Big data powers design of 'smart' cell therapies for cancer

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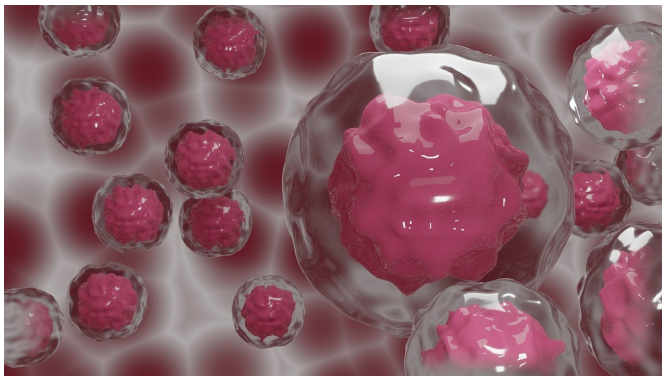

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Finding medicines that can kill cancer cells while leaving normal tissue unscathed is a Holy Grail of oncology research. In two new papers, scientists at UC San Francisco and Princeton University present complementary strategies to crack this problem with "smart" cell therapies—living medicines that remain inert unless triggered by combinations of proteins that only ever appear together in cancer cells.

Biological aspects of this general approach have been explored for several years in the laboratory of Wendell Lim, Ph.D., and colleagues in the UCSF Cell Design Initiative and National Cancer Institute-sponsored Center for Synthetic Immunology. But the new work adds a powerful new dimension to this work by combining cutting-edge therapeutic cell engineering with advanced computational methods.

For one paper, published September 23, 2020 in *Cell Systems*, members of Lim's lab joined forces with the research group of computer scientist Olga G. Troyanskaya, Ph.D., of Princeton's Lewis-Sigler Institute for Integrative Genomics and the Simons Foundation's Flatiron Institute. Using a machine learning approach, the team analyzed massive databases of thousands of proteins found in both cancer and normal cells. They then combed through millions of possible protein combinations to assemble a catalog of combinations that could be used to precisely target only cancer cells while leaving normal ones alone.

In another paper, published in *Science* on November 27, 2020, Lim and colleagues then showed how this computationally derived protein data could be put to use to drive the design of effective and highly selective cell therapies for cancer.

"Currently, most cancer treatments, including cell therapies, are told 'block this,' or 'kill this,'" said Lim, also professor and chair of cellular and molecular pharmacology and a member of the UCSF Helen Diller Family Comprehensive Cancer Center. "We want to increase the nuance and sophistication of the decisions that a therapeutic cell makes."

Over the past decade, chimeric antigen receptor (CAR) T cells have been in the spotlight as a powerful way to treat cancer. In CAR T cell therapy, immune system cells are taken from a patient's blood, and manipulated in the laboratory to express a specific receptor that will recognize a very particular marker, or antigen, on cancer cells.

While scientists have shown that CAR T cells can be quite effective, and sometimes curative, in blood cancers such as leukemia and lymphoma, so far the method hasn't worked well in solid tumors, such as cancers of the breast, lung, or liver. Cells in these solid cancers often share antigens with normal cells found in other tissues, which poses the risk that CAR T cells could have off-target effects by targeting healthy organs. Also, solid tumors also often create suppressive microenvironments that limit the efficacy of CAR T cells.

For Lim, cells are akin to molecular computers that

can sense their environment and then integrate that information to make decisions. Since solid tumors are more complex than blood cancers, "you have to make a more complex product" to fight them, he said.

In the *Cell Systems* study—led by Ruth Dannenfelser, Ph.D., a former graduate student in Troyanskaya's team at Princeton, and Gregory Allen, MD, Ph.D., a clinical fellow in the Lim lab—the researchers explored public databases to examine the gene expression profile of more than 2,300 genes in normal and tumor cells to see what antigens could help discriminate one from the other. The researchers used machine learning techniques to come up with the possible hits, and to see which antigens clustered together.

Based on this gene expression analysis, Lim, Troyanskaya, and colleagues applied Boolean logic to antigen combinations to determine if they could significantly improve how T cells recognize tumors while ignoring normal tissue. For example, using the Booleans AND, OR, or NOT, tumor cells might be differentiated from normal tissue using markers "A" OR "B," but NOT "C," where "C" is an antigen found only in normal tissue.

To program these instructions into T cells, they used a system known as synNotch, a customizable molecular sensor that allows synthetic biologists to fine-tune the programming of cells. Developed in the Lim lab in 2016, synNotch is a receptor that can be engineered to recognize a myriad of target antigens. The output response of synNotch can also be programmed, so that the cell executes any of a range of responses once an antigen is recognized.

To demonstrate the potential power of the data they had amassed, the team used synNotch to program T cells to kill kidney cancer cells that express a unique combination of antigens called CD70 and AXL. Although CD70 is also found in healthy immune cells, and AXL in healthy lung cells, T cells with an engineered synNotch AND logic gate killed only the cancer cells and spared the healthy cells.

"The field of big data analysis of cancer and the field of cell engineering have both exploded in the last few years, but these advances have not been brought together," said Troyanskaya. "The computing capabilities of therapeutic cells combined with machine learning approaches enable actionable use of the increasingly available rich genomic and proteomic data on cancers."

The work described in the new *Science* paper, led by former UCSF graduate student Jasper Williams, shows how multiple synNotch receptors can be daisy-chained to create a host of complex cancer recognition circuits. Since synNotch can activate the expression of selected genes in a "plug and play" manner, these components can be linked in different ways to create circuits with diverse Boolean functions, allowing for precise recognition of diseased cells and a range of responses when those cells are identified.

"This work is essentially a cell engineering manual that provides us with blueprints for how to build different classes of therapeutic T cells that could recognize almost any possible type of combinatorial antigen pattern that could exist on a cancer cell," said Lim.

For example, a synNotch receptor can be engineered so that when it recognizes antigen A, the cell makes a second synNotch that recognizes B, which in turn can induce the expression of a CAR that recognizes antigen C. The result is a T cell that requires the presence of all three antigens to trigger killing. In another example, if the T cell encounters an antigen present in normal tissues but not in the cancer, a synNotch receptor with a NOT function could be programmed to cause the T cell carrying it to die, sparing the normal cells from attack and possible toxic effects.

In the *Science* paper, using complex synNotch configurations like this, Lim and colleagues show they can selectively kill cells carrying different combinatorial markers of melanoma and breast cancer. Moreover, when synNotch-equipped T cells were injected into mice carrying two similar tumors with different antigen combinations, the T cells efficiently and precisely located the tumor they had been engineered to detect, and reliably executed the cellular program the scientists had designed.

Lim's group is now exploring how these circuits could be used in CAR T cells to treat glioblastoma, an aggressive form of brain cancer that is nearly always fatal with conventional therapies.

"You're not just looking for one magic-bullet target. You're trying to use all the data," Lim said. "We need to comb through all of the available cancer data to find unambiguous combinatorial signatures of cancer. If we can do this, then it could launch the use of these smarter cells that really harness the computational sophistication of biology and have real impact on fighting cancer."

More information: "Precise T cell recognition programs designed by transcriptionally linking multiple receptors" *Science* (2020). science.sciencemag.org/lookup/ … 1126/science.abc6270

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