Revealing a New Way Cancer Evades Immunotherapy

How a new technology solved a mystery and honors one man's legacy

October 17, 2018 By Susan Keown

Monica Bristow, PhD, smiles up at a photo on the living-room wall. She remembers when they took that picture: Her husband was just finishing a course of chemotherapy, and his hair was starting to regrow. In a silly mood, the family arrayed themselves around him on the front stoop and piled their hands on his downy-topped pate, the grins on their faces reflecting his.

Life was full of things for her husband to smile at. A clinical psychologist, Gregg Schimmel, PhD, had a passion to help his patients live better lives, but he also plunged himself with enthusiasm into his tennis game and his favorite classic-rock bands, whose albums still dominate the dining-room wall.

Each time his rare skin cancer came back — again, and again, and again, for eight and a half years — his will to stay in the world that brought him so much joy propelled him forward, Bristow says.

Then, there came the time last year, when Schimmel's Seattle doctors told the couple that they had run through every treatment option they could find for his Merkel cell carcinoma, both standard and experimental.

Bristow had long sensed that this conversation would happen one day. But that didn't make it easier to hear those words.

At home with family, Schimmel passed away in his sleep on July 21, 2017.

His story, however, was hardly finished.

As a participant in clinical trials, Schimmel had donated tissue samples and data to researchers studying his disease in the Fred Hutchinson/University of Washington Cancer Consortium, where he was treated for much of his illness. As Schimmel and his family faced the end of his life, those scientists were back in the lab, consumed with a vexing question: Why did his most-advanced treatment work for nearly two years and then suddenly fail?

For months they hit only dead ends. Now, they have an answer.

New knowledge, future cures?

“We learn a lot from research samples. Even though it is harder, we’re not going to stop studying a patient just because their tumor doesn’t do what we want it to do,” explained Kelly Paulson, MD, PhD, of Fred Hutchinson Cancer Research Center, who led the key experiments that unraveled the mystery.

Using a high-powered new technology for analyzing samples from Schimmel and another man with a similar case, Paulson and her colleagues at Fred Hutch and UW located the escape hatch through which the cancers had wriggled free from their immune-harnessing therapies, or immunotherapies. The research team published their findings on Monday in the journal Nature Communications.

Immunotherapies hold the potential for long-term responses — perhaps cures — for patients with many cancers, including certain skin cancers. Usually, if the cancer shrinks with immunotherapy, it stays dormant. But an increasing number of patients who receive immunotherapy for Merkel cell carcinoma or for another deadly skin cancer, melanoma, have initial responses to the therapies but then relapse, Paulson said. It happens in other cancers, too.

“We’re really interested in understanding what causes that, because we want to turn those immunotherapy responses into immunotherapy cures,” she said. With what they have learned from Schimmel and the other man, the scientists are beginning to develop what they hope will be better therapies for patients with Merkel cell carcinoma and other cancers.

Bristow can imagine her husband’s reaction to the news.

“He would be joyful,” she says. “He would be so happy that that has come out of this.”

Merkel cell carcinoma: rare and deadly

The list of treatments that Schimmel received for his Merkel cell carcinoma, or MCC, fills an entire page of Bristow’s yellow legal pad. And it all started with a little red bump on his left ankle, which he spotted in 2008.

That’s a common start to the stories of many patients with MCC, a cancer of certain cells in the skin that are involved in the sense of touch. About 2,500 Americans, and growing, are diagnosed with MCC each year, and the disease is notorious for its ability to spread.

Until recently, treatment options for advanced MCC were extremely limited. Then, a new class of therapies that harness the power of the immune system to fight cancer — immunotherapies — burst onto the scene and transformed the care of advanced MCC. Toward the end of Bristow’s long list of her husband’s treatments are several immunotherapies, including immune-boosting drugs called checkpoint inhibitors and an experimental strategy called T-cell therapy.

From initial hope, a mystery arises

T-cell therapy is a specialty of Fred Hutch researcher Aude Chapuis, MD, one of Schimmel’s many

doctors, Paulson's mentor, and a senior scientist on the new study. In T-cell therapy, the killing might of patients' own immune-system assassins, called T cells, is aimed at their cancer cells.

It was in 2015, on a clinical trial led by Chapuis, that Schimmel received two infusions of his own cancer-specific T cells that had been isolated, multiplied and stimulated in a lab. That was followed by courses of two different checkpoint inhibitors.

"It was a very optimistic time," says Bristow. Schimmel's tumors shrunk by more than 90 percent. He was feeling good, and his doctors could detect the special T cells on patrol. Bristow and Schimmel took a long-anticipated trip to Italy.

Then, once again, his cancer came back.

The researchers did test after test on Schimmel's samples and those of the other patient with a similar story. They used every technology at their disposal, but they could not find anything amiss: Even after relapse, the men's immune cells looked armed and ready to go, and their cancers looked as vulnerable as before.

What went wrong?

A 'revelatory' new research tool

At that impasse, the scientists caught wind of a new tool that changed the course of their research.

It was called single-cell RNA sequencing, or scRNA-seq for short. It's a method that harnesses genomic and computational technologies together to see the activities of each individual cell in a sample containing thousands of different cells, all at once.

This had simply never been possible before. Standard sequencing methods can tell you if there are changes in the DNA code. But they can't tell you how cells are accessing that code, turning different programs in their DNA on or off. At least, not on the massive scale of scRNA-seq: the scale you need if you're looking, as Paulson and teammates were, for a needle in a haystack.

The researchers used the method to analyze tumor samples from Schimmel and the other man that had been collected throughout their course of treatment, including after their relapses.

It was "revelatory," Chapuis said, "absolutely revelatory."

A surprising answer offers opportunity

scRNA-seq showed that the cancer-fighting T cells were indeed responsible for the men's reprieves. But faced with the immune cells' onslaught, the cancers began to hide the target the T cells were looking for — a little bit of the virus that infects Merkel cells and causes most cases of this cancer.

Cells, including cancer cells, use molecules called HLAs to hold out little bits of their innards — such as viruses that infect them — for the immune system to see during its constant patrol for disease. The cancers were hiding by turning down their production of the HLA that held the virus fragments out for inspection.

What was especially interesting to the researchers was that the cancer cells weren't turning down HLAs across the board — only the very specific one, different for each man, that worked with the cancer-killing T cells flooded into his body.

"It's something we couldn't see with the older technology. We didn't know that the cancer could tune just one of them [HLAs] down," Paulson said.

Because the change was happening outside of the hard-wiring of the cells' DNA code, it offered the research team a valuable opportunity: to fix it.

"That's the key question in that situation: Can you do something about it?" Paulson said.

Pointing toward a 'smart combination therapy'

The research team grew some of Schimmel's cancer cells in the lab and treated them with two existing medications that can change cells' immune-system displays. Both are already FDA-approved for use in people: one for a precancerous bone marrow disorder; the other, for illnesses ranging from cancers to inherited conditions involving bone or nerves.

Both drugs worked. Schimmel's cancer cells were forced to display his T cells' specific HLA partner once again. This "shows hope that you could rescue somebody out of that kind of situation in the future with a smart combination therapy," Paulson explained.

That's exactly what the team is working on. They are developing an approach using a mix of T cells that work with different HLA partners, reasoning that it will be significantly less probable that cancer cells can figure out how to escape each different kind of attack, all at once.

As Chapuis put it: "One dagger you can probably escape. But if you put in five daggers, it's difficult."

The researchers suspect that many cancers may be using this particular escape technique to hide from immune-based therapies. This should become apparent as more research groups apply scRNA-seq technologies and report their findings.

Fulfilling a legacy

Schimmel was a person who remembered everyone's name.

Since his death, many Merkel cell carcinoma patients have told Bristow how much he meant to them. He helped lead a Seattle support group for patients with the rare disease. He organized an annual coping workshop for patients and caregivers. He relished sharing his knowledge and was

grateful for the support of others with the same disease.

Bristow hadn't been aware of the depth of the ongoing research on Schimmel's cells. But she hopes it continues. She hopes that scientists wring every last bit of knowledge they can out of the precious pieces of him that he left behind.

"I believe his hope would be that in anything he did — both in his involvement with the MCC research and patients, but also his involvement with all the patients he saw over the years as a psychologist — that he made a contribution," Bristow said. "He wanted other people to see improvement, joy, quality of life that could come from work he did."

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