CAR T drives acute myeloid leukemia into submission in pre-clinical studies

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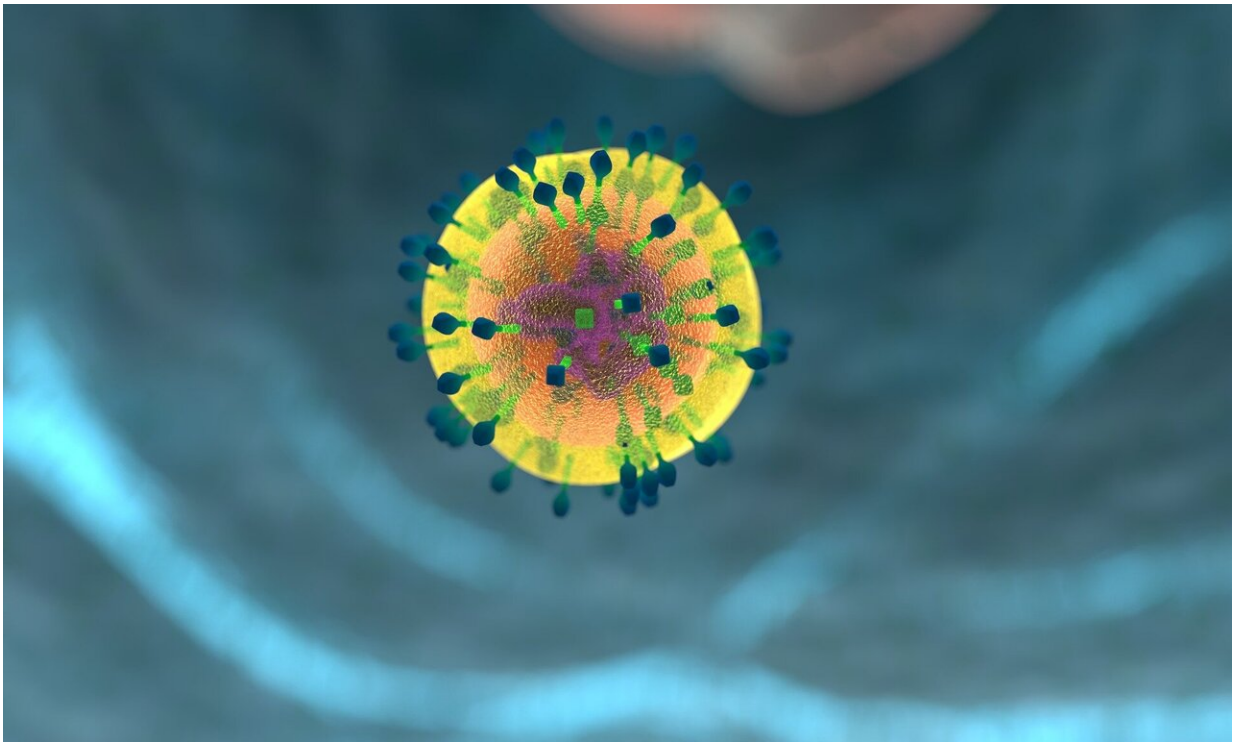

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Massachusetts General Hospital (MGH) researchers have developed a novel treatment strategy that has the potential to bring the life-saving benefits of chimeric antigen receptor T-cell therapy (CAR T) to patients with acute myeloid leukemia (AML) the most common form of leukemia in adults.

The method involves a combination of drug therapy to expand the number of targets on tumor cells, and an engineering approach to help the therapy adhere more tightly and durably to those targets.

They describe their work in a study published online in the journal *Cancer Cell*.

CAR T therapy has revolutionized the care of patients with advanced cancers of the blood system. It involves harvesting a patient's T cells, which are key components of the immune system, and genetically engineering them to recognize a specific target (antigen) on the surface of cancer cells. The cells are then expanded in the laboratory and returned to the patient's bloodstream, where they mount an enhanced tumor-killing immune response.

CAR T therapy relies on the ability of T cells to identify antigens that are either unique to cancer cells or are present in much greater numbers on normal cells than on malignant cells.

For lymphoid malignancies such as acute lymphoblastic leukemia and B-cell lymphomas, which arise from white blood cells, targeting tumors can also deplete the population of normal antibody-producing B cells, but clinicians can compensate for the loss of normal cells by replacing immunoglobulins that B cells normally make.

"In contrast, the normal counterparts to acute myeloid leukemia are myeloid cells, which are involved in fighting infections. Unfortunately, you can't live without these for very long," says lead author Mark B. Leick, MD, investigator the Cellular Immunotherapy program at the MGH Cancer Center,

Previous attempts to treat advanced AML with CAR T therapy have been stymied by the lack of a suitable antigen, and by "off-target"

effects when the treatment kills large numbers of healthy normal cells as well as cancer cells.

Leick, with senior researcher Marcela V. Maus, MD, Ph.D., director of Cellular Immunotherapy at the MGH Cancer Center, and colleagues, started with a CAR T construct directed against an antigen called CD70 that is present in larger numbers on AML cells than on normal myeloid cells. The CAR T alone was only modestly effective against AML in animal models, but combining it with the FDA-approved AML drug azacitidine increased the number of CD70 antigens on cancer cell surfaces.

"We were able to show that through the combination of the two, we got better killing of the tumor cells," he says.

In addition, unlike most CARs that use antibodies derived from mice to target the antigen, which can cause an unwanted immune reaction, the CAR used in this study relies on a kind of a natural molecular bond known as a ligand to bind tightly to the antigen, thereby avoiding the possibility that the immune system would recognize the tumor-killing machinery as foreign and try to reject it.

Lastly, they overcame a problem that bedeviled an older version of the CAR T cell to target AML.

"AML cells secrete an enzyme, a proteinase, that is essentially able to decapitate the CAR T cell, and so we localized where that cut takes place, and we modified that region, so now the CAR T cells bind tighter to the tumor and kill it more effectively," Leick says.

"We are excited for the therapeutic potential of this new CAR T cell product, and hope that we can offer it to patients with acute myeloid leukemia soon," says Maus.

More information: Mark B. Leick et al, Non-cleavable hinge enhances avidity and expansion of CAR-T cells for acute myeloid leukemia, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.04.001