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The Quest to Deliver Alzheimer's Drugs Directly to the Brain

10–13 minutes

An experimental Alzheimer's treatment is testing a nearly 40-year-old idea: Could drugs hitch a ride through the blood-brain barrier by exploiting the brain's own transport system?

About 400 miles of blood vessels run through the human brain. The smallest are lined with endothelial cells joined by tight junction proteins, forming a nearly impenetrable barrier that keeps unwanted substances in the bloodstream from entering the brain.

The blood-brain barrier acts like passport control at an airport, tightly regulating what can enter. Hormones, iron, and other nutrients can pass through because their molecular shapes act as passports, recognized by specialized proteins called receptors and transporters along the barrier.

But that protection creates a problem: [Drugs](#) targeting the brain cannot easily enter from the bloodstream, making brain cancers, neurodegenerative diseases, and genetic disorders difficult to treat. Doctors may have to use high doses to ensure that even a small amount reaches the brain or rely on invasive injections into the spinal canal—approaches that can increase costs and side effects.

In the late 1970s, UCLA endocrinologist [William M. Pardridge](#) began studying the pathways that allow hormones and nutrients to pass through the blood-brain barrier. In 1989, that work led to a patent for the Molecular Trojan Horse platform. Pardridge envisioned laboratory-engineered antibodies that could smuggle drugs into the brain by exploiting the barrier's own receptors.

That strategy has now begun to work. Two treatments for a rare genetic disorder called [Hunter syndrome](#) hitch a ride on one of these proteins, the transferrin receptor. Roche's experimental Alzheimer's therapy trontinemab uses the same route and is now being tested in [multiple Phase III trials](#)

"That's a huge validation for the shuttle field," says [James Gorman](#), principal investigator of the Wyss Institute's Brain Targeting Program. The progress has generated excitement among scientists and pharmaceutical companies hoping to target difficult-to-treat brain diseases using the same strategy.

The challenge now is determining how broadly these shuttles can be used—and whether researchers can develop more precise routes for carrying different treatments into the brain.

The [transferrin receptor](#) ferries an iron-carrying protein called transferrin from the bloodstream into the brain. Its rapid cycling made it a promising route for smuggling drugs past the blood-brain barrier.

"It's going from the surface into the cell, back to the surface and into the cell, all the time, pretty quickly," says Gorman. "That's not like any other transporter that we know." Many other transporters and receptors don't take cargo all the way into the brain or cycle as quickly.

Scientists engineered antibody-based shuttles that could be attached to drugs. In theory, these antibodies would bind to the transferrin receptor on the cell surface, allowing their cargo to enter the brain. But for a long time, researchers, including Pardridge, couldn't make the approach work.

While working at Genentech in the 2000s, [Ryan Watts](#) and his colleagues cracked the decades-old problem. Antibodies used to treat other diseases were generally designed to bind as tightly as possible to their targets. But that strategy repeatedly failed with transferrin-receptor shuttles. "That's why [the technology] was in the backwaters for so long," says Watts.

The eureka moment came when Watts and his colleagues discovered that [binding weakly](#) to the receptor allowed antibody shuttles to cross the barrier and spread throughout the brains of mice. Gorman calls it a "revolutionary insight." Watts and several colleagues later left Genentech to start Denali Therapeutics, where they developed the technology into a platform called TransportVehicle. The company pairs these shuttles with drugs intended to treat rare genetic diseases and more common neurodegenerative conditions.

[Hunter syndrome](#) would provide crucial evidence that the same strategy could work in people.

The inherited disorder is caused by genetic variants that disrupt the function of an enzyme called iduronate-2-sulfatase, or I2S. The enzyme normally breaks down complex sugar molecules called glycosaminoglycans. Without it, these molecules accumulate throughout the body and brain. Existing enzyme-replacement therapy can treat some effects of Hunter syndrome, but because it

[doesn't reach the brain](#), children can still develop cognitive decline, behavioral issues, and seizures.

([Why Some People Are Born With Devastating Gene Mutations—And Never Get Sick.](#))

In 2021, Japan [approved](#) Izcargo, developed by JCR Pharmaceuticals, a treatment that fuses the I2S enzyme with a transferrin receptor shuttle called J-Brain Cargo, allowing it to enter the brain. The drug reduced levels of toxic sugars, and early results suggested it may slow neurocognitive impairment, though researchers noted that more long-term data are needed to confirm the impact.

In March 2026, Denali Therapeutics' [Avlayah](#) received accelerated approval in the U.S. for treating neurological symptoms in children who have not yet progressed to advanced impairment. The approval was based on a [trial](#) showing that the drug reduced levels of heparan sulfate, one of the sugar molecules that accumulates in people with Hunter syndrome. The FDA determined that this reduction was “reasonably likely to predict” clinical benefit. Denali is conducting a confirmatory trial to determine the drug's effects on cognition and daily function.

For [Miriam Pedroza](#) and her 14-year-old son Adam, who was diagnosed with Hunter syndrome at four, the effects of Avlayah feels tangible. Five years ago, her family moved from Southern California to the Bay Area to participate in Denali's clinical trial. Adam is still taking Avlayah today.

“We were told it was a life-limiting disease,” says Pedroza. But since starting the medication, she says Adam's hearing has improved, and he's become more talkative. Adam talks with all his

neighbors and the clinic staff, who affectionately call him “The Mayor” because he knows everyone.

For families affected by Hunter syndrome, the possibility itself can be meaningful. “I think it gives people hope that it is possible, that there are these medical breakthroughs that can happen and that will happen,” Pedroza says.

But Hunter syndrome is a relatively straightforward target: A faulty gene disrupts a single enzyme, producing a measurable buildup of specific molecules. Alzheimer’s is far more complicated and could provide a much bigger test of the shuttle strategy.

Roche’s Alzheimer’s drug [trontinemab](#) is now being tested in multiple Phase III trials testing whether it could [prevent](#) or [slow Alzheimer’s](#). Trontinemab is an anti-amyloid antibody that targets and clears [beta-amyloid](#) plaques in the brain. While two similar drugs are approved, they [frequently cause side effects](#) including temporary brain swelling and bleeding, known as amyloid-related imaging abnormalities, or ARIA, which can be serious and, in rare cases, fatal.

Roche’s approach combines the anti-amyloid antibody with BrainShuttle technology, which lets the drug enter the brain via the transferrin receptor. In early trials, it cleared plaques within a few infusions at lower doses than approved medications, which require several months of treatment, and with [far fewer side effects](#).

([The biggest scientific breakthroughs of the last 25 years.](#))

These findings will need to be confirmed in Phase III trials. It also remains unclear whether it will slow or prevent the disease, as there’s still debate over the impact of clearing beta-amyloid in the brain, as current drugs aimed at the same target only show a

[small-to-modest effects](#).

[Richard Keep](#), a University of Michigan professor who studies the blood-brain barrier but isn't directly involved in developing this technology, says these findings have "caused a lot of excitement" and calls the development of this technology "an important event."

Many companies are now developing their own versions of transferrin receptor shuttles. Researchers are also targeting other proteins, including [insulin receptor](#), [LDL receptor-related proteins](#), and [CD98](#).

The Hunter syndrome treatments and early trontinemab results suggest that shuttles can carry therapies into the brain to clear harmful protein buildup or act directly on neurons and other cells. Researchers are exploring similar approaches for [glioblastoma](#), [multiple sclerosis](#), and a handful of [neurodegenerative diseases](#).

Gorman believes the technology could also open doors for other rare genetic disorders in which cells cannot properly recycle waste. "There's a huge amount of interest in ultra-rare diseases," Gorman adds, where there might only be one or two people worldwide afflicted with a genetic disorder affecting the brain.

Shuttles may make it possible to efficiently deliver small strands of genetic material, oligonucleotides, that could potentially treat these one-off disease-causing mutations that scientists weren't able to target before. "I think that's the next big unlock that's going to happen in the next, frankly, months to years," says Watts.

But drugmakers may need a much larger repertoire of shuttles. Caltech neuroscientist [Viviana Gradinaru](#) says she was "somewhat puzzled" that so much of the biotechnology and pharmaceutical industries was relying on "this one receptor, transferrin."

Because the transferrin receptor is present throughout the body, drugs may cause side effects in other organs. For people with Hunter syndrome, who need the missing enzyme throughout the body, that broad distribution can be an advantage. Other diseases may require a more targeted approach.

To find alternative routes, Gradinaru's team engineered viral vectors that could cross the blood-brain barrier and then identified the receptors they used. "We ended up as a field with thousands and thousands of interesting delivery vectors," she says.

One of those routes involves carbonic anhydrase IV, a receptor enriched on the blood-facing surface of the brain's blood vessels. In a recent [*Nature Chemical Biology* study](#), Gradinaru and her colleagues developed a nonviral shuttle that used the receptor to deliver antibodies into the brains of mice and rhesus macaques. Although the approach remains preclinical, it suggests researchers may eventually choose different shuttles based on the treatment being delivered and where it needs to go.

"The big vision for the future is not one receptor or one shuttle, but a collection of blood-brain barrier shuttles that can be engaged depending on the needs," says Gradinaru.

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