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Novel genetic experiment shrinks tough-to-treat cancer

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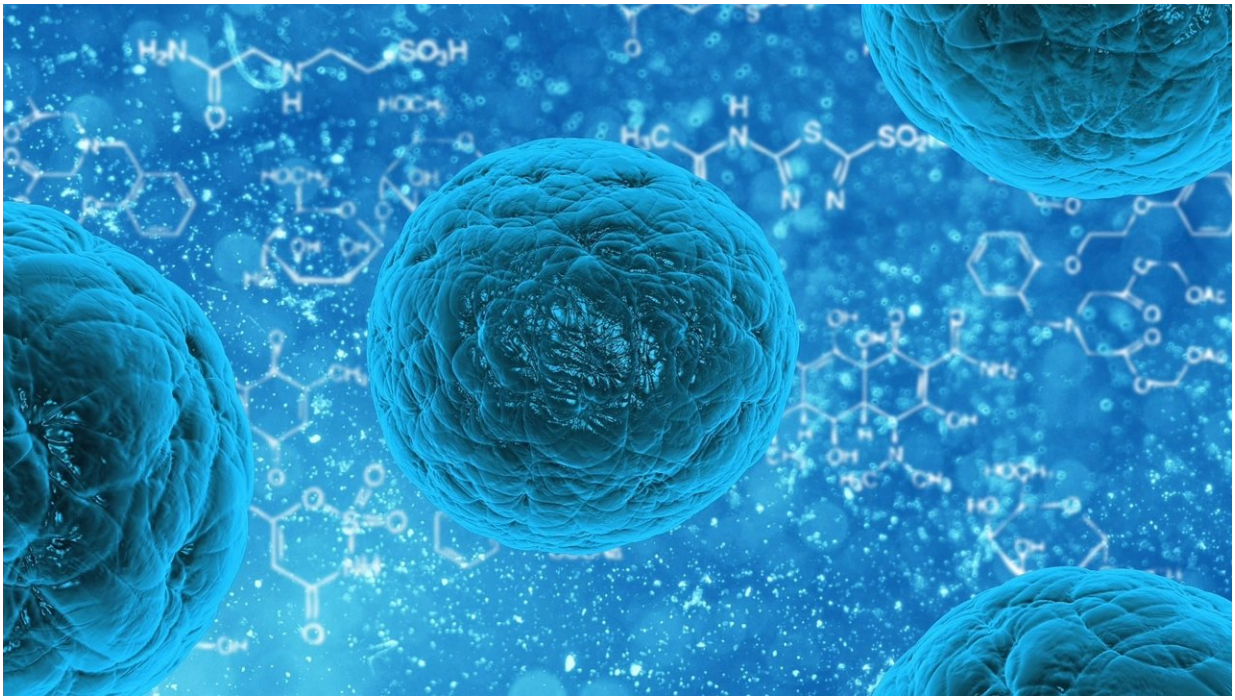

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In a novel experiment, a woman with advanced pancreatic cancer saw her tumors dramatically shrink after researchers in Oregon turbocharged her own immune cells, highlighting a possible new way to someday treat a variety of cancers.

Kathy Wilkes isn't cured but said what's left of her cancer has shown no

sign of growth since the one-time treatment last June.

"I knew that regular chemotherapy would not save my life and I was going for the save," said Wilkes, of Ormond Beach, Florida, who tracked down a scientist thousands of miles away and asked that he attempt the experiment.

The research, published Wednesday in the *New England Journal of Medicine*, explores a new method of harnessing the immune system to create "living drugs" able to seek and destroy tumors.

"It's really exciting. It's the first time this sort of treatment has worked in a very difficult-to-treat cancer type," said Dr. Josh Veatch of the Fred Hutchinson Cancer Research Center in Seattle, who wasn't involved with the experiment.

It's just a first step and far more research is needed, he cautioned—noting that Wilkes is one of only two people known to have tried this exact approach and it failed in the other patient.

Still, Veatch said the findings are "a proof of principle that this is possible" and that other researchers also are testing this type of immunotherapy.

T cells are key immune soldiers, able to kill off diseased cells—but too often cancer evades them. Doctors already have learned how to strengthen T cells to fight some types of leukemia and lymphoma. They add an artificial receptor to patients' T cells so the immune fighters can recognize a marker on the outside of blood cancer cells, and attack.

But that CAR-T therapy doesn't work against more common solid tumors, which don't carry that same danger marker.

The new twist: At Oregon's Providence Cancer Institute, researcher Eric Tran genetically engineered Wilkes' T cells so they could spot a mutant protein that's hidden inside her tumor cells—and only there, not in healthy cells.

How? Certain molecules sit on the surface of cells and give the immune system a sneak peek of what proteins are inside. If a complex receptor on the T cell recognizes both the person's genetically distinct "HLA" molecule and that one of the protein snippets embedded in it is the targeted mutant, that immune fighter can latch on.

It's an approach known as T cell receptor, or TCR, therapy. Tran stressed that the research remains highly experimental but said Wilkes' remarkable response "provides me with optimism that we're on the right track."

Dr. Eric Rubin, the New England Journal's top editor, said the study raises the possibility of eventually being able to target multiple cancer-causing mutations.

"We're talking about the chance to distinguish tumor cells from non-tumor cells in a way that we never could before," he said.

Wilkes underwent chemotherapy, radiation and surgery for her pancreatic cancer. Later doctors discovered new tumors in her lungs—the pancreatic cancer had spread, a stage when there is no good treatment.

Wilkes knew researchers were testing immunotherapy to fight different hard-to-treat tumors, and a biopsy showed a specific mutation was fueling her cancer. Her search led to Tran, who in 2016 had co-authored a study about a subset of T cells that naturally harbored receptors able to spot that same so-called KRAS mutation.

Wilkes also had the right type of HLA molecule. So Tran and his colleague Dr. Rom Leidner, an oncologist, got Food and Drug Administration permission to reprogram her T cells to bear the special mutant-fighting receptor.

They culled T cells from Wilkes' blood, genetically engineered them in the lab and then grew billions of copies. Six months after a transfusion of the altered cells, her tumors had shrunk by 72%—and Wilkes said recent checkups show her disease remains stable.

Tran said it's not clear why the experiment failed in another patient, although lessons from that case that prompted some changes to Wilkes' treatment.

The Oregon team has opened a small study to further test TCR therapy for patients with incurable cancers fueled by what Tran calls "hot-spot" mutations.

More information: Rom Leidner et al, Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer, *New England Journal of Medicine* (2022). DOI: 10.1056/NEJMoa2119662