How Does Leukemia Escape From Immunotherapy?

New tech enables deep dive into mysterious results, sets stage for future improvements

May 25, 2018 By Susan Keown

When an experimental new cancer treatment shows promising results for many patients, these successes are exciting. But cancer researcher Kelly Paulson, PhD, says that the most important insights — those that will lead to better therapies for even more patients — come from studying the failures.

A new study by Paulson and colleagues does just that, highlighting one way that an aggressive leukemia can wriggle its way free of targeted attack by a high-tech strategy for immune-based therapy. With these insights in hand, the researchers say, they're already making progress on what they hope will be an improved version of the experimental therapy that will help more people in the future.

Paulson, a senior fellow at Fred Hutchinson Cancer Research Center, presented the results on Monday afternoon at the annual meeting of the American Association for Cancer Research, which is being held through Wednesday in Chicago.

"It's important for our clinical trial participants, for our patients and our families to know that, even if the trial doesn't go the way that we want it to for that particular patient, we don't stop working," she said. "That we don't stop asking what we can do better next time. That we don't stop working hard to understand how we can fight cancer better, and how we can make the next treatment better and stronger."

In an immunotherapy trial, more promising results for some than others

Paulson, a medical oncology fellow in the laboratory of Aude Chapuis, MD, led the study alongside Fred Hutch colleague Thomas Schmitt, PhD, a research associate in the lab of Fred Hutch immunotherapy pioneer Phil Greenberg, MD.

p>Their study was a deep dive into the cells of certain patients enrolled on a recent early stage trial of an experimental immunotherapy. In this small trial, people who'd undergone bone marrow

transplant for a type of advanced, aggressive leukemia received an infusion of donor T cells genetically engineered with a special receptor. This special T-cell receptor enabled the immune cells to recognize cancer cells with a telltale molecular signature. At the AACR meeting, Paulson presented updated data on the results of the trial, which was led by Chapuis, Greenberg and Daniel Egan, MD, also of Fred Hutch.

Every participant whose cancers were in remission at the time they received the engineered cells has continued in remission for several years — "truly wonderful," said Paulson, given how aggressive their cancers were. But the engineered cells do not seem to be helping improve the survival of patients whose cancers were not completely in remission after transplant when they received the special T cells, Paulson reported.

Why? The research team dived in to find out.

A cancer's escape

Paulson and Schmitt focused on certain patients whose cases were especially mysterious: like that of one man, who was only in his early twenties when he enrolled on the trial after his acute myeloid leukemia came back. On the trial, he received genetically engineered T cells after his second bone marrow transplant failed to put his cancer into full remission.

With the engineered cells, his cancer did go into remission, but only for 12 months. And the reason his cancer came back wasn't obvious. His genetically modified, cancer-targeting T cells were still circulating en masse throughout his blood. And his leukemia cells still displayed the molecular signature — a protein called WT1 — that the modified cells recognized.

Paulson, Schmitt and colleagues harnessed an emerging technology called single-cell RNA sequencing, or scRNA-seq to help them understand what was going on. scRNA-seq enables researchers to look at the identity and activity of many different cells at once. In scRNA-seq, sequencing technology records the gene activity of the thousands of diverse cells contained within a small sample of tissue — a blood sample, say. Then, sophisticated statistical techniques sort through the billions of sequences the technique generates to create maps showing which kinds of cells are present and what each one is doing.

By analyzing samples from the man's remission and his relapse, the researchers found that the genetically modified, cancer-targeting T cells stayed present, but they had lost their activity. "It suggested to us that the T cells weren't seeing the leukemia cells very well anymore," Paulson said.

Digging a bit deeper, they found out the likely reason for this: The man's relapsed cancer cells had a slightly modified version of the molecular machinery cells use to process the proteins like WT1 that reveal their identity. With this tweak to their processing machinery, the cancer cells were still displaying their WT1 signatures. But they were displaying them in a different way — a way that the T cells had not been engineered to recognize.

And that's why the modified T cells were inactive, the team realized. From the T cells' perspective, it was as if the cancer cells floating alongside them in the blood weren't even there.

To their surprise, the researchers then discovered that the man had a few of the leukemia cells with the altered processing machinery months earlier, at a time when his cancer appeared to be in remission and his engineered T cells were active. The researchers deduced that these treatment-resistant cells, initially vanishingly rare, multiplied steadily, flying under the T cells' radar, until the man became sick again.

"It's patients like that that show why you need to find more [treatments]," Paulson said.

The power of scRNA-seq

Schmitt said that "it is well-appreciated" that tumors can change to avoid attack by genetically modified T cells. Many of the details are still to be determined, he added, but this will change. "Single-cell RNA-seq will help elucidate the precise mechanisms and frequency of such events," Schmitt wrote by email.

scRNA-seq "is wildly powerful," Paulson said, flipping through color-coded maps on her computer that were generated by the technology. With the help of biostaticians in the research group of Raphael Gottardo, PhD, at the Hutch, scRNA-seq allowed the team to learn secrets of the experimental therapy's success and failure, insights that are laying the groundwork for improvements. But also, she added, as scRNA-seq develops further, it could play an important role in patient care, she said, by providing doctors with insights that would help them choose therapies.

The next iteration of a T-cell therapy on the horizon?

Back in the Greenberg Lab, Schmitt looked for different versions of the cancer-targeting receptor used in this trial. What he was searching for were T-cell receptors that could recognize WT1 processed with a variety of cell machineries. All told, he estimates, he has synthesized and tested about 40 different T-cell receptors for their leukemia-killing abilities in lab dishes, and he's found some that show promise.

Within the next few weeks, he should know which one of these new WT1-specific T-cell receptors might make the best leukemia therapy, he said. And by the end of the summer, he hopes to have the results of the essential laboratory testing that would pave the way toward a new clinical trial of what the team hopes will be an escape-thwarting genetically engineered T-cell strategy.

"The hope is to have it in the clinic in the not-too-distant future," Paulson said.

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