CAR-T cell Therapy - A powerful Immunotherapeutic tool

Dr. Archana Kumari Srivastava[1], Senior Executive; Mr. Vijayanand K[1], Deputy General Manager; Mr. Sudip Kumar Majumder[1], Vice President

[1]Department of Biotechnology, Jodas Expoim Pvt. Ltd

In the journey of our Cancer Immunotherapy blog series, let us introduce CAR-T cell therapy, another milestone in recent years in the field of immunotherapy that has revolutionized the modern medicine. Chimeric Antigen Receptor (CAR) T cell therapy utilizes T-cells, a type of white blood cell (immune cells), to fight cancer by engineering them *ex vivo* prior to infusing back into the patient. These CAR T-cells can specifically find and destroy cancerous cells. CAR T-cell therapy is a type of cell-based gene therapy or Adoptive Cell Therapy (ACT) as it involves gene alteration of T-cells that enables them to attack specific cancer cells.

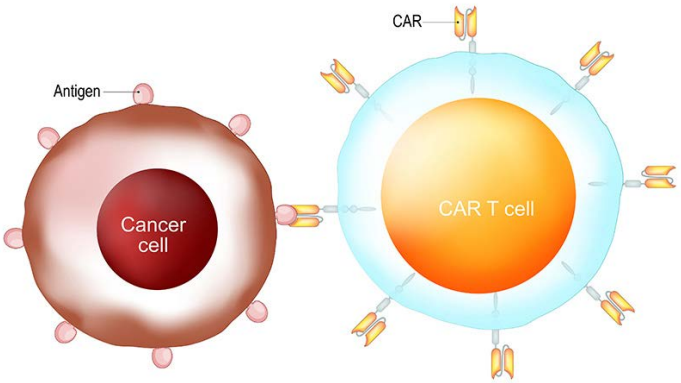


Figure 1: Pictorial representation of T cell and its modification to generate CAR-T cell

[Source: Critical Care Medicine ACEP.org (https://www.acep.org/criticalcare/newsroom/newsroom-articles/jun2020/car-t-therapy-and-the-cytokine-storm/)]

As depicted in Figure 1, on the surface of the CAR-T cells, there are certain proteins called “receptors” that possess the ability to bind specific antigen present on the malignant cells and thereby orchestrating the immune response against the specific antigen. CAR-T cell therapy as illustrated in Figure 2 ameliorate the body’s ability to detect and fight cancer cells by genetically engineering the body’s own T-cells in the lab by adding a gene for a receptor generating a chimeric receptor which ultimately helps the T-cells attach to a specific cancer cell antigen and hence this therapy is known as Chimeric Antigen Receptor (CAR)-T cell therapy. The U.S. Food and Drug Administration (FDA) has approved CAR-T cell therapy because of its dramatic efficacy to treat different types of hematological malignancies like leukemia, lymphoma, multiple myeloma for patients where chemotherapy and other treatments no longer works. Numerous clinical trials were conducted with the most prevalent

CAR-T cells i.e., CD19 CAR-T cells that targets CD19 expressed on the surface of the B cell Lymphomas or leukemias. On the other hand, some of the CAR-T cell therapy targets TNF (Tumor Necrosis Factor).

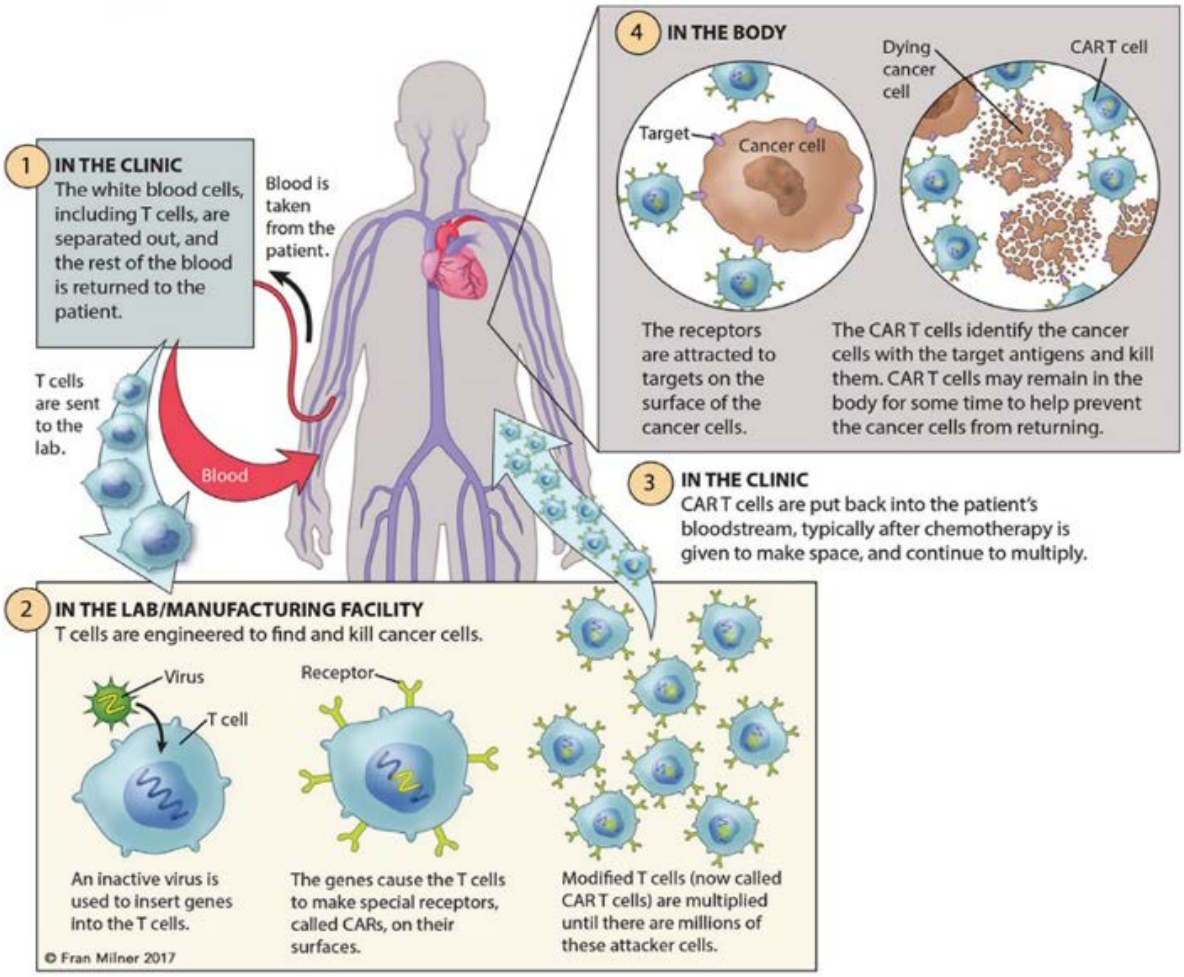


Figure 2: Working Mechanism of CAR-T cell Therapy

[Source: Leukemia and Lymphoma Society (https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy)]

CAR T-cell therapy process

As different cancerous cells have different antigens which necessitates to generate unique CAR for it. Moreover, CAR T-Cell Therapy is patient specific, thus manufacturing of autologous engineered CAR T-Cells is dedicated for one patient at a time. CAR-T cells manufacturing involves the following steps (Figure 3 diagrammatically demonstrates the process of CAR-T Cell Therapy):

1. **Cell Collection and Cryopreservation**

   In specific treatment centres, patient's blood is collected and White Blood Cells (T Cells) are extracted from it through a process known as leukapheresis while Red

Blood Cells and plasma are transferred back to the patient. Usually, this process takes 2-3 hours. Collected T cells are cryopreserved within 24 hours.

2. **Engineering of the T-cells in the manufacturing Unit:**

   Cryopreserved T-cells are shipped to the specific manufacturing facility. In these manufacturing facilities, T-cells are genetically reprogrammed into CAR-T cells and endowed with defined specificity by using viral vectors that helps these modified CAR-T cells in targeting surface antigens on cancer cells leading to destruction of malignant cells. As this therapy requires enormous quantity of engineered CAR-T cells during treatment, these cells are multiplied *ex vivo* in large number which often takes several weeks before infusing in the patient.

3. **Infusion of the CAR-T cells**

   Prior to infusion of these CAR T-cells, the patient might be given lymphodepleting chemotherapy to lower the number of other immune cells and thereby preparing the body for receiving CAR-T cells. Lymphodepleting chemotherapy is followed by the activation of CAR-T cells by binding with the cancerous cells resulting in its elimination in the due process.

4. **Monitoring of the patient infused with CAR-T cells**

   Once the infusion of the CAR-T cells was completed, patient must be monitored at least 2-3 times in the first week. In addition, to monitor any potential side effects after CAR-T cells infusion patient should remain in proximity of their treatment centre up to 4 weeks.

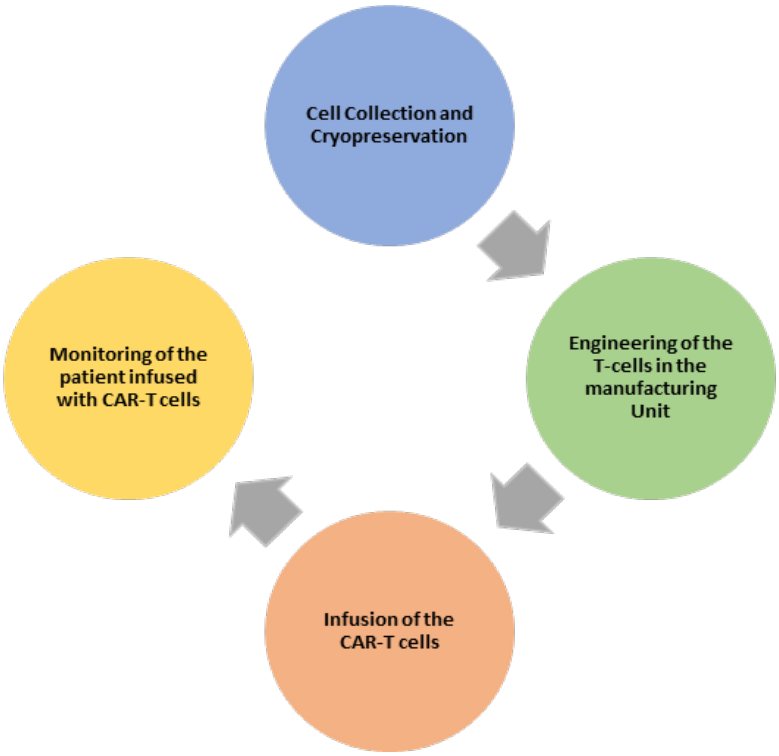


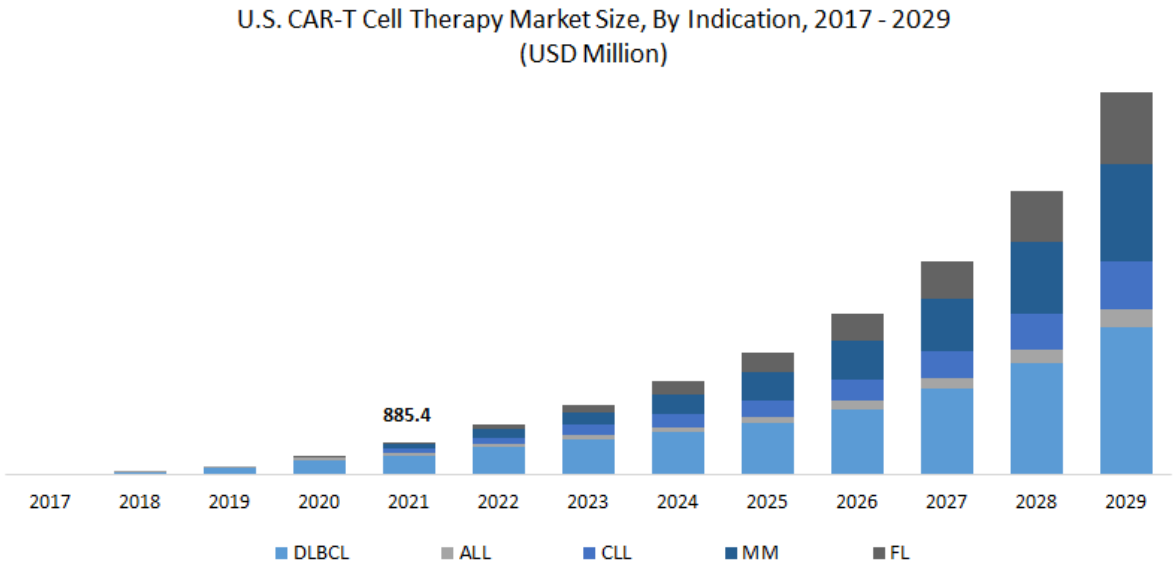
Figure 3: Diagrammatic representation of the steps involved in the CAR T-cell Therapy

List of U.S. Food and Drug Administration (FDA) approved CAR-T cell Therapies

Sl. No.	*Approved CAR-T cell Therapy*	*Trade Name*	*Manufacturer*	*FDA Approval Year*	*Indications*
1.	**Tisagenlecleucel**, also known as tisa-cel	Kymriah	Novartis Pharmaceuticals Corporation	2017	Used to treat B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
2.	**Axicabtagene ciloleucel**, also known as axi-cel	Yescarta	Kite Pharma Inc.	2017	Used For the treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
3.	**Brexucabtagene autoleucel**, also known as brexu-cel	Tecartus	Kite Pharma Inc.	2020 for MCL 2021 for ALL	Used to treat adults with mantle cell lymphoma (MCL) or acute lymphoblastic leukemia (ALL).
4.	**Lisocabtagene maraleucel**, also known as liso-cel	Breyanzi	Juno Therapeutics, Inc., a Bristol-Myers Squibb Company	2021	For treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
5.	**Idecabtagene vicleucel**, also known as ide-cel	Abecma	Celgene Corporation, a Bristol-Myers Squibb Company	2021	Used for the treatment of multiple myeloma in patients who have received at least four kinds of treatment regimens that have not worked or have stopped working.
6.	**Ciltacabtegene autoleucel**, also known as cilta-cel	Carvykti	Janssen Biotech, Inc.	2022	Treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody.

Estimated market value of CAR-T cell therapy

As per Polaris market research, global market value of CAR-T cell therapy was USD 1,965.8 million in 2021 and expected to grow at a CAGR (Compound Annual Growth Rate) of 31.16 % during the forecast period (2022 – 2029). Figure 4 demonstrates estimated market value of CAR-T cell therapy.



Source: Polaris Market Research Analysis

DLBCL: Diffuse Large B-Cell Lymphoma, ALL: Acute Lymphoblastic Leukemia,
CLL: Chronic Lymphocytic Leukemia, MM – Multiple Myeloma, FL – Follicular Lymphoma

Figure 4: Estimated market size of CAR-T cell therapy

Challenges of CAR-T cell Therapy

Though CAR-T cell therapy comes up with an edge over other technologies in cancer treatment, however it is also associated with few shortcomings that includes toxic side effects on the patient after receiving CAR-T cell therapy such as CRS (Cytokine Release Syndrome) resulting in high fever and chills, nausea, breathing trouble etc. In addition to CRS, Macrophage Activation Syndrome (MAS), neurologic toxicities, and anaphylaxis are other side effects. To address the regulation of proliferation and toxicity associated with CAR-T, construction of a “suicide gene” system capable of destroying infused CAR T cells is under progress. Beside high cost of this therapy, current technology also requires expert workforce.

Further, limited efficacy of CAR-T cell therapy on solid tumor treatment alongwith poor trafficking and tumor infiltration are some of the limitations that must be addressed in order to make it ultimate choice of therapy for cancer treatment.

To overcome the above-mentioned hurdles in CAR-T cell therapies, innovative strategies have to be designed to make CAR-T cells with decreased toxic side effects when

administered for hematological malignancies and with improved clinical efficacy in anti-tumor activity.

Recent advancement and Future Perspective

CAR-T cell therapy is the new face of immunotherapeutics involved in combating hematological diseases. It is profoundly promising even in nonmalignant targets such as HIV-infected cells by modifying CAR structure and the choice of the adoptive immune cells. In order to overcome the inefficiency of current CAR-T against solid tumors, Yan et al., (2023) suggested a new strategy of combined targeting TMAs (Tumor microenvironment associated antigens) to create a tumor-hostile microenvironment and leading to better CAR-T cell infiltration into solid tumors. Current research work has just scratched the tip of the ice-berg indicating the immense embedded potential of CAR-T cell therapy.

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