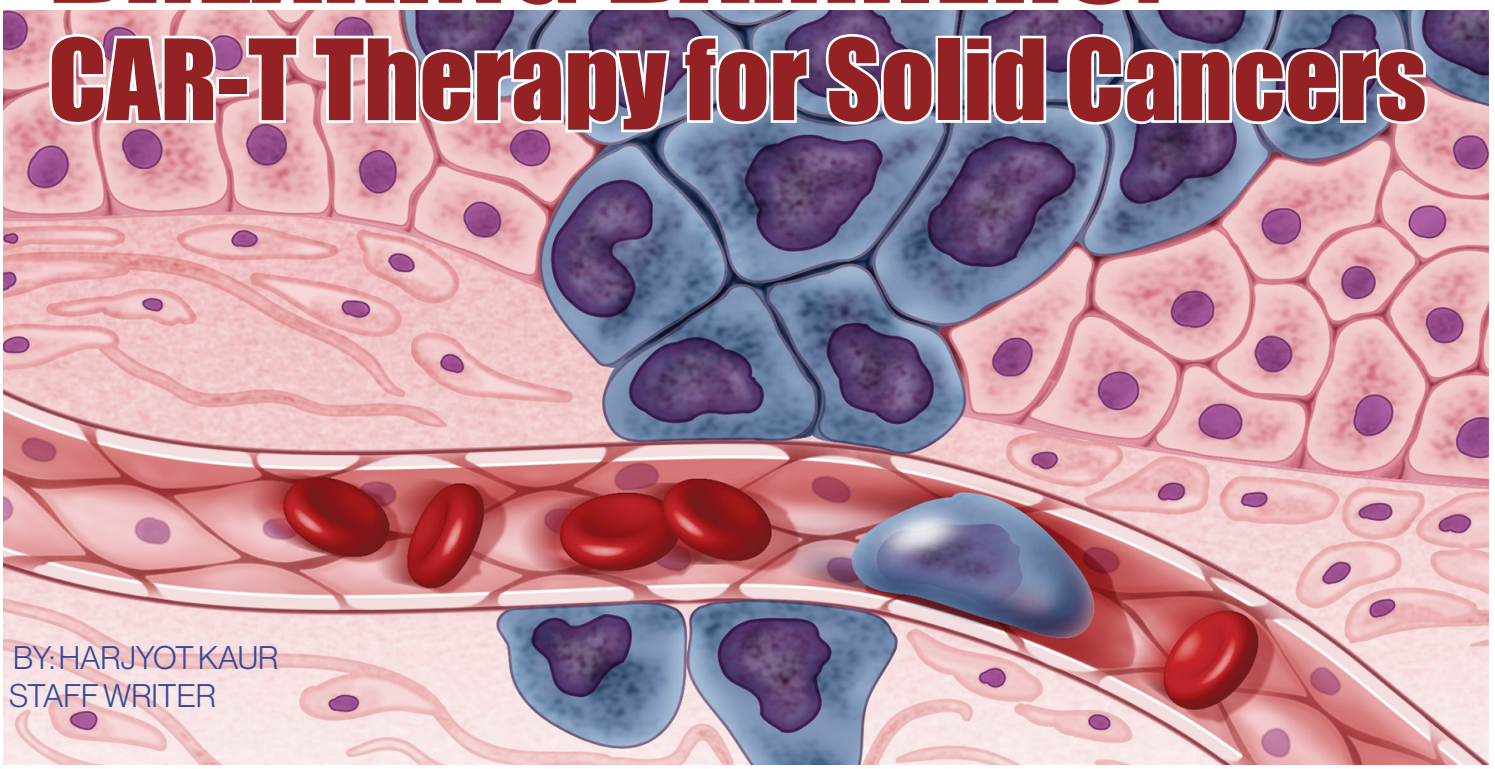
BREAKING BARRIERS:

CAR-T Therapy for Solid Cancers



BY: HARJYOT KAUR
STAFF WRITER

A cure for cancer is a fallacy. At least, the idea of a singular cure for all cancers is impossible, as every type of cancer is distinct and thus many require unique therapeutic approaches. While people with cancer are living longer due to modern scientific advances, most therapies only extend lives by a few years. In recent decades, one incredible, innovative therapeutic breakthrough has shown immense clinical promise and even reversed certain death diagnoses: Chimeric Antigen Receptor T-cell (CAR-T) therapy.

HOW DOES CAR-T THERAPY WORK

CAR-T therapy harnesses the power of the immune system. The adaptive immune system is the body's long-term defense against disease-causing pathogens and includes B-cells and T-cells. B-cells create antibodies, proteins that bind and neutralize specific foreign pathogens and cells. T-cells can also recognize and destroy foreign and harmful cells. Cancerous cells often mutate to hide themselves from the adaptive immune system by not expressing antigens—or targets—for such receptors, allowing them to grow unchecked.[1]

CAR-T therapy directly addresses this issue by genetically engineering a

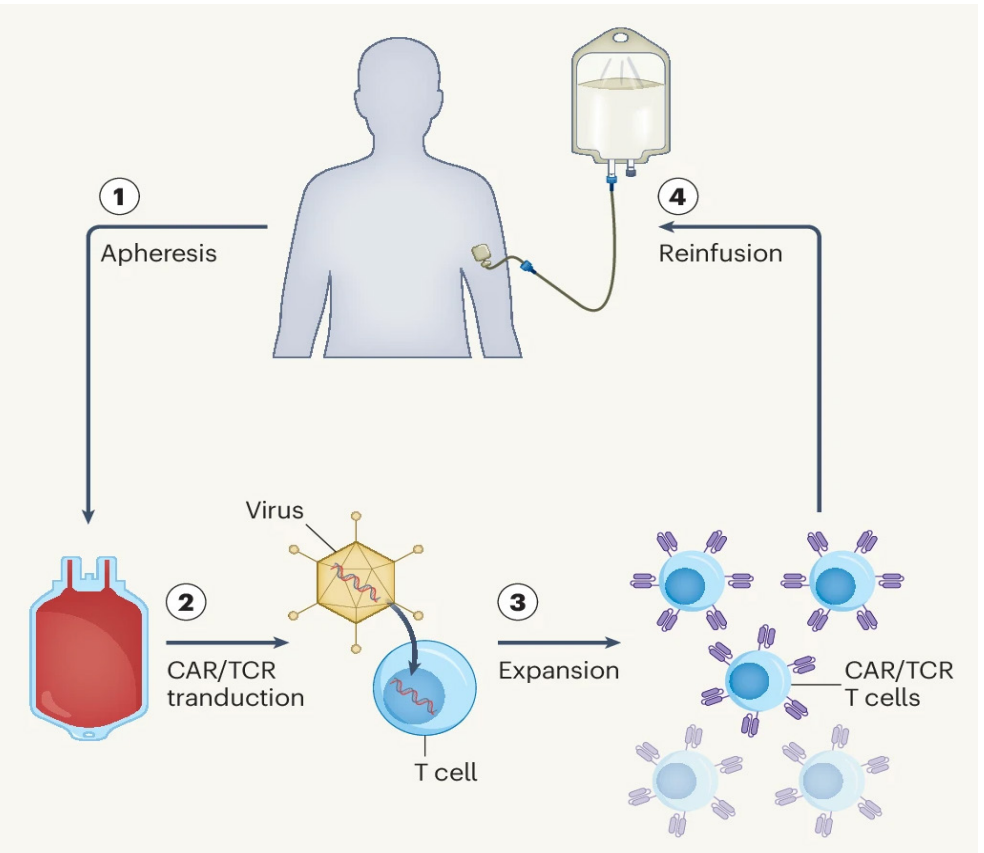


Figure 1. Process of CAR-T Therapy. First, the patient undergoes apheresis, where their blood is extracted, immune cells are collected, and the remaining components of the blood are returned to the body. During transduction, a virus delivers and inserts the CAR gene, reprogramming its T-cells to recognize specific antigens on target cells. These CAR-T cells are multiplied and reinfused back into the patient.

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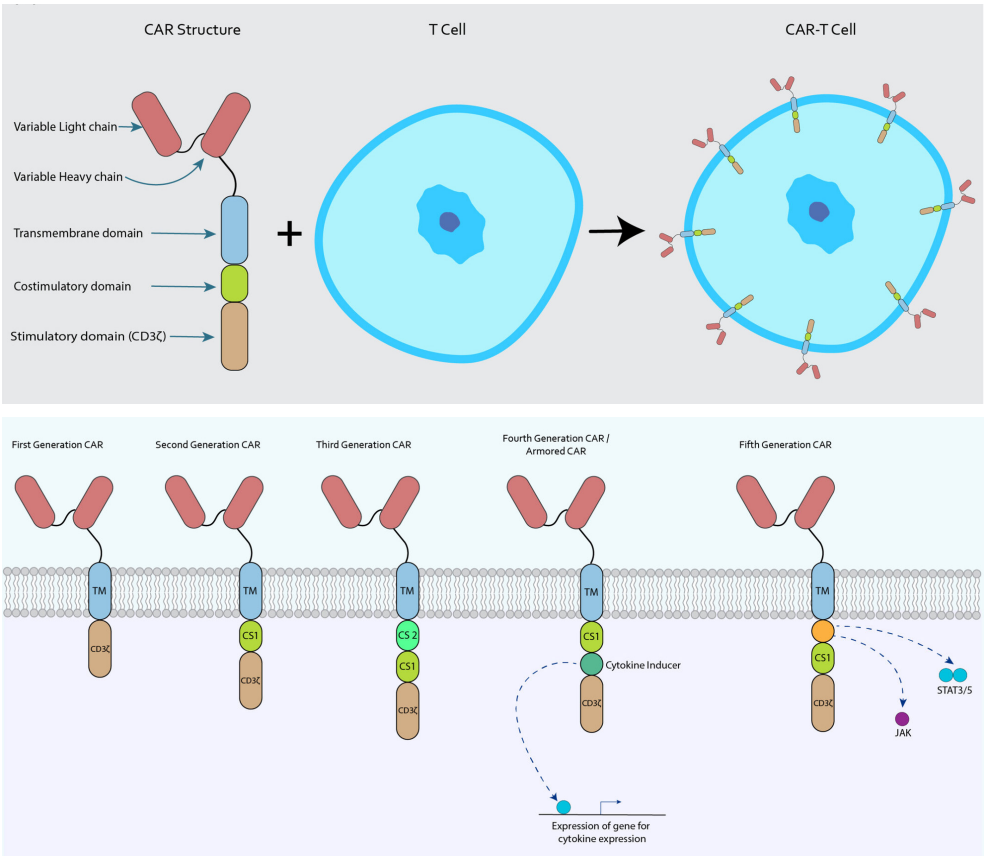

Figure 2: (a) The structure of a CAR construct. The variable heavy and light chains are antibody fragments that comprise the antigen recognition domain. The transmembrane domain allows the construct to implant in the cell, the costimulatory domain(s) enhance the signal and response, and the stimulatory domain is the primary signaling domain that is responsible for T-cell activation. **(b)** Each generation of CAR constructs, each more complex, better enhances CAR-T cell activation and proliferation.

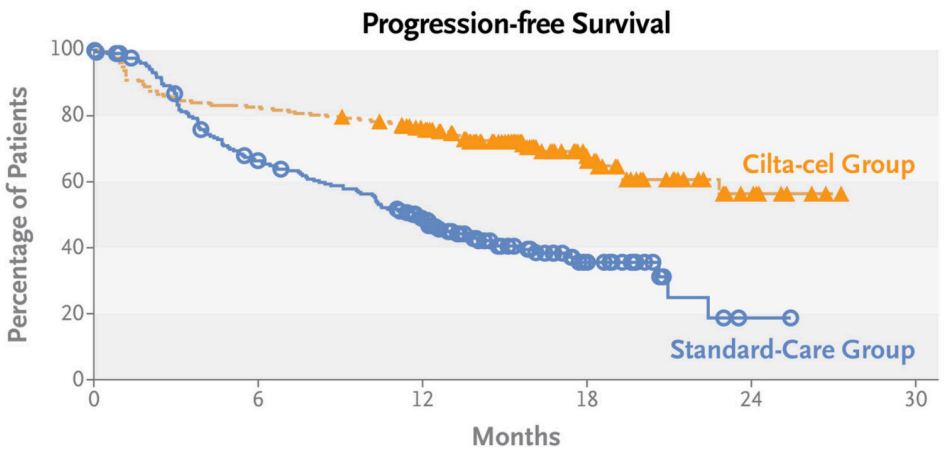

Figure 3: Phase 3 clinical trial data showing progression-free survival for Carvykti, a CAR-T therapy for multiple myeloma. At 12 months, 75.9% of patients who received Carvykti had no cancer progression compared to 48% of patients receiving standard-of-care treatment. Even after 2 years, more than 50% of patients who received Carvykti had not progressed.[8]

patient's T-cells to express a synthetic receptor that binds to a specific antigen on the surface of cancer cells. When the cells are infused back into the patient, they encounter, recognize, and destroy the cancer cells that express the antigen (see figure 1). When CAR-T therapy works for patients, it eradicates the majority or all of their cancer cells, putting them in remission, even if they had a poor prognosis and frequent relapses—effectively "curing" them.[2]

First-generation CARs consisted of an antigen recognition domain made of antibody fragments and an internal signal transduction motif that activates the T-cell. Once the recognition domain is attached to the specific antigen on the tumor cell, it triggers a cell death pathway, effectively killing the cancer cell (see figure 2a).[3] Scientists have developed newer generations of CARs to enhance antigen identification, strengthen the CAR-T cell response, and promote immune responses. This is primarily accomplished by engineering the CAR constructs to contain elements such as costimulatory domains—additional signals that promote activation—and secrete cytokines, which are secreted hormone-like proteins that enhance immune responses (see figure 2b).[2]

CAR-T THERAPY IN HEMATOLOGICAL CANCERS

Historically, hematological (blood-cell related) cancers have been treated with aggressive chemotherapy and radiation. However, many patients relapse and quickly run out of options for treatment. According to the Leukemia and Lymphoma Society, one person in the United States is diagnosed with a type of blood cancer approximately every three minutes, and dies from it every nine minutes.[4] CAR-T therapy shows promise in changing this reality.

In 2012, the first infusion of CAR-T cells was given to Emily Whitehead, a six-year-old patient with relapsed B-cell acute lymphoblastic leukemia (B-ALL) and on the verge of death. After a single dose of CAR-T therapy, her cancer vanished within weeks. To this day, 13 years later, she is still cancer-free.[5] In 2017, this CAR-T therapy, called Kymriah, was approved by the Food and Drug Administration for treating patients

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with B-ALL.[6] Since then, CAR-T therapy has shown impressive efficacy in particularly aggressive blood cancers. Different antigens are identified and targeted for each cancer, and currently, seven therapies are approved for various hematological indications.[7] Remission rates after CAR-T therapy range from 60% to 93%6, which is unprecedented for this patient population with aggressive, progressed, and non-responsive cancers. therapy has shown impressive efficacy in particularly aggressive blood cancers. Different antigens are identified and targeted for each cancer, and currently, seven therapies are approved for various hematological indications.[7] Remission rates after CAR-T therapy range from 60% to 93%[6], which is unprecedented for this patient population with aggressive, progressed, and non-responsive cancers (see figure 3).

Despite CAR-T therapy's efficacy, there are still dangerous side effects, the most common being Cytokine Release Syndrome (CRS), which develops in the weeks after CAR-T infusion. Since CAR-T cells trigger cytokine release to activate the immune response, this inflammatory reaction may become too intense and cause CRS. This can lead to infection, organ failure, and even death.[6] Emily Whitehead also suffered from acute CRS but was successfully treated.[5] CAR-T can induce additional toxicities, called on-target/off-tumor side effects, where healthy cells expressing the target antigen are destroyed, leading to further complications.[6] However, these adverse effects are usually treatable and carefully monitored in patients.

Another downfall of CAR-T therapy is the extremely high costs associated with receiving CAR-T therapy—about $500,000 to $1,000,000 per patient. While it is covered by most private and public insurance when medically necessary, other potentially crippling costs remain. Patients have to stay near a certified treatment center for weeks, which is expensive for those living in rural areas. It may be questionable to consider CAR-T therapy a cure for cancer with its current price tag limiting access.[9]

BARRIERS TO CAR-T THERAPY IN SOLID TUMORS

CAR-T Therapy is miraculously successful in hematological cancers, however, several obstacles are preventing similar efficacy in solid tumors.

A significant challenge is identifying unique target antigens that are expressed primarily by cancer cells and not healthy tissues. Interestingly, some approved hematological CAR-T therapies target CD19, a protein expressed on many B-cells, and therefore may destroy all of a patient's B-cells, including healthy ones. Yet, physicians can still manage the long-term harm from the patient's weakened immune system.[10] Despite this alleviation, the same approach cannot be applied to solid tumors.

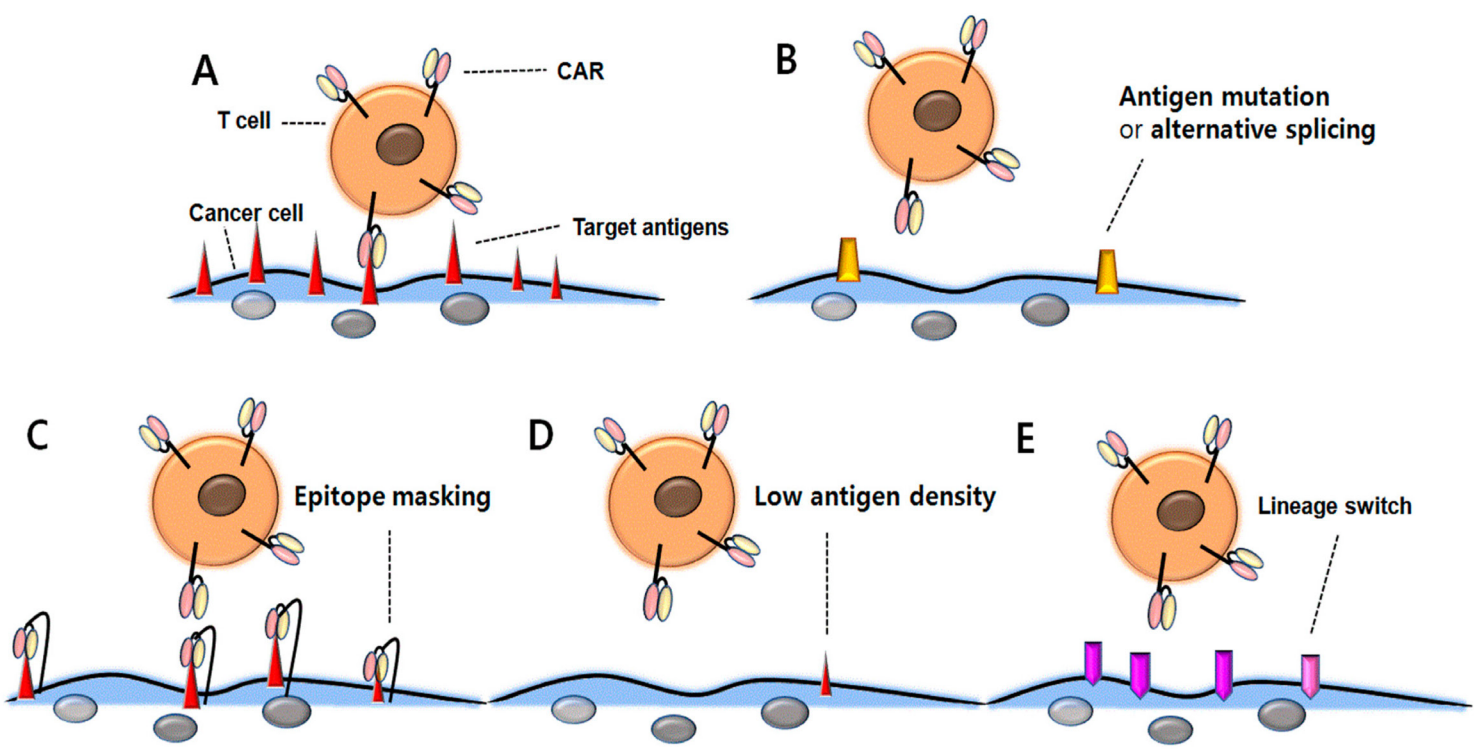

Figure 4: Different ways that cancer cells can escape identification through complications with antigen recognition. (a) Ideally, CAR-T cells bind to specific antigens expressed on cancer cells. **(b)** Cancer cells may change the way the antigen is expressed, preventing the CAR-T cells from binding. **(c)** Epitope masking occurs when the antigen is hidden or blocked from the CAR-T cells. In one rare case, a patient's cells were contaminated, and one tumor cell was transduced with the CAR. It was shielded from detection and the patient eventually became resistant to the therapy. **(d)** Rare mutations by cancer cells can create cells with reduced or no target antigen expression. These cells proliferate and can't be effectively targeted by CAR-T therapy. **(e)** Another rare phenomenon is lineage switch, where cancer cells change their cell lineage and express different antigens, allowing them to escape recognition.

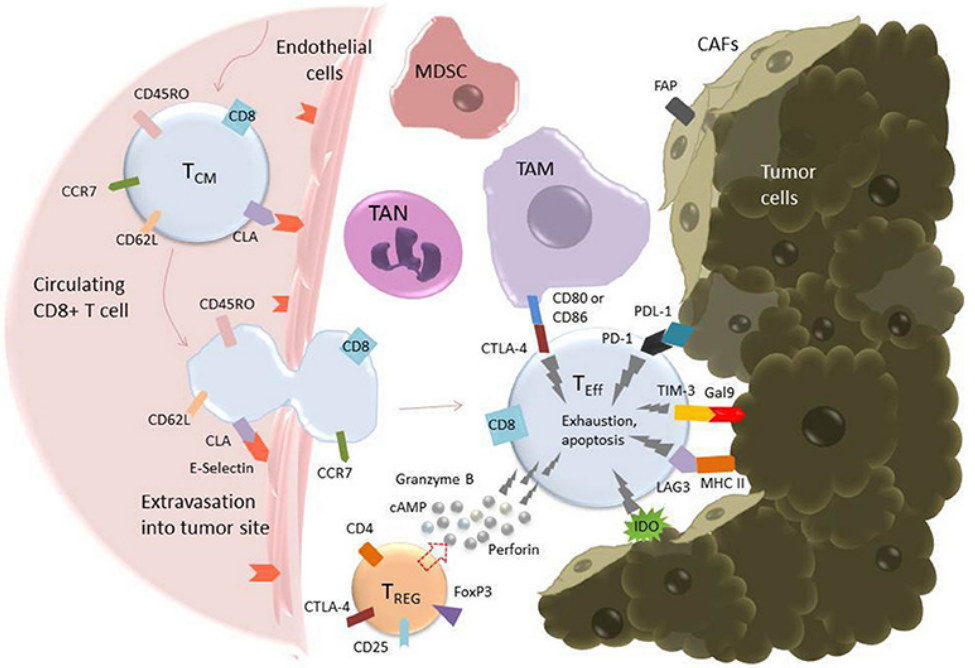

Figure 5. The hostile TME has many different mechanisms to inhibit T-cell function.

Consider liver cancer: if all of a patient's liver cells are targeted and destroyed, the patient cannot survive. Even if the target antigen is not expressed by all cells, if it is not specific enough, the on-target/off-tumor toxicities may still be devastating. This barrier is quite significant, thus, CAR-T therapy is currently only being developed for solid cancers that have known specific antigens, like HER2 in breast cancers, IL-13Rα2 in glioblastomas, and GD2 in neuroblastomas.[11]

Tumors also present high variation in antigen expression (see figure 4), so while CAR-T therapy may kill the antigen-containing cancer cells, the cancer cells that don't have the antigen may continue to grow and dominate—a phenomenon called antigen escape. This limitation is being addressed through pooled CAR-T therapy, where multiple CARs targeting different antigens are used to treat these heterogeneous cancers, and bispecific CAR-T cells, where one CAR-T cell expresses multiple CARs that recognize different antigens.[11]

Another challenge is CAR-T cell guiding, infiltration, and expansion in the tumor site. Compared to blood cancers, solid tumors are aggressive and localized. In order to attack the cancer, the CAR-T cells must navigate complicated vasculature, dense extracellular matrix, and excessive immunosuppressive molecules and signals.[12] One way to deal with this challenge is by directly injecting the therapy into the tumor site. In a Phase 0 trial, which tested if the CAR-T cells reached the tumor site, scientists found that injections into breast tumors were well tolerated and encouraged immune responses.[13] Another approach for non-injectable solid tumors is utilizing chemokines, which are molecules that guide immune cells. In cancer, their function of guiding CAR-T cells directly is often compromised, therefore, current research is focused on directly delivering chemokines to the tumor, which will them aid CAR-T cells in their journey to the site uncompromised.[12]

Even if CAR-T cells reach the tumor, they face another issue: persisting and functioning in the hostile tumor microenvironment (TME), which is nutrient-deprived, low in pH, hypoxic, and immunosuppressive—all of which can render CAR-T cells ineffective (see figure 5).[14] One approach to increase CAR-T cell persistence is engineering the cells to also express cytokines that modulate the TME, but this is limited by the potential for toxic CRS from the excess cytokine expression. Another avenue is to develop the fitness of CAR-T cells, allowing them to thrive in these difficult conditions. One such innovation in its early stages is hypoxia-responsive CAR-T cells, which have demonstrated superior persistence and efficacy, and are also only active in hypoxic conditions, limiting toxicities.[14] CRISPR gene-editing is also being explored to enhance CAR-T cell survival by eradicating genes limiting T-cell persistence and function.[12]

These innovations may optimize CAR-T cell function in solid tumors and are currently being tested. Currently, several CAR-T therapy clinical trials are running for the following cancers: lung, breast, gastric, liver, pancreatic, colorectal, esophageal, ovarian, gliomas, and more.[12] While it is too early to be sure, the ability to engineer complex behaviors in CAR-T cells suggests that efficacy in solid tumors will eventually be achieved.

CONCLUSION

CAR-T therapy has revolutionized cancer therapy. Following decades of research and development, its successes in blood cancers have reversed terminal diagnoses and even effectively cured patients. Currently, research aims to harness the immense power and potential of this therapy to treat solid tumors and even autoimmune diseases. Despite the current limitations of CAR-T therapy in solid tumors, medical innovations continue to overcome obstacles and instill hope for more cancer cures.

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REFERENCES

1. Carter, D. (2021, November 10). *T cells, B cells and the immune system*. The University of Texas MD Anderson Cancer Center. https://www.mdanderson.org/cancerwise/t-cells--b-cells-and-the-immune-system.h00-159465579.html
2. Sun, D., Shi, X., Li, S., Wang, X., Yang, X., & Wan, M. (2024). CAR-T cell therapy: A breakthrough in traditional cancer treatment strategies (Review). *Molecular Medicine Reports,* 29, 47. https://doi.org/10.3892/mmr.2024.13171
3. Muñoz-López, P., Ribas-Aparicio, R. M., Becerra-Báez, E. I., Fraga-Pérez, K., Flores-Martínez, L. F., Mateos-Chávez, A. A., & Luria-Pérez, R. (2022). Single-Chain Fragment Variable: Recent Progress in Cancer Diagnosis and Therapy. *Cancers*, 14(17), 4206. https://doi.org/10.3390/cancers14174206
4. *Facts and statistics overview. Leukemia and Lymphoma Society.* (n.d.). https://www.lls.org/facts-and-statistics/facts-and-statistics-overview
5. *Emily Whitehead.* Cancer Research Institute. (2013, December). https://www.cancerresearch.org/stories/patients/emily-whitehead
6. Khan, A. N., Asija, S., Pendhari, J., & Purwar, R. (2023). CAR-T cell therapy in hematological malignancies: Where are we now and where are we heading for? *European Journal of Haematology*, 112(1), 6–18. https://doi.org/10.1111/ejh.14076
7. *Which cell and gene therapies are approved to treat cancer?*. Alliance for Cancer Gene Therapy. (2024, November 11). https://acgtfoundation.org/for-patients/approved-cell-and-gene-therapies/
8. San-Miguel, J., Dhakal, B., Yong, K., Spencer, A., Anguille, S., Mateos, M.-V., Fernández de Larrea, C., Martínez-López, J., Moreau, P., Touzeau, C., Leleu, X., Avivi, I., Cavo, M., Ishida, T., Kim, S. J., Roeloffzen, W., van de Donk, N. W. C. J., Dytfeld, D., Sidana, S., … Einsele, H. (2023). CILTA-CEL or standard care in lenalidomide-refractory multiple myeloma. *New England Journal of Medicine*, 389(4), 335–347. https://doi.org/10.1056/nejmoa2303379
9. Robinson, K. M. (2024, June 26). Car T-cell therapy: How to manage costs and get financial assistance. *WebMD*. https://www.webmd.com/cancer/lymphoma/features/navigate-finances-car-t-cell-therapy
10. Cappell, K. M., & Kochenderfer, J. N. (2023). Long-term outcomes following car T cell therapy: What we know so far. *Nature Reviews Clinical Oncology*, 20(6), 359–371. https://doi.org/10.1038/s41571-023-00754-1
11. Chen, T., Wang, M., Chen, Y., & Liu, Y. (2024). Current challenges and therapeutic advances of CAR-T cell therapy for solid tumors. *Cancer Cell International,* 24(1). https://doi.org/10.1186/s12935-024-03315-3
12. Martinez, M., & Moon, E. K. (2019). Car T cells for solid tumors: New strategies for finding, infiltrating, and surviving in the tumor microenvironment. *Frontiers in Immunology*, 10. https://doi.org/10.3389/fimmu.2019.00128
13. Tchou, J., Zhao, Y., Levine, B. L., Zhang, P. J., Davis, M. M., Melenhorst, J. J., Kulikovskaya, I., Brennan, A. L., Liu, X., Lacey, S. F., Posey, A. D., Williams, A. D., So, A., Conejo-Garcia, J. R., Plesa, G., Young, R. M., McGettigan, S., Campbell, J., Pierce, R. H., … June, C. H. (2017). Safety and efficacy of intratumoral injections of chimeric antigen receptor (CAR) T cells in metastatic breast cancer. *Cancer Immunology Research,* 5(12), 1152–1161. https://doi.org/10.1158/2326-6066.cir-17-0189
14. Uslu, U., & June, C. H. (2024). Beyond the blood: Expanding car T cell therapy to solid tumors. *Nature Biotechnology*. https://doi.org/10.1038/s41587-024-02446-2

IMAGE REFERENCES

1. Banner image: U.S. Department of Health and Human Services. (2018, April 5). NIH completes in-depth genomic analysis of 33 cancer types. *National Institutes of Health.* https://www.nih.gov/news-events/news-releases/nih-completes-depth-genomic-analysis-33-cancer-types
2. Figure 1: Uslu, U., & June, C. H. (2024). Beyond the blood: Expanding car T cell therapy to solid tumors. *Nature Biotechnology.* https://doi.org/10.1038/s41587-024-02446-2
3. Figure 2: Khan, A. N., Asija, S., Pendhari, J., & Purwar, R. (2023). CAR-T cell therapy in hematological malignancies: Where are we now and where are we heading for? *European Journal of Haematology,* 112(1), 6–18. https://doi.org/10.1111/ejh.14076
4. Figure 3: San-Miguel, J., Dhakal, B., Yong, K., Spencer, A., Anguille, S., Mateos, M.-V., Fernández de Larrea, C., Martínez-López, J., Moreau, P., Touzeau, C., Leleu, X., Avivi, I., Cavo, M., Ishida, T., Kim, S. J., Roeloffzen, W., van de Donk, N. W. C. J., Dytfeld, D., Sidana, S., … Einsele, H. (2023). CILTA-CEL or standard care in lenalidomide-refractory multiple myeloma. *New England Journal of Medicine,* 389(4), 335–347. https://doi.org/10.1056/nejmoa2303379
5. Figure 4: Song, M.-K., Park, B.-B., & Uhm, J.-E. (2019). Resistance mechanisms to car T-cell therapy and overcoming strategy in B-cell hematologic malignancies. *International Journal of Molecular Sciences*, 20(20), 5010. https://doi.org/10.3390/ijms20205010
6. Figure 5: Martinez, M., & Moon, E. K. (2019). Car T cells for solid tumors: New strategies for finding, infiltrating, and surviving in the tumor microenvironment. *Frontiers in Immunology*, 10. https://doi.org/10.3389/fimmu.2019.00128