Is this a faster, better treatment for blood and solid tumor cancers?

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Credit: Alyssa Stone/Northeastern University

A Northeastern researcher in the Department of Pharmaceutical Sciences and the New England Inflammation and Tissue Protection Institute (NEITPI) says his lab has employed a novel gene editing technology that might make personalized treatments for cancer available "off the shelf" against solid tumors.

The platform is called base editing, says Stephen Hatfield, assistant professor at Northeastern's Bouvé College of Health Sciences.

He says it allows multiple gene edits of cancer-fighting immune cells called CAR T cells without causing substantial DNA damage.

Enhancing a cancer killer

CAR T cell treatments have been on the market since 2017 and are considered a valuable tool in fighting blood cancers such as leukemia, particularly recurring cases.

They are genetically engineered to find hidden cancer cells in tumors and kill them.

However, to date they have been unsuccessful at eliminating solid cancers, likely due to resistance of CAR T cells to conditions in the tumor microenvironment, Hatfield says.

"One big problem with CAR T cells is they are patient specific," Hatfield says.

It can take months to remove T cells from a patient, genetically engineer the cells to attack cancer markers on the patient's tumor and reinfuse them back into the patient, Hatfield says.

"T cells are complex. I can't take my T cells and give them to you. It would cause immune reactions that would be detrimental in terms of the cells attacking tissues in your body. Or your immune system could just eliminate them altogether, making the treatment ineffective."

"What we've done is edited these CAR T cells in such a way that they don't have the molecules that would cause graft versus host disease or cause them to be eliminated by the host immune system."

"We're making them so that CAR T cell therapy would not be just

personalized medicine. It could be off the shelf," Hatfield says. "You could use it for any patient that has a tumor that expresses a particular antigen."

That means CAR T cells could be produced in larger, scalable amounts in shorter periods of time and frozen in anticipation of patient use, he says.

Fighting solid tumors

A major problem is that CAR T cell therapy has not proven effective against solid tumors such as those that occur in lung and pancreas cancer, Hatfield says, adding that most cancer cases involve solid tumors.

The type of molecules that are produced in the oxygen-depleted environment created by fast-growing tumors, such as adenosine, bar immune cells from doing their job, he says.

Adenosine molecules, for instance, are able to engage an "off switch" on the T cell to prevent it from working. "These off switches are much more prominent in the solid tumor microenvironment," says Hatfield, whose preprint paper on the topic is published on *bioRxiv*.

"We want to selectively edit out those off switches that are most relevant for a type of tumor," he says.

Hatfield says the way to do that is through the multiplex base editing platform employed by his lab at Northeastern and developed in collaboration with a Cambridge-based biotech company, Beam Therapeutics.

"This highly synergistic collaboration was enabled by the unique industrial Ph.D. program pioneered by Northeastern which allowed a

talented young scientist, Ryan Murray, to spearhead this program on the bench level between Beam Therapeutics and the Hatfield laboratory," Hatfield says.

With standard CRISPR editing of genes, DNA is more vulnerable to significant damage after multiple edits, Hatfield says. But the base-editing platform has allowed the researchers to genetically engineer cells by changing a single base in the DNA, sidestepping potential problems associated with CRISPR-based multiplex editing strategies, he says.

Hatfield and his colleagues have used the platform to make CAR T cells with six edits, the most his team has seen reported in scientific literature.

Three of the edits help turn the cells into "off-the-shelf" cells while the other three edits make CAR T cells effective in attacking solid tumors by avoiding immune suppressive barriers, according to an article in New Scientist magazine.

Hatfield believes this platform in its current form may even allow researchers to make up to eight edits in the future. He says applying the edits to human tumors grown on mice was effective in curing all the mice treated with these engineered CAR T cells.

"We're applying the base-editing technology to manufacturing CAR T cells that can be used as off-the-shelf medicine instead of personalized medicine. And they're highly effective against solid tumors in humanized mouse models, which so far has not been the case in human clinical studies" Hatfield says.

He says he is optimistic that "off the shelf" tumor-destroying CAR T cells are such an attractive weapon the technology "will be translated into clinical trials as soon as possible."

More information: Ryan Murray et al, Comprehensive genome editing confers 'off-the-shelf' CAR-T cells superior efficacy against solid tumors, *bioRxiv* (2023). DOI: 10.1101/2023.08.03.551705

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