New technique reinforces immune cells that seek and destroy cancer

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In what could be a shot in the arm for adoptive immunotherapy, new Stanford University research shows promise in enhancing and controlling the growth of T cells in living mice and in human cell cultures, potentially overcoming one of the therapy's drawbacks.

The engineers altered the T cells using synthetic biology, an emerging field in which researchers can build new functions into cells by integrating pre-designed genetic components. Adoptive immunotherapy is an experimental technique meant to boost the immune response to a number of diseases, most notably some cancers.

"This is an integration of a cell-based therapy application with new synthetic biology tools that have come up from foundational research," said Christina Smolke, PhD, assistant professor of bioengineering. "The unique aspect is that we're taking new tools for controlling cell function and gene expression, and looking at them in the context of a specific and clinically relevant system."

The research will be published online April 26 in the Proceedings of the National Academy of Sciences. Smolke is the senior author of the paper and the advisor of the lead author, California Institute of Technology chemical engineering graduate student Yvonne Chen. Chen has worked with Smolke since 2006 and became a visiting researcher at Stanford in 2009 when Smolke left Caltech for Stanford.

Immune boost

Adoptive immunotherapy is targeted to situations when the immune system fails to detect a disease. The adoptive immunotherapy strategy is to harvest T cells from the patient, engineer them to spot the disease and then send them back in, like police detectives with a reliable tip. A major drawback, however, has been that the T cells still need to call for back-up forces from a variety of other cell types in the body, but they can't. They die out quickly without doing enough good.

The new approach is to further engineer the T cells to be able to support themselves rather than relying on other immune cells — perhaps a bit like Robocop — and to insert the ability to switch that self-support on or off, to ensure that they don't grow out of control. That way, the T cells can persist in fighting the disease without becoming a cancer themselves.

Biologically speaking, T cells will only thrive in the presence of certain chemicals called cytokines that are normally delivered or triggered by other cells that are part of a proper immune response. In its work, the team implanted genes in the T cells, enabling the cells to produce the cytokines for themselves. This ability, however, is controlled by another addition: a series of switches, encoded in RNA, that allow cytokine production to proceed only in the presence of a drug.

With the help of co-author Michael Jensen, MD, cancer immunology researcher at the City of Hope's Beckman Research Institute in Duarte, Calif., the team tested a variety of modifications both in mice and in cultures of human T cells. They used different drugs to trigger the production of different cytokines. Generally, the results showed that their engineering produced healthier, faster-growing populations of the T cells, until the drugs were withdrawn and growth shut down. In the human cell cultures, for example, the technology led to a 24 percent increase in the live T-cell population compared to controls and 50

percent fewer cells dying off.

Synthetic biology

The research can be traced back to 2007 at Caltech, when Smolke led the development of the ribozyme-based RNA switches. At the time the switches were synthesized as fundamental, generally useful components. Now they have found an advanced use. By analogy, they are light switches that have now been successfully integrated into a working circuit.

"Originally we were looking at how can you design an RNA molecule that can detect a chemical and then translate that into a gene-regulatory event in a cell," Smolke said. "Yvonne took some of that foundational research and asked, what if the downstream output is a T-cell proliferation response and what if the input is a drug molecule you can apply to a patient."

Because they are essentially components, different versions of the switches can be swapped in or out, as interchangeably as any two of the light switches at a hardware store. The researchers, for example, swapped in and out switches that are responsive to two different drugs: tetracycline and theophylline.

Smolke said the next phase for the project will be to develop new versions of the switch that will make the cells responsive to drugs with ideal clinical properties, such as good permeation into tissue but with low side effects. From there, the team could begin testing with therapeutically engineered T cells, such as the ones used in adoptive immunotherapy, to gauge whether their approach indeed translates into an improvement in the efficacy of the therapy against disease.

"An important point for us is that, as a proof of concept, it has the

behavior we programmed it to have," Chen said. "The fact that it's modular allows us to explore other parts that can make it more suitable for whatever application you want to use it for."

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