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Researchers program cancer-fighting cells to resist exhaustion, attack solid tumors in mice

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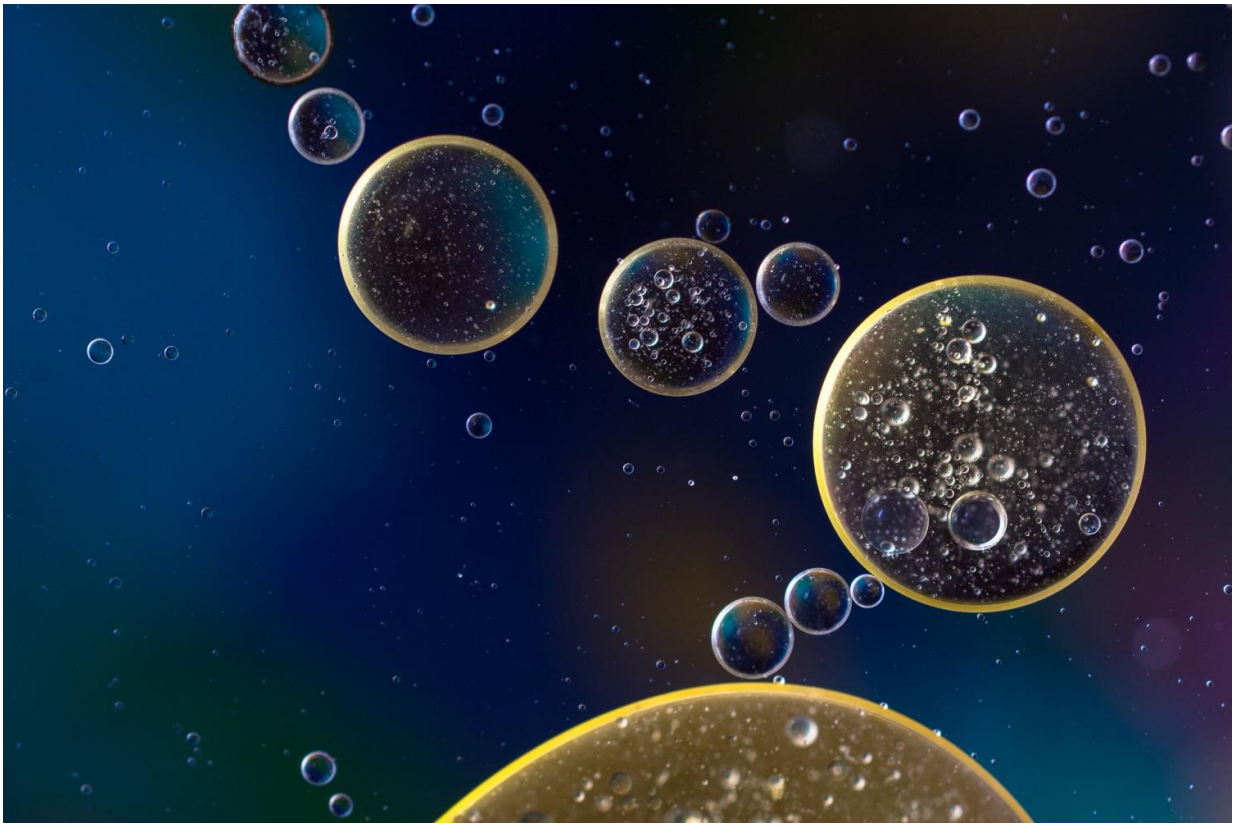

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A new approach to programing cancer-fighting immune cells called CAR-T cells can prolong their activity and increase their effectiveness against human cancer cells grown in the laboratory and in mice,

according to a study by researchers at the Stanford University School of Medicine.

The ability to circumvent the exhaustion that the genetically engineered cells often experience after their initial burst of activity could lead to the development of a new generation of CAR-T cells that may be effective even against solid cancers—a goal that has until now eluded researchers.

The studies were conducted in mice harboring human leukemia and bone cancer cells. The researchers hope to begin clinical trials in people with leukemia within the next 18 months and to eventually extend the trials to include solid cancers.

"We know that T cells are powerful enough to eradicate cancer," said Crystal Mackall, MD, professor of pediatrics and of medicine at Stanford and the associate director of the Stanford Cancer Institute. "But these same T cells have evolved to have natural brakes that tamp down the potency of their response after a period of prolonged activity. We've developed a way to mitigate this exhaustion response and improve the activity of CAR-T cells against blood and solid cancers."

Mackall, who is also the director of the Stanford Center for Cancer Cell Therapy and of the Stanford research center of the Parker Institute for Cancer Immunotherapy, treats children with blood cancers at the Bass Center for Childhood Cancer and Blood Diseases at Stanford Children's Health.

Mackall is the senior author of the study, which will be published Dec. 4 in *Nature*. Former postdoctoral scholar Rachel Lynn, Ph.D., is the lead author.

Genetically modified cells of patient

CAR-T cells is an abbreviation for chimeric antigen receptor T cells. Genetically modified from a patient's own T cells, CAR-T cells are designed to track down and kill cancer cells by recognizing specific proteins on the cells' surface. CAR-T cell therapy made headlines around the world in 2017 when the Food and Drug Administration fast-tracked their approval for the treatment of children with relapsed or unresponsive acute lymphoblastic leukemia. Later that year, a version of CAR-T treatment was also approved for adults with some types of lymphoma.

But although blood cancers often respond impressively to CAR-T treatment, fewer than half of treated patients experience long-term control of their disease, often because the CAR-T cells become exhausted, losing their ability to proliferate robustly and to actively attack cancer cells. Overcoming this exhaustion has been a key goal of cancer researchers for several years.

Lynn and Mackall turned to a technique co-developed in the laboratory of Howard Chang, MD, Ph.D., the Virginia and D.K. Ludwig Professor of Cancer Genomics and professor of genetics at Stanford, to understand more about what happens when T cells become exhausted and whether it might be possible to inhibit this exhaustion. The technique, called ATAC-Seq, pinpoints areas of the genome where regulatory circuits overexpress or underexpress genes.

"When we used this technique to compare the genomes of healthy and exhausted T cells," Mackall said, "we identified some significant differences in gene expression patterns." In particular, the researchers discovered that exhausted T cells demonstrate an imbalance in the activity of a major class of genes that regulate protein levels in the cells, leading to an increase in proteins that inhibit their activity.

When the researchers modified CAR-T cells to restore the balance by

overexpressing c-Jun, a gene that increases the expression of proteins associated with T cell activation, they saw that the cells remained active and proliferated in the laboratory even under conditions that would normally result in their exhaustion. Mice injected with human leukemia cells lived longer when treated with the modified CAR-T cells than with the regular CAR-T cells. In addition, the c-Jun expressing CAR-T cells were also able to reduce the tumor burden and extend the lifespan of laboratory mice with a human bone cancer called osteosarcoma.

"Those of us in the CAR-T cell field have wondered for some time if these cells could also be used to combat solid tumors," Mackall said. "Now we've developed an approach that renders the cells exhaustion resistant and improves their activity against solid tumors in mice. Although more work needs to be done to test this in humans, we're hopeful that our findings will lead to the next generation of CAR-T cells and make a significant difference for people with many types of cancers."

More information: Rachel C. Lynn et al, c-Jun overexpression in CAR T cells induces exhaustion resistance, *Nature* (2019). DOI: 10.1038/s41586-019-1805-z

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