

## Liftoff: First humans treated with gene silencing drugs for HD!



Major Announcement: First HD patients treated with gene silencing drugs

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*Today brings news that the first Huntington's Disease patients have been successfully dosed with gene silencing drugs targeting the HD gene. These brave volunteers are the first HD patients to ever be treated with drugs designed to attack HD at its root cause, a treatment approach with huge potential. What about this news has us so excited?*

### Gene Silencing

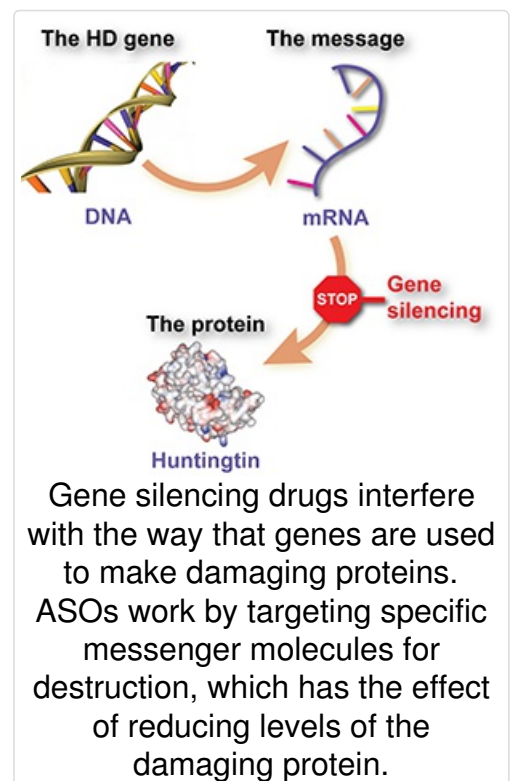
Many HD researchers, including the editors of HDBuzz, believe that a treatment approach called *gene silencing* is the most exciting thing happening in HD research right now. To understand why, we need to cover a little bit of HD basics.

Every HD patient has inherited a mutated version of a gene that we sometimes call the *HD gene*. In scientific circles, the gene is actually called *Huntingtin*, and abbreviated *HTT*, but that can be a bit confusing.

Everyone on earth has two copies of the HD gene, one they inherited from mom and one from dad. In every HD patient, one of these copies has a sort of genetic stutter, a repetitive bit of code near one end of the gene that tweaks the way this gene does its job. This turns out to be bad news - Huntington's Disease is the consequence of this stutter lengthening beyond a critical threshold.

We still don't understand a lot about HD. What the HD gene normally does, why does it have this repetitive stretch of DNA, and what makes it stretch out are questions that we still don't have scientific consensus on.

But what's clear beyond a shadow of a doubt is that every single HD patient has the same type of mutation - a lengthening of the repetitive stretch of DNA in the HD gene. In the code scientists use to describe genetic sequences, the stuttering letters



are abbreviated “C-A-G”, which is why you might have heard of people talking about “C-A-G repeats”.

This genetic certainty is terrifying for family members - if your mom or dad has HD you have an exactly 50% chance of inheriting this awful mutation. But there’s a flip side to this bad news, which is that this certainty gives us a really good target for trying to attack HD. Since every single HD patient has a mutant HD gene, why don’t we just try to get rid of the mutant gene itself?

In previous generations, this would have been like asking someone to reach up into the sky and pluck out your favorite star, but we live in amazing times. It turns out that this kind of thing might actually be possible now because over the last 20-30 years, techniques have been developed by scientists that let us pretty much switch off a given gene at will.

At root, scientists are a curious bunch. As they’ve poked and prodded how cells achieve particular tasks, they’ve uncovered a wide range of ways to shut off certain genes. You might hear about “antisense oligonucleotides (ASOs)”, or “zinc finger nucleases (ZFNs)” or even “transcription activator-like effector nucleases (TALENs)”. The idea behind this zoo of approaches is the same: trick cells into shutting off the HD gene and only the HD gene.

## Isis and ASOs

A wide range of scientists are applying all of the above approaches (and more!) to the problem of shutting off the HD gene. The most advanced program uses a type of drugs called “antisense oligonucleotides”, or “ASOs”. Basically, ASO drugs are short heavily modified bits of DNA that instruct a cell to destroy a particular gene.

Compared to some of the other technologies that turn on or off genes, ASOs have been around for a long time. The company with the most advanced HD gene silencing program is called Isis Pharmaceuticals, which was founded in 1989. For those of us that remember the fall of the Berlin Wall, 1989 might not seem like so long ago, but in the biotechnology world that’s a long run.

The benefit of all this experience is that Isis has a long history in applying ASOs to the problem of human diseases. Versions of their various ASO drugs have been tested in thousands of humans with a wide range of health problems. They’ve also successfully had drugs approved by regulatory agencies like the FDA, so they’ve got a realistic idea of what it takes to get a drug to people.

Luckily for us, Isis has developed an ASO drug they call “ISIS-HTTRx” which targets the HD gene for silencing. Animals treated with the mouse version of this drug show remarkable and important improvements in HD-like symptoms, which has a lot of scientists very excited.

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The success of HD silencing drugs in mice is neat science, but actually running a trial for HD patients is a big and expensive problem. Isis understands that they need partners with deep pockets and even more clinical trial experience to get drugs to patients as quickly as possible. For this reason, they've partnered with pharmaceutical giant Roche to test ISIS-HTTRx as quickly and competently as possible.

## The first HTTRx study

As we recently described at HDBuzz (<http://en.hdbuzz.net/203>), getting drugs approved is a long and complicated process. The first step along the way is what's called a *Phase 1* trial. Any phase 1 study has a single, essential, goal: to make sure that an experimental drug is safe in people. Not mice, not monkeys, not rats, but people.

Often phase 1 studies are conducted in healthy volunteers, but in this case the phase 1 study of ISIS-HTTRx is being carried out in 36 HD patients in Canada, the United Kingdom and Germany. This may seem like a small number of patients, but remember the goal of this study is to establish safety, so what we want is to treat a small number of volunteers to look for any problems before we test the drug in a larger group.

This is especially true for a drug like ISIS-HTTRx which must be delivered directly into the brain. After a lot of experimenting, Isis developed a plan to deliver ASOs directly into the fluid that bathes the brain, the *cerebrospinal fluid* (or CSF). Because this fluid circulates throughout the brain, delivering a small amount of drug at the base of the spine should result in the drug getting carried throughout the entire brain.

A lot of homework has been done in both animals and humans to figure out this delivery trick, but of course anytime we deliver an experimental drug to someone's brain we have to exercise extreme caution. That is why a relatively small number of patients are enrolled in this first phase 1 study of ISIS-HTTRx.

This question of the spread of the drug within the brain raises an important concern. The data collected by Isis so far suggests that the drug gets to many parts of the brain, but not very much into part of brain called *the striatum*.

This is too bad, because the striatum is the most damaged part of the brain in HD. The hope is that fixing other parts of the brain with an ASO may prove a big benefit for the striatum -figuring out if this is true is one of the goals of these studies.

## What's happened?



So what's the big news? Simple - Isis has just announced that the first few patients have been successfully dosed with ISIS-HTTRx. Professor Sarah Tabrizi, global chief clinical investigator of the study at University College London, has said: "I'm thrilled that this antisense drug has now been safely administered to the first patients. Families ravaged by Huntington's disease have been waiting for this milestone for decades. I look forward to ensuring the smooth running of this first trial and hopefully seeing ISIS-HTTRx through to efficacy testing and licensing".

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This means that the trial is underway, and that the first volunteers have been treated without any immediate complications. The next year or so will be a period of intense study of these trial volunteers to make sure that they don't have unexpected complications from the treatment. They'll also be examined for a range of measures of whether or not the drug is working, which will provide critical information for planning future HD gene silencing studies.

## Where's this going?

This announcement represents a huge milestone, but it's only one step on the path towards developing a gene silencing approach to HD. If this phase 1 study is successful and the drug is proven safe, another trial will be required to prove that the drug has an impact on HD symptoms. And also remember that these trials are experiments that we don't know the outcome of - it's possible the drug will be safe, but not have enough impact in the brain to significantly impact HD symptoms.

This sounds daunting, but patients and families can be comforted by the knowledge that planning for this next trial is already underway. Everyone involved in this project wants safe and effective drugs for HD in the clinic as soon as possible.

Today's announcement represents a remarkable step the long fight against HD. We feel great excitement, as well as a deep sense of gratitude to the researchers and participants in this pivotal trial. Stay tuned to HDBuzz for more updates as these trials progress.

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*Ed Wild, co-editor-in-chief of HDBuzz, is an investigator in the ISIS-HTTRx trial. Dr. Wild was not involved in the writing or editing of this article, or the decision to publish it. Jeff Carroll, the author, has a long-standing non-financial collaboration with Isis pharmaceuticals that does not involve the drug being investigated in the HTTRx trial. No Isis or Roche employees were involved in the writing or editing of this article. For more information about our disclosure policy see our FAQ...*

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## Article history

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## Glossary

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

**CSF** A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

**gene silencing** An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

**clinical trial** Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

**transcription** the first step in making a protein from the recipe stored in a gene.

Transcription means making a working copy of the gene from RNA, a chemical messenger similar to DNA.

**efficacy** A measure of whether a treatment works or not

**HTT** one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15