

# Engineering a 'Trojan horse' to sneak drugs into the brain

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Beset by a host of debilitating and potentially fatal disorders, the human brain is in desperate need of a few good drugs. The catch, however, is that nature has set up a roadblock known as the blood-brain barrier — intended to keep harmful agents out — that prevents clinicians from administering effective medicine.

Now, scientists have hit upon a scheme that could be used to sneak drugs past the barrier to treat afflictions such as Parkinson's, Alzheimer's, brain tumors and stroke. The idea, according to Eric V. Shusta, a University of Wisconsin-Madison professor of chemical and biological engineering, is to exploit human antibodies by transforming them into "Trojan horses" capable of ferrying payloads of drugs from the blood across the barrier and into the parts of the brain where they will do the most good.

Describing the new work in San Francisco today (Sept. 13) at a meeting of the American Chemical Society, Shusta described a system where antibodies capable of penetrating the blood-brain barrier could be used to carry drugs, DNA or even therapeutic nanoparticles to the brain.

"There are many drugs that show promise in the Petri dish," Shusta explains. "We just can't deliver them."

The scheme being explored by Shusta and his colleagues rests on the ability of antibodies, protein molecules that circulate in the blood and whose job, typically, is to seek out and neutralize foreign pathogens and

toxins before they do harm. Antibodies are good at such work because they are built to recognize the surface features of targeted cells.

Using engineered yeast as microscopic factories to produce human antibodies customized to recognize the surface features of cells that compose the blood-brain barrier, Shusta has developed a set of unique antibodies that may one day be used to ferry drugs to specified regions of the brain.

"Antibodies bind tightly and specifically to cells, and we're trying to find those that home in on the blood-brain barrier endothelial cells," Shusta says.

When antibodies bind to cells, they can sometimes gain access to the cell and, potentially, open a gateway for the delivery of drugs or other therapeutic agents.

"We'd like to use the bloodstream to deliver drugs, but most small molecule pharmaceuticals as well as larger protein and gene medicines cannot pass the blood-brain barrier," he says.

With roughly 400 miles of blood vessels, the human brain is equipped with its own expansive delivery network for therapy — provided scientists are able to figure out a way to get past the blood-brain barrier. With different cell surface features in different parts of the circulatory system and also in different regions of the brain, it might be possible to customize antibodies to carry drugs to only those parts of the brain that would benefit from treatment.

So far, Shusta and his colleagues have identified a panel of unique antibodies that avidly bind to the plasma membranes of brain endothelial cells. In some cases, the antibodies engineered by the Wisconsin team have demonstrated the capacity to gain access to the cell, showing their

"potential to act as molecular Trojan horses and allow blood-to-brain transfer of a wide range of pharmaceuticals."

The idea of using antibodies to tote drugs into the brain is not new, according to Shusta, but the antibodies used to date are not particularly efficient. The work of Shusta's group, however, has shown it is possible to identify novel transporting antibodies that could one day provide effective alternatives. "Ours is a novel system," Shusta adds. "We're still trying to work out the specifics, but we're pretty excited."

Source: University of Wisconsin-Madison

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