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New technique could make human T cells 100 times more potent at killing cancer cells

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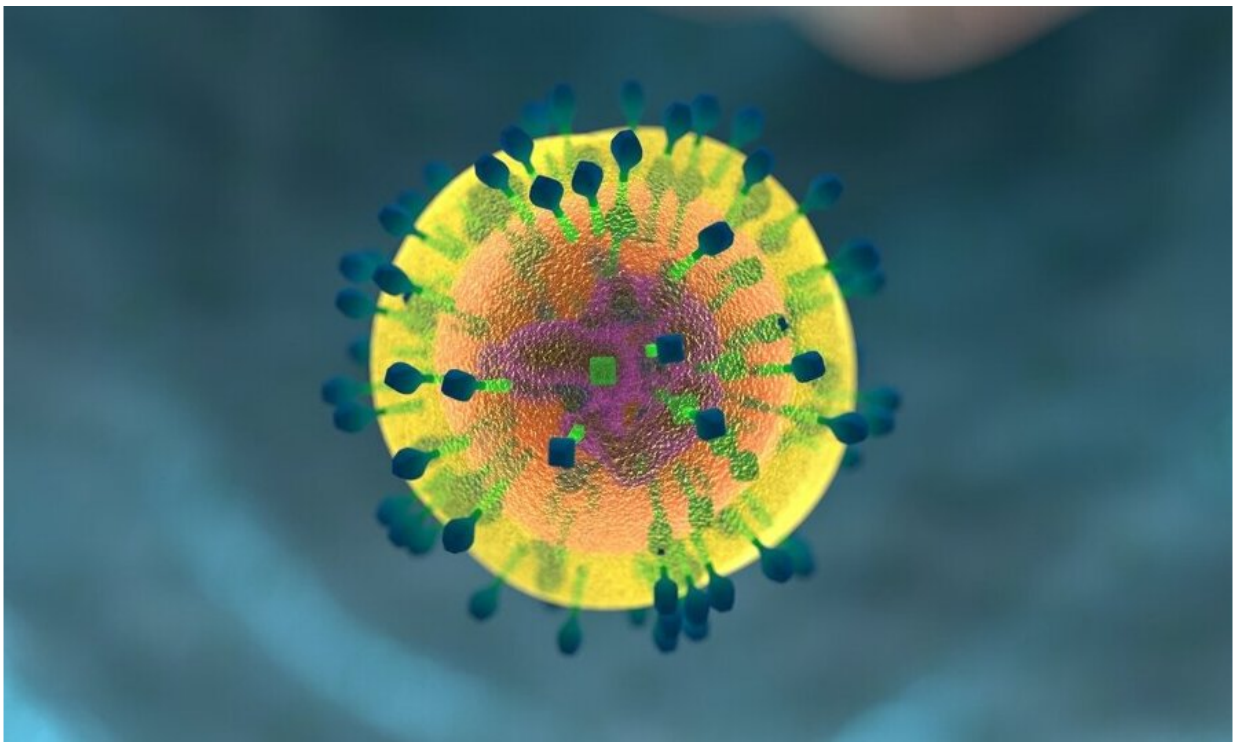

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Scientists at the UC San Francisco (UCSF) and Northwestern Medicine may have found a way around the limitations of engineered T cells by borrowing a few tricks from cancer itself.

By studying mutations in malignant T cells that cause lymphoma, they zeroed in on one that imparted exceptional potency to engineered T cells. Inserting a gene encoding this unique mutation into normal human T cells made them more than 100 times more potent at killing cancer cells without any signs of becoming toxic. The study appears in *Nature*.

While current immunotherapies work only against cancers of the blood and bone marrow, the T cells engineered by Northwestern and UCSF were able to kill tumors derived from skin, lung and stomach in mice. The team has already begun working toward testing this new approach in people.

"We used nature's roadmap to make better T cell therapies," said Dr. Jaehyuk Choi, an associate professor of dermatology and of biochemistry and molecular genetics at Northwestern University Feinberg School of Medicine. "The superpower that makes cancer cells so strong can be transferred into T cell therapies to make them powerful enough to eliminate what were once incurable cancers."

"Mutations underlying the resilience and adaptability of cancer cells can super-charge T cells to survive and thrive in the harsh conditions that tumors create," said Kole Roybal, associate professor of microbiology and immunology at UCSF, center director for the Parker Institute for Cancer Immunotherapy Center at UCSF, and a member of the Gladstone Institute of Genomic Immunology.

A solution hiding in plain sight

Creating effective immunotherapies has proven difficult against most cancers because the tumor creates an environment focused on sustaining itself, redirecting resources like oxygen and nutrients for its own benefit. Often, tumors hijack the body's immune system, causing it to defend the cancer, instead of attacking it.

Not only does this impair the ability of regular T cells to target cancer cells, it undermines the effectiveness of the engineered T cells that are used in immunotherapies, which quickly tire against the tumor's defenses.

"For cell-based treatments to work under these conditions," Roybal said, "we need to give healthy T cells abilities that are beyond what they can naturally achieve."

The Northwestern and UCSF teams screened 71 mutations found in patients with T cell lymphoma and identified which ones could enhance engineered T cell therapies in mouse tumor models. Eventually, they isolated one that proved both potent and non-toxic, subjecting it to a rigorous set of safety tests.

"Our discoveries empower T cells to kill multiple cancer types," said Choi, a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "This approach performs better than anything we've seen before." Their discoveries can be incorporated into treatments for many types of cancer, the scientists said.

"T cells have the potential to offer cures to people who are heavily pretreated and have a poor prognosis," Choi said. "Cell therapies are living drugs, because they live and grow inside the patient and can provide long-term immunity against cancer."

In collaboration with the Parker Institute for Cancer Immunotherapy and Venrock, Roybal and Choi are building a new company, Moonlight Bio, to realize the potential of their groundbreaking approach. They are currently developing a cancer therapy that they hope to begin testing in people within the next few years.

"We see this as the starting point," Roybal said. "There's so much to learn from nature about how we can enhance these cells and tailor them to different types of diseases."

Roybal and Choi are inventors on patents related to these discoveries and are co-founders and equity holders in Moonlight Bio.

More information: Jaehyuk Choi, Naturally occurring T cell mutations enhance engineered T cell therapies, *Nature* (2024). DOI: 10.1038/s41586-024-07018-7. www.nature.com/articles/s41586-024-07018-7

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