically, even after they have begun to experience symptoms of HD.
Gene silencing therapy

The HD gene (which is made from DNA) is like a recipe for the huntingtin protein. When the gene is switched on (transcription), a messenger molecule called mRNA is produced before the protein is built by the cell (translation).

Gene silencing therapy is already used successfully in human patients in other diseases.

One major problem with gene silencing is getting the molecules where they are needed. RNA and DNA molecules don’t enter the brain easily, and getting them to spread through the whole brain is difficult. New methods of designing the molecules have improved the efficiency of spread through the brain, and there are now devices that can deliver drugs directly into the fluid surrounding the brain.

Using these techniques, researchers have recently been able to slow down the progression of HD in mouse models. Gene silencing is very promising in HD because, unlike in many other diseases, the exact genetic cause of HD is known. Switching off the HD gene may be a relatively simple way to prevent the many things that the mutation causes to go wrong in cells.
Before it can be tried in humans, gene silencing therapy needs to be tested in HD model animals that have brains as large as a human brain, to test whether the combination of new molecules and new delivery techniques can get the treatment to where it is needed. It will probably also need refining to minimise any side effects of switching off the gene.

**Cystamine & cysteamine**

These drugs decrease the activity of a group of enzymes called transglutaminases. These enzymes are thought to be involved in the formation of huntingtin aggregates — the lumps of protein that are seen in unhealthy brain cells in HD. Cystamine is converted into cysteamine by the human body. Cystamine has been tried in mice with HD and shown to slow down progression and improve movement. A trial of cysteamine was carried out in humans, and showed that it was tolerated quite well, but the trial was too small to tell whether the treatment slows down the disease. More trials are needed.

**Autophagy enhancers**

Autophagy is a clearance process that cells use to get rid of unwanted proteins. HD researchers think that the abnormal protein in HD, huntingtin, is disposed of using autophagy. Looking for drugs that make autophagy happen more efficiently might help cells get rid of huntingtin and live longer. Rapamycin belongs to a group of drugs called mTOR inhibitors, which activate autophagy, and it has been shown to slow down HD in a mouse model. However, rapamycin causes lots of side-effects in humans and when tested in patients, it was not shown to be effective. HD researchers looking for more efficient, less toxic activators of autophagy have identified several drugs that might be better than rapamycin, and these now need testing in animal models of HD.

**Inflammation and the KMO pathway**

Microglia are the brain’s immune system cells, like white blood cells that protect the body against infections. Our own research has shown that the immune system is overactive in HD, and evidence is mounting that microglia are overactive, too. HD researchers have shown that KMO, an enzyme found in microglia, can affect how fast HD progresses. Researchers are now working on drugs that will switch off KMO, reducing the damage microglia do to brain cells, and preliminary results have shown that KMO inhibitors may be effective at slowing down the damage done by HD in mice.
**HDAC inhibitors**

HDAC (histone deacetylase) is an enzyme involved in regulating which genes are switched on and which are switched off — a process known to malfunction in HD. Drugs called HDAC inhibitors — in particular one drug called SAHA — have been shown to be effective in slowing down the cellular damage in HD, and HD mice treated with SAHA have less severe disease. However, HDAC inhibitors, which are sometimes used to treat cancer, are toxic drugs with serious side effects. Researchers are looking for more effective HDAC inhibitors with less severe side effects, to try in humans.

**Memantine**

In some neurodegenerative illnesses, some of the damage is thought to be caused by too much stimulation of brain cells by incoming transmitter chemicals. This is called excitotoxicity. It is not clear whether excitotoxicity is to blame for any of the cell damage in HD, but it is a possibility. Memantine is a drug sometimes used to help the memory symptoms of Alzheimer’s disease. It prevents excessive stimulation by a transmitter chemical called NMDA. Memantine has been suggested as a possible therapy for Huntington’s disease, to help with the symptoms and possibly to slow down the disease process. A couple of small studies have been performed, but so far the evidence on memantine is inconclusive. Further studies are going on in the USA into whether memantine is helpful in HD.

**Caspase inhibitors**

In cells, the abnormal HD protein (huntingtin) is cut into smaller proteins by enzymes called caspases. Some of the smaller fragments that are produced by this are more damaging to cells than the original full-length huntingtin. So, by turning off the caspases, the dangerous huntingtin fragments might be prevented from forming. Minocycline is a drug that acts as a caspase inhibitor. Initially there was some optimism that minocycline might help in HD but so far no double-blinded, controlled trial (the most reliable kind of clinical trial) has shown evidence that minocycline is helpful in HD, but these clinical trials are underway.

There are 11 types of caspase, and caspase 6 is thought to be the one that generates the most toxic huntingtin fragment. Work is underway to develop and test inhibitors of caspase 6 that might be more powerful than minocycline, but with fewer side effects.
p53 pathway

p53 is a cell protein with many functions, but it’s known to be involved in energy production, the response to stress and controlling when cells divide. Recently, it has been shown that p53 accumulates in the brain cells most affected by HD, and that the huntingtin protein and p53 interact with each other. That means that some effects of huntingtin might be due to abnormalities of the p53 pathway — or even that p53 controls levels of abnormal huntingtin. Work is underway to identify targets in the p53 pathway that drugs might be able to alter, so that the negative effects of huntingtin on cells can be minimised.

Apoptosis

Apoptosis is the programmed death of cells — a form of cell suicide — that usually happens when a cell is so damaged, it is likely to do more harm than good by staying alive. Cells in HD patients’ brains are malfunctioning, and do undergo apoptosis, but it’s also possible that the abnormal huntingtin is making cells undergo apoptosis earlier than necessary, so that relatively healthy cells die prematurely. HD researchers are looking for drugs that influence the cells’ decision to undergo apoptosis and help HD cells to live longer.

Transplantation of fetal stem cells

Stem cells are cells that can develop into any kind of cell, including brain cells. They could potentially be used to replace dead or damaged cells in the brains of HD patients. Research into stem cell therapy is difficult, and it is not clear at the moment whether it is a useful treatment in people with HD. In a study in France, 3 out of 5 patients maintained or slightly improved movement and thinking function after the procedure. There have also been promising, but mixed, results in the UK from Cardiff and Cambridge. The treatment involves a major brain operation, so much more study is needed to assess whether it is effective.
Dietary supplements

Creatine and coenzyme Q10 are dietary supplements that may increase the energy efficiency of cells. Research has suggested that a reduced supply of cellular energy may have a role in nerve cell death in HD. These supplements may therefore have some ability to protect brain cells. These treatments are currently being studied in large clinical trials. Whatever the final results, these drugs are at least much less toxic than more powerful drug treatments. LAX101, also known as EPA, comes from fish oil and it was thought that it might protect brain cells against damage in HD. We recently participated in a large international study of fish oil and the overall results showed that it was not effective.

The need for HD biomarkers

Even if we can find promising possible treatments for HD, and get them to where they’re needed, one problem will remain. It is very difficult to determine how effective a therapy is, because our tests are not sensitive enough to pick up significant changes in patients over short time periods.

So, even if a patient was taking a treatment that was effective at slowing down HD progression, we might not be able to detect that slowing from the outside, even over several years.

Some drugs also have direct effects on the symptoms of HD (such as mood, or movements), without actually slowing down the damage to brain cells. If a patient looks or feels better, we can’t tell from the outside whether this is due to actual slowing of the disease, or simply a direct effect on symptoms — an important difference.

So, other markers that could also be used to track disease progression would be very useful — things like blood tests, brain scans or computerised clinical measurements. Monitoring the disease more accurately, in ways that reflect what is happening to brain cells, is crucial for the development of therapies that will slow the disease.

We call these measures biomarkers and at the moment, there is no single test or combination of tests that accurately measures and predicts the progression of HD.
In addition, markers that can detect changes in patients who have the HD gene but do not yet have any symptoms of the disease (carriers), will be essential to decide when to start treatment to delay progression and in monitoring their success.

One of the main aims of our work here in London is the identification of biomarkers that will be used to monitor the success or failure of possible treatments. Our **blood biomarkers project, ICE-HD and LOOK-HD** have been making progress towards finding biomarkers already. We are also participating in the international **PREDICT-HD** study of premanifest gene carriers. Our newest study, **TRACK-HD** aims to study all the possible biomarkers head-to-head in the most comprehensive biomarker study performed to date, to find out which combination of biomarkers is best — so that when HD-slowing therapies are ready to be tested, we will be ready to test them.

**Symptomatic treatments**

As well as all the research that is being done into finding drugs that will slow down the progression of HD, there is already lots that can be done to treat the symptoms. Even though symptomatic treatments may not increase life expectancy, they do often make great differences to patients and improve their quality of life.

Some examples of symptomatic treatments are:

- Drug treatments and other therapies for anxiety, irritability, depression and other psychiatric problems in HD
- Drug treatments to reduce involuntary and unwanted movements
- Physiotherapy, to improve balance, stability and walking
- Treatments and techniques to improve quality and quantity of sleep in HD
- Speech and language therapy, to help with speech and swallowing.

The European Huntington’s Disease Network (EHDN) has a major programme of research into these symptomatic treatments. It aims to establish which treatments and combinations are most effective, in order to develop guidelines to help guide treatment choices in patients with symptoms of HD.
Find out more

Our **UCL HD Clinical Research website** has information on research HD therapies, our own clinical research and HD in general, as well as links to reliable HD sites.

[www.hdresearch.ucl.ac.uk](http://www.hdresearch.ucl.ac.uk)

The **HD Association** provides information, advice and practical support for HD patients, carers and families.

[www.hda.org.uk • 020 7022 1950](http://www.hda.org.uk)

The **Euro-HD Network** is a Europe-wide collaboration of HD researchers sharing information and ideas about HD, studies and possible treatments. EURO-HD also funds and runs clinical studies in HD.

[www.euro-hd.net](http://www.euro-hd.net)

**HD Lighthouse** is a US-based web site with a global focus on presenting and explaining the latest research.

[www.hdlighthouse.org](http://www.hdlighthouse.org)