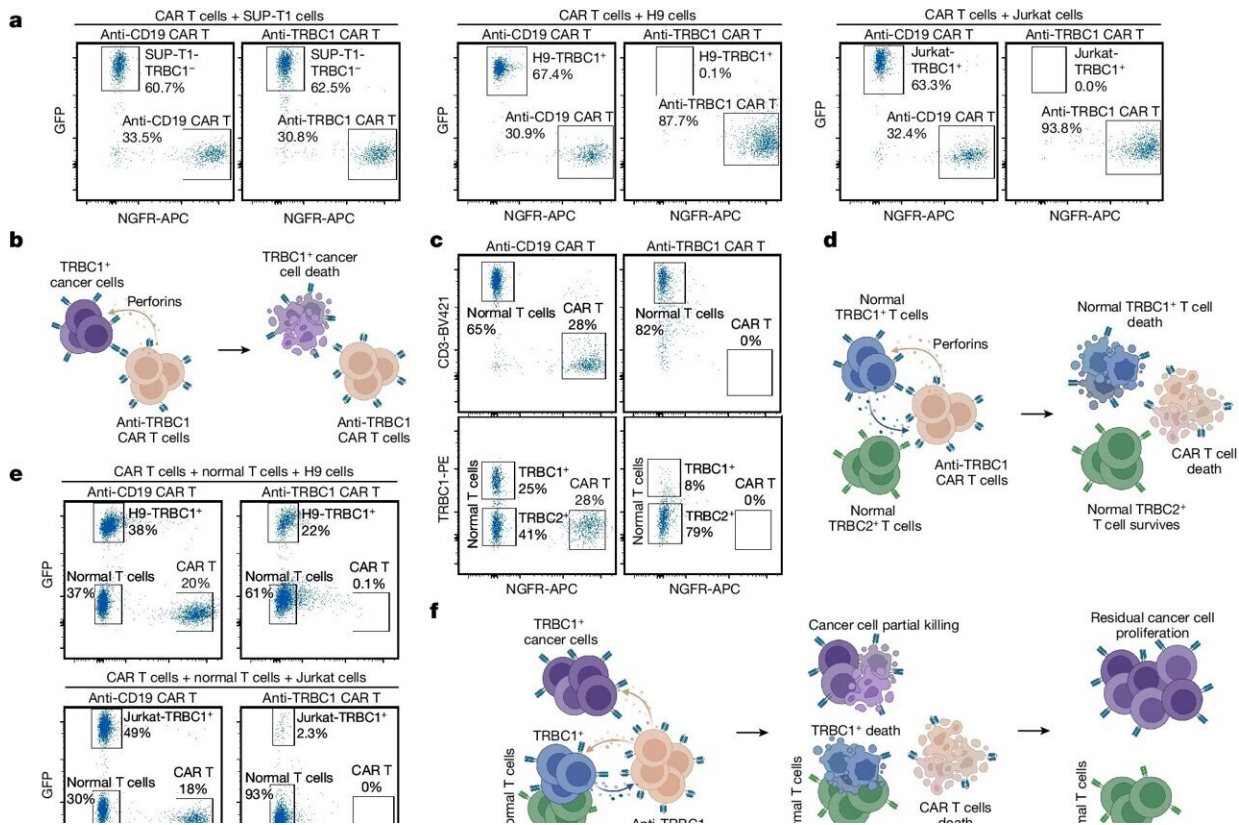


# Investigators develop novel treatment for T-cell leukemias and lymphomas

April 2 2024



Anti-TRBC1 CAR T cell activity is limited by normal T cell-mediated killing of the CAR T cells. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07233-2

A novel treatment for leukemias and lymphomas that arise from immune system T cells, developed by investigators at the Johns Hopkins Kimmel

Cancer Center and its Ludwig Center and Lustgarten Laboratory, was found to be effective at killing these cancers in mice bearing human T-cell tumors.

The therapy, an antibody-drug conjugate (ADC), combines an antibody that targets a protein called TRBC1 expressed on the surface of T-cell cancers with an anti-cancer drug called SG3249. The ADC works by using the antibody to seek out the cancer cells that express TRBC1. Then, those cancer cells ingest the ADC, where SG3249 is released and kills the [cancer cells](#). A description of the work was published [in Nature](#).

Each year, about 100,000 patients worldwide are affected by T-cell leukemias and lymphomas. Adults with relapsed T-cell cancers have limited therapeutic options and five-year survival rates of 7–38%.

"Developing treatments for T-cell leukemias and lymphomas is much more difficult than for leukemias and lymphomas arising from immune system B cells," explains senior study author Suman Paul, M.B.B.S., Ph.D., an assistant professor of oncology at the Johns Hopkins University School of Medicine.

Effective therapies for B-cell cancers wipe out both cancerous and noncancerous B cells, but patients still do well even without the immune system B cells that help fight infections. However, if similar approaches are used and a treatment wipes out both normal and cancerous T cells, it would leave patients without a functioning immune system and at high risk of dying from infections.

"Not much drug development has happened in this space of T-cell leukemias and lymphomas," Paul says. "We need new therapies for these cancers, but whatever therapies we develop in the space have to be cancer-specific. We have to preserve some of the normal T cells and wipe out cancerous T cells at the same time."

T-cell cancers express either TRBC1 or TRBC2, while normal T-cells express a mix of TRBC1 and TRBC2. Therefore, selective targeting of TRBC1 can potentially eradicate the normal and cancerous T cells expressing TRBC1 while preserving normal T cells expressing TRBC2. A recent clinical trial conducted elsewhere attempted to target TRBC1 cancers using [chimeric antigen receptor](#) (CAR) T-cell therapy.

These CAR T cells are genetically engineered T cells that bind to and kill TRBC1 cells. CAR T-cell therapies are FDA-approved treatment options used in several B-cell cancers. However, after administering the TRBC1-targeting CAR T cell therapy in [human patients](#), trial investigators reported that the CAR T cells were not persisting inside the patients.

Such persistence is required for effective cancer cell-killing. Interested to understand why, Paul and colleagues found that the CAR T cells targeting TRBC1 could be killed by normal T cells, limiting their persistence.

This lack of CAR T-cell persistence led the team to try TRBC1 targeting with the use of antibody-drug conjugates. Paul and colleagues tried two different formulations of ADCs in mouse models of T-cell cancers. After a single injection of one formulation of the treatment, the cancers initially regressed but then recurred. After a single treatment with the anti-TRBC1-SG3249 ADC combination, investigators observed signs of cancer elimination within seven days, and the cancers were eventually undetectable, with no recurrences.

"The tumors didn't come back, and we followed the mice for more than 200 days," Paul explains.

The treatment was able to eliminate the cancer while preserving half of the remaining normal T cells. "The residual normal T cells should be

sufficient to maintain some immune system protection against [infectious diseases](#)," Paul says.

"Witnessing the successful elimination of T-cell cancers while sparing normal T cells in preclinical models was truly gratifying," adds Jiaxin Ge, a co-author of the study and third-year Ph.D. student in the Ludwig Center. "We believe this approach has the potential to address a critical unmet need in oncology, and we're committed to advancing it through further research."

Tushar Nichakawade, first author on the study and a fourth-year Ph.D. student at the Ludwig Center, says, "There are so many lessons to learn from the clinic, and it has been exciting to be a part of the iterative process of drug discovery. Every therapy has its pros and cons, but the preclinical efficacy of our ADC gives me hope that it can make a difference for patients suffering from these terrible cancers."

Investigators are now working with an industry partner to conduct early-phase safety and efficacy trials in human patients.

**More information:** Tushar D. Nichakawade et al, TRBC1-targeting antibody–drug conjugates for the treatment of T cell cancers, *Nature* (2024). [DOI: 10.1038/s41586-024-07233-2](https://doi.org/10.1038/s41586-024-07233-2)

Provided by Johns Hopkins University School of Medicine

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