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CAR-T - In Cancer: A "Living Drug"

New Era of Cancer Therapy

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[1]O Krishnasai Reddy, [2]Puvvula Vijaya Durga, [3]Swapna Kannabathula, [4]R. Shivani, [5]Kreena Parmar, [6*]S P Srinivas Nayak

[1,2] Department of Genetics, PIAS, Parul University, Vadodara, Gujarat. India. [3]Drug Safety Associate, IQVIA, Bangalore, Karnataka, India. [4]Department of Pharmacy Practice, PIPR, Parul University, Vadodara, Gujarat. India. [5]Department of Pharmacy Practice, PIPR, Parul University, Vadodara, Gujarat. India. [6] Assistant Professor, PIPR, Parul University, Vadodara, Gujarat. India.

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ABSTRACT

The CAR-T cell therapy is a ground-breaking new component in the treatment of cancer. The therapeutic efficiency of CAR-T cells in solid tumours and haematological malignancies is constrained by a number of obstacles, despite the fact that treatment with CAR-T cells has shown significant clinical responses with some subsets of B cell leukemia or lymphoma. Severe toxicities that can be fatal, poor anti-tumor effectiveness, antigen evasion, restricted trafficking, and minimal tumor penetration are all obstacles to effective CAR-T cell therapy. Additionally, CAR-T cell activity is significantly changed by interactions between the host and tumor microenvironment. These treatments must also be developed and implemented by a sophisticated staff. Innovative tactics and methods to create more potent CAR-T cells with greater anti-tumor activity and less toxicity are required to address these important difficulties. The CRISPR approach is expected to make genetically edited T cell immunotherapies safe, well-tolerated, and effective medicines that will give cancer patients hope. In this review, we cover recent developments in CAR-T cell engineering to enhance clinical effectiveness in solid tumors and haematological malignancies, as well as the benefits and drawbacks of CAR-T cell treatment using CRISPR.

INTRODUCTION:

There is a paradox at the base of cancer. Several immune cells, including the T cells that are normally fighting cancer which is spreading through numerous tumors. However, these T cells frequently stop functioning, allowing the tumor to continue to grow uncontrolled. This dilemma has a title in science: the Hellstrom paradox, why immune cells ignore the deadly threat arising in their surroundings is a mystery. T cells are vital immune cells that occasionally have the ability to combat cancer but, T cells frequently degenerate inside tumors, losing their capacity to assault cancer cells. Immunotherapy as a cancer treatment approach seeks to restore these damaged cells. Traditional cancer treatments include hematopoietic stem cell transplantation, radiation, chemotherapy, small molecule targeted medicines, and monoclonal antibodies. Cancer cells that have spread to other organs cannot be removed surgically; radiotherapy and chemotherapy are more common but have poorer specificity and cause significant harm to other tissues.[1] The most advanced kind of cancer treatment is cellular immunotherapy. Recent years have seen tremendous advancements in cancer treatment.[2] Gene therapy has emerged as one of the current therapeutic trends due to its potential to treat a variety of diseases such as autoimmune disorders, diabetes, malignancies and cardiac ailments that are resistant to traditional treatments.[3] Suicide gene therapy, oncolytic viro therapy, anti-angiogenesis, and therapeutic gene vaccines are just the few of the gene therapy treatments that have been developed to treat a range of tumours. Two thirds of all gene therapy studies are for cancer, and several are already at advance stages, including a phase III study of Ad.p53 for head and neck cancer and two phase III gene vaccine trials for prostate and pancreas cancer.[3] In addition to improving awareness of many solid and blood malignancies, research has also enhanced the application and significance of numerous immunotherapy techniques. The field of immunotherapy is one that is rapidly and remarkably expanding. For a number of patients with solid tumors and blood cancers, immunotherapy has produced novel therapeutic alternatives.[4] CAR-T cells are thought to be an important scientific advance and a major milestone in cancer immunotherapy.[5] Chimeric antigen receptors (CARs) T cells are found to possess the effector capabilities of a cytotoxic T cell along with the targeting specificity of a monoclonal antibody. With the ability to recognize antigens independently of the MHC and the ability to be properly customized to target the unique and crucial antigen epitopes, CARs have potential benefits over pathogen-specific T cells. This enables them to combat pathogen escape mechanisms.[6]

1. CAR-T CELL THERAPY

A cutting-edge tumor immunotherapy method for cancer treatment is CAR-T cell therapy. Acute B lymphocytic leukemia has been successfully treated using CAR-T cells, and other clinical trials using CAR-T cell therapy to treat different types of cancers have been described.[7] Due to the ability to target different tumor targets with the antigen-binding domain, this strategy is also more specialized and adaptable. Additionally, CAR-T cells can create memories in people with advanced leukemia.[8] The main element of CAR-T cells is a CAR, which provides T cells MHC unrestricted. This process, which is unrestricted by major histocompatibility complex (MHC) molecules, enables the modified T cells to recognize a broader range of targets than the normal TCR on the T cell surface. A CAR is a recombinant receptor that can both attach to tumor antigens and activate T cells.[9,10]

2. ENGINEERED T-CELL THERAPY

Modern adaptive immunotherapy mostly involves reinfusion of allogeneic or autologous tumor-responsive T cells into the patient's body to combat cancers.[11] This approach has worked well. However, due to the lack of invasive lymphocytes and the inability of this therapy to enhance the body's autoimmune system's capacity to fight tumors, it has not been widely employed.[12] T cell genetic engineering therapies can, to some extent, solve the problems of low T cell survival, motility, and immune escape. Blood is drawn from the patient, and T cells are genetically altered to produce receptors that identify antigens specific to malignancy.[13] To increase survival and encourage T cell infiltration into cancer tissue, additional genes can also be altered. These genes include those that encode cytokines. The newest and most potent immunotherapy techniques, CAR-T cell treatment and T cell receptor (TCR)-T cell therapy, have received a lot of attention recently.

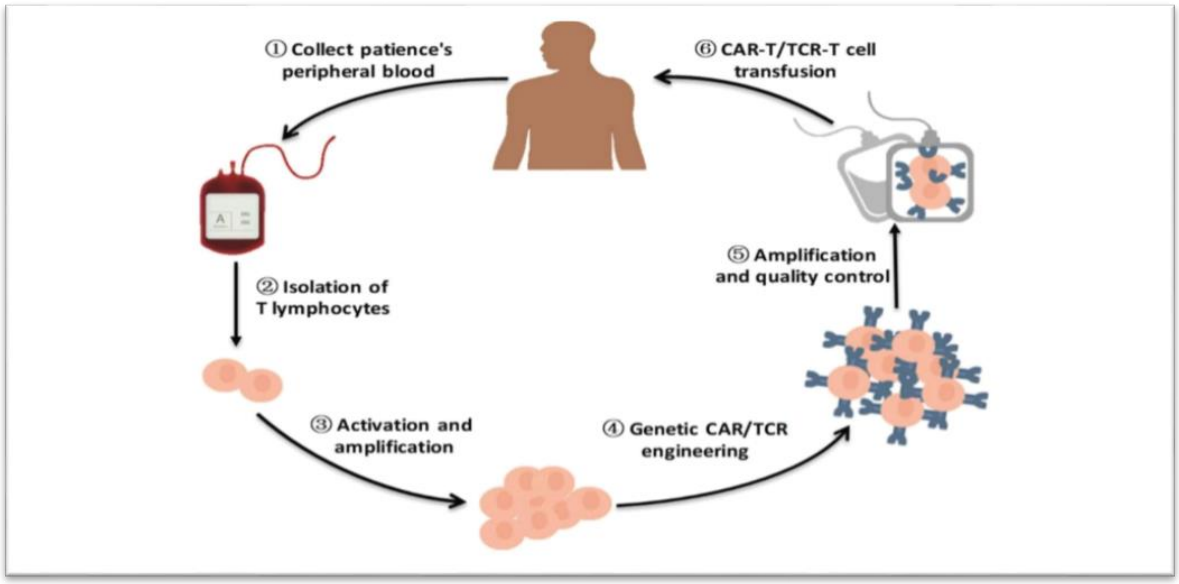

Figure No. 1: A flow chart of engineered-T cell therapy. A sufficient amount of blood is drawn from patients to obtain enough peripheral blood mononuclear cells (PBMCs) for engineered T cell manufacturing. The PBMCs of patients are used to purify the T lymphocytes. T cells are altered via viral vector transfection, like lentivirus transfection or retrovirus transfection, to exhibit particular CARs/TCRs on the T cell surface after activation and amplification in vitro. Following amplification and quality control, CAR-T cells/TCR-T cells are infused into the patient body to improve antitumor ability. [14,15]

3. CAR-T CELL THERAPY BEYOND CANCER

Recent research indicates that CAR-T therapy may be extremely effective in treating a variety of autoimmune illnesses, which are brought on when the immune system assaults host cells or tissues improperly. Individuals occasionally develop autoantibodies via B cells against a non-pathogenic endogenous protein. Numerous autoimmune disorders have been described, but only a small number of them are caused by autoantibodies, and in the majority of these instances, it is unknown what exact antigenic targets the autoantibodies are directed against. In some situations, it is believed that autoimmune illness is brought on by overexpression T cell responses (which may also be dependent on B cells through antigen presentation) or other immune system components.[16]

4. THE FIRST "LIVING DRUGS" FOR CANCER

Researchers and medical professionals now have a brand-new, cutting-edge method of treating some severe B-cell blood cancers that are entirely distinct from all previous

therapies. Through a process known as chimeric antigen receptor T (CAR-T) cell therapy, a patient's T cells—the white blood cells that guard the body against sickness and infection are transformed into a specialized, one-time treatment that may identify and eradicate cancer cells. It represents a significant improvement over several common cancer medicines, which must be supplied over time to huge populations of patients uniformly Dr. Bruce Levine of the University of Pennsylvania states, we recognized that we had a prospective therapeutic that could be helpful at treating untreatable malignancies. [17]

5. HOW CAR-T FINDS AND ELIMINATES CANCER CELLS

Step 1: T cells are essential in the fight against illness, but they struggle to identify cancer cells.

Step 2: After that, a manufacturing facility receives those cells to be reprogrammed.

Step 3: The genetic modification of the patient's T cells enables them to identify a certain marker on some cells, including cancer cells.

Step 4: Before being sent to the approved facility, the reprogrammed cells - now known as CAR-T cells - are replicated and put through a series of quality checks.

Step 5: After being given to the patient, the transformed cells start to recognize the markers on both healthy and malignant cells, adhere to them, and start cell death.

6. CASE STUDY

The first patient, a 63-year-old man with rapidly advancing and primary resistant DLBCL, within 8.5 months of diagnosis Additional (Figure No.2) provides a summary of this case. The patient's right trunk skin, subcutaneous soft tissue, right pleural space, peritoneum, bilateral cervical lymph nodes, supraclavicular lymph nodes, and bilateral axillary lymph nodes all exhibited significant tumor burdens. He had preconditioning therapy with a total dosage of 1.5 3 106 /kg universal CAR-T cells in 2 consecutive doses, followed by a total dose of fludarabine (30 mg/kg) and cyclophosphamide (15 mg/kg), all without experiencing any acute infusion-related toxicity. The patient had grade 4 cytokine release syndrome within 21 hours of cell infusion, as evidenced by his fever, respiratory distress, drop in blood pressure, severe pulmonary edema, and the presence of pleural effusion on chest X-ray (CRS). Tocilizumab, etanercept, and methylprednisolone were subsequently given in many cycles, but the patient's fever and CRS were not much reduced (Figure No.1A-B). Following

global CAR T-cell infusion, thrombocytopenia, anemia, and leukocytopenia were noticed; these toxicities may have been brought on by preconditioning regimens, but they were corrected after the infusion.

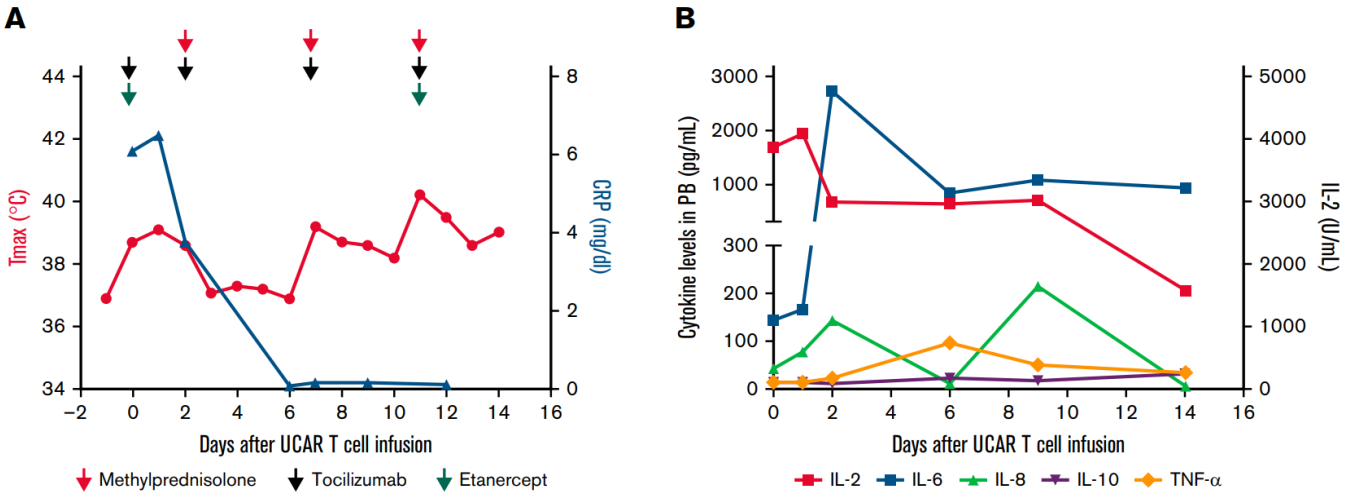

Figure No.2: After the delivery of universal CAR-T cells, toxicities, persistence, and response in patient 2. Before and after receiving universal CAR (UCAR) T cells, patient 2's maximum temperature (Tmax) and blood level of C-reactive protein (CRP) were observed in (A), and Tmax and CRP recovered without any treatment. (B) The serum levels of cytokines, including interleukin-2 (IL-2), IL-6, IL-8, IL-10, and tumor necrosis factor-a (TNF-a), were tested before and after UCAR T-cell infusion.[18]

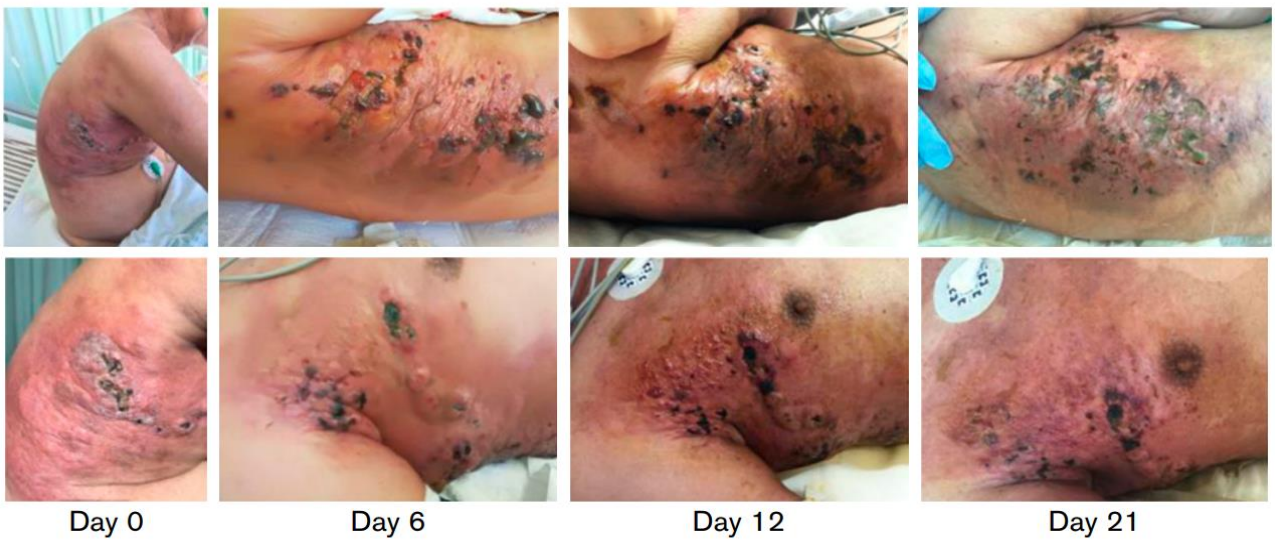

Figure No.3: Skin damage in the right trunk developed after UCAR T-cell infusion. The swelling improved after methylprednisolone treatment.[18]

7. FDA-APPROVED CART THERAPIES

The use of CAR-T cells in treating both adults and children with various forms of leukemia and other blood cancers holds great potential. So far, five CAR T-cell treatments have received approval from the US Food and Drug Administration (FDA), which is in charge of examining innovative medicines and approving their release to the market. In 2017, the first CAR T-cells with FDA approval hit the market. The 5 FDA approved CAR T-cell therapies. In the US, there are five CAR T-cell immunotherapies that have received FDA approval:

Kymriah™ (tisagenlecleucel)

Yescarta™ (axicabtagene ciloleucel)

Tecartus™ (brexucabtagene autoleucel)

Breyanzi® (lisocabtagene maraleucel)

Abecma® (idecabtagene vicleucel) [19]

In April 2017, the FDA designated Novartis KymriahTM as a breakthrough drug for the treatment of complicated diffuse large B-cell lymphoma, and it later acquired FDA approval for the treatment of B cell acute lymphoblastic leukemia and acute lymphoblastic leukemia (ALL). Later that year, the FDA granted YescartaTM breakthrough therapy recognition, new drug status, and priority review for diffuse large B-cell lymphoma, transformed follicular lymphoma, and primary mediastinal B-cell lymphoma. Non-Hodgkin lymphomaAcute lymphoblastic leukemia and the uncommon non-Hodgkin lymphoma known as mantle cell lymphoma were both authorized for TecartusTM in 2020.For the treatment of refractory large B-cell lymphomas, such as diffuse large B-cell lymphoma (DLBCL), difficult-to-treat follicular lymphoma, high-grade B-cell lymphoma, and primary mediastinal large B-cell lymphoma, the FDA approved Breyanzi® in the first few months of 2021.The FDA most recently approved the use of Abecma® for the treatment of multiple myeloma in March 2021.[19] The first CAR-modified T-cell clinical trials were carried out in the 1990s, but there were no clinical advances. The breakthrough in CAR T-cell persistence and cancer cell clearance came about during the course of the next 20 years when CAR T-cells were improved and activation domains were added to the CAR components. The US Food and Drug Administration has approved five CAR T-cell treatments in the previous five years for difficult-to-treat blood and bone marrow malignancies. Despite the fact that the relevant

clinical trials revealed serious side effects (such as an overly active immune system and neurological toxicity), the agency recognized the potential of CAR T-cell therapy and the need for effective treatment options for those diseases in the interest of the public health. Additionally, CAR T-cells are potential candidates to treat additional conditions, such as challenging solid tumors.

8. CRISPR DRIVES CAR

An effective technique to make precise genetic alterations to the human genome is through the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas)9 platform. This enables a new class of genetic therapies that can be used to treat hematological disorders because it can be used to destroy, add, and correct genes. Technological developments in the CRISPR/Cas9 approach and applications in hematology for treating hematological malignancies and correcting monogenic genetic abnormalities as well as generating innovative chimeric antigen receptor (CAR) T cells are advanced.[20] Although gene editing could enhance cell engineering, it would be a while before CAR-T cells and CRISPR would come into contact. The ability of CAR-T cells to treat cancer was evident from the start, but producing these cells was laborious and challenging. Lentiviral or retroviral vectors were initially required for T cell engineering in order to introduce DNA fragments into a cell for homologous recombination. DNA fragments can be permanently integrated and expressed using viral vectors. The cost of the clinical-grade chemicals necessary to obtain these vectors.[21] Because the vectors can only transport a certain quantity of DNA, some of which may randomly merge into the genome. Long CAR sequences needed to be engineered more effectively for CAR T cell therapy to develop. CRISPR initially seemed like the best method for creating T cells. It operates on a variety of cell types, is straightforward, and has few off-target consequences. But CRISPR has had trouble in one particular area. By specifically causing double-stranded DNA (dsDNA) breaks, which are later repaired by the cell's non-homologous end joining process, CRISPR-Cas9 is excellent in producing modest alterations. However, CRISPR editing can be dreadfully ineffective when it comes to introducing foreign DNA utilizing homology-directed repair mechanisms. However, DNA insertion is essential for creating CAR T cells. A gene engineer at the University of Nebraska Medical Center in Omaha named Channabasavaiah Gurumurthy claims that "CRISPR is a far better instrument when it comes to homology-directed repair.[22] Gurumurthy and his colleagues found that lengthy single-stranded DNA (ssDNA) is a more efficient template than double-stranded when utilizing CRISPR to insert DNA into a cell.

Long ssDNA and a preassembled complex containing Cas9 and guide RNAs are injected using EasiCRISPR, leading to increased rates of on-target editing and reduced rates of off-target editing. It was beginning to look as though CRISPRCas9 could be a useful tool for producing both deletions and insertions within T cells, especially in light of prior reports demonstrating that chemically synthesized single guide RNAs (sgRNA) with 2'-O-methyl and phosphorothioate end modifications enhanced intracellular stability and editing efficiency in primary cells. [23,24] The way researchers approach cell engineering is changing as a result of gene editing. CAR-T cell engineering efforts are set to be significantly strengthened by techniques like CRISPR and advancements in DNA and RNA synthesis, ultimately enhancing cancer therapy and human health.[25]

9. ADVANTAGES OF CAR-T THERAPY

The first child with ALL to get CAR-T cell therapy was Emily Whitehead. Emily's leukemia was entirely cured by the University of Pennsylvania CAR-T cell clinical study, and she has since become a spokesperson for the therapy. To demonstrate the potential of CAR-T cell immunotherapy in the treatment of cancer. Tisagenlecleucel (Kymriah), a CAR-T cell treatment, was effective in 52 of 63 patients in a clinical trial for children and young adults with cancer who had not responded to traditional therapy. Three out of every four individuals in the trial did not experience a relapse after six months. The FDA authorized tisagenlecleucel in August 2017 for the treatment of patients with relapsed or resistant B-cell precursor ALL based on the findings of this trial.[26] MHC molecules do not impose limitations on CAR-T cells. They more specifically identify antigens and eradicate tumour cells. effectively. TCRs and tumour infiltrating lymphocytes (TILs) can only detect antigens presented by particular MHC molecular downregulation or MHC molecule mutation in malignant cells may allow molecules and malignancies to evade immune monitoring leading to clinical restrictions.[27]

10. FAILURES OF CAR-T THERAPY

The HER2-targeted CAR-T treatment and indications for metastatic melanoma were included in the first third-generation CAR-T cell clinical investigations. The NCI decided to treat HER2+ melanoma with a CAR-T cell that contains a scFv targeting HER2. A total dose of 1 x 1011 cells were administered to the first patient, giving them a high concentration of CAR-T cells. After the procedure, the patient immediately went into severe discomfort and quickly fell into a coma. Five days after receiving a high-dose hormone intervention, the patient

passed away. The patient's body was then found to contain CAR-T cells all throughout it, with the lungs being the organ most severely affected. Further investigation may reveal that the primary driver of this deadly lung T cell infiltration was HER2 expression in pulmonary epithelial cells.[28]

Certain types of immunotherapy can fight cancer or stop it from spreading to other body areas. Others facilitate the immune system's ability to eliminate cancer cells, but immunotherapy can occasionally trigger the immune system to attack healthy cells, causing in negative side effects. Immunotherapy can have a variety of unwanted consequences. Numerous adverse effects are influenced by the type of therapy, the type and location of the cancer, and the general health of the patient. Immunotherapy frequently causes side effects such skin redness, blistering, and dryness. Immunotherapy side effects might include fatigue, fever, chills, weakness, nausea, vomiting, disorientation, body aches, and hypertension or hypotension. Before beginning treatment, it is important to weigh the substantial dangers associated with this innovative method to cancer treatment. There are frequently potential therapeutic adverse effects, such as CRS and neurological issues.[29]

CONCLUSION

In contrast to conventional medicines, immunotherapy uses the autoimmune system to attack tumors and directly affect cancer cells. This cycle can be repeated to increase the anti-tumor immune response. The anti-tumor immune response can constantly recognize and store tumor antigens throughout time. Some cytotoxic T cells develop into mature memory T cells as the immune response progresses, and these cells can offer long-term immunological memory even in the absence of primary antigen stimulation. Immunotherapy can therefore help patients live longer and experience permanent benefits. The field of CAR-T cell-based therapeutics for adoptive cell therapy is expanding as genomic editing tools advance. Among the many technologies that can be used, CRISPR/Cas9 exhibits remarkable multiplex genome engineering capabilities while being relatively simple to use, simple to design, and affordable. Today, CRISPR/Cas9-based genome editing offers the potential to further streamline immune cell-based therapies, particularly through the creation of an all-encompassing "off-the-shelf" cellular product or engineering these redirected effector cells to overcome tolerance in human malignancies, which range from solid tumors to haematological malignancies. Designing and enhancing large-scale methods for CRISPR/Cas9-mediated target ablation in mature T cells, however, is of primary significance for future human

clinical trials. These procedures must facilitate the transfer of sgRNA, Cas9, and a gene encoding the CAR, sustain cell viability, and enable robust in vitro genetically modified T cell growth. This deal is a life-changer for young people with this severe illness and their families. More patients seek this inventive therapy, treatment centres should prepare to deal with and manage the drug.[30]

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