

# Vaccine-like mRNA injection can be used to make CAR T cells in the body

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An experimental immunotherapy can temporarily reprogram patients' immune cells to attack a specific target via only a single injection of messenger RNA (mRNA), similar to the mRNA-based COVID-19

vaccines, according to a new study from researchers in the Perelman School of Medicine at the University of Pennsylvania.

The researchers, whose work is published today in *Science*, demonstrated the new approach with an mRNA preparation that reprograms T cells—a powerful type of immune cell—to attack heart fibroblast cells. Heart failure is often driven in part by these [fibroblast cells](#), which respond to heart injury and inflammation by chronically overproducing fibrous material that stiffens the [heart muscle](#), impairing heart function—a condition called fibrosis. In experiments in mice that model [heart failure](#), the reduction in cardiac fibroblasts caused by the reprogrammed T cells led to a dramatic reversal of fibrosis.

"Fibrosis underlies many serious disorders, including heart failure, [liver disease](#), and kidney failure, and this technology could turn out to be a scalable and affordable way to address an enormous medical burden," said senior author Jonathan A. Epstein, MD, chief scientific officer for Penn Medicine and executive vice dean and the William Wikoff Smith Professor of Cardiovascular Research in the Perelman School of Medicine. "But the most notable advancement is the ability to engineer T cells for a specific clinical application without having to take them out of the patient's body."

The new technique is based on [chimeric antigen receptor](#) (CAR) T cell technology, which, until now, has required the harvesting of a patient's T cells and their genetic reprogramming in the lab to recognize markers on specific cell types in the body. These specially targeted T cells can then be multiplied using cell culture techniques and re-infused into the patient to attack a specific cell type. The first CAR T cell therapy was developed by researchers from Penn and Children's Hospital of Philadelphia and approved by the U.S. Food and Drug Administration in 2017 for use against certain leukemias—and later approved for lymphoma—that arise from [immune cells](#) called B cells.

Although CAR T cell technology is currently used primarily for treating cancers, with dramatic results in many otherwise hopeless cases, its developers have long envisioned harnessing the approach for other diseases. Indeed, Epstein and colleagues showed in a [2019 study](#) that the standard CAR T cell approach can be used to attack overactive cardiac fibroblasts and restore heart function in a mouse model of heart failure.

However, this standard CAR T cell strategy would be problematic when directed against heart failure or other fibrotic diseases in humans. Fibroblasts have a normal and important function in the body, especially in wound-healing. CAR T cells that are reprogrammed genetically to attack fibroblasts could survive in the body for months or even years, suppressing the fibroblast population and impairing wound-healing for all that time.

Therefore, in the new study, Epstein and colleagues devised a technique for a more temporary and controllable, and procedurally much simpler, type of CAR T cell therapy. They designed mRNA that encodes a T-cell receptor targeting activated fibroblasts and encapsulated the mRNA within tiny, bubble-like lipid nanoparticles (LNPs) that are themselves covered in molecules that home in on T cells. That technology is also crucial to the mRNA COVID-19 vaccines now in use across the globe.

"Standard CAR T cell technology involves modifying patients' T cells outside the body, which is expensive and difficult to scale for common diseases or for use in less wealthy countries," said study co-author Drew Weissman, MD, Ph.D., the Roberts Family Professor in Vaccine Research at Penn. "Making functional CAR T cells inside the body greatly extends the promise of the mRNA/LNP platform."

Injected into mice, the encapsulated mRNA molecules are taken up by T cells and act as templates for the production of the fibroblast-targeting receptor, effectively reprogramming the T cells to attack activated

fibroblasts. This reprogramming is very temporary, however. The mRNAs are not integrated into T-cell DNA and survive within T cells for only a few days—after which the T cells revert to normal and no longer target fibroblasts.

The scientists found that, despite this brief duration of activity, injections of the mRNA in mice that model heart failure successfully reprogrammed a large population of mouse T [cells](#), causing a major reduction of heart fibrosis in the animals and a restoration of mostly normal [heart](#) size and function with no evidence of continued anti-fibroblast T cell activity one week after treatment.

The researchers are continuing to test this mRNA-based, transient CAR T cell technology, with the hope of eventually starting clinical trials.

Along with Epstein and Weissman, the other co-corresponding authors are Haig Aghajanian, Ph.D., vice president of research at Capstan Therapeutics and adjunct assistant professor of cardiology at Penn; and Hamideh Parhiz, PharmD, Ph.D., a research assistant professor of medicine at Penn. Joel Rurik, the lead author, is a Ph.D. candidate in Epstein's laboratory.

**More information:** Joel Rurik et al, CAR T cells produced in vivo to treat cardiac injury, *Science* (2022). [DOI: 10.1126/science.abm0594](https://doi.org/10.1126/science.abm0594). [www.science.org/doi/10.1126/science.abm0594](https://www.science.org/doi/10.1126/science.abm0594)

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Provided by Perelman School of Medicine at the University of Pennsylvania

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