

Findings pave way for three-drug combination treatment for childhood leukemia

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

UCLA researchers have developed a new approach that could eventually help young people respond better to treatment for acute lymphoblastic leukemia. The scientists discovered in mice that when the production of nucleotides—also known as the building blocks of life—is stopped, a



"DNA replication stress response" is activated. The replication stress response is a cellular monitoring system that usually senses and resolves DNA damage, but instead allows cancer cells to survive.

The team, led by Dr. Caius Radu, a member of UCLA's Jonsson Comprehensive Cancer Center, used results of the study to devise a threedrug combination treatment regimen, which has proven to kill <u>cancer</u> <u>cells</u> and eradicate <u>acute lymphoblastic leukemia</u> in mouse models.

The three-drug combination has been shown to block both of the nucleotide <u>biosynthetic pathways</u> and inhibit the replication stress response. Biosynthetic pathways are components of metabolism that allow cells to produce nucleotides, needed to grow and survive. When the pathways are blocked by drug molecules, cancer cells can stop growing and can die.

Two of the experimental drugs, triapine (3-AP) and DI-82, were used to lower nucleotide levels. The third drug, VE-822, inhibits an enzyme called ATR, which is known as the master regulator of the DNA replication stress response and renders the cancer cells sensitive to low levels of nucleotides. Then VE-822 disables the brakes applied by the replication stress response and allows the three-drug combination to kill lymphoblastic leukemia cells. It also promotes long-term survival of treated animals without causing toxicity that would harm them.

Acute lymphoblastic leukemia is the most common childhood cancer diagnosed in the United States annually. It occurs when <u>bone marrow</u> <u>cells</u> aren't functioning properly and struggle to fight infections.

This study builds and improves upon previous work investigating how lymphoblastic leukemia <u>cells</u> produce nucleotides. Mouse models were used in the pre-clinical research to assess the effectiveness of the threedrug combination over a four-year period. The next stage of research



will aim to test the individual components of the combination therapy in clinical trials.

The study is published online in the journal Nature Communications.

More information: Thuc M. Le et al. ATR inhibition facilitates targeting of leukemia dependence on convergent nucleotide biosynthetic pathways, *Nature Communications* (2017). DOI: 10.1038/s41467-017-00221-3

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