

## Could mesenchymal stem cells deliver gene silencing drugs?

Stem cells can deliver HD gene silencing drugs into cells in a dish. Do we need another delivery technology?



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**M**any people consider gene silencing the best candidate therapy for Huntington's disease. A group led by Dr Jan Nolte has described a new method of getting silencing drugs into cells in a dish using modified bone marrow stem cells. Does this new approach offer benefits over existing technologies?

### Gene silencing

Like most HD researchers, we think gene silencing, or shutting off the expression of the HD gene, is the most exciting treatment option on the short term horizon. To achieve this goal, drugs that block expression of the HD gene must be delivered to the brain in some way.



*Mesenchymal stem cells are harvested from bone marrow*

The problem is twofold: we must first develop drugs that silence the HD gene, and then get them to the brain. Luckily, the first part of this problem has been pretty well worked out - there are a large number of described drugs that reduce expression of the HD gene. Getting these drugs to the right spot has turned out to be the hard part.

# Delivery

For good reasons, your body goes to great lengths to protect your brain. The skull is a rigid container that protects your brain from bumps and bruises.

When we zoom in and look closer, we realize that the brain is even better protected than it appears from the outside. Within the skull, a water tight barrier separates your brain from the bloodstream and the rest of your body. This 'blood-brain barrier' is a nearly perfect wall, keeping the brain safe from bugs and poisons.

This is great, normally, but when we want to treat the brain with a drug, the wall stands in our way and we've got to find a way to get around it to have a therapeutic effect - in this case, reducing the expression of the HD gene.

So far, gene silencing studies have used one of two methods to deliver drugs to the brain. Scientists have tried directly injecting the drugs into the brain, physically by-passing the wall of the blood brain barrier. Other approaches have also used this injection approach, but used modified virus particles to carry other types of silencing drugs throughout the brain. Our last article on two new gene silencing trials contains an example of each method.

Once the drugs are in the brain, they still need a way into brain cells. Some gene silencing drugs, called RNAi drugs, aren't readily taken up by cells. These drugs need some help to get them into cells. Historically, this is where the virus packaging has come in.

## Mesenchymal stem cells

A group of scientists led by Dr. Jan Nolte of the University of California Davis, have tested a unique method to pass RNAi drugs into cells. This group has a long-standing interest in a special kind of cell called a 'mesenchymal stem cell', or MSC.

“MSCs carrying HD silencing drugs were able to reduce mutant huntingtin levels in the target cells, when they were grown on top of them.”

Found in various parts of the body including the fat and bone marrow, MSCs are easily isolated from adult donors. These cells have a bunch of normal roles in the body, but what interests Nolte is their ability to 'home in' on sites of injury and release beneficial chemicals.

More recently, it has been shown that MSCs can actually fuse with injured cells, directly injecting with 'spare parts' to help aid healing. Given this ability, Nolte is interested in modifying MSCs to release new payloads, including HD gene silencing drugs.

Her vision is that MSCs, isolated from a patient, would be modified to carry silencing drugs. These modified cells would then be injected back into the patient's brain, or possibly blood, where it is hoped they will find their way to injured brain cells. These sick cells would then be injected by MSCs with HD silencing drugs.

# New data

In a paper just published in *Molecular and Cellular Neuroscience*, Nolta's lab describes the first steps in testing this plan. So far, the described work takes place in purified cells in a dish - no cells were injected into brains in this published study.

First, they tested the RNAi gene silencing drug directly in the target cells. The silencing drug was somewhat effective, reducing the amount of huntingtin in cells that it reached.

Next, they genetically engineered MSCs so that they produced the RNAi drug, and measured their ability to directly connect with other cells. They grew these genetically modified MSCs in the same dish as other cells that expressed a short piece of the mutant huntingtin gene. Their hope was that MSCs would deliver enough silencing drugs to the mutant HD cells by a direct connection.

This seemed to work. These genetically modified MSCs carrying HD silencing drugs were able to reduce mutant huntingtin levels in the target cells, when they were grown on top of them. The reduction was not complete, or permanent, but it serves as a proof that MSCs can indeed deliver HD silencing drugs to other cells.

## Limitations of the MSC approach



*Mesenchymal stem cells might be able to deliver gene silencing molecules to neurons, but it's very early days for the approach and there are many unanswered questions.*

The study was positive but has some limitations. First, modified MSCs were directly placed onto cells expressing mutant HD genes. Recall, the idea is that these cells can find sick cells independently. That **might** happen, but this paper doesn't show that it can.

Furthermore, the silencing achieved by MSC-delivered drugs was less effective than what we'd expect with existing approaches like virus-delivered RNAi. For MSCs to be useful for patients, they'll have to provide some benefit above and beyond what's currently possible with these drugs. This may come from the sick-cell targeting ability of MSCs, but again, we haven't seen that yet.

Finally, in this study, the number of MSCs used was equal to the number of cells targeted. Given that there are about 200 billion cells in the brain, it seems unlikely that we'll be able to infuse in that many MSCs for treatment. It would be nice to know the smallest number of cells needed to have an effect, so we can tell whether it'll be feasible to transfer enough.

## Predictions versus reality

Dr Nolta's MSC work has attracted quite a bit of attention, not least because Nolta herself addressed HD families at the Huntington Study Group Clinical Research Symposium in November 2009. She gave strikingly optimistic predictions for the work, notably of a clinical trial of a "treatment" for HD from this work within 12 months.

To give you an idea of how long therapies research takes, the first paper describing mutant HD gene silencing in a mouse was published by Beverly Davidson's group in 2005. In 2012, we're just seeing safety studies with similar molecules in monkeys. That's a seven year gap, and Davidson's team are a hard-working bunch.

This first publication by Nolta's group describes the very earliest cellular work with their delivery system, not its application in mice or monkeys. Though we look forward to seeing what comes next, any clinical application of this work is likely years away.

As we've said before, we **love** optimism, but it has to be accompanied by realism if disappointment is to be avoided. We call on scientists to consider this when reaching out to the public.

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*Front page image credit: PNAS (cover image, 11 August 2009). This article was amended on February 10th, 2012, removing mention of a concern that MSC-RNAi therapy would require independent cell lines for each patient. This may not be the case. [For more information about our disclosure policy see our FAQ...](#)*

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## GLOSSARY

**blood-brain barrier** A natural barrier, made from reinforcements to blood vessels, that prevents many chemicals from getting into the brain from the bloodstream

**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

**bone marrow** The gooey stuff in the middle of bones, that manufactures blood cells. When eaten, gives dogs a healthy coat and vitality

**stem cells** Cells that can divide into cells of different types

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

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