Replacing What Is Lost: Regrowing Damaged Brain Cells for Huntington's Disease

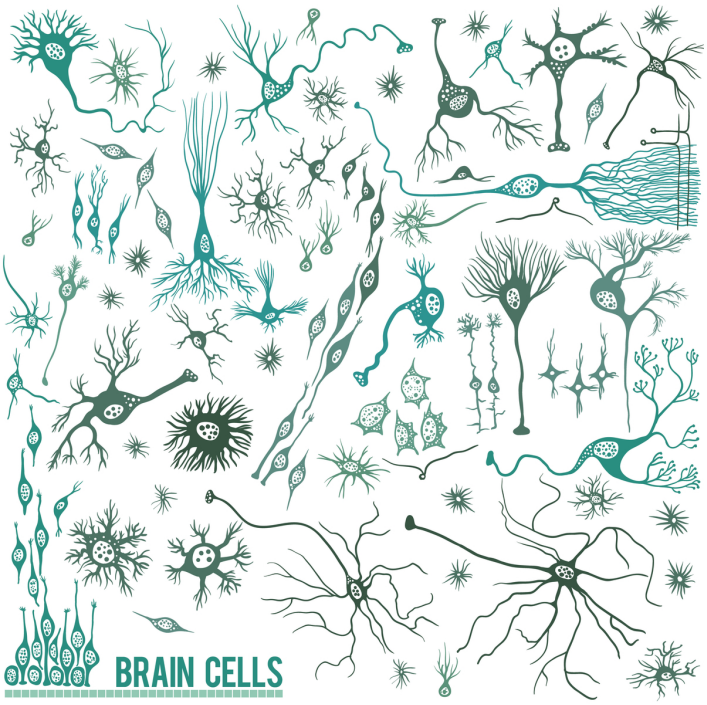
Cell replacement therapy is making massive strides for other diseases. But what about Huntington's disease? Can we use technological advancements in this area to replace lost brain cells with the hope of repairing and reversing disease?

By Carlos Chillon Marinas | **January 13, 2025** | **Edited by Dr Sarah Hernandez**

It's exciting to think about the treatments currently in trials that aim to halt or slow Huntington's disease. But can we dream big and start thinking beyond that now? Could we one day not only stop Huntington's disease but actually repair the damage it causes by growing and replacing the brain cells that have been lost?

Can we replace what is lost?

When we think about finding a cure for Huntington's disease (HD), the first idea that often comes to mind is stopping or correcting the CAG expansion in the huntingtin (HTT) gene—the genetic mutation that we know causes this devastating condition.



The brain is made up of more than just neurons. A type of cell called a "glia" works to support neurons. Scientists are working on experiments that could be used to convert glia into neurons to replace lost brain cells for diseases like Huntington's disease.

Over the decades, we've learned a lot about the genetic root of HD, but this raises an important question: Even if we could fix the gene, what about the nerve cells in the brain

already lost and the damage caused by the disease's progression?

Replacing brain cells that have been lost offers an exciting possibility to restore lost brain function and, perhaps, reverse the devastating effects of the condition. By harnessing advancements in cell replacement, researchers are opening new doors for potential treatments.

The brain's building blocks

To understand this possibility, it's helpful to look at how the brain works. The brain is composed of many different types of cells, including neurons and glial cells. Neurons are the stars of the show—responsible for transmitting signals and forming the networks that control everything we think, feel, and do.

Most types of cells are "dividing cells". For example, if a skin or liver cell is damaged, a nearby cell will divide in two to replace the damaged cell. But neurons are "non-dividing cells". This means that if you lose a neuron to aging or disease, a nearby neuron won't divide to replace it.

However, this isn't the case for all cell types in the brain! The brain is also made up of a cell type called "glia". Glia are support cells that provide structure, nutrients for neurons, and help to maintain a healthy brain environment. Importantly, glial cells can divide and replenish their numbers. Scientists are increasingly focusing on glial cells because we might be able to use them to regenerate neurons.

Remove, reprogram, replace

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Thanks to decades of groundbreaking research, there's now hope that even the brain's inability to replace lost neurons could be overcome. One approach involves reprogramming cells outside the body. This means taking a specific type of cell—often bone marrow cells or other accessible cell types—out of the body, reprogramming them using genetic tools, and implanting them back into the desired area of the brain to complete their transformation into replacement neurons.

Leading researchers in this field, called regenerative medicine, like Dr. Malin Parmar, are translating scientific discoveries into clinical applications. Her trailblazing work focuses on developing techniques to generate dopamine-producing neurons, an approach currently being explored as a treatment for Parkinson's disease.

These advancements are not only laying the groundwork for treating other neurodegenerative disorders, but also highlight the potential for tailored, cell-based therapies that could one day regenerate the neurons lost in HD. By demonstrating the

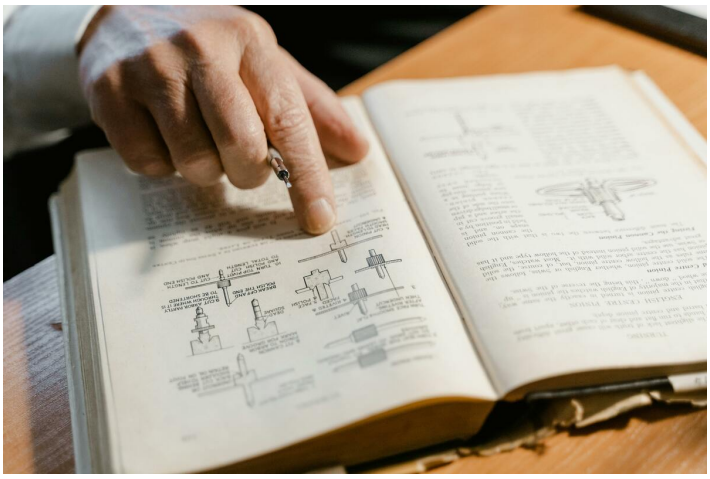
feasibility of reprogramming and transplanting functional neurons into the brain, her research brings us closer to transforming these experimental approaches into clinical realities.

Although implanting new neurons into the brain comes with significant challenges—such as ensuring the new cells survive, integrate into existing networks, and function properly—clinical trials in this area for other diseases have already begun, demonstrating both feasibility and promise. The hope is that these advancements could help repair the damage caused by diseases, like Huntington's, and restore lost brain function.

Conversions in the brain

Another exciting approach to generate replacement neurons is converting cells already present in the brain into neurons, all without the need for removing any cells and transplanting new ones. This is where glial cells, the brain's "support team," come into the spotlight. Glial cells share a similar developmental origin with neurons (we could even call them cellular cousins!), making them a natural and compatible choice for reprogramming.

The process involves "convincing" glial cells to activate specific genetic programs that guide them into becoming neurons. Think of it as flipping a switch in the cell's genetic instruction manual, activating previously dormant neuron-making instructions.



The genetic code is like an instruction manual. Every cell has the same manual, but cells only use certain parts, allowing them to become specialized, like a heart cell or a brain cell.

Image credit: Tima Miroshnichenko

Scientists like Drs. Magdalena Goetz and Benedikt Berninger (and many more) have identified certain molecules, called transcription factors, that act like master regulators to unlock specific genetic pathways. These transcription factors guide the glial cells through a carefully choreographed transformation, allowing them to acquire the structure and function of neurons.

This approach is particularly exciting because it sidesteps some of the challenges associated with cell transplantation, like immune rejection or difficulty integrating new cells into existing brain networks. By working directly within the brain's existing cellular environment, reprogramming glial cells offers a promising, less invasive alternative for regenerating neurons lost in neurodegenerative diseases like HD.

But, how do you turn one cell type into another?

If you think about it, every cell in your body has the same DNA. When you were just an 8 cell blastocyst, those cells divided with the same DNA until you got to the person you are today. So the genetic code throughout every cell of your body is identical.

But why do certain cells look so different? Why do some become muscle cells that assemble into fibers to form your muscles, while others become cells that beat in your heart, and still others form the intricate networks of neurons in your brain? The answer lies in which parts of their DNA they "read" and use.

You can think of the genetic code as a massive instruction manual containing all the directions needed to create any cell type in your body. Every cell has access to this manual, but they only read the sections relevant to their specific role. For example, a neuron reads the instructions necessary for developing and maintaining its complex tree-like structure that allows them to communicate with other cells. Meanwhile, other parts of the genetic code remain unopened, like chapters that aren't needed for a neuron's job.

Cellular cousins

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Neurons and glial cells come from the same family tree, so glial cells already have access to the genetic blueprints for becoming neurons—they just need the right push to open those chapters of the book. Scientists are exploring how to provide that push, using tools like antisense oligonucleotides (ASOs), short hairpin RNA (shRNA), or viral vectors—the same kinds of technologies being investigated for HD treatments.

While this approach is still in its early stages, researchers have shown in animal studies that it's possible to generate new neurons in the brain from glial cells. These studies offer hope, though translating these findings to humans remains a challenge.

Heading to the clinic

This research is still far from being prescribed by your doctor, but it is marching its way to the clinic. Some clinical studies have already tested transplanting engineered cells back into patients for conditions like spinal cord injuries, HIV/AIDS, and immune diseases.

This type of approach requires the use of medication to suppress the immune system to prevent rejection of the transplanted cells. If we could reprogram glial cells within the brain itself, we might be able to sidestep some of these challenges and create a treatment that's both more effective and less invasive.

In fact, there are drug companies that are taking both of these approaches, working to develop cell replacement therapies for HD right now. Sana Biotechnology is a company working to transplant new brain cells to replace those that are lost in HD. NeuExcell Therapeutics is a company working in the HD space to convert glial cells already in the brain to new neurons.

In the fight against HD, stopping the disease would be a game changer—but imagining a future where we can also repair the brain is an exciting and inspiring possibility. The ability to regenerate neurons could transform not only how we treat HD but could also unlock the potential of the brain to heal itself.

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

GLOSSARY

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

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

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.

therapeutics treatments

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

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

neuron Brain cells that store and transmit information

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

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