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New research identifies potential approach to mitigate CAR T-cell therapy toxicity

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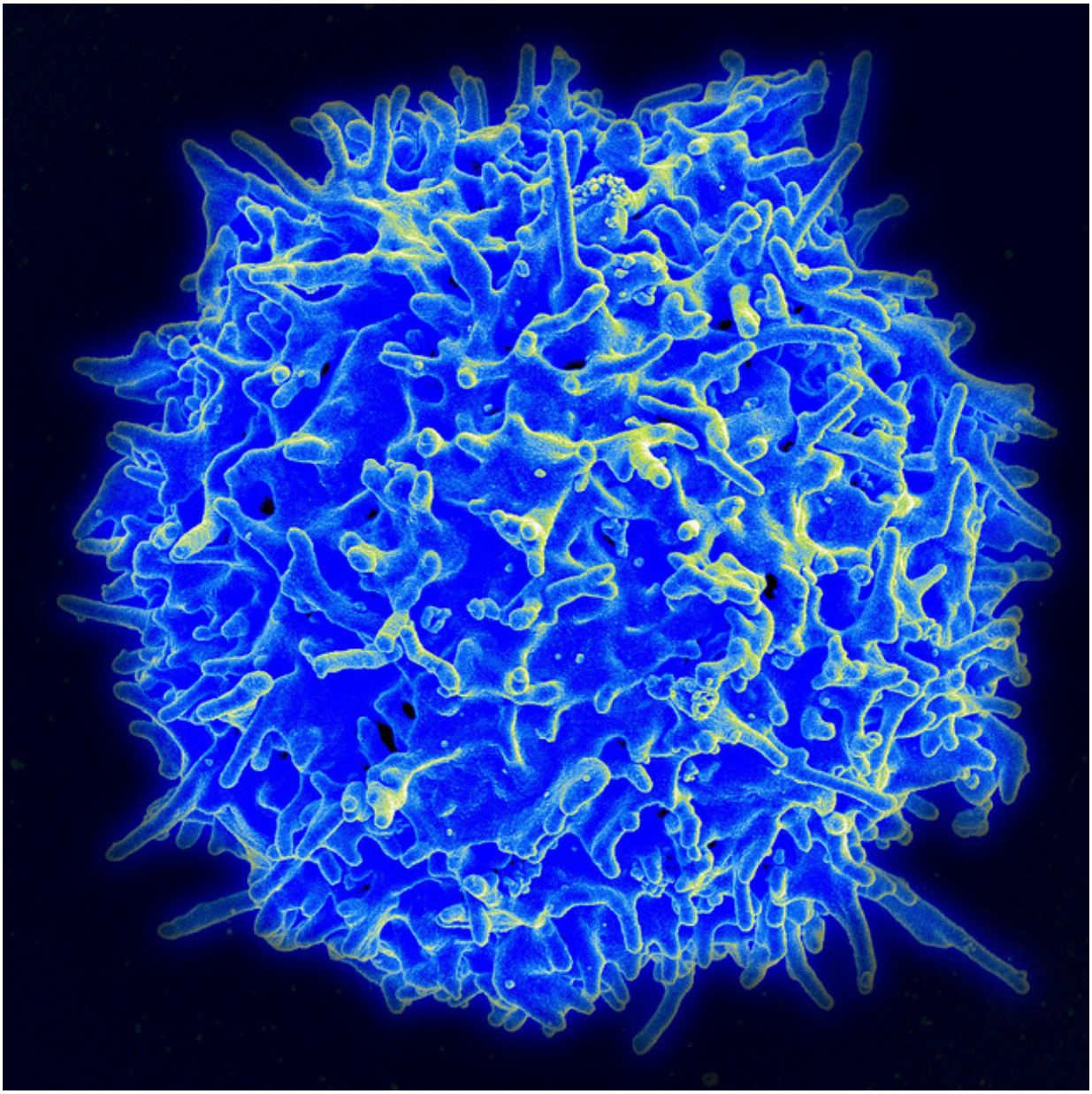

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

Blood Cancer Discovery, a journal of the American Association for Cancer Research, has published a research article demonstrating a novel approach that may reduce a serious adverse effect associated with chimeric antigen receptor (CAR) T-cell therapy, a form of immunotherapy.

This research was presented at the American Society of Hematology Annual Meeting in Atlanta, Georgia by the study's senior author, Marcela Maus, MD, Ph.D., director of the Cellular Immunology Program at Massachusetts General Hospital Cancer Center and associate professor of Medicine at Harvard Medical School.

"One of the main limitations to CAR T-cell therapy is the temporary side effects that it causes: High fevers, low blood pressure, and other signs of what is known as the 'cytokine release syndrome,'" said Maus. In severe cases, patients experiencing cytokine release syndrome may require intensive care, she added.

Interferon gamma (IFNγ) is a cytokine produced by CAR T cells that initiates the cellular events that lead to cytokine release syndrome, but its contribution to the antitumor effects of CAR T-cell therapy remained unclear. "We've generally thought that this cytokine is part of how CAR T cells work. We wanted to ask the question, is this cytokine really necessary for the antitumor effect [of CAR T cells] in blood cancers? Or, if we block it or knock it out… do we still get antitumor effects, and would we expect there to be less cytokine release syndrome?" Maus explained.

Using in vitro and in vivo models of blood cancers, Maus and colleagues demonstrated that suppressing IFNγ, either by blocking its function or deleting it from CAR T cells, had no observable adverse impact on the antitumor effects of CAR T cells. In contrast, suppression of IFNγ appeared to prevent the activation of macrophages and other immune cells that help drive cytokine release syndrome. Deletion of IFNγ led to a greater reduction in macrophage activation than current clinical approaches.

"Together, this implies that we can separate toxicity from efficacy," Maus summarized. "It may be possible that blocking or knocking out this cytokine from CAR T cells could prevent or treat cytokine release syndrome, while still preserving the antitumor effects [of CAR T-cell therapy]. This could make CAR T cells an easier and more accessible therapy for patients." Maus noted that additional research will be needed to understand the role of IFNγ for the treatment of solid tumors.

More information: Stefanie R Bailey et al, Blockade or deletion of IFNg reduces macrophage activation without compromising CAR-T function in hematologic malignancies, *Blood Cancer Discovery* (2021). DOI: 10.1158/2643-3230.BCD-21-0181

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