New 'SLICE' tool can massively expand immune system's cancer-fighting repertoire

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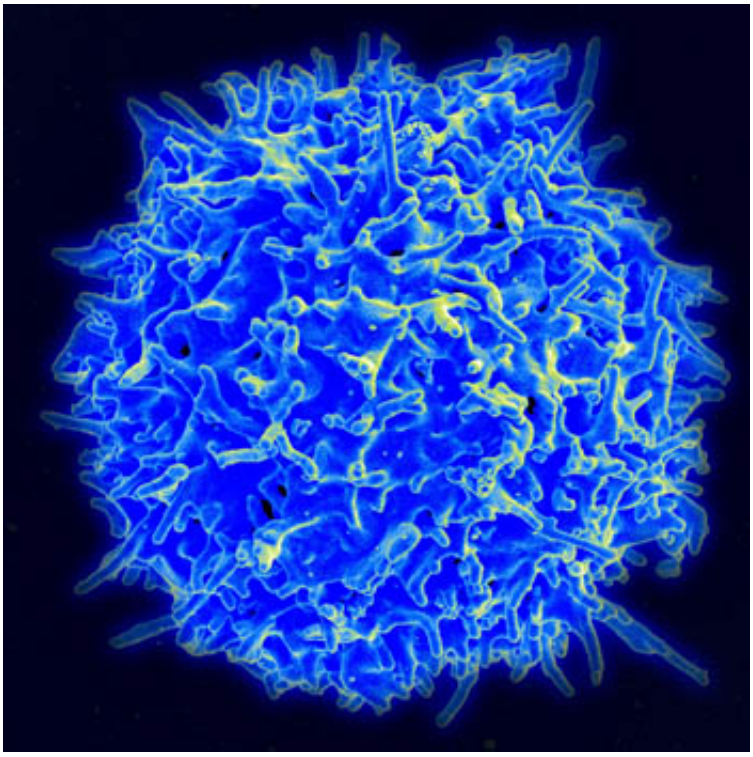

Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

Immunotherapy can cure some cancers that until fairly recently were considered fatal. In addition to developing drugs that boost the immune system's cancer-fighting abilities, scientists are becoming expert at manipulating a patient's own immune cells, turning them into cancer-killing armies. But cancers have tricks to evade attack, so scientists are

racing to outmaneuver cancer and boost the effectiveness of immune cell therapies. Today's scientists are skilled immune system engineers, but they're working off of an incomplete blueprint: while they know a great deal about how to reprogram immune cell pathways, they often can't determine precisely which circuits they should rewire in order to fabricate a more potent immune system.

Now, UC San Francisco researchers have devised a CRISPR-based system called SLICE, which will allow scientists to rapidly assess the function of each and every gene in "primary" immune cells—those drawn directly from patients. The new method, described in the Nov. 15 issue of *Cell*, provides researchers with a powerful tool that will guide their decision-making when determining how best to engineer immune cells to fight cancer and a host of other diseases.

"SLICE allows us to perform genome-wide screens in which we mutate every gene in the genome to see which genes have the biggest effect on the cellular behavior we're interested in," explained Alex Marson, MD,Ph.D., associate professor of microbiology and immunology at UCSF and co-senior author of the new study. "We change one gene at a time in each cell and see which change causes the cell to do what we want it to do. SLICE is the discovery engine that will point us towards pathways that we can reprogram to generate the most effective next-generation cell therapies."

SLICE Finds Genes That Ramp Up Cancer-Killing Immune Activity

As a proof of principle, the researchers tested whether they could use SLICE to identify genes that make T cells—a common type of immune cell—replicate more effectively. This is especially important for cancer immunotherapy, which employs artificially stimulated and engineered T

cells to kill cancer. So far, these therapies have only been effective against certain malignancies, but scientists believe that identifying genes that promote T cell proliferation can make cancer immunotherapy available to a wider range of patients.

Using SLICE, the researchers were able to identify genes that promote T cell replication, and others that suppress it. Though some of these genes had been previously characterized using other discovery methods, many were entirely new, demonstrating that SLICE could reveal key regulators of proliferation that other methods failed to capture.

After identifying these genes, the researchers obtained primary T cells from multiple human donors and deleted the genes that had been found to inhibit replication. When these CRISPR-modified T cells were cultured in the presence of cancer, they exhibited a markedly improved cancer-killing capacity, demonstrating that scientists could edit genes identified by SLICE and turn ordinary T cells into a potent potential therapy.

Outsmarting Cancer's Defenses

But cancer has tricks of its own. Cancer immunotherapy often fails because tumors thrive in so-called microenvironments that are teeming with compounds that suppress immune activity and prevent T cells from realizing their full cancer-killing potential.

"T cells seem to become 'suppressed' in tumor microenvironments," said UCSF Health oncologist Julia Carnevale, MD, a Damon Runyon Cancer Foundation fellow and co-first author of the new study. "We wanted to know if SLICE could help us find a way to help T cells overcome this suppression."

The researchers showed that SLICE can indeed be employed to

invigorate suppressed T cells. Utilizing SLICE, the researchers identified genes targeted by adenosine, an immunosuppressor found in tumor microenvironments, and found that deleting these genes allowed T cells to proliferate, even in the presence of adenosine.

"SLICE functions as a flexible platform that allows scientists to model the interaction between immune cells and the tumor microenvironment. We've shown that SLICE can help researchers identify genes that allow immune cells to escape the immunosuppressive forces they encounter in these microenvironments," said Alan Ashworth, Ph.D., the E. Dixon Heise Distinguished Professor in Oncology at UCSF, president of the UCSF Helen Diller Family Comprehensive Cancer Center, and co-senior author of the new study.

SLICE Is the Discovery Engine for Next-Generation Immune Cell Therapies

SLICE builds on a recent discovery from the Marson lab. In July 2018, researchers in Marson's lab reported in Nature that they could deliver CRISPR-based gene-editing constructs into immune cells using electroporation, a technique in which cells are literally shocked into absorbing molecules from outside the cell. SLICE takes a hybrid approach, incorporating the best aspects of the Marson lab's electroporation method alongside more conventional methods that employ viruses to deliver components of the CRISPR system. Once SLICE identifies genomic targets, the electroporation-based CRISPR method could be used to re-engineer those targets and reprogram immune cells, thus boosting their therapeutic capacity.

SLICE also represents a major advance over the current crop of tools that scientists use to study gene function. Though the existing methods—including RNA interference (RNAi) and a handful of

CRISPR-based approaches—have yielded important insights, their use is limited to cell lines that often fail to capture the real-life biology that researchers are most interested in. Furthermore, SLICE could be used to interrogate regions of the genome that don't code for proteins—a major advance over RNAi, which was limited to coding regions of the genome.

But most importantly, the potential applications for SLICE are not limited to what's described in the new paper, said Marson, who serves as scientific director of biomedicine at the UC Berkeley-UCSF Innovative Genomics Institute, and is also affiliated with the Parker Institute for Cancer Immunotherapy, which funded the new study.

"Given the flexibility of this approach," Marson said, "SLICE may one day help scientists to create personalized immune cells with novel disease-fighting properties."

Provided by University of California, San Francisco

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