

## Multiplex edited universal CAR T cells without the genomic cost

by Ofrat Beyar-Katz and Eric Shifrut

Received: February 13, 2026

Accepted: February 19, 2026.

Citation: Ofrat Beyar-Katz and Eric Shifrut. Multiplex edited universal CAR T cells without the genomic cost. *Haematologica*. 2026 Mar 5. doi: 10.3324/haematol.2025.300382 [Epub ahead of print]

### *Publisher's Disclaimer.*

*E-publishing ahead of print is increasingly important for the rapid dissemination of science.*

*Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.*

*E-publishing of this PDF file has been approved by the authors.*

*After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal.*

*All legal disclaimers that apply to the journal also pertain to this production process.*

## Editorial

Multiplex edited universal CAR T cells without the genomic cost

Ofrat Beyar-Katz<sup>1,2</sup> and Eric Shifrut<sup>3,4,5</sup>

<sup>1</sup>Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel; <sup>2</sup>The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel;

<sup>3</sup>The George S. Wise Faculty of Life Sciences, Tel Aviv University, Israel;

<sup>4</sup>Gray Faculty of Medical and Health Sciences, Tel Aviv University, Israel;

<sup>5</sup>Dotan Center for Advanced Therapies, Tel Aviv Sourasky Medical Center, Israel;

### **Declaration of Interests:**

Authors declare no competing interests.

### **Author contribution:**

Authors equally contributed

### **Corresponding author:**

Ofrat Beyar-Katz, MD, PhD

Department of Hematology and Bone Marrow Transplantation

Rambam Health Care Campus

8, Ha'Aliya Street

Haifa 3109601, Israel

Tel: +972-544980188

Fax: +972-47772343

Email: [o\\_katz@rmc.gov.il](mailto:o_katz@rmc.gov.il)

The study by Preece et al. presenting multiplex base-edited CAR38-T cells as an “off-the-shelf” platform, arrives at an inflection point in cellular immunotherapy<sup>1</sup>. After nearly a decade of remarkable clinical success with autologous CAR-T cell therapies, the field continues to struggle with slow manufacturing, high costs, and variable product quality, the factors that ultimately limit patient access, with some patients deteriorating or dying before their CAR-T product is ready<sup>2</sup>. Efforts to generate allogeneic or “universal” CAR-T products aim to untether cell therapy from individualized production. Yet, the same immunoregulation that provides protection against pathogens, namely T-cell receptor (TCR) mediated alloreactivity and human leukocyte antigen (HLA) mismatch, has made universal CAR-T cell development a formidable challenge. This study directly confronts these barriers using precise base editing to create a TCR-null, HLA-null, anti-CD38 CAR-T platform with enhanced allo-resilience. The result is a product that is immunologically “quiet”, while remaining functionally potent.

### **Why CD38? Revisiting a familiar target**

The transmembrane glycoprotein CD38 is a well-validated target in multiple myeloma, and anti-CD38 monoclonal antibodies have reshaped the therapeutic landscape. Yet, the CD38 expression across additional cells makes it attractive far beyond myeloma<sup>3</sup>. Targeting CD38 introduces the major challenge of fratricide among CD38-positive T cells<sup>4</sup>. The authors address this elegantly through base-editing-mediated disruption of CD38, which prevents fratricide and enables stable CAR38 expression. The antigen breadth is notable. CAR38-T cells demonstrated robust activity across B-cell, T-cell, and myeloid leukemias, suggesting a platform with the potential to treat malignancies currently underserved by CAR-T therapies, including T-cell neoplasms where fratricide, product contamination, and antigen overlap have stymied progress<sup>5</sup>. Of note, CD38 is expressed on immature hematopoietic cells; therefore, hematopoietic toxicity with CAR38-T is expected and should be carefully monitored when advancing this therapy into clinical use.

### **A New concept: Allo-defense as an engineered function**

Perhaps the most intriguing element of the study is the demonstration that CAR38-T cells can actively eliminate CD38-expressing allo-reactive host cells in mixed lymphocyte cultures. Rather than passively evading host immunity, these universal CAR-T cells establish a controlled counterattack against the very cells that would mediate rejection. This “allo-defense” is a conceptual shift: an allogeneic therapy that not only avoids elimination but reshapes the immunological landscape to protect itself. While this phenomenon will require validation in vivo, it raises compelling possibilities. A universal CAR-T product with both anti-tumor and anti-rejection functionality could reduce the need for heavy lymphodepletion, potentially improving tolerability and expanding access for older or frail patients.

### **When breaks become a problem**

To generate immunologically quiet CAR-T cells, multiple genetic edits are required, and the way these edits are introduced has real consequences for genomic stability<sup>6</sup>. Double-strand breaks create structural instability in primary T cells. Nahmad et al. have demonstrated this by targeting the TCR locus with CRISPR Cas9 and observing high rates of chromosome 14 loss in human T cells<sup>7</sup>. These chromosomal aberrations become even more pronounced when multiple edits are needed as in case of allogeneic CAR-T cells. These findings were notable because the structural changes appeared quickly and remained detectable after expansion. Other groups have also shown that multiplex cutting increases translocations and larger rearrangements<sup>8,9</sup>, which reinforces the idea that the editing burden itself becomes the limiting factor. In this context, the use of base editing becomes the practical solution. It enables parallel modification of several loci without triggering the repair pathways that create chromosomal errors. This creates an editing framework that is better suited for designs that require coordinated disruption of TCR, HLA, and lineage markers in the same manufacturing run.

### **Why base editing fits the allogeneic path**

Allogeneic platforms rely on third-party donors, and once a donor is established, every manufactured dose inherits the same genomic background. Regulators evaluate these products as standardized biologics rather than individualized treatments, which places real weight on genomic consistency. Base editing supports this expectation because it produces a more stable and predictable edit profile and reduces the chance of structural variants that would complicate release testing. It also allows developers to qualify a donor bank with greater confidence, since the product is less likely to accumulate editing-related chromosomal errors across batches. This is important for any multi-edited design, but especially for universal CAR-T programs that depend on simultaneous changes in TCR, HLA class I and II, and target antigens. The approach described in the study aligns with where allogeneic cell therapy is heading. A well-characterized donor and an editing strategy that minimizes genomic disruption create a practical route for advancing complex engineered products into clinical use.

### **Clinical Promise and Questions Ahead**

The *in vivo* xenograft models demonstrate clear anti-leukemic activity, but several translational challenges remain. Base editing may alter differentiation pathways or metabolic fitness. Durable remission in humans will require long-lived, functionally competent cells and achieving this in an HLA-deficient context is not trivial. The capacity to target pathogenic plasma cells invites potential applications in autoimmunity. However, depletion of healthy long-lived plasma cells raises concerns about sustained hypogammaglobulinemia and infection risk<sup>10</sup>.

Each of these hurdles is addressable, and the field is rapidly evolving. This CAR38 platform represents one of the most comprehensive attempts to engineer a universal cell therapy with

functional, immunologic, and safety considerations built into its DNA. Universal CAR-T cells will not replace autologous therapies overnight. But studies like this one – precise, intentional, and mechanistically grounded – demonstrate that the path forward is no longer theoretical. It is engineered, multiplexed, and increasingly within reach.

## References

1. Preece R, Gough O, Joshi A, et al. Allo-defensive, multiplex base-edited, anti-CD38 CAR T cells for 'off-the-shelf' immunotherapy. *Haematologica*. xxx
2. Kim SJ, Yoon SE, Kim WS. Current Challenges in Chimeric Antigen Receptor T-cell Therapy in Patients With B-cell Lymphoid Malignancies. *Ann Lab Med*. 2024;44(3):210-221.
3. van de Donk N, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood*. 2018;131(1):13-29.
4. Mihara K, Yanagihara K, Takigahira M, et al. Activated T-cell-mediated immunotherapy with a chimeric receptor against CD38 in B-cell non-Hodgkin lymphoma. *J Immunother*. 2009;32(7):737-743.
5. Glisovic-Aplenc T, Diorio C, Chukinas JA, et al. CD38 as a pan-hematologic target for chimeric antigen receptor T cells. *Blood Adv*. 2023;7(16):4418-4430.
6. Su J, Zeng Y, Song Z, et al. Genome-edited allogeneic CAR-T cells: the next generation of cancer immunotherapies. *J Hematol Oncol*. 2025;18(1):90.
7. Nahmad AD, Reuveni E, Goldschmidt E, et al. Frequent aneuploidy in primary human T cells after CRISPR-Cas9 cleavage. *Nat Biotechnol*. 2022;40(12):1807-1813.
8. Sasu BJ, Opiteck GJ, Gopalakrishnan S, et al. Detection of chromosomal alteration after infusion of gene-edited allogeneic CAR T cells. *Mol Ther*. 2023;31(3):676-685.
9. Aussel C, Cathomen T, Fuster-Garcia C. The hidden risks of CRISPR/Cas: structural variations and genome integrity. *Nat Commun*. 2025;16(1):7208.
10. Kampouri E, Walti CS, Gauthier J, Hill JA. Managing hypogammaglobulinemia in patients treated with CAR-T-cell therapy: key points for clinicians. *Expert Rev Hematol*. 2022;15(4):305-320.

**Figure legend:**

**Figure 1. Off-the-shelf multiplex base-edited CAR38-T cells.**

Schematic illustration of universal anti-CD38 CAR-T cell generation. Donor T cells undergo multiplex base editing to disrupt TCR, HLA class I, and CD38, preventing graft-versus-host disease, immune rejection, and fratricide. The edited cells are engineered to express an anti-CD38 CAR, yielding an allo-resilient, off-the-shelf CAR-T product with preserved anti-tumor activity and the ability to eliminate CD38-expressing allo-reactive host cells.

