# Researchers change human leukemia cells into harmless immune cells

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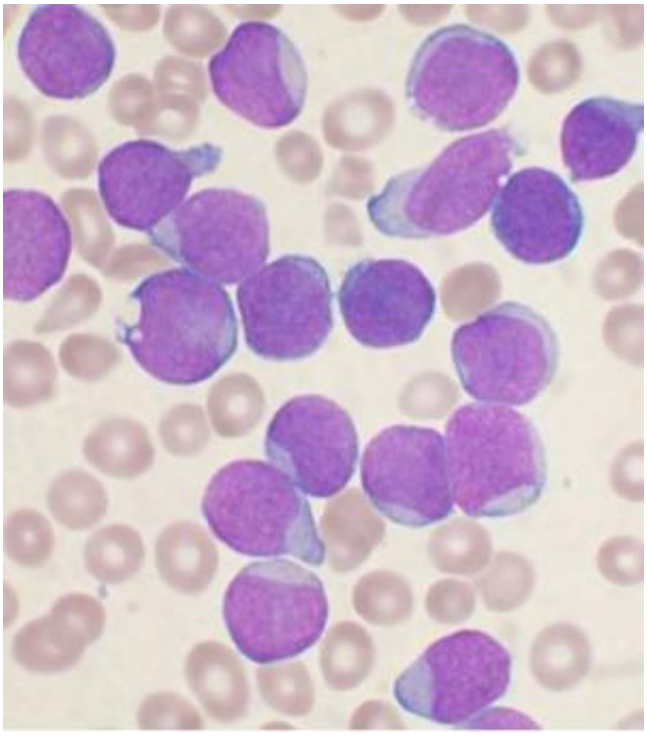

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Researchers at the Stanford University School of Medicine have discovered that when a certain aggressive leukemia is causing havoc in the body, the solution may be to force the cancer cells to grow up and behave.

After a chance observation in the lab, the researchers found a method that can cause dangerous leukemia cells to mature into harmless immune cells known as macrophages.

The findings will be described in a paper that will be published online March 16 in the *Proceedings of the National Academy of Sciences*.

B-cell acute lymphoblastic leukemia with a mutation called the Philadelphia chromosome is a particularly aggressive cancer with poor outcomes, said Ravi Majeti, MD, PhD, an assistant professor of medicine and senior author of the paper. So finding potential treatments is particularly exciting.

Majeti and his colleagues made the key observation after collecting leukemia cells from a patient and trying to keep the cells alive in a culture plate. "We were throwing everything at them to help them survive," said Majeti, who is also a member of the Stanford Cancer Institute and the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

## An unusual metamorphosis

Postdoctoral scholar Scott McClellan MD, PhD, a lead author of the paper, mentioned that some of the cancer cells in culture were changing shape and size into what looked like macrophages. Majeti concurred with that observation, but the reasons for the changed cells were a mystery until he remembered an old research paper, which showed that early B-cell mouse progenitor cells could be forced to become macrophages when exposed to certain transcription factors—proteins that bind to certain DNA sequences.

"B-cell leukemia cells are in many ways progenitor cells that are forced to stay in an immature state," Majeti said. So he, McClellan and student

Christopher Dove, an MD/PhD student and the paper's other lead author, did more experiments and confirmed that methods shown to have altered the fate of the mouse progenitor cells years ago could be used to transform these human cancer cells into macrophages, which can engulf and digest cancer cells and pathogens.

Majeti and his colleagues have some reason to hope that when the cancer cells become macrophages they will not only be neutralized, but may actually assist in fighting the cancer. Like a bloodhound owner who gives the dog a sniff of an object that was associated with the person or animal he wants to track, macrophage cells present recognizable bits of abnormal cells to other immune cells so that they can launch an attack. "Because the macrophage cells came from the cancer cells, they will already carry with them the chemical signals that will identify the cancer cells, making an immune attack against the cancer more likely," Majeti said.

## The hope for a therapy

The researchers' next steps will be to see if they can find a drug that will prompt the same reaction and that could serve as the basis for a therapy for the leukemia. There is some precedent for such a treatment. Retinoic acid is commonly used to treat another cancer called acute promyelocytic leukemia. In that case, retinoic acid is used to turn cancer cells into mature cells called granulocytes. This treatment is the only well-established therapy that matures, or "differentiates," cancer cells, but researchers around the world are hopeful of finding many more. "There's big-time interest in differentiation therapies for cancer," Majeti said.

**More information:** Reprogramming of primary human Philadelphia chromosome-positive B cell acute lymphoblastic leukemia cells into nonleukemic macrophages, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1413383112

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