New cell type, called Co-STAR, fights cancer cells. Credit: Elizabeth Cook

Using genetic engineering techniques, investigators at the Johns Hopkins Kimmel Cancer Center and its Ludwig Center, the Lustgarten Laboratory and Bloomberg~Kimmel Institute for Cancer Immunotherapy have designed a novel type of cell to recognize and fight cancer.
To produce the cells, called Co-STAR (Co-stimulatory Synthetic T-cell receptor and Antigen Receptor) cells, the researchers combined genetic components of four types of cells that the body normally uses to defend against invaders to make a powerful new cell type: T-cell receptors (TCRs) from T cells, antibodies from B cells, MyD88 from white blood cells called monocytes, and CD40 from dendritic and other cells.

The TCR and antibody components served as an "invader-detecting device," recognizing cancer cells as foreign, and the "alarm" triggered by this hybrid detector was boosted by the MyD88 and C40 components.

In laboratory studies, Co-STARs led to a sustained anti-tumor response against human cancer cells growing in test tubes and in mice. A description of the work was published July 10 in Science Translational Medicine.

T cell-based therapies are among the most promising approaches to treat advanced cancer and are the subject of intense research, explains lead study author Brian Mog, M.D., Ph.D., an internal medicine resident at Brigham and Women's Hospital in Boston. He was a medical and graduate student at the Johns Hopkins University School of Medicine when the research was conducted.

However, TCR and CAR (chimeric antigen receptor, usually using an antibody as the detector), which are aimed at stimulating an immune response by activating T cells, each have limits. The combination of the two can overcome these limitations.

"We needed to make a new type of cell, because we were trying to target specific antigens called peptide-HLA (human leukocyte antigen) antigens, which are peptide fragments from mutant proteins inside the cancer cell that are displayed on the cell surface by peptide-holding proteins called HLAs," Mog explains.
Their specific target was a peptide containing the R175H mutation of p53 (the 175th amino acid of p53 is mutated from arginine to histidine), displayed on the HLA-A2 allele (gene variation). This is the most common mutation in the tumor suppressor protein p53, which is in turn the most commonly mutated gene in human cancers.

However, these antigens are present in very low numbers (just one to 10) in a cancer cell, and the classic CAR format would not be able to react to such a small amount.

"Our goal was to combine some of the advantages of the CAR format with those of the natural T cell receptor on T cells, supplemented with additional signaling boosters, so that they could fight cancers more effectively," Mog says.

The team went through multiple rounds of engineering to come up with the final design, testing their receptors in model cancer cell lines in test tubes and then in mouse models of cancer. The final Co-STAR T cells were able to continuously kill human cancer cells in test tubes.

When tested in mouse models of cancer, Co-STARs induced a robust, long-lasting proliferation of T cells that were able to induce profound remissions and often cure human cancer cells growing in mice. By contrast, more conventional T cells or CAR T cells were not able to eradicate the cancer cells in vitro and only brought about temporary tumor control in mice, with the cancers re-emerging days later.

"Brian's results demonstrated that Co-STAR T cells combine the advantages of many features of immune cells that normally fight infection in a way that allowed them to effectively kill cancer cells in mouse models," says co-senior investigator Bert Vogelstein, M.D., Clayton Professor of Oncology, Howard Hughes Medical Institute investigator and co-director of the Ludwig Center. "Co-STARs address
some, but certainly not all, challenges confronting T cell-based therapeutics but are certainly worthy of continued investigation.

"I was, honestly, incredibly surprised that the Co-STARs worked so well in mice, given that I had generated so many different types of T cells over four years that could only slow the growth of cancers in mice," adds Mog. "Witnessing those cures was a very exciting moment."

Study co-authors were Nikita Marcou, Sarah DiNapoli, Alexander Pearlman, Tushar Nichakawade, Michael Hwang, Jacqueline Douglass, Emily Han-Chung Hsiue, Stephanie Glavaris, Katharine Wright, Maximilian Konig, Suman Paul, Nicolas Wyhs, Jiaxin Ge, Michelle Miller, P. Aitana Azurmendi, Evangeline Watson, Drew Pardoll, Sandra Gabelli, Chetan Bettegowda, Nickolas Papadopoulos, Kenneth Kinzler and Shibin Zhou of Johns Hopkins.


Provided by Johns Hopkins University School of Medicine

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