Hunting for immune cells' cancer targets

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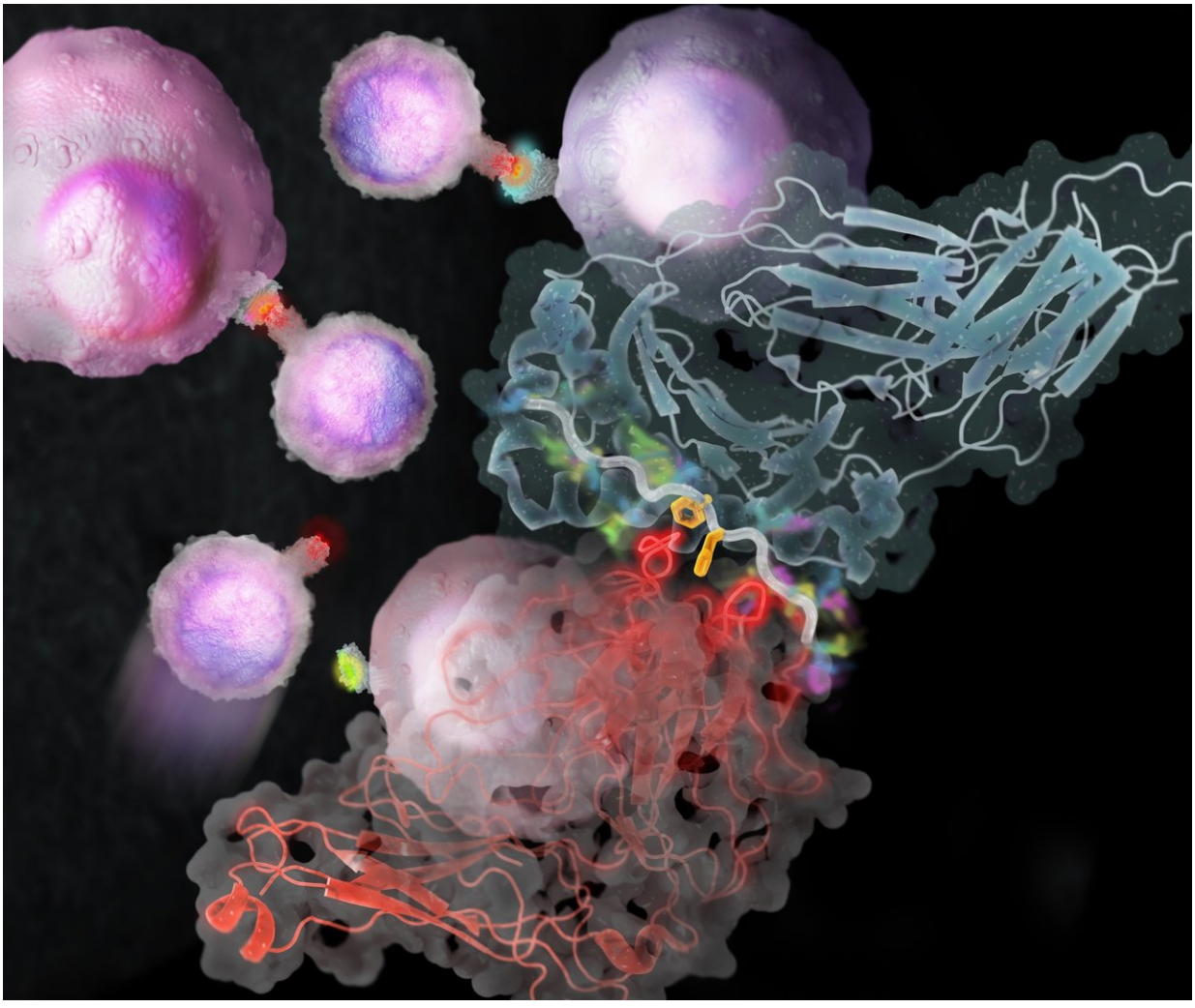

Proteins on immune cells called T-cell receptors (red) detect specific protein snippets (yellow) on the surface of other cells, including tumor cells. A new technique lets researchers find snippets linked to cancer. Credit: Eric Smith and Christopher Garcia

By screening millions of molecular targets, researchers have uncovered a tumor beacon detected by the immune cells of two patients with colorectal cancer.

The screening technology, developed by Howard Hughes Medical Institute Investigator (HHMI) Christopher Garcia and colleagues after almost 20 years of basic molecular studies of the immune system, may ultimately lead to more effective immunotherapies, which harness the body's immune system to fight cancer. "This is going to widen the scope of our understanding for how tumors are recognized," says Garcia, a protein engineer at the Stanford University School of Medicine.

More broadly, the method, reported online December 21, 2017, in the journal *Cell*, promises to illuminate how immune cells lock onto targets, the cellular recognition at the heart of autoimmune disorders and infections. Without a systematic way to look for these signals, many details of immune cells' recognition capabilities have remained a mystery.

One type of immune cell, called a tumor-infiltrating lymphocyte, can invade tumors and help destroy cancer cells. Tumor-infiltrating lymphocytes have captured the attention of cancer researchers eager to supercharge these cells' tumor-killing abilities. This destruction depends on lymphocytes correctly detecting cancer signals - bits of protein called antigens that cancer cells display on their surface. Lymphocytes use proteins called T-cell receptors to lock on to these cancer signals, many of which are unknown.

In 2014, Garcia and colleagues published an article in *Cell* reporting a discovery that T-cell receptors were far more specific for their targets than originally thought. They were able to make this discovery by developing a biochemical method to sift through millions of antigens that might be detected by T-cell receptors. In the new work, they apply a

similar method to tumor samples from two colorectal cancer patients, this time searching for the actual targets of patients' tumor-invading lymphocytes.

Along with graduate student Marvin Gee, Garcia enlisted the collaboration of Mark Davis, an HHMI investigator at Stanford University. Davis's laboratory has developed ways to read the DNA sequences of single lymphocytes - information that helped researchers hunt for immune cells' targets. First, Davis and post-doctoral fellow Arnold Han isolated and characterized T-cell receptors from two patients with colorectal cancer. Next, the researchers used those precise T-cell receptors as bait, a labor-intensive process that involves searching through hundreds of millions of signals that cancer cells might display. These signals, short strings of amino acids, represent molecular needles in an enormous haystack.

But the method worked. And the researchers discovered something surprising: Out of a huge number of possibilities, the T-cell receptors from both patients recognized the same tumor antigen. The results support the approach of developing broadly effective cancer treatments based on the immune system. "We have to find antigens that are shared across multiple different patients, so that one treatment can serve many different people," Garcia says.

These shared signals could prove useful in several ways. In laboratories, researchers could genetically engineer T-cell receptors to recognize common cancer antigens. Once introduced into a patient's body, these cells would make a beeline to the tumor cells. A related approach would turn the cancer antigen itself into a vaccine. After an injection, this cancer vaccine would teach existing immune cells to recognize and combat the rogue cells.

The new results have implications that reach far beyond cancer, too. The

method could illuminate the cellular details of autoimmune disorders, infectious diseases or any other process that involves T-cell receptors, Garcia says.

The current findings were rooted in a result from 1996, when Garcia and colleagues first solved the 3-D structure of a T-cell receptor bound to a target. Since then, the work has moved steadily from basic research to clinically relevant insights, Garcia says. "This is a great example of how starting with the most reductionist approach can lead you to very powerful insights with clinical relevance," he says. "If you invest in the most basic discovery science, and you go deep enough on an important problem, here's what can come out the other end."

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