Genome-edited immune cell therapy shows promise for treating aggressive blood cancer

University College London Dec 8 2025

A groundbreaking new treatment using genome-edited immune cells, developed by scientists at UCL (University College London) and Great Ormond Street Hospital (GOSH), has shown promising results in helping children and adults fight a rare and aggressive form of blood cancer called T-cell acute lymphoblastic leukemia (T-ALL).

The world-first gene therapy (BE-CAR7) uses base-edited immune cells to treat previously untreatable T-cell leukemia and help patients achieve remission, offering new hope for families facing this aggressive cancer. Base-editing is an advanced version of CRISPR technology, that can precisely change single letters of DNA code inside living cells.

In 2022, researchers from GOSH and UCL delivered the world's first treatment made using 'base-editing' to a 13-year-old girl from Leicester, Alyssa.

Now a further eight children and two adults have undergone the treatment at GOSH and King's College Hospital (KCH).

The results of the clinical trial have been published in the *New England Journal of Medicine and* presented at the 67th American Society of Hematology Annual Meeting. Key findings from the study include:

- 82% of patients achieved very deep remissions after BE-CAR7, enabling them to proceed to stem cell transplant without disease
- 64% remain disease-free, with the first patients now three years disease-free and off treatment
- Anticipated side effects including low blood counts, cytokine release syndrome and rashes were tolerable, with the greatest risks arising from virus infections until immunity recovered

New technology

Immunotherapy using CAR-T cells has recently become available to treat several types of blood cancer. This therapy uses immune cells, called T-cells, and modifies them to have specific proteins on their surface called chimeric antigen receptors (CARs). The CARs can recognize and target specific 'flags' on the surface of cancer cells, and the T-cell can then destroy that cancer cell. Developing CAR T-cell therapy for leukemia which itself has arisen from abnormal T-cells has been challenging.

BE-CAR7 T-cells are engineered using base editing, a new-generation of genome editing that avoids cutting DNA, reducing the risk of chromosomal damage. Very precise chemical reactions were carried out using CRISPR guidance systems to change single letters of DNA code in order to modify the T cells. As reported in 2022, these complex DNA changes generated storable banks of 'universal' CAR T-cells that can find and attack T-cell leukemia when given to patients.

The 'universal' CAR T-cells in this study were made from healthy donor white blood cells and engineering steps were undertaken in a clean room facility at Great Ormond Street Hospital, using custom made RNA, mRNA and a lentiviral vector in an automated process previously developed by the research team. These steps were:

- **Removing existing receptors so that T-cells from a donor can be banked and used without matching the recipient**– making them 'universal'.
- **Removing a 'flag' called CD7 that identifies them as T-cells (CD7 T-cell marker).** Without this step, T-cells programmed to kill T-cells would simply end up destroying the product through 'friendly-fire'.
- **Removing a second 'flag' called CD52.** This makes the edited cells invisible to one of the strong antibody drugs given to patients to subdue their immune system.
- **Adding a Chimeric Antigen Receptor (CAR) which recognizes the CD7 T-cell flag on leukemic T-cells.** A disabled virus added extra DNA code into the cells so they become armed against CD7 and recognize and fight T-cell leukemia.

When base-edited CAR T-cells are given to the patient they rapidly find and destroy all T-cells in the body, including leukemic T-cells. If the leukemia is eradicated within four weeks, the patient's immune system is then rebuilt from

a bone marrow transplant over a period of several months.

"We previously showed promising results using precision genome editing for children with aggressive blood cancer and this larger number of patients confirms the impact of this type of treatment," said Professor Waseem Qasim who led the research and is professor of cell and gene therapy at UCL and honorary consultant immunologist at GOSH. "We've shown that universal or 'off the shelf' base-edited CAR T-cells can seek and destroy very resistant cases of CD7+ leukemia."

He also added: "Many teams were involved across the hospital and university and everyone is delighted for patients clearing their disease, but at the same time, deeply mindful that outcomes were not as hoped for some children. These are intense and difficult treatments - patients and families have been generous in recognising the importance of learning as much as possible from each experience."

> *Although most children with T-cell leukemia will respond well to standard treatments, around 20% may not. It's these patients who desperately need better options and this research provides hope for a better prognosis for everyone diagnosed with this rare but aggressive form of blood cancer.*
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> *Seeing Alyssa go from strength-to-strength is incredible and a testament to her tenacity and the dedication of an array of small army of people at GOSH. Team working between bone marrow transplant, haematology, ward staff, teachers, play workers, physiotherapists, lab and research teams, among others, is essential for supporting our patients."*
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> *Dr. Rob Chiesa, study investigator and bone marrow transplant consultant at GOSH*

Dr Deborah Yallop, consultant haematologist at KCH said "We've seen impressive responses in clearing leukemia that seemed incurable – it's a very powerful approach."

The trial was sponsored by GOSH and supported by the Medical Research

Council, Wellcome, and the National Institute for Health and Care Research (NIHR), for patients eligible for NHS care in the UK. Any patients eligible to receive treatment under the NHS and interested in this trial should approach their specialist healthcare provider.

As well as providing early funding to Professor Qasim to help pave the way for new cutting-edge treatment options, Great Ormond Street Hospital Charity (GOSH Charity) has now agreed to support treatment for another 10 patients as part of an extended cohort of T-ALL patients. Funding over £2m so that more children can access the clinical trial, this ties into GOSH Charity's ongoing fundraising appeal to build a world-leading new Children's Cancer Centre at GOSH, which will help create an environment where pioneering research can thrive.

First patient going from strength to strength

Alyssa Tapley, 16 from Leicester, was the first patient in the world to receive a base-edited cell therapy and originally shared her story in 2022 when she was 13. At the time, she was cautiously optimistic with her leukemia undetectable, but was under close monitoring. She has now been discharged to long-term follow up and is throwing herself into life with her friends.

Alyssa was diagnosed with T-cell leukemia in May 2021, after a long period of what the family thought were colds, viruses and general tiredness. She did not respond to standard therapies - chemotherapy or a first bone marrow transplant - and she was discussing the option of palliative care when the research opportunity was proposed.

Alyssa said: "I chose to take part in the research as I felt that, even if it didn't work for me, it could help others. Years later, we know it worked and I'm doing really well. I've done all those things that you're supposed to do when you're a teenager.

"I've gone sailing, spent time away from home doing my Duke of Edinburgh Award but even just going to school is something I dreamed of when I was ill. I'm not taking anything for granted. Next on my list is learning to drive, but my ultimate goal is to become a research scientist and be part of the next big discovery that can help people like me."

BE-CAR7 cells were manufactured as part of a long-standing research programme led by Professor Waseem Qasim at UCL Great Ormond Street Institute of Child Health, honorary consultant at GOSH. Thanks to funding from NIHR, Wellcome, the Medical Research Council and GOSH Charity, Professor Qasim has been a pioneer in developing new gene therapy derived treatments, including using innovative genome editing techniques. The team is now based at the Zayed Centre for Research into Rare Disease in Children, a partnership between UCL and GOSH. This state-of-the-art research institution was made possible thanks to the extraordinary philanthropic support of Her Highness Sheikha Fatima bint Mubarak. In 2014 Her Highness made a £60 million gift to GOSH Charity in honour of her late husband, Sheikh Zayed bin Sultan Al Nahyan.

The research team wish to thank Anthony Nolan and their volunteer blood and stem cell donors, and the patients and their families for participating in the research.

Source:

University College London

Journal reference:

Chiesa, R., *et al*. (2025). Universal Base-Edited CAR7 T Cells for T-Cell Acute Lymphoblastic Leukemia. *New England Journal of Medicine*. doi: 10.1056/nejmoa2505478. https://www.nejm.org/doi/10.1056/NEJMoa2505478