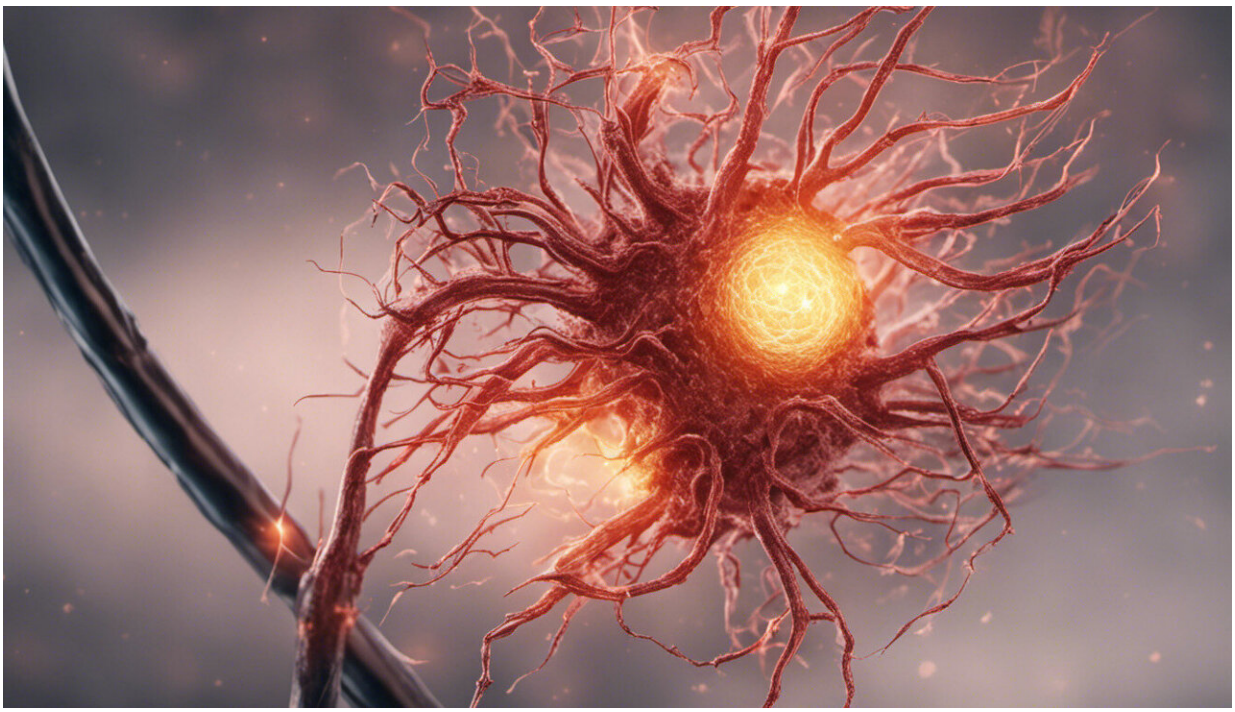
'Inverse vaccine' shows potential to treat multiple sclerosis and other autoimmune diseases

September 11 2023, by Sarah C.P. Williams



Credit: AI-generated image (disclaimer)

A new type of vaccine developed by researchers at the University of Chicago's Pritzker School of Molecular Engineering (PME) has shown in the lab setting that it can completely reverse autoimmune diseases like multiple sclerosis, type 1 diabetes, and Crohn's disease—all without

shutting down the rest of the immune system.

A typical vaccine teaches the human immune system to recognize a virus or bacteria as an enemy that should be attacked. The new "inverse vaccine" does just the opposite: it removes the immune system's memory of one molecule. While such immune memory erasure would be unwanted for infectious diseases, it can stop autoimmune reactions like those seen in multiple sclerosis, type I diabetes, rheumatoid arthritis or Crohn's disease, in which the immune system attacks a person's healthy tissues.

The inverse vaccine, described this week in *Nature Biomedical Engineering*, takes advantage of how the liver naturally marks molecules from broken-down cells with "do not attack" flags to prevent autoimmune reactions to cells that die by natural processes.

PME researchers coupled an antigen—a molecule being attacked by the immune system—with a molecule resembling a fragment of an aged cell that the liver would recognize as friend, rather than foe. The team showed how the vaccine could successfully stop the autoimmune reaction associated with a multiple-sclerosis-like disease.

"In the past, we showed that we could use this approach to prevent autoimmunity," said Jeffrey Hubbell, the Eugene Bell Professor in Tissue Engineering and lead author of the new paper. "But what is so exciting about this work is that we have shown that we can treat diseases like multiple sclerosis after there is already ongoing inflammation, which is more useful in a real-world context."

Unwinding an immune response

The job of the immune system's T cells is to recognize unwanted cells and molecules—from viruses and bacteria to cancers—as foreign to the

body and get rid of them. Once T cells launch an initial attack against an antigen, they retain a memory of the invader to eliminate it more quickly in the future.

T cells can make mistakes, however, and recognize healthy cells as foreign. In people with Crohn's disease, for instance, the immune system attacks cells of the small intestine; in those with multiple sclerosis, T cells mount an attack against myelin, the protective coating around nerves.

Hubbell and his colleagues knew that the body has a mechanism for ensuring that immune reactions don't occur in response to every damaged cell in the body— a phenomenon known as peripheral immune tolerance and carried out in the liver. They discovered in recent years that tagging molecules with a sugar known as N-acetylgalactosamine (pGal) could mimic this process, sending the molecules to the liver where tolerance to them develops.

"The idea is that we can attach any molecule we want to pGal and it will teach the immune system to tolerate it," explained Hubbell. "Rather than rev up immunity as with a vaccine, we can tamp it down in a very specific way with an inverse vaccine."

In the new study, the researchers focused on a multiple-sclerosis-like disease in which the immune system attacks myelin, leading to weakness and numbness, loss of vision and, eventually mobility problems and paralysis. The team linked myelin proteins to pGal and tested the effect of the new inverse vaccine. The immune system, they found, stopped attacking myelin, allowing nerves to function correctly again and reversing symptoms of disease in animals.

In a series of other experiments, the scientists showed that the same approach worked to minimize other ongoing immune reactions.

Toward clinical trials

Today, autoimmune diseases are generally treated with drugs that broadly shut down the immune system.

"These treatments can be very effective, but you're also blocking the immune responses necessary to fight off infections and so there are a lot of side effects," said Hubbell. "If we could treat patients with an inverse vaccine instead, it could be much more specific and lead to fewer side effects."

More work is needed to study Hubbell's pGal compounds in humans, but initial phase I safety trials have already been carried out in people with celiac disease, an autoimmune disease that is associated with eating wheat, barley and rye, and phase I safety trials are under way in multiple sclerosis. Those trials are conducted by the pharmaceutical company Anokion SA, which helped fund the new work and which Hubbell cofounded and is a consultant, board member and equity holder. The Alper Family Foundation also helped fund the research.

"There are no clinically approved inverse vaccines yet, but we're incredibly excited about moving this technology forward," says Hubbell.

More information: Andrew C. Tremain et al, Synthetically glycosylated antigens for the antigen-specific suppression of established immune responses, *Nature Biomedical Engineering* (2023). DOI: 10.1038/s41551-023-01086-2

Provided by University of Chicago