

Ultrasound remotely triggers immune cells to attack tumors in mice without toxic side effects

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Credit: Martha Sexton/public domain

Bioengineers at the University of California San Diego have developed a cancer immunotherapy that pairs ultrasound with cancer-killing immune cells to destroy malignant tumors while sparing normal tissue.

The new experimental therapy significantly slowed down the growth of solid cancerous tumors in mice.

The team, led by the labs of UC San Diego bioengineering professor Peter Yingxiao Wang and bioengineering professor emeritus Shu Chien, detailed their work in a paper published Aug. 12 in *Nature Biomedical Engineering*.

The work addresses a longstanding problem in the field of cancer immunotherapy: how to make [chimeric antigen receptor](#) (CAR) T-cell therapy safe and effective at treating [solid tumors](#).

CAR T-cell therapy is a promising new approach to treat cancer. It involves collecting a patient's T cells and genetically engineering them to express special receptors, called CAR, on their surface that recognize specific antigens on [cancer cells](#). The resulting CAR T cells are then infused back into the patient to find and attack cells that have the cancer antigens on their surface.

This therapy has worked well for the treatment of some blood cancers and lymphoma, but not against solid tumors. That's because many of the target antigens on these tumors are also expressed on normal tissues and organs. This can cause toxic side effects that can kill cells—these effects are known as on-target, off-tumor toxicity.

"CAR T cells are so potent that they may also attack normal tissues that are expressing the target antigens at low levels," said first author Yiqian (Shirley) Wu, a project scientist in Wang's lab.

"The problem with standard CAR T cells is that they are always on—they are always expressing the CAR protein, so you cannot control their activation," explained Wu.

To combat this issue, the team took standard CAR T cells and re-engineered them so that they only express the CAR protein when ultrasound energy is applied. This allowed the researchers to choose where and when the genes of CAR T cells get switched on.

"We use ultrasound to successfully control CAR T cells directly in vivo for [cancer immunotherapy](#)," said Wang, who is a faculty member of the [Institute of Engineering in Medicine](#) and the [Center for Nano-ImmunoEngineering](#), both at UC San Diego. What's exciting about the use of ultrasound, noted Wang, is that it can penetrate tens of centimeters beneath the skin, so this type of therapy has the potential to non-invasively treat tumors that are buried deep inside the body.

The team's approach involves injecting the re-engineered CAR T cells into tumors in mice and then placing a small ultrasound transducer on an area of the skin that's on top of the tumor to activate the CAR T cells. The transducer uses what's called focused ultrasound beams to focus or concentrate short pulses of ultrasound energy at the tumor. This causes the tumor to heat up moderately—in this case, to a temperature of 43 degrees Celsius (109 degrees Fahrenheit)—without affecting the surrounding tissue. The CAR T cells in this study are equipped with a gene that produces the CAR protein only when exposed to heat. As a result, the CAR T cells only switch on where ultrasound is applied.

The researchers put their CAR T cells to the test against standard CAR T cells. In mice that were treated with the new CAR T cells, only the tumors that were exposed to [ultrasound](#) were attacked, while other tissues in the body were left alone. But in mice that were treated with the standard CAR T [cells](#), all tumors and tissue expressing the target antigen were attacked.

"This shows our CAR T-cell therapy is not only effective, but also safer," said Wu. "It has minimal on-target, off-[tumor](#) side effects."

The work is still in the early stages. The team will be performing more preclinical tests and toxicity studies before it can reach clinical trials.

More information: Wu, Y. et al, Control of the activity of CAR-T cells within tumours via focused ultrasound, *Nat Biomed Eng* (2021). doi.org/10.1038/s41551-021-00779-w

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