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Researchers engineer T cells to recognize tumor-specific expression patterns, enhancing tumor response

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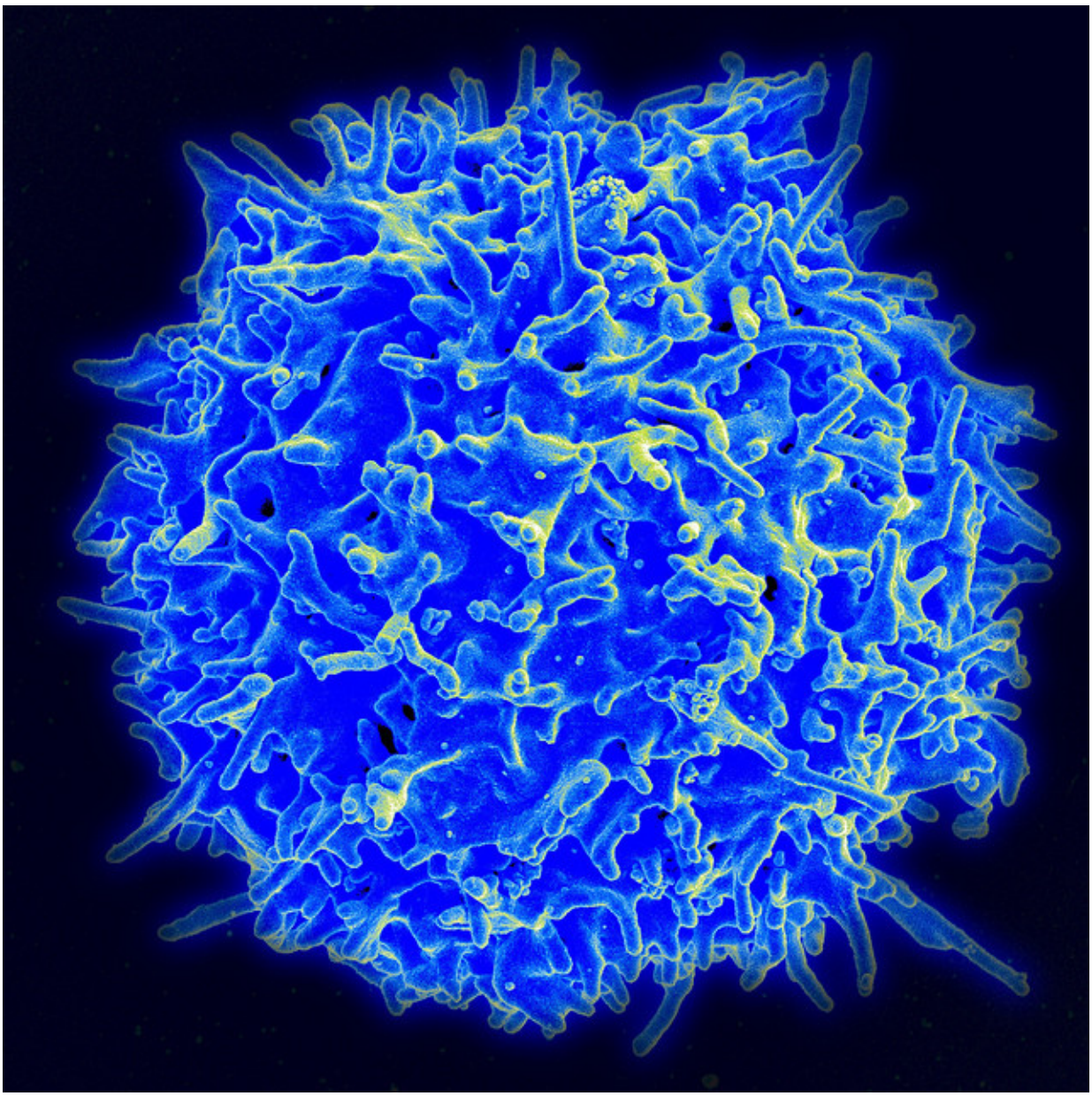

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

The advent and advancement of T cell therapy, especially chimeric antigen receptor (CAR)-modified T cells, has demonstrated therapeutic potential in treating previously treatment-resistant tumors. However, few CAR targets are absolutely tumor-specific, resulting in "on-target, off-tumor" toxicities that can be severe. Researchers in the Center for Cell and Gene Therapy at Baylor College of Medicine, Texas Children's Hospital and Houston Methodist have found a new way to ensure that engineered T cells can reliably discriminate between normal and malignant cells. This was achieved by modifying T cells to express a trio of molecules designed to recognize a pattern of antigens that are present, in combination, only on tumor cells. When tested in preclinical studies, these engineered T cells exhibited enhanced anti-tumor activity and selectivity, without side effects. The study appears in *Cancer Discovery*.

"In the past, CAR T cell therapy has worked through the specific targeting of a single antigen present on the tumor surface. However, this can be limiting, and even result in toxicity, when the CAR T cells find the antigen on normal tissues, which is called 'on-target, off-tumor,'" said Dr. Juan Vera, associate professor in the Center for Cell and Gene Therapy at Baylor. "In this study, we engineer CAR T cells to recognize a cohort, or a pattern, of molecules uniquely present in the tumor microenvironment. What this means is that our 'smarT cells' are able to better discriminate between tumor-proliferating cells and bystander cells."

In addition to a lack of signature, traditional T cell therapy also has been

limited by the suppressive nature of the tumor microenvironment, which limits the long-term survival and population growth of the T cells in solid tumors.

The research team chose to incorporate receptors into their engineered T cells that would protect them from such suppressive elements and ensure their sustained tumor killing capacity until all malignant cells were eliminated.

"The tumor signature detected by these smarT cells results in the delivery of three key signals to T cells: antigen activation, co-stimulation, and cytokine, which are delivered in a manner similar to physiological T cell activation," said Vera, who also is a member of the Dan L Duncan Comprehensive Cancer Center at Baylor. "When the T cells detect the signature, they are activated and grow and expand at the tumor site. Simultaneously, these signals congregate T cells resistant to the inhibitory effects of the tumor site and ensure their sustained long-term survival and effector function."

Engineering T cells to recognize tumor patterns is an example of the next generation of genetic editing, where engineered T cells are emulating the natural T cell response as closely as possible.

"Our study demonstrates the feasibility of reprogramming T cells to recognize a signature rather than a single antigenic marker expressed by tumors, thus enabling our modified cells to specifically target malignant tissues. By utilizing sophisticated genetic engineering approaches, we designed synthetic receptors that enhance both the potency and safety profile of the infused cells, which are key factors that underlie the success of CAR T cell therapy," said Dr. Sujita Sukumaran, first author on the paper and now a scientist in the T cell engineering group at Kite Pharma, Inc.

More information: Sujita Sukumaran et al. Enhancing the potency and specificity of engineered T cells for cancer treatment, *Cancer Discovery* (2018). DOI: 10.1158/2159-8290.CD-17-1298

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