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Alzheimer's drug sneaks through blood–brain barrier

A double-sided antibody targets enzyme to reduce levels of harmful amyloid-β protein in monkeys.

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Two-sided antibody
The anti-Alzheimer's antibody has two binding sites — one for crossing the blood-brain barrier, the other for disabling an enzyme that produces the plaques associated with the disease.

Courtesy of Genentech

Delivering medications to the brain could become easier, thanks to molecules that can escort drugs through the notoriously impervious sheath that separates blood vessels from neurons. In a proof-of-concept study in monkeys, biologists used the system to reduce levels of the protein amyloid-β, which accumulates in the brain plaques associated with Alzheimer's disease[1].

The blood–brain barrier is a layer of cells lining the inner surface of the capillaries that feed the central nervous system. It is nature's way of protecting the delicate brain from infectious agents and toxic compounds, while letting nutrients and oxygen in and waste products out. Because the barrier strictly regulates the passage of larger molecules and often prevents drug molecules from entering the brain, it has long posed one of the most difficult challenges in developing treatments for brain disorders.

Several approaches to bypassing the barrier are being tested, including nanoparticles that are small enough to pass through the barrier's cellular membranes and deliver their payload; catheters that carry a drug directly into the brain; and ultrasound pulses that push microbubbles through the barrier. But no approach has yet found broad therapeutic application.

Neurobiologist Ryan Watts and his colleagues at the biotechnology company Genentech in South San Francisco have sought to break through the barrier by exploiting transferrin, a protein that sits on the surface of blood vessels and carries iron into the brain. The team created an antibody with two ends. One end binds loosely to transferrin and uses the protein to transport itself into the brain. And once the antibody is inside, its other end targets an enzyme called β-secretase 1 (BACE1), which produces amyloid-β. Crucially, the antibody binds more tightly to BACE1 than to transferrin, and this pulls it off the blood vessel and into the brain. It locks BACE1 shut and prevents it from making amyloid-β.

Forward and back

When Genentech first described tests of the antibody in 2011, the results seemed promising: in mice engineered to produce the human version of BACE1, a single injection of the antibody knocked down amyloid concentrations in the brain by 47% . But the project was set back in 2013, when the researchers discovered[2] that the antibody attacked immature red blood cells that have transferrin on the outer surface of their membranes, suggesting that the treatment could be harmful.

In their most recent study, published today in *Science Translational Medicine*[1], the researchers adjusted the strength with which the antibody binds to transferrin.

When they tested the drug in both mice and crab-eating macaques (*Macaca fascicularis*), they found that it spread throughout the animals' brains and decreased levels of amyloid-β in their blood plasma by more than 50%. The antibody did not seem to affect the monkeys' blood cells. It remains to be seen, however, whether the drug would mitigate the behavioural symptoms of Alzheimer's, because monkeys do not develop the disease or amyloid plaques in the way that humans do.

"It's a very elegant, clever approach," says Robert Vassar, a molecular biologist at Northwestern University Feinberg School of Medicine in Chicago, who studies the role of BACE1 in Alzheimer's disease. The key, he says, seems to be engineering the antibody so that it binds neither too tightly nor too loosely to transferrin.

Over the wall

BACE1 has become a popular target for potential Alzheimer's treatments: pharmaceutical companies including Merck, Eli Lilly and AstraZeneca are conducting clinical trials with small-molecule drugs that attack the enzyme. An advantage of the antibody approach, says Vassar, is that it is less likely to be toxic to the liver and other organs than a small molecule might be.

Watts says that he and his colleagues are now working on ways to manufacture the antibody at a quality high enough for testing in humans. "We're beside ourselves with excitement," he says.

Yet the real advance, he adds, is that the BACE1 study shows that the transferrin-binding antibody is safe and can successfully enter the brain. The method can now be modified to carry any number of antibodies or drugs across the blood–brain barrier. One compound that could be used is Genentech's drug crenezumab, an antibody that targets amyloid itself. It is currently being tested in clinical trials treating healthy young people at risk of Alzheimer's, in the hope that it will prevent plaques from building up before the brain has been irreparably damaged.

Watts says that participants in these trials are currently being given very high levels of crenezumab, so that at least some can make it into their brains. The antibody platform could make the treatment both safer and more efficient, and Watts says that Genentech is currently testing it with crenezumab and other drugs in animals.

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References

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2. Couch, J. A. *et al*. *Sci. Transl. Med.* **5**, 183ra57 (2013).