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Programmable T cells chase down cancer, deliver drugs directly to tumors

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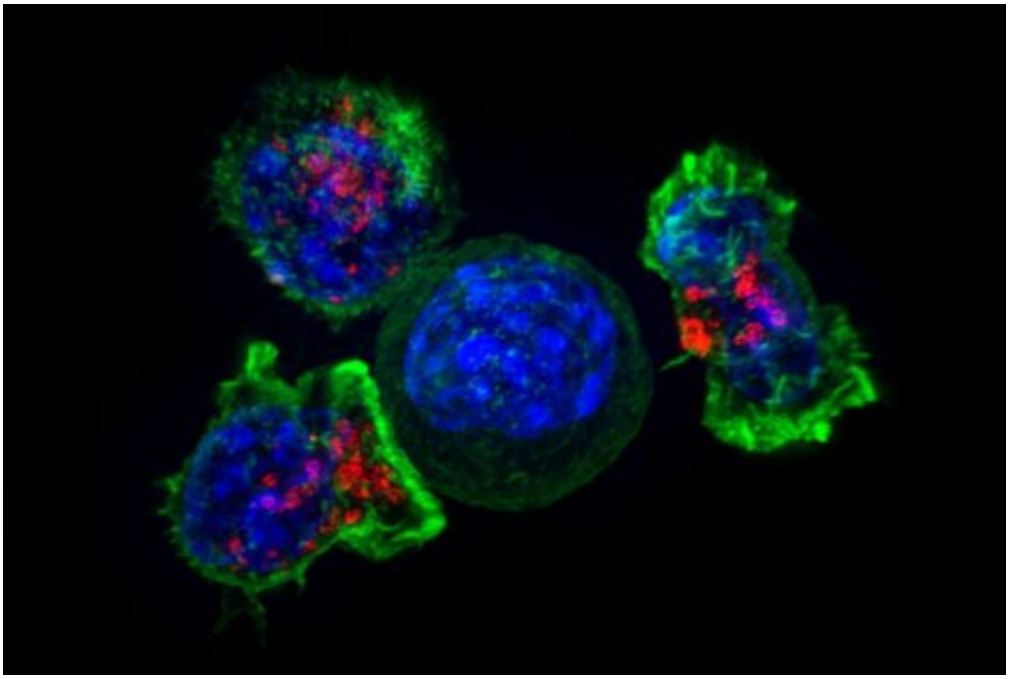

Killer T cells (green and red) surrounding a cancer cell. Credit: Alex Ritter, Jennifer Lippincott Schwartz, Gillian Griffiths/National Institutes of Health

UC San Francisco scientists have engineered human immune cells that can precisely locate diseased cells anywhere in the body and execute a wide range of customizable responses, including the delivery of drugs or other therapeutic payloads directly to tumors or other unhealthy tissues. In experiments with mice, these immune cells, called synNotch T cells, efficiently homed in on tumors and released a specialized antibody

therapy, eradicating the cancer without attacking normal cells.

As reported in the Sept. 29, 2016, online edition of *Cell*, in addition to delivering therapeutic agents, synNotch cells can be programmed to kill cancer cells in a variety of other ways. But synNotch cells can also carry out instructions that suppress the immune response, offering the possibility that these cells could be used to treat autoimmune diseases such as type 1 diabetes or to locally suppress immune system rejection of transplanted organs.

"SynNotch is a universal molecular sensor that allows us to program immune cells as if they were microscopic robots," said Wendell Lim, PhD, chair and professor of cellular and molecular pharmacology at UCSF, Howard Hughes Medical Institute investigator, and member of the UCSF Helen Diller Family Comprehensive Cancer Center. "They can be customized with different features and functions, and when they detect the appropriate signals in a diseased tissue, they can be triggered to deploy diverse therapeutic weapons."

Sidestepping Limitations of CAR T Therapy

The new research broadens and deepens previous research on synNotch T cells in Lim's laboratory, which has shown, among other things, that the synNotch sensor platform can be used to create custom "logic gates" in T cells that allow them to recognize and kill cancer cells, while protecting closely related healthy cells. These cellular "AND gates" require two separate conditions to be met in target cells before the T cells take steps to eliminate the target.

T cells are highly motile, and roam throughout the body seeking out diseased or infected cells. A form of T cell therapy known as CAR (Chimeric Antigen Receptor) T therapy has been widely publicized for its unprecedented success in treating a form of blood cancer known as

acute lymphoblastic leukemia, or ALL.

But because CAR T therapy largely relies on the "built-in" sensing and response properties of T cells, some of which can be deleterious, it can have serious side effects. Moreover, because T cells are often unable to overcome properties of tumors that suppress immunity, CAR T therapy has so far not been effective against the solid tumors that affect the breast, prostate, brain, lungs and other organs. Lim said that the synNotch technology developed at UCSF can be used on its own, but can also be added to CAR T cells to sidestep many of that therapy's current limitations.

SynNotch is so called because it is the product of several synthetic alterations of Notch, a protein involved in cell-to-cell communication in diverse organisms that is especially crucial for normal development. First of all, the synNotch receptor acts as a "universal sensor" – it has a component protruding from the T cell that can be swapped out to specifically recognize many different types of disease signals. And synNotch's other end, inside the cell, is an "effector" component that can be engineered to cause the cell to carry out diverse responses.

Versatility of synNotch

In the new Cell paper, a research team at the UCSF Center for Systems and Synthetic Biology, led by postdoctoral fellow and first author Kole T. Roybal, PhD, demonstrated the versatility of synNotch T cells in several ways.

- When activated, conventional T cells, including CAR T cells, secrete a "native" suite of cytokines, chemical signals that summon other immune cells to the disease site and determine the overall immune response. But some native cytokines, when overproduced, can be also be highly toxic. Members of the Lim

laboratory demonstrated that synNotch T cells can be directed to secrete single, predetermined cytokines or customized selections of cytokines that can be tailored to elicit a specific desired immune response.

- SynNotch cells can be outfitted with other receptors that cause the disease cells they target to "commit suicide" by triggering built-in cell-death pathways.
- When T cells reach a disease site and are activated, they may transform into particular T cell subtypes. As with cytokines, however, the T cell varieties that emerge from this differentiation process may not be the optimal combination. Lim and colleagues show that, with synNotch, this T cell differentiation process can be "skewed" so that the activated T cells emerge as a subtype of T cell optimized to combat cancer.
- The use of so-called "checkpoint inhibitor" drugs that unleash the immune response have achieved unprecedented remissions in metastatic melanoma and other forms of cancer that until recently were considered fatal. In the work published in Cell, synNotch cells were engineered to manufacture two effective checkpoint inhibitor drugs when the synNotch cells were in direct contact with cancer. Lim said that this on-site drug delivery may increase response among cancer patients while reducing side effects. SynNotch delivery of another therapy, known as a Bispecific T Cell Engager (BiTE; in this case, a BiTE known as Blincyto was delivered) eliminated tumors in mice without affecting normal cells.
- Intriguingly, the group showed that synNotch cells can produce immunosuppressive signals at disease sites, indicating that synNotch T cells could be used to tamp down the immune system attacks that occur in inflammatory and autoimmune diseases.

Lim is scientific founder and advisory board member of Cell Design Labs, a San Francisco company devoted to advancing cell-based

therapies to treat cancer, autoimmune diseases, and other conditions. Based on technology licensed from UCSF, Cell Design Labs is developing a portfolio of anticancer therapies and creating partnerships with leading oncology companies.

"Using synNotch cells to deliver powerful therapeutic molecules or to shape the immune response directly at the site of disease will not only be more effective, but will likely prevent the side effects that occur when drugs are delivered systemically, and indiscriminately affect every tissue in the body," said Roybal. "The local production of molecular therapies by therapeutic immune cells is a radically new approach – one that could be both more effective and far safer than the systemic administration of therapeutics being used today."

More information: To learn more about Cell Design Labs, please visit their website: www.celldesignlabs.com/

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