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News

Cell therapy fights leukaemia

Patchwork receptors target immune cells against cancer.

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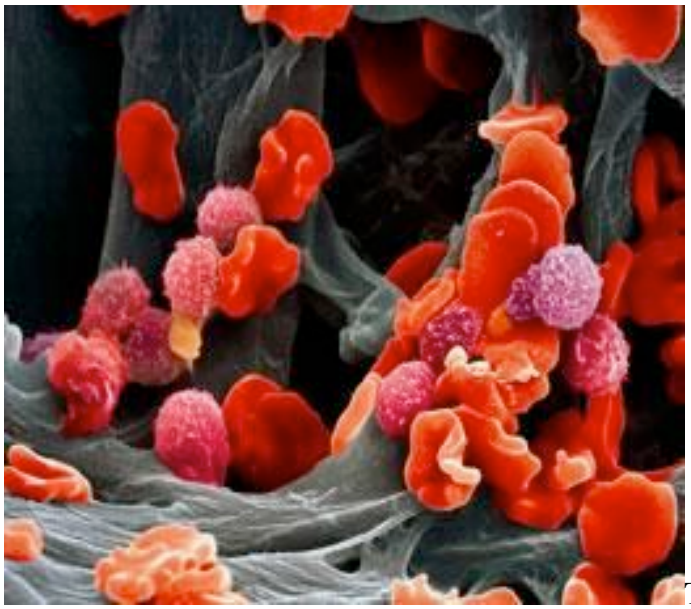

Trials of immune cells reprogrammed to attack cancer are producing encouraging results.STEVE GSCHMEISSNER/SCIENCE PHOTO LIBRARY

Two weeks after receiving an experimental treatment for his cancer, David Porter's 65-year-old leukaemia patient seemed to take a turn for the worse. Fatigue and fever drove the patient back to hospital, where his temperature surged to more than 39° C and he began to shake, his body racked with nausea and diarrhoea.

But rather than being a clinical failure, the patient's return to hospital heralded the treatment's success. His symptoms were the dying scream of more than a kilogram of leukaemia cells under attack by genetically engineered immune cells called T cells that Porter, an oncologist at the University of Pennsylvania Medical Center in Philadelphia, and his colleagues had infused two weeks earlier. As the T cells destroyed their targets, the sheer volume of cellular debris temporarily overwhelmed the patient's body.

"I was sure the war was on," the patient, who has asked to remain anonymous, wrote in a statement released to reporters. "It was another week later that I got the news that my bone marrow was completely free of detectable disease."

“It vindicates the cancer researchers who believe that cells are very smart drugs.”
Michel Sadelain
Memorial Sloan-Kettering Cancer Center, New York

The dramatic results from this patient and two others, published this week in the New England Journal of Medicine[1] and Science Translational Medicine[2], are among the first successes for a

long-sought therapy based on reprogramming immune cells to attack cancers.

The approach aims to harness the lethal capabilities of T cells. Porter and his colleagues, including immunologist Carl June, engineered each patient's T cells to recognize a protein called CD19 that is displayed on the surface of cancerous cells as well as on normal immune cells called B cells.

Researchers have long sought to kill cancer with T cells containing such "chimeric antigen receptors", but early results were disappointing. Then, last year, the field was rocked by the reports of two deaths in clinical trials of similar therapies[3,4].

Advocates of the technique hope that Porter's results and others like them will spark a renaissance. "These are very encouraging findings," says Michel Sadelain, a cancer researcher at Memorial Sloan-Kettering Cancer Center in New York. "It really vindicates this small but growing field of cancer researchers who believe that cells are very smart drugs."

Promising leads

Cells may be smart, but researchers have struggled to harness that intelligence to fight cancer. Early attempts to engineer T cells with chimeric antigen receptors failed to coax the cells to proliferate in the body. As a result, the modified cells soon died off, leaving little impact on the disease.

Porter's group is one the first to report results from a generation of chimeric receptors that include both an antibody to target the cancer and part of a receptor that amplifies the T-cell response. This time, the doctored T cells proliferated more than 1,000-fold in the body, and were still present at high levels six months after the treatment.

June credits this expansion and persistence for the study's dramatic results: two patients in complete remission and a third showing a partial response. The treatment kills off normal antibody-producing B cells too, but patients can be given regular infusions of antibodies to compensate for this, Porter says.

Other laboratories have also reported success with this generation of receptors. Last year, Steven Rosenberg's group at the National Cancer Institute (NCI) in Bethesda, Maryland, published a similarly promising case report: a person with lymphoma given T cells modified to target CD19 experienced a partial remission of his cancer[5]. That patient, treated initially in 2009, received a second treatment in March 2010 and is "still having a fabulous response", says Rosenberg.

Safety first

Rosenberg's team has since treated six more patients with lymphoma or leukaemia, and the NCI plans to sponsor chimeric antigen receptor trials against pancreatic cancer, brain tumours called glioblastomas and a rare lung cancer called mesothelioma.

Meanwhile, results from Sadelain's trial of CD19-targeting T cells in nine patients are due to be published soon, and Robert Hawkins, a cancer researcher at the University of Manchester, UK, says that his team is in the midst of a CD19 trial that is showing "encouraging" results.

All these trials are small, and the results, although promising, are preliminary. That means the field still needs to come to grips with the potential toxicity of such treatments, cautions Walter Urba, an oncologist at the Providence Cancer Center in Portland, Oregon.

In the wake of the case reports describing the deaths of the two clinical trial participants last year[3,4], some trials were put on hold, and the US Food and Drug Administration convened a meeting to discuss the need for added safety measures.

"That really set the field back," says John Maher, a clinical immunologist at King's College London. "But the recent results are great news."

As for Porter's patient; he is still marvelling over his experience. "When I was a young scientist, like many I'm sure, I dreamed that I might make a discovery that would make a difference to mankind," he wrote. "I never imagined I would be part of the experiment."

References

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