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Getting more mileage from a T-cell therapy for acute myeloid leukemia

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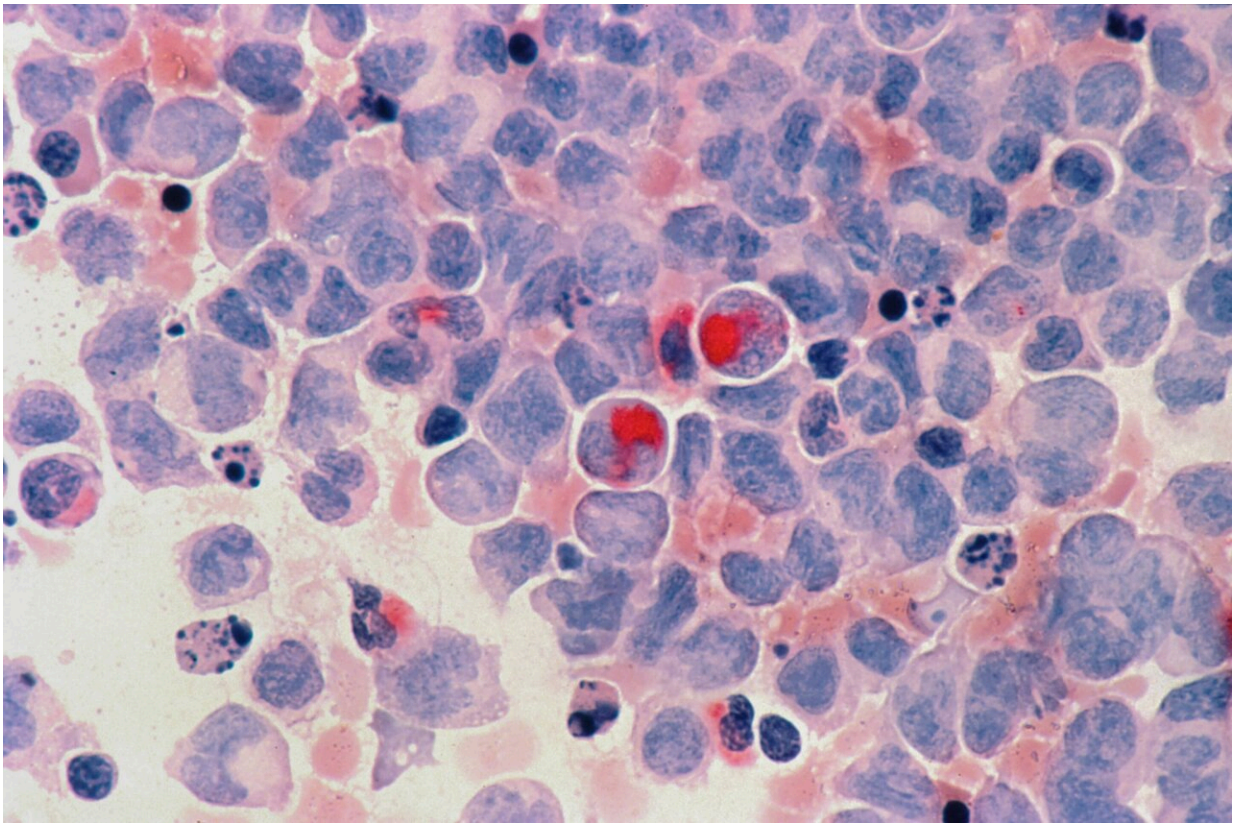

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Scientists at St. Jude Children's Research Hospital developed a strategy to improve the ability of engager (ENG) T cells to kill acute myeloid leukemia (AML). The approach showed promise in preclinical models

against hard-to-treat relapsed disease. The results were pre-published today in the journal *Haematologica*.

Despite advances in pediatric leukemia treatment, clinical outcomes remain poor for relapsed AML. Researchers are exploring multiple potential therapies. One approach uses ENG T cells. These cells are immune cells that have been modified to secrete antibodies that bring T cells and cancer cells together, promoting tumor killing. Scientists at St. Jude developed a way to improve on ENG T cells, making the therapy more efficient and effective. They added a co-stimulation system controlled by an activating drug to the ENG construct. Preclinical findings show that the approach increased the anti-AML activity of ENG T cells.

"We're basically having the T cells express a battery that we can control," said corresponding author Paulina Velasquez, M.D., St. Jude Department of Bone Marrow Transplantation and Cellular Therapy. "ENG T cells secrete a protein that allows the T cells to kill leukemia. In this case, when they also express the controlled battery that we added, we are getting extra mileage out of these cells."

ENG T cells for AML improve with inducible co-stimulation

Regular ENG T cells quickly become exhausted after encountering tumor cells, ending their therapeutic effect. The St. Jude team found that co-stimulation can counteract exhaustion, making the ENG T cells work better. The team tested inducible co-stimulatory proteins that only function in the presence of a small molecule (drug). The drug gives the researchers more control, even after the ENG T cells are infused into a patient. In addition to preventing exhaustion, this system can serve as an important safety feature because the inducible co-stimulation can be

easily curtailed if the drug is stopped.

Velasquez and her team tested whether expression of inducible co-stimulatory proteins that activate MyD88, CD40, or both MyD88 and CD40 immune pathways in ENG T cells improves their antitumor activity. AML-specific ENG T cells in which both signaling pathways were activated outperformed their unmodified counterparts or ENG T cells in which only one of the pathways was active in laboratory studies as well as animal models.

ENG T cells: A promising alternative to treat relapsed AML

At present there are many genetic approaches to render T cells specific for AML. This includes, for example, expression of chimeric antigen receptors (CARs). In contrast to CAR T-cell therapy for acute lymphoblastic leukemia (ALL), the clinical experience with AML-specific CAR T cells has presented challenges.

"Based on the results of our study, ENG T cells that express inducible co-stimulatory proteins, might be a promising alternative to other AML-specific T-cell therapy approaches that are actively being explored," Velasquez said. "There are currently no clinical trials with ENG T cells, but our study should provide the impetus to explore the safety and efficacy of AML-specific ENG T cells in early phase clinical studies in the future."

More information: Abishek Vaidya et al, Improving the anti-acute myeloid leukemia activity of CD123-specific Engager T cells by MyD88 and CD40 costimulation, *Haematologica* (2022). DOI: 10.3324/haematol.2021.279301

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