# What the 'big neurodegeneration breakthrough' means for Huntington's disease

**Are recent findings in mice injected with 'prions' as important for Huntington's disease as widely reported?**

**By Eric Minikel** | **October 15, 2013** | **Edited by Dr Jeff Carroll**

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Many people in the Huntington's disease community have noticed reports highlighting a recent study from the University of Leicester, which the BBC claimed "could treat Alzheimer's, Parkinson's, Huntington's and other diseases". The underlying study is well-executed research of some importance. However, the press hype is out of all proportion to the impact of this research. What does this study actually show, and what does it mean for HD?

## Prion disease

When patients die after battling Huntington's disease, doctors have long observed that their brains are full of debris that shouldn't be there. It's as if the cells of the brain forgot to take out the trash and let it pile up before they died. Scientists call these clumps of junk **aggregates** when they are found in HD patient brains.

*In many brain diseases, proteins overwhelm the trash collection systems of cells. The PERK signal slows protein manufacture to help cells catch up. In prion disease, it does more harm than good — but is that true of other diseases?*

This littering of the brain with different proteins is observed in many heurodegenerative' diseases, including Alzheimer's and Parkinson's disease. Because of this common feature, some scientists believe there may be a common root cause for all these diseases. Other researchers note that while these piles of trash are observed in many conditions, they're full of different stuff in each case. Essentially, each brain disease is associated with **different** kinds of litter, so it's not clear if the origin of these problems is the same in each case.

Yet another family of brain diseases associated with the accumulation of junk are the so-called "prion diseases". Prions are infectious particles made up of protein - unlike viruses or bacteria, they don't have any DNA or RNA. Once so obscure that their existence was hotly debated by the scientists, they are now a well-known cause of brain disease.

Everyone has a protein called prion protein (PrP), which is usually perfectly healthy. But sometimes PrP folds up the wrong way, and once one PrP molecule decides to do this, all the others follow suit, like a line of dominoes tumbling down one after the other.

Unlike HD, which is always caused by a genetic mutaiton, prion diseases can happen three different ways: you can have a genetic mutation in your PrP gene, you can get infected with prions (most famously, from animals with 'Mad Cow' disease) or sometimes it just seems to come out of nowhere. Once the dominoes start to fall, cells have trouble cleaning them up and throwing them out, and eventually the cell gets so full of junk that it dies.

# Cells PERK up and take out the trash

Last year, a group of researchers led by Prof Giovanna Mallucci, from the University of Leicester, described a cellular communications network that they believe contributes to brain cell death in prion disease.

Mallucci and colleagues showed in mice that once cells are full of enough misfolded PrP - the fallen dominoes - eventually this triggers something called the 'unfolded protein response'. This is a normal cellular process that instructs the cell to clean up, because the trash is backing up and things are starting to smell.

As part of this house cleaning response, cells activate a specific cellular signal called **PERK**. Activation of the PERK signal has the effect of dramatically reducing the overall rate at which new proteins are generated. This draconian mechanism might have evolved as a way to give the cell a break from the accumulation of cellular junk.

In the case of prion disease, this response backfires, because prions have tricky ways of escaping the 'clean up' signal. In fact, in 2012 Mallucci and her colleagues showed that PrP is actually produced in even greater-than-usual quantities when the unfolded protein response is activated.

In the 2012 study, the authors looked for ways to interfere withprion disease by interfering with the unfolded protein response. Inhibiting unfolded protein response with genetic tricks extended survival of prion-infected mice by 10%. Meanwhile, treating prion-infected mice with salubrinal, a drug that promotes the unfolded protein response, accelerated disease, leading to death a few days earlier.

The interpretation of these results was that, contrary to expectations, the unfolded protein response is bad in prion disease. It accelerates brain cell death by reducing protein production, while simultaneously failing to halt the production of the protein at the root of the problem: PrP. It's as if your house was filling up with fallen dominoes so you threw out all your food and furniture, while still buying more dominoes.

> **"While these are findings interesting, we don't think they deserve the hype they are receiving. "**

In the same year, British drug company GlaxoSmithKline published its discovery of a drug called GSK2606414 which can reach the brain and specifically inhibit PERK. This opened up an opportunity to attack the same cellular signal with a potent drug that could be given orally and reach all areas of the brain. Good news, right?

# The new findings

In the new study that has received so much attention, Mallucci and colleagues used the new drug to inhibit the unfolded protein response and delay the clinical signs of disease in prion-infected mice. Somewhat like the "pre-symptomatic" phase of HD, prion diseases have a long silent incubation period in which prions build up but there are no symptoms. Mice in this stage act normal and everything looks fine in their brains.

The group of scientists led by Mallucci are pioneers of looking for the very earliest indicator signs of prion disease in prion-infected mice. The earliest signs of prion disease they have found occur about 56 days after mice are infected with prions - the mice eventually succumb to disease after about 84 days.

In this new study, Mallucci treated mice with GSK's new drug to see what effect this would have on the progression of prion disease. Some of the mice they treated were free of symptoms, while some mice already had early symptoms of prion disease at the start of the trial.

While all of the untreated mice had became sick by 84 days, none of the drug-treated mice had done so. Behavioral tests and examination of the brains of treated mice this stage revealed early signs of prion disease in some mice, but no severe signs in any of them. However, the mice were not monitored for longer to see how long they would survive, or how long they would remain disease-free.

# Trouble outside the brain

Importantly, this GSK drug doesn't affect the PERK signal only in the brain, but acts throughout the whole body. Drug treatment appeared to particularly effect the pancreas, an organ critical to normal processing of sugar by the body. In fact, it appeared to cause pre-diabetic changes in treated mice, who had increased blood sugar and weight loss of about 20%. According to the animal welfare rules of Mallucci's institution, the weight loss meant that the mice could no longer be studied, and so they weren't monitored further to see when disease would set in.

Therefore, we are left to guess just how effective this treatment was. Since all untreated mice clearly had prion disease by 84 days but none of the treated mice did, the treatment must surely have delayed illness. This delay was probably at least 10 days, or about 12%. Of course, it could have been even more – but we can't conclude that from this study.

In general, it is always hard to say how percentages like these will project onto the human disease course. It's especially hard in this case because the PERK inhibitor approach does not target the underlying cause of the disease – the accumulation of prions – but rather seeks to allow neurons to tolerate a greater accumulation of prions before dying.

# The devil is in the details

*Problems shared between brain diseases can help us understand how things go wrong. But it's very unlikely a single drug will make a huge impact on several major diseases.*

Despite the unknowns, this study is exciting because it provides a proof of principle that targeting the PERK pathway can be therapeutically valuable for prion disease. But it is unlikely that the unfolded protein response is the only thing toxic about prions – there are several other types of dysfunction that may kill neurons if the unfolded protein response doesn't get them first.

For this reason, we find these findings exciting, but believe they don't deserve the hype they are receiving. We believe that there's a few reasons for a more moderate view than the one taken by most of the press. First: there is no evidence this compound 'prevented'

neurodegeneration. In a statement to BBC, Prof Mallucci is quoted as saying: “What’s really exciting is a compound has completely prevented neurodegeneration and that’s a first”.

For some perspective, consider that treatment with several other drugs have given delays in onset of at least the same magnitude as this study. In any of these earlier studies, if the mice had been examined just a few weeks after the time of disease onset in the control mice and then monitored no further, it probably would have appeared that these treatments too had “completely prevented” neurodegeneration. However, by following the mice for longer those authors were able to observe that the treatments merely delayed neurodegeneration.

Second: the adverse effects may be unavoidable. Commenting on the adverse effects that led to the premature termination of the study, the BBC writes: “Side effects are an issue. The compound also acted on the pancreas, meaning the mice developed a mild form of diabetes and lost weight”.

In fact, this is probably not a side effect. It’s more likely a **main** effect. In the paper, the authors cite evidence that suggests that the observed changes in the pancreas could be due to the drug’s intended effect – PERK inhibition – rather than due to an ‘off-target’ interactions. If so, then avoiding this adverse effect while trying to develop a drug for human use will be challenging indeed.

Addressing this issue, the BBC responds that “Any human drug would need to act only on the brain.” Derek Lowe, a well-known drug development chemist currently working at Vertex Pharmaceuticals, noted on his blog that “if you could just keep an inhibitor out of the pancreas, you might be in business. Good luck with that. I can’t imagine how you’d do it.” Neither can we!

Third: the relevance to Huntington’s and Alzheimer’s disease remains to be shown. Noted news outlets such as Time, CBS, BBC and The Independent all structured their articles mostly around Alzheimer’s disease. No doubt, there are links between prion disease and other diseases like Huntington’s and Alzheimer’s. But **there is not much evidence to say that the specific pathway targeted in this study is shared between these diseases**. You wouldn’t treat food poisoning and the flu in the same way, just because they both involve vomiting. Each has its own cause, and probably needs its own treatment

# Take home for HD families

This is a well-conducted, well-conceived, study designed to investigate the connections between prion disease and the unfolded protein response in cells. Excitingly, it demonstrates that if you understand the science sufficiently, you can come up with drugs that can delay the death of brain cells in previously untreatable brain diseases.

But it’s a long way from having anything specific to say about how to develop drugs for Huntington’s disease.

*This story originally appeared as a blog post on the CureFFI blog at cureffi.org, and has been edited in line with HDBuzz style.*

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

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## GLOSSARY

**Parkinson's Disease** A neurodegenerative disease that, like HD, involves motor coordination problems

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

**aggregate** Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases

**neuron** Brain cells that store and transmit information

**prion** special proteins that can become harmful, and cause disease called prion disease. Like falling dominoes, prion proteins can 'infect' other proteins, making them become harmful.

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

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