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New cell-engineering technique may lead to precision immunotherapies

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UC San Francisco scientists have created a new class of highly customizable biological sensors that can be used to form "logic gates" inside cells of the immune system, giving these cells the capability to home in on and kill a wide range of cancer cells while preventing them from attacking normal tissue.

As reported in two companion papers published Jan. 28 in the online edition of *Cell*, in addition to their potential to bring much-needed precision and safety to the form of cancer immunotherapy known as CAR T cell therapy, these versatile new sensors, known as synNotch receptors, can also be inserted into cells such as nerve and muscle cells. The receptors may have uses in regenerative medicine, in the treatment of autoimmune diseases, and in basic biological research.

"SynNotch receptors provide us with one of the most flexible ways we have to reprogram the behavior and function of almost any cell," said Wendell A. Lim, PhD, chair and professor of cellular and molecular pharmacology at UCSF, and senior author of the two new papers. "One of the most exciting applications is in engineering therapeutic cells – we can now provide these cells with highly precise instructions about how to recognize and respond to disease."

CAR T cell therapy has been much in the news for its unprecedented success in treating a form of blood cancer known as acute lymphoblastic leukemia, or ALL. CAR T cells are so-called because an engineered Chimeric Antigen Receptor – a T cell receptor with an antibody "head"

that recognizes a specific cancer-associated molecule called an antigen – is inserted into the immune system's T cells to guide them to tumor cells, which they then kill.

The therapy works well in ALL because the disease affects white blood cells known as B cells, all of which carry a unique antigen known as CD19. By designing the CAR antibody head to target CD19, B cells can be selectively eradicated. A major side effect of this treatment, however, is that healthy B cells carrying the CD19 antigen are also eliminated by CAR T therapy, a loss that patients are generally able to tolerate.

But CAR T cell therapy has not been effective against the solid tumors that affect the breast, prostate, brain, lungs, and other organs, because – unlike in B cells – there is no single target antigen present in these tumors that is not also found in healthy cells. As a result, CAR T cell therapy directed at antigens in solid tumors has caused serious, sometimes lethal side effects when healthy tissues are also attacked by the CAR T cells.

To get around this problem, said Lim, a Howard Hughes Medical Institute investigator and director of the UCSF Center for Systems and Synthetic Biology, CAR T cells need to be able to finely discriminate between cancer cells and healthy cells. The UCSF team accomplished this goal with synNotch, using the new sensor to create a cellular "AND gate" that endows T cells with the sort of precision that Boolean search terms bring to Internet search engines. In effect, synNotch can direct T cells to perform tasks such as "find cells with tumor antigen A, but activate the T cell's killing program only when tumor antigen B is also present."

The synNotch receptor is an engineered version of a naturally occurring receptor called Notch, which plays crucial roles in the body's development from embryo to adult. Notch, which sticks through cell

walls like a straw though a coconut shell, works in a unique fashion. When the portion of Notch protruding outside the cell recognizes a particular target molecule, the section within the cell is released, freeing this portion to travel to the cell nucleus, where it switches specific genes on or off.

The UCSF team, led by Leonardo Morsut, PhD, and Kole T. Roybal, PhD, both postdoctoral fellows in the Lim laboratory, found that they could exploit this unusual configuration by swapping out the Notch components that lie outside and inside the cell with components that match a desired biological function. The product of this modular engineering strategy is synNotch, a receptor that can recognize any target molecule, and in response, execute any genetic program.

For the version of synNotch described in Cell, Roybal customized the extracellular portion of Notch so the receptor would recognize an antigen found on tumors, and inserted the synNotch receptor into T cells. The intracellular portion of Notch was also tweaked, so that it would activate the genes necessary to create a CAR in the same cell. The CAR was designed to recognize a tumor antigen different from the antigen recognized by the synNotch receptor.

The researchers then implanted two distinct tumors into mice, one expressing only the antigen targeted by the CAR, and the other expressing both the antigen recognized by the CAR and that recognized by the synNotch receptor.

When synNotch-equipped T cells were injected into the mice, the T cells did not attack tumors expressing only the antigen targeted by the CAR, because the synNotch activation necessary for the CAR to be present did not occur. If both antigens were present, however, synNotch activation prompted the expression of the CAR receptor, which then recognized the second antigen and launched the T cell's killing program.

The synNotch-equipped T cells were remarkably effective and selective: they completely eradicated tumors expressing both antigens, and the effect was durable – all the mice who carried these double-antigen tumors remained alive when the experiments were concluded, 30 days after treatment.

Lim said it is possible to insert multiple synNotch receptors into CAR T cells, but he believes that only one to three synNotch receptors may be necessary to considerably enhance the selectivity of these cells. Through genomic sequencing it should be possible to identify unique combinations of proteins that occur only in a patient's tumor and not in his or her healthy cells, he said, and then create synNotch CAR T cells to precisely target the cancer.

"The kinds of engineered T cells that we can now construct give us the exciting potential to create precision cancer therapeutics that take advantage of all the genomic and proteomic information we are currently gathering on disease," said Lim. "This genomic information now becomes actionable."

Provided by University of California, San Francisco

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