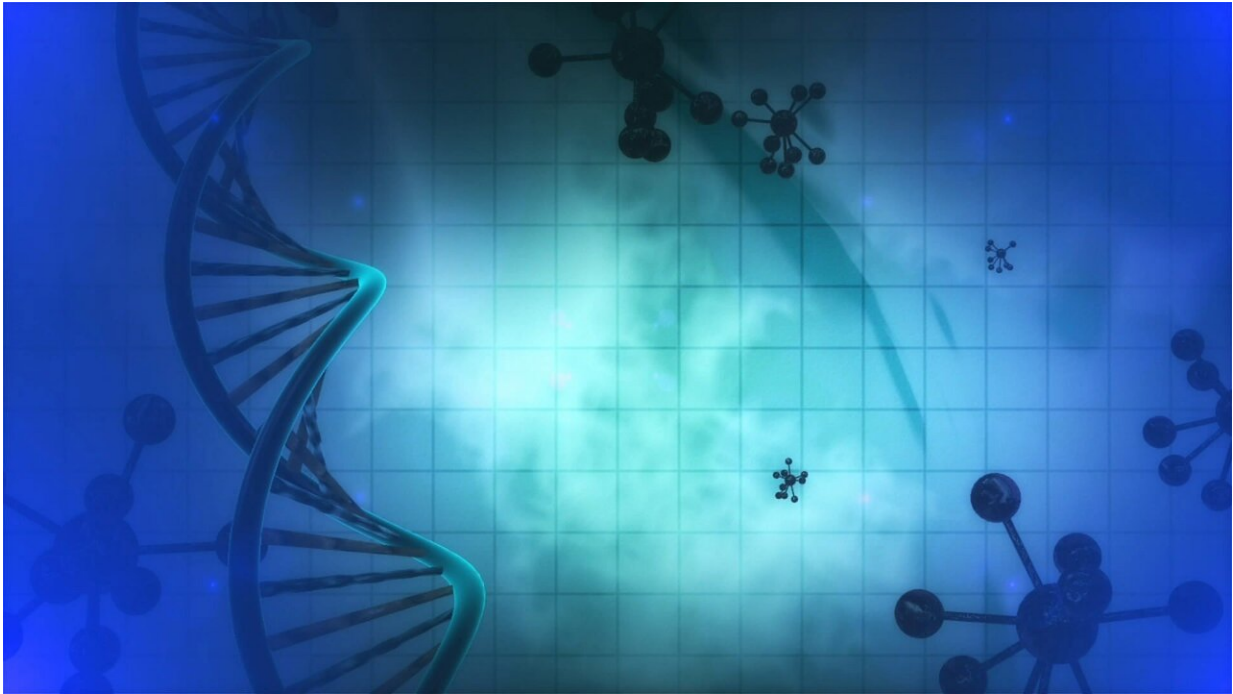


Getting gene therapy to the brain

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A lone genetic mutation can cause a life-changing disorder with effects on multiple body systems. Lysosomal storage diseases, for example, of which there are dozens, arise due to single mutations that affect production of critical enzymes required to metabolize large molecules in cells. These disorders affect multiple organs including, notably, the brain, causing intellectual disability of varying degrees.

Gene therapy holds promise to address these conditions, but the brain's own protective mechanism—the blood-brain barrier—has been a formidable challenge for researchers working to develop one.

In a new study published in the journal *Brain*, a team led by John H. Wolfe, a researcher with Penn's School of Veterinary Medicine and Perelman School of Medicine and the Children's Hospital of Philadelphia, successfully applied a [gene therapy](#) platform to completely correct brain defects in a large animal model of a human genetic disease.

"This is the first example of a large-brain mammal with a bona fide human genetic disease that has intellectual disability as part of the human syndrome where we've been able to correct the biochemistry and pathologic lesions in the whole brain," says Wolfe.

Wolfe has worked on models of human genetic diseases that impact the brain for many years. With gene therapy, a delivery vehicle—typically a [viral vector](#)—is used to provide the normal version of a mutated gene to correct a condition. Wolfe and other scientists working in this area have made steady progress to treat neurogenetic diseases in rodents. However, applying the same treatment to the much larger brain of higher mammals has only been able to produce partial corrections.

"There's been a lot of excitement for the last 10 years or so that specific vectors can be injected into the blood and enter the brain," says Wolfe. "They do cross the blood-brain barrier." One such treatment with restricted distribution has been effective in treating a disease that primarily affects the spinal cord.

And while scientists have shown these therapies can reverse the pathology throughout the brains of mice, it's been hard to judge what effect it would have in patients, as the rodent brains have a much smaller cerebral cortex than larger mammals, like humans.

In the current study, the team used an animal model with a brain more similar to humans, cats, to assess the effectiveness of a gene-correcting therapy for one type of lysosomal storage disease: a condition called alpha-mannosidosis, which naturally occurs in cats and results from a mutated copy of the alpha-mannosidase gene.

Having refined the gene-delivery technique during many years of work, the researchers selected a specific vector that they showed, in mice, was capable of crossing the [blood-brain barrier](#) to reach sites throughout the brain.

They next delivered the vector, containing a reporter gene, to normal cats. Several weeks later, they were able to find evidence that the corrected gene had distributed to various parts of the brain, including the cerebral cortex, hippocampus, and mid-brain.

Finally the research team assessed the therapy in cats with alpha-mannosidosis, using either a low or high dose of the vector. They injected the therapy into the carotid artery, so that it would go directly to the brain before traveling to other parts of the body. Compared to untreated cats, treated animals had a significant delayed onset of certain neurological symptoms and a longer lifespan; those that received the higher dose of the vector delivered through the carotid artery lived the longest.

"It's a big advance," says Wolfe. "Nobody has been able to treat the whole brain of a large-brained animal before. We're hopeful that this will translate into clinical use in humans."

Wolfe cautions, however, the findings don't amount to a cure.

"These were significant improvements, but they were only just improvements on a serious condition," Wolfe says. "The cats weren't

cured, and we don't know what impact this has on mental ability. However, since the pathology is found throughout the brain, it is thought that complete correction will be necessary."

As alpha-mannosidosis is a childhood-onset disease with no cure, however, any improvements that lessen the severity of symptoms are welcome. The approach the researchers developed may potentially be employed to treat many other diseases that affect the whole central nervous system.

In future work, Wolfe and his collaborators hope to refine their methods to achieve the same outcomes with a lower dose, making an effective treatment safer as well as more affordable. And they will continue to work to understand the details of why their treatment works, including precisely how the vector travels through the [brain](#), a line of investigation that could shed light on additional strategies to address these serious disorders.

More information: Sea Young Yoon et al. Global CNS correction in a large brain model of human alpha-mannosidosis by intravascular gene therapy, *Brain* (2020). [DOI: 10.1093/brain/awaa161](https://doi.org/10.1093/brain/awaa161)

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