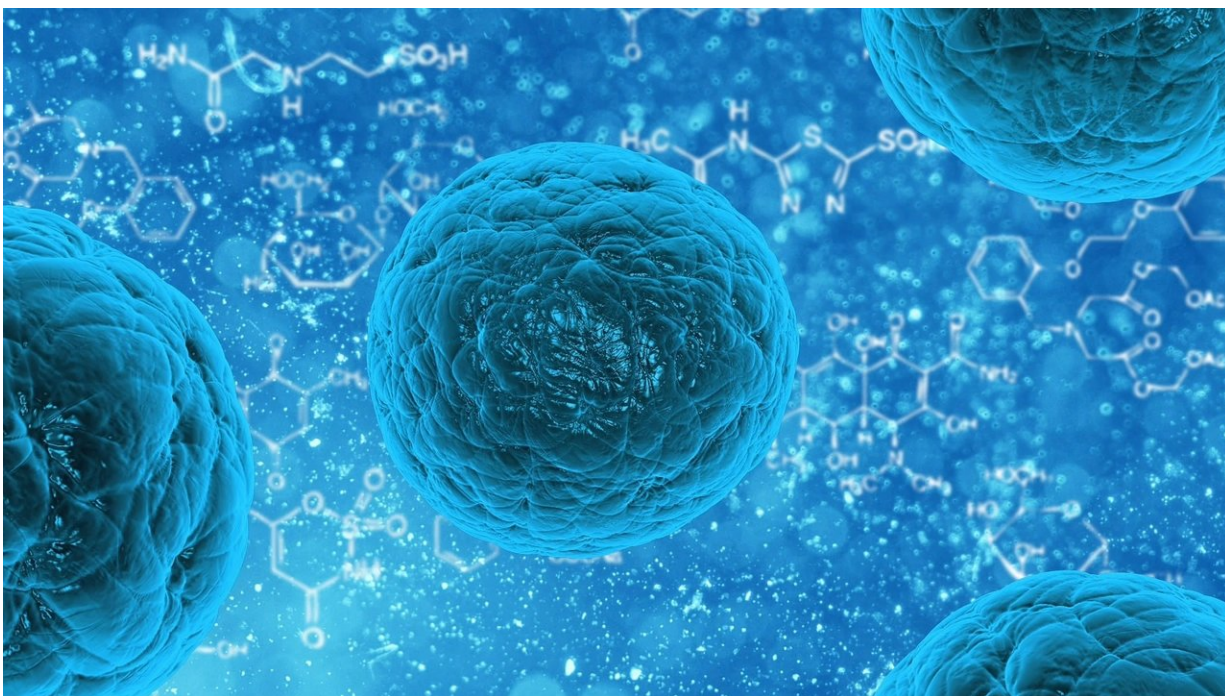


# A method to engineer immune cells so they grow even in hostile tumors

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Tumors can create a hostile environment for cancer-fighting immune cells. In a new study, University of North Carolina Lineberger Comprehensive Cancer Center researchers have developed a method for engineering immune cells to improve their survival and proliferation, even within a hostile tumor.

Researchers led by UNC Lineberger's Gianpietro Dotti, MD, report in the journal *Nature Biotechnology* they have created a method for providing a stimulatory signal to super-charge cancer-hunting [immune cells](#), called chimeric antigen receptor T-cells, that have been genetically engineered to hunt and kill specific cancers. Their preclinical finding offers an alternative method to amplifying the modified T-cells while avoiding activating other immune cells that could cause off-target side effects.

"Our study was trying to see if we could find an alternative strategy so that we could still provide the T-cells with proliferation signals, but also when and where we want them to proliferate, causing less of a global effect in terms of the cells' activities," said Yang Xu, Ph.D., postdoctoral research associate at UNC Lineberger and the study's senior author.

## **Researching CAR-T immunotherapy for solid tumors**

Cellular immunotherapy, or CAR-T immunotherapy, involves extracting specific immune cells from patients, engineering the cells in the lab to hunt [tumor](#) cells displaying a specific molecular target, and then re-infusing them into the patient to fight their cancer.

Through the Clinical Immunotherapy Program, UNC Lineberger researchers have designed novel investigational CAR-T therapies for Hodgkin and non-Hodgkin lymphoma, multiple myeloma, neuroblastoma and leukemia that are being studied in clinical trials.

Researchers are working to find ways to make CAR-T effective in solid tumors, which can be a hostile environment for the modified T-cells, Xu said. Inside solid tumors, the immune cells don't have as much access to nutrients from the blood that can help them grow and proliferate.

"One way that we could improve this is to provide a secondary signal to

these T-cells so they can sustain their proliferation, even when the cells are in a very hostile environment," Xu said.

## **Research findings**

First, researchers discovered important insights about the function of the stimulatory molecule interleukin 23, or IL-23. They determined the receptor for this stimulatory signal is present only when the cancer-fighting T-cells get activated.

Based on this finding, they wondered whether they could engineer the cells to self-produce this proliferation signal, and only in T-cells that are fighting the tumor.

"We thought: Maybe we could use this in a way to selectively provide the proliferation signal to the cells that encounter the tumor without activating bystander cells within the tumor," Xu said. "We found when we added IL-23 to the cells, when these T-cells were activated, these cytokines improved their proliferation, and this method does not have any effect on the T-cells that are not activated."

Researchers then reported a method of engineering the T-cells to produce the IL-23. More specifically, researchers engineered the cells so when they recognized the tumor and were stimulated to kill, they would also be stimulated to produce IL-23, which helps them to proliferate.

"If you think about your immune system—it's regulated in a very strict way," Xu said. "You want the cells that are recognizing an infection or a tumor to proliferate, to increase in number inside the tumor. You do not want other cells that are not specific for that infection to be reactive. If that's the case, you could get a global immune activation throughout the body, and end up with side effects like skin allergies. We envision IL-23 would only be produced by and act on the cells getting activated, which

are the CAR-T cells that are encountering the tumor cells."

Researchers demonstrated their method of increasing proliferation using mouse models of neuroblastoma and pancreatic cancer. Researchers are planning to continue their work to find ways to improve the modified T-cells' functions in other ways, such as boosting their metabolic activities so they can function better in nutrient-poor tumors.

They also believe that this new discovery could improve investigational CAR-T therapies currently under study in clinical trials. Dotti said other investigational CAR-T designs, such as those under study at UNC for pediatric neuroblastoma, incorporate a different strategy for boosting the CAR-T [cells](#) within tumors that utilizes a stimulatory signal called interleukin-15, or IL-15.

"We are currently evaluating an investigational CAR-T immunotherapy approach for pediatric patients with neuroblastoma that utilizes CAR-T that constitutively make another cytokine named IL-15," Dotti said.

"The IL-23 engineering seems even superior to the IL-15 strategy in preclinical models. We hope to clinically develop this approach in the near future in [solid tumors](#) such as pancreatic cancer."

**More information:** Xingcong Ma et al. Interleukin-23 engineering improves CAR T cell function in solid tumors, *Nature Biotechnology* (2020). [DOI: 10.1038/s41587-019-0398-2](https://doi.org/10.1038/s41587-019-0398-2)

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