CRISPR Can Reprogram T Cells to Fight Cancer Without Viruses

New immunotherapy approach could make engineering immune cells faster and cheaper.

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A new method using CRISPR gene editing technology could allow scientists to create cancer-fighting T cells more easily, which could potentially increase their availability and reduce their cost, according to a study published this week in Nature.

“This is a rapid, flexible method that can be used to alter, enhance and reprogram T cells so we can give them the specificity we want to destroy cancer, recognize infections or tamp down the excessive immune response seen in autoimmune disease,” lead author Alex Marson, MD, PhD, of the University of California at San Francisco said in a UCSF press release.

Unlike traditional chemotherapy, which directly poisons cancer cells, immunotherapy helps the immune system recognize and fight cancer, usually by boosting the activity of T cells. One method uses a harmless virus to insert new genes into a patient’s T cells to make them express naturally occurring T-cell receptors (TCRs) that can recognize cancer antigens. Another technique, chimeric antigen receptor T-cell therapy, or CAR-T, uses a virus to insert artificial receptors that bind to cancer cells more readily than natural TCRs.

However, using viral vectors to ferry new genetic material into cells is a slow and laborious process—and therefore expensive—and viruses have limits regarding the size of the genetic sequences they can carry and the precision with which they can place them. In addition, a shortage of clinical-grade viral vectors has led to a manufacturing bottleneck, according to the UCSF release.

Marson’s team developed a cut-and-paste genome editing system using CRISPR-Cas9 to get around these limitations.

CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats), which bacteria use to defend against viruses, can locate a specific sequence in the genome. Then the Cas-9 enzyme acts as molecular scissors to cut and disable DNA at that location. Variations of the technique can be used to activate rather than disable specific genes or to alter the genome at a particular location by pasting in a new sequence.

In a laboratory study the researchers used an electrical field—a process known as electroporation—to make T-cell membranes temporarily more permeable and allow the entrance of CRISPRs and the bits of DNA they wished to insert.

This technique allowed “rapid and efficient” insertion of large DNA sequences (greater than one kilobase) at specific sites in the T-cell genome while preserving the cells’ ability to function, according to the study authors.

The researchers then used this technique to correct a harmful gene mutation in cells from children with a rare autoimmune disease and to replace an existing T-cell receptor with a new TCR that targets a cancer antigen.

In collaboration with researchers at the Parker Institute for Cancer Immunotherapy at UCLA, Marson’s team showed that these engineered human T cells were able to recognize and mount an effective response against human melanoma tumors implanted in mice.

“I anticipate that this new technology will revolutionize the field of genetically engineered cell therapy for cancer,” Antoni Ribas, MD, PhD, of UCLA’s Jonsson Comprehensive Cancer Center said in a Parker Institute press release. “In the next three to five years, we will see many more approaches to treat cancer based on this nonviral targeted method.”

“This is a huge advance for the cell therapy and CAR-T field, opening the door for us to create more robust, personalized cancer immunotherapy treatments in less time,” added Parker Institute vice president of research Fred Ramsdell, PhD. “What takes months or even a year may now take a couple weeks using this new technology. If you are a cancer patient, weeks versus months could make a huge difference.”

Click here to read the study abstract.
