New trials following successful approach to producing and using anti-CD19 CAR T cells against B-cell malignancies

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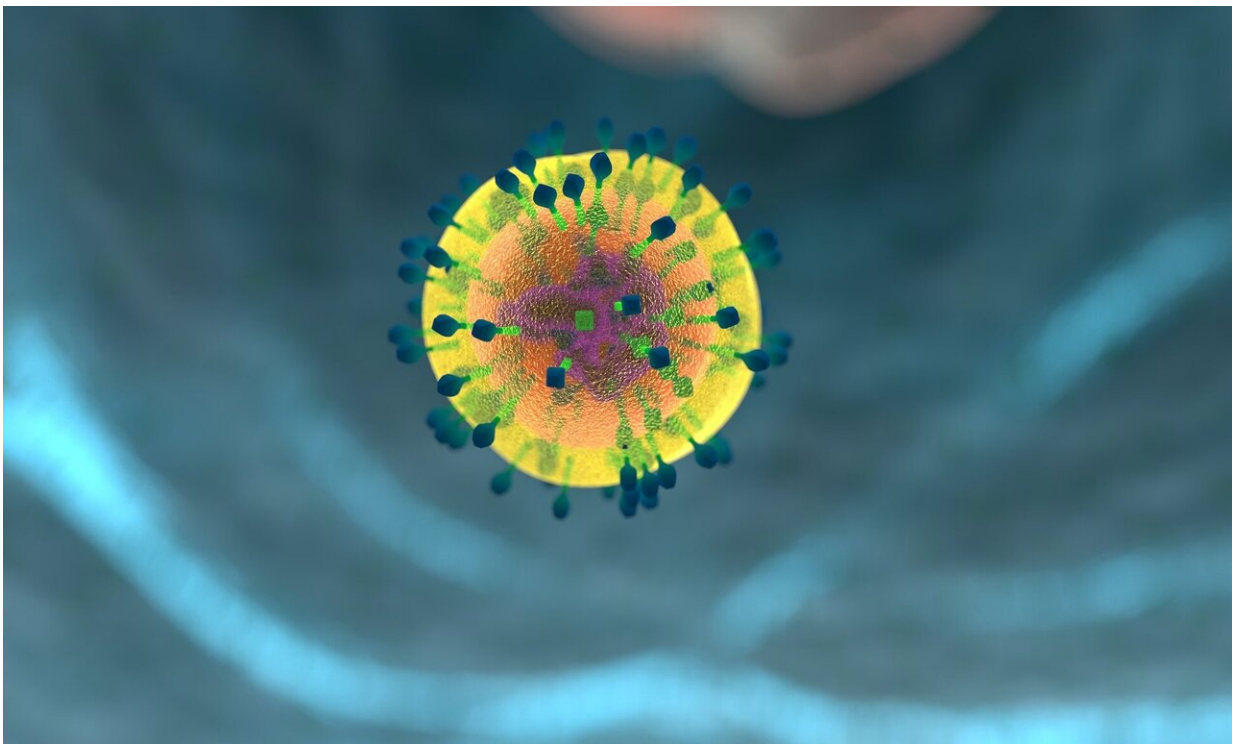

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Newly designed chimeric antigen receptor (CAR) T-cells targeting the CD19 antigen are effective in treating adults and children with B-cell malignancies, especially when produced under place-of-care

manufacturing which is available at University Hospitals (UH) Seidman Cancer Center. That's the conclusion of a recent study published in the journal *Nature Communications,* detailing two Phase I clinical trials of CAR19 T-cells used to treat patients with relapsed/refractory pediatric B-cell Acute Lymphocytic Leukemia (ALL) or adult B-cell Lymphoma.

"Place-of-care manufacturing may improve performance and accessibility by obviating the need to cryopreserve and transport cells to centralized facilities," says study co-author Jane Reese Koc, Cellular Therapy Operations Director at UH Seidman Cancer Center and the National Center for Regenerative Medicine at Case Western Reserve University. The Cellular Therapy Lab is shared by the National Center for Regenerative Medicine, Case Comprehensive Cancer Center and UH Seidman Cancer Center. "The results of this study support the safety and efficacy of this approach."

"One of the major advantages of this approach is the ability to treat patients significantly quicker than is feasible with commercial CAR T products," adds study co-author David Wald, MD, Ph.D., Associate Director for Basic Research at the Wesley Center for Immunotherapy at UH Seidman Cancer Center and Associate Professor of Pathology Case Western Reserve University School of Medicine. "Commercial products can take three to six weeks to be manufactured. The time savings to treatment with the method is important for these patients that have advanced malignancies. We are working with partners to develop even more rapid methods to shorten the manufacturing method down to a single day."

The Phase I trials involved 31 pediatric and 23 adult patients, located in both Russia and Cleveland. After a median follow-up of 17 months, one-year survival rate of ALL complete responders was 79.2% and median duration of response is 10.2 months. For non-Hodgkin lymphoma (NHL), complete responders one-year survival was 92.9%, and median

duration of response has not been reached. The CAR19 T-cells were first tested in cancer cell lines and mouse xenograft models, with positive results.

"For NHL, the results were excellent," says hematologist Leland Metheny, MD, who is also involved in these clinical trials at UH Seidman Cancer Center. "The results showed they were curative for a significant portion."

Importantly, in the mouse xenograft experiments, fresh CAR19 T-cells produced in the local facility were shown to provide an advantage over cryopreserved cells more commonly used in CAR T applications. Administration of fresh CAR19 T-cells yielded significantly lower tumor burden as compared to dose-matched frozen CAR19 T-cells on study days 11 and 13. On study days 21 and 28, tumors were similarly and potently rejected by both fresh and frozen cell-treated groups. However, fresh cells reduced the tumor burden sooner by eight days, and immediately started reducing the tumor burden, while frozen CAR19 T-cells first permitted tumor growth before controlling growth.

"The cells that were given fresh acted much better and more effective in mice in getting rid of the NHL than the frozen cells," Dr. Metheny says. "There is something we don't know yet about the impact of the freezing technique that is impacting the CAR T-cells."

In addition to these two clinical trials, Dr. Metheny's colleagues at UH Seidman Cancer Center are also conducting a CAR T trial that uses fully human protein—one just a handful of sites nationwide to offer this option to patients.

"The antibody part of the antigen receptor that we're putting on the surface of the T cell is a fully human sequence," says UH Seidman oncologist Benjamin Tomlinson, MD, who is leading this trial. "In

theory, it may have fewer adverse events, so be slightly safer, while still attacking the same target. The biggest question is whether by not having a foreign component, it may be a little bit more effective in instigations in the signaling. Human to human should connect a little bit better than human to mouse, and it may not generate the type of reactions that we are used to seeing with a regular CAR Ts. So that's what we're exploring. We have opened this humanized CAR T trial and have treated patients with lymphoma and ALL successfully."

In addition, Dr. Wald and colleagues recently reported at the American Society of Hematology meeting on their work identifying potential biomarkers that may help predict outcomes of the patients receiving CAR T-cell therapy.

"We hope this will help to design next generation CAR T-cell therapies," he says.

More information: Michael Maschan et al, Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients, *Nature Communications* (2021). DOI: 10.1038/s41467-021-27312-6

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