Cancer immunotherapy may get a boost by disabling specific T cells

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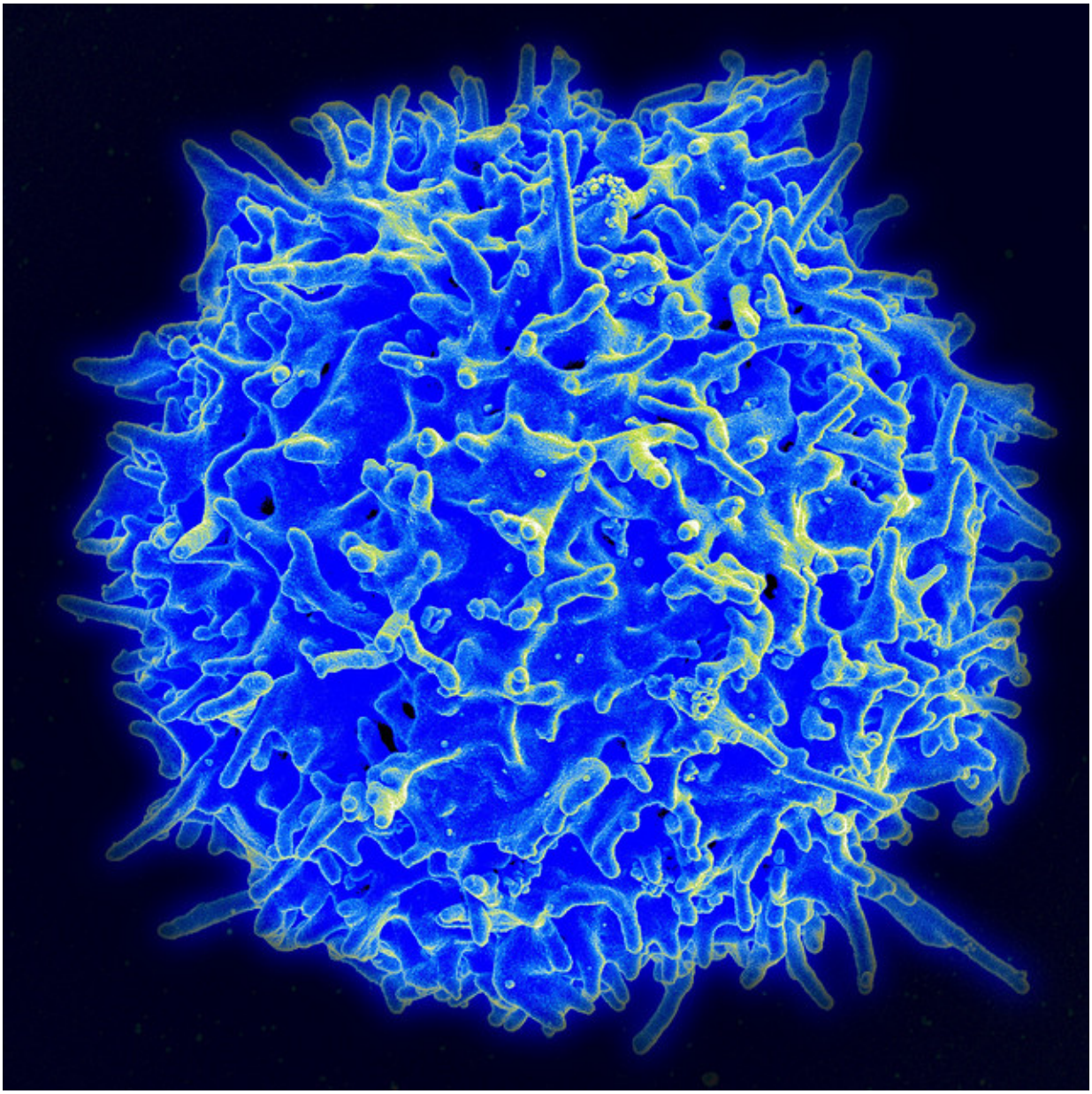

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

Cancer immunotherapy drugs only work for a minority of patients, but a generic drug now used to increase blood flow may be able to improve those odds, a study by Columbia University Medical Center (CUMC) researchers suggests.

In mice with melanoma, the researchers found that the drug - called pentoxifylline - boosts the effectiveness of immune-checkpoint inhibitors, a type of immunotherapy now commonly used in the treatment of melanoma and other cancers.

The study was published today in the online edition of *Cell*.

Checkpoint-blockade immunotherapy drugs - the first drugs were approved in 2011 - target proteins on tumor cells or cells of the immune system that prevent "killer" T cells from attacking cancer. These drugs have revolutionized cancer care, but do not work for all patients. "In advanced melanoma, for example, the cure rate is only about 20 percent. That's a remarkable improvement over previous therapies," says study leader Sankar Ghosh, PhD, Chair and Silverstein and Hutt Family Professor of Microbiology & Immunology. "But why doesn't it work for the other 80 percent? There must be another mechanism that contributes to the suppression of the immune response."

Dr. Ghosh and other cancer biologists suspected that a different type of T cell, known as regulatory T cells, or Tregs, may also suppress the immune system's attack on cancer. Large numbers of these cells are found within several types of tumors. "One possible therapy would be to get rid of Tregs," he said. "But Tregs are also needed to keep the

immune system in check, and shutting down Tregs completely would unleash an attack against the body's healthy cells and organs."

This point is underscored by a related study, published today in Immunity, in which Dr. Ghosh and colleagues found that removing NF-B from Tregs caused widespread and lethal autoimmunity in mice. However, a partial inhibition of NF-?B, achieved by removing only one, specific, NF-B protein, called c-Rel, changed Treg function without causing widespread autoimmunity. In the *Cell* study Ghosh and colleagues showed that these c-Rel deficient Tregs were specifically crippled in their ability to protect cancer cells. As a result, when c-Rel is blocked, killer T cells mounted a more robust attack on cancer cells without causing autoimmunity.

Pentoxifylline is a drug that is used in patients to increase blood flow in the hands and feet of people with poor circulation, but it's also known to inhibit the c-Rel protein. In the *Cell* study, the researchers demonstrated that pentoxifylline blocked Treg function and boosted the effectiveness of standard checkpoint-blockade immunotherapies. As a result, mice treated with both drugs showed significantly reduced melanoma tumor burden, compared to animals that received the standard therapy alone.

"The next step is to test this drug combination in human clinical trials," Dr. Ghosh says. "If trials are successful, the use of c-Rel inhibitors could become a standard addition to immune checkpoint therapy for many types of cancer."

The *Cell* paper is titled, "NF-?B c-Rel is crucial for the regulatory T cell immune checkpoint in cancer."

Provided by Columbia University Medical Center