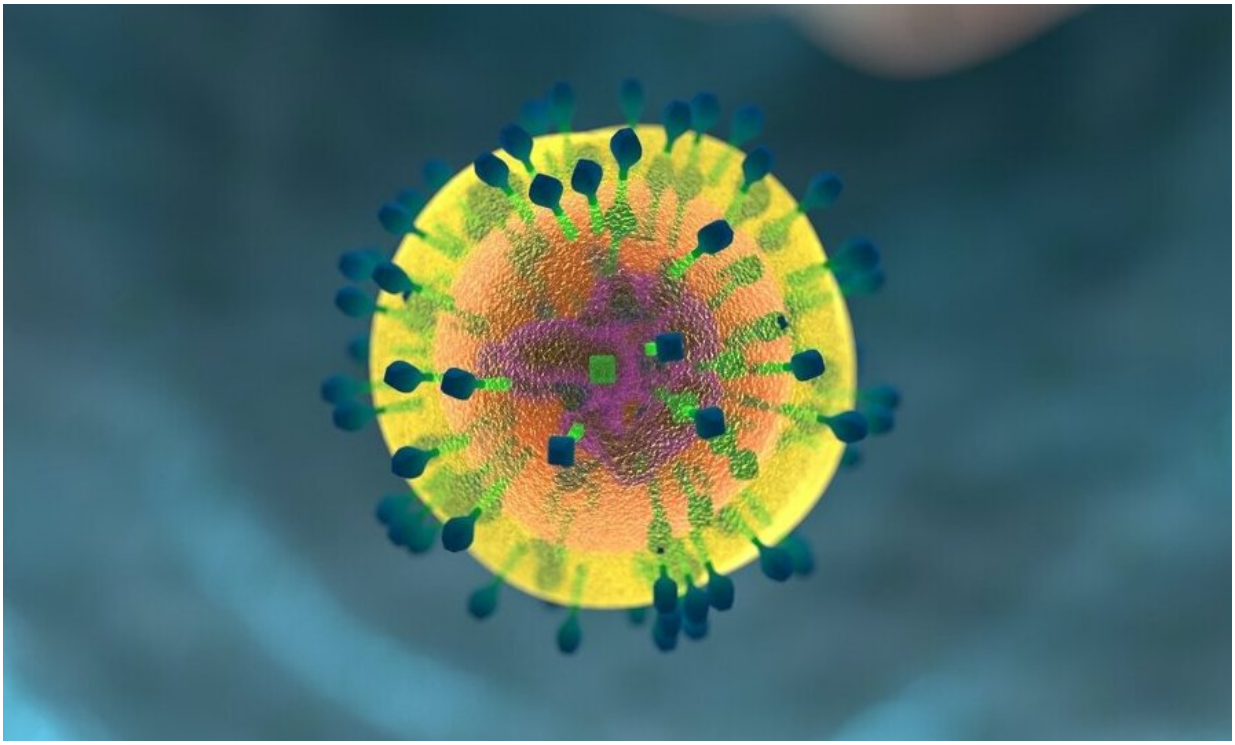
Further hope for base-edited T-cell therapy to treat resistant leukemia

June 14 2023



Credit: Pixabay/CC0 Public Domain

Three young patients with relapsed T-cell leukemia have now been treated with base-edited T-cells, as part of a "bench-to-bedside" collaboration between University College London (UCL) and Great Ormond Street Hospital for Children (GOSH).

The data from the NHS clinical trial, published in *The New England Journal of Medicine*, shows how donor CAR T cells were engineered using cutting-edge gene-editing technology to change single letters of their DNA code so they could fight leukemia.

The experience of using the cells in three patients is shared, and includes 13-year-old Alyssa from Leicester, who last year was the first person in the world to be treated on the trial for T-cell acute lymphoblastic leukemia (T-ALL)*. This is a cancer of white blood cells and is usually treated with chemotherapy, but if it comes back, can be hard to clear.

Within four weeks of her receiving the cells, Alyssa's leukemia was undetectable and she went on to have a successful bone marrow transplant, and is still well and at home almost a year later.

A second teenager cleared their leukemia within a similar time period and is now recovering at home after their transplant. Sadly, while a third child responded to the CAR T cell therapy, their course was complicated by serious infections and their family agreed with the clinical team to move to palliative care.

This first human application of base-editing technology was designed and developed by a team of researchers at UCL, led by Professor Waseem Qasim (UCL Great Ormond Street Institute of Child Health and Honorary Consultant at GOSH), working with Dr. Robert Chiesa and the Bone Marrow Transplant/CART/Haematology teams at GOSH.

Professor Waseem Qasim, Professor of Cell and Gene Therapy at UCL, said, "It's nice to be able to see the fruits of a long period of work coming together from multiple teams and being brought into play for new treatments. It's still early, and we need more follow up and to treat more patients to know how it might impact treatments long term."

Dr. Robert Chiesa said, "It is really crucial that children affected by cancer who failed standard of care have access to innovative strategies in the context of clinical trials such as this. A research hospital such as GOSH offers the ideal setting for developing experimental approaches that might offer hope to children with otherwise very poor prognosis. This is possible due to the dedication of scientists, doctors, nurses and allied professionals working for these children and their families."

To generate banks of "universal" anti T-cell CAR T-cells for the study, the researchers used healthy donor T-cells. They then made changes to the cells using "base editing," which works by chemically converting single nucleotide bases (letters of the DNA code) which carry instructions for a specific protein, in order to prevent them being produced.

The steps were:

1. Removing existing receptors so that T-cells from a donor could be banked and used without matching—making them "universal."
2. Removing a "flag" called CD7 that identified them as T-cells (CD7 T-cell marker). Without this step the T-cells—which are designed to recognize and attack cancerous cells—could have also killed each other.
3. Removing a second "flag" called CD52. This made the edited cells invisible to some of the strong drugs given to the patient during the treatment process.
4. Adding a Chimeric Antigen Receptor (CAR) that recognized the CD7 T-cell receptor on leukemic T-cells. The cells became armed against CD7, and recognized and fought T-cell leukemia.

Professor Qasim said, "Base editing involves making changes to single letters of DNA code to change signals and stop genes being expressed,

without having to make a cut to the chromosomes. It works really well for engineering T cells."

The clinical trial for this treatment is still open and aims to recruit up to 10 NHS patients with T-cell leukemia, who have exhausted all conventional treatment options, referred by NHS children's leukemia specialists. Patients are treated in the Bone Marrow Transplant Department at GOSH under the care of the BMT/CART/Haematology teams. Any patients eligible to receive treatment under the NHS and interested in this trial should approach their specialist healthcare provider.

If shown to be widely successful, the teams hope that it can be offered to more children and earlier in their treatment journey when they are less sick. With additional funding, they also hope to make it available for adults in the future.

The researchers also believe the base editing technique could be used for multiple other conditions, where changes in single letters of DNA cause illness such as sickle cell disease.

Professor Qasim explained, "The technology itself could also have wide-reaching applications for corrections of certain inherited conditions such as sickle cell disease. As the technology matures and is shown to be safe, it could be applied quite widely, although there will need to be careful testing and longer-term studies."

The cells were manufactured as part of a long-standing research program led by Professor Qasim at UCL Great Ormond Street Institute of Child Health. Professor Qasim has been a pioneer in developing new CAR T-cell treatments using innovative gene editing techniques.

More information: Base-edited CAR7 T Cells for relapsed T-cell

acute lymphoblastic leukaemia, *New England Journal of Medicine* (2023). doi.org/10.1056/NEJMoa2300709