New discovery would allow researchers to fine-tune CAR-T activity

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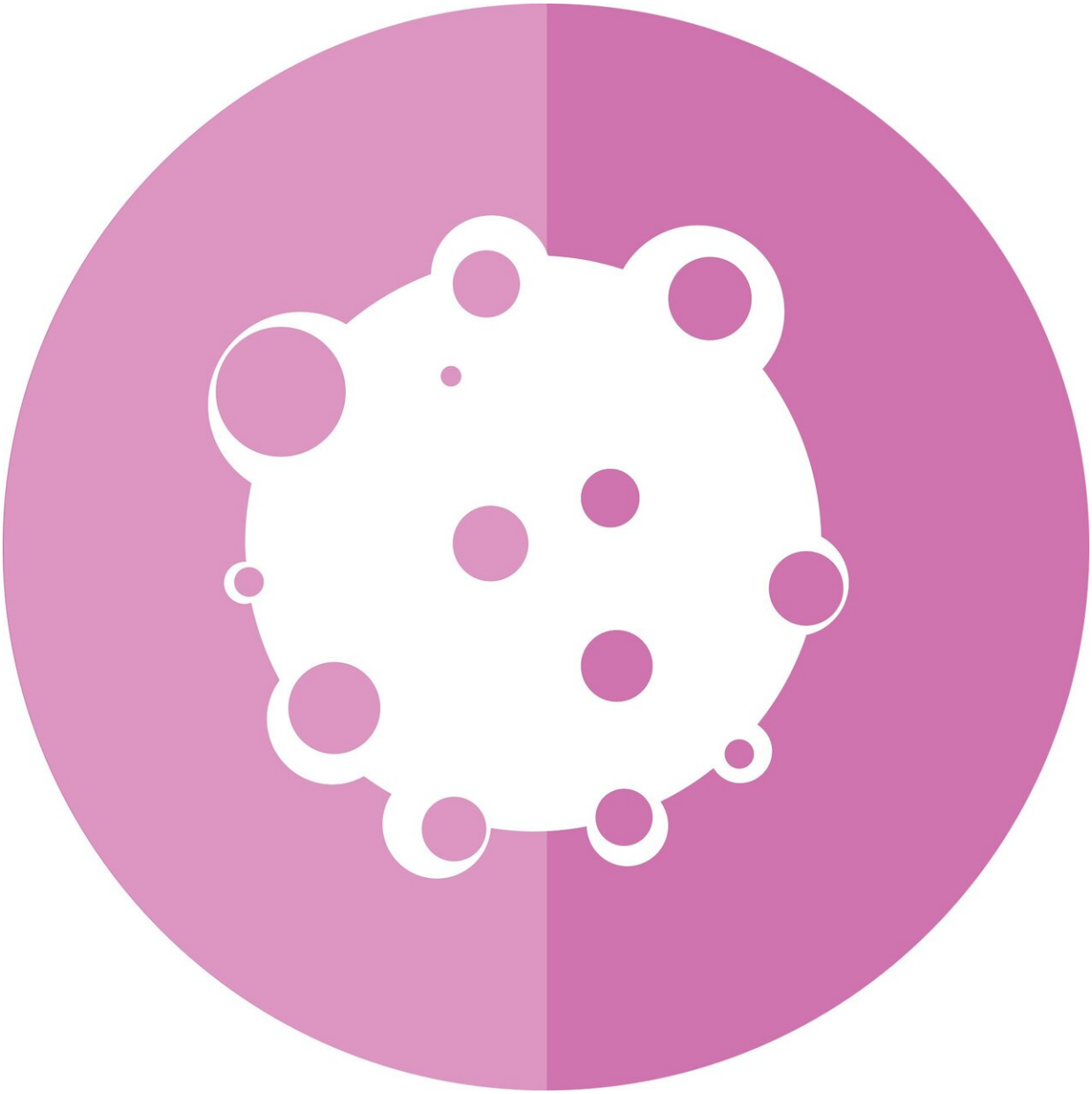

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A discovery by University of North Carolina Lineberger Comprehensive Cancer Center researchers could allow scientists to fine-tune genetically engineered immune cells to heighten their killing power against tumors or to decrease their activity level in the case of severe side effects.

In a study published in *Cancer Cell*, researchers led by UNC Lineberger's Gianpietro Dotti, MD, reported new findings about the regulation of co-stimulatory molecules that could be used to activate cancer-killing immune cells—chimeric antigen receptor T-cells, or CAR-T—or decrease their activity.

"In immunology, it's always about balance; you don't want to have too much T-cell activation, and you don't want T-cell activation to be too low," said Peishun Shou, Ph.D., postdoctoral research associate at UNC Lineberger and the study's co-first author. "We wanted to keep the T-cell activation and tumor killing at a suitable or sustainable level."

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 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.

"We are conducting and developing clinical studies with CAR-T cells in both liquid and solid tumors. In these studies, we are testing what we call

the 'new generation' of CAR-T cells, hoping to further enhance the therapeutic index of this technology," said Dotti, the study's corresponding author, a professor in the UNC School of Medicine Department of Microbiology and Immunology and director of the UNC Lineberger Cellular Immunotherapy Program. "This latest study highlights how when translational and basic science come together, we can hopefully improve therapeutic strategies."

In the *Cancer Cell* study, researchers revealed new strategies for engineering investigational CAR-T to either increase the activity of modified T-cells to more effectively kill tumor cells or decrease their activity in case the therapies trigger severe side effects.

They developed strategies for improving two different types of modified T-cells. These two types of CAR-T cells are differentiated by the signals that activate them. First, they have a receptor that recognizes a specific marker on the tumor—the first signal. They also need a second signal that helps to fully activate them and increase their response. There are two different types of T-cells that have different "second signals" that activate them.

One type of CAR-T is co-stimulated by the CD28 protein, and another is stimulated by 4-1BB. UNC Lineberger researchers wanted to find a way to regulate these proteins in order to "fine-tune" the cells' disease-fighting response, since researchers reported each type of CAR-T has differences in terms of how long it typically lasts in the body to fight cancer, how quickly it responds and the strength of its response.

"T-cells have to be activated to kill tumor cells," Shou said. "If you have better activation, you have more cytokine release ... and the cells can better target a tumor and kill it. In some cases, we want to make the T cells stronger, more active, and depending on the tumor type, we may want to tune down the T-cell activation to help the T-cells survive and

expand."

For CAR-T co-stimulated by 4-1BB, scientists found they could increase expression of the LCK molecule to increase the cells' activity.

"What we found is that the LCK molecule can bind to the CAR, enhancing the CAR-T cell activation and signaling transduction, which therefore will help CAR-T cells get a better tumor-killing effect," Shou said.

They also reported on the discovery of a new "safety switch" mechanism to reduce activity of CAR-T co-stimulated by CD28. Doctors could use the safety switch should patients experience severe side effects from the experimental therapy.

They found they could use a molecule called SHP1 to reduce T-cell activity. When they added a certain drug, SHP1 bound to the CAR to reduce the activity of CAR-T cells.

"In the presence of the drug, we can cool down or tune down the CAR-T cell activation," Shou said. "The advantage of this switch is that it will not kill the CAR-T cells; it's just temporarily tuning down the activity."

Researchers want to investigate using these findings to improve CAR-T treatments against blood cancers like leukemia, and to potentially improve experimental treatments for solid tumors.

"Researchers in the CAR-T immunotherapy field now want to solve the solid tumor problem," Shou said. "Solid tumors have an immunosuppressive microenvironment, so you need stronger CAR-T activation."

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