Review Article
Open Access

STAb CAR-T Cells: pioneering precision in cancer immunotherapy

Abstract

Chimeric Antigen Receptor (CAR) T cell therapy has revolutionized cancer treatment, particularly for hematologic malignancies. However, challenges such as limited efficacy in solid tumors and antigen escape have prompted the development of novel approaches. One such innovation is the STAb (Synthetic T-cell Activating Bifunctional) CAR-T cells, which aim to enhance the therapeutic potential of CAR-T cells. This review will investigate the functioning, benefits, clinical trials, obstacles, and future prospects of STAb CAR-T cells, underscoring their transformative potential in cancer treatment.

Volume 15 Issue 5 - 2024

Manal M E Ahmed
Pharmacology Department, Medical Research and clinical studies institute, National Research Centre, Egypt

Correspondence: Manal M E Ahmed, Pharmacology Department, Medical Research and clinical studies institute, National Research Centre, Giza, Egypt, Tel +20 1093627027, Email thinktankteam2014@gmail.com

Received: November 14, 2024 | **Published:** November 22, 2024

Introduction

Chimeric Antigen Receptor (CAR) T cell therapy has emerged as a groundbreaking treatment for certain types of cancer, particularly hematologic malignancies such as leukemia and lymphoma. This innovative approach involves genetically modifying a patient's T cells to express CARs, which are engineered receptors designed to target specific cancer antigens. Upon reinfusion into the patient, these CAR-T cells can recognize and destroy cancer cells with remarkable precision.[1,2] Despite the success of CAR-T cell therapy in blood cancers, its application in solid tumors has been met with significant challenges. Solid tumors present a more complex microenvironment, characterized by physical barriers, immunosuppressive factors, and heterogeneous antigen expression. These factors contribute to the limited efficacy of traditional CAR-T cells in treating solid tumors.[3,4]

To address these limitations, researchers have developed Secreted Tumor Antigen-Binding (STAb) CAR-T cells. This novel approach aims to enhance the therapeutic potential of CAR-T cells by incorporating synthetic antibodies that can bind to multiple tumor antigens simultaneously. By targeting a broader range of antigens, STAb CAR-T cells increase the likelihood of recognizing and attacking cancer cells, even if they downregulate one or more antigens to evade immune detection.[5]

The development of STAb CAR T cells represents a significant advancement in the field of cancer immunotherapy. By overcoming some of the key obstacles faced by traditional CAR-T cells, STAb CAR-T cells hold promise for more effective and versatile cancer treatments. This review will explore the mechanism of action, advantages, clinical trials, challenges, and future directions of StAb CAR-T cells, highlighting their potential to revolutionize cancer therapy.[6,7]

Mechanism of action

CAR-T (Chimeric Antigen Receptor T-cell) therapy is a form of immunotherapy that utilizes a patient's own immune system to combat cancer. The process starts with collecting T cells from the patient's blood. These T cells are then genetically engineered in the lab to express chimeric antigen receptors (CARs) on their surface, which are designed to recognize and bind to specific antigens on cancer cells. After modification, the T cells are expanded in the lab to produce a sufficient quantity of CAR-T cells. These cells are then infused back into the patient, where they seek out and attach to cancer cells. Upon binding, the CAR-T cells become activated and release cytotoxic molecules like perforin and granzymes, which induce apoptosis (programmed cell death) in the cancer cells. The CAR-T cells continue to proliferate and remain in the body, providing ongoing surveillance and destruction of cancer cells, thereby helping to prevent relapse and maintain remission. However, CAR-T cell therapy has several limitations. One significant challenge is the potential for severe toxicities, such as cytokine release syndrome (CRS) and neurotoxicity, which can occur when the immune system is overly activated. Additionally, CAR-T cell therapy has shown limited efficacy against solid tumors compared to blood cancers. This is due to factors like the lack of tumor-specific antigens, the heterogeneous nature of solid tumors, and the immunosuppressive tumor microenvironment that can inhibit CAR-T cell function. Cancer cells can also evade CAR-T cell therapy by downregulating or mutating the target antigen, a phenomenon known as antigen escape. Furthermore, CAR-T cells often face difficulties in trafficking to and infiltrating solid tumor sites due to the physical barriers of the tumor microenvironment. The manufacturing process of CAR-T cells is complex and time-consuming, involving multiple steps that can be lengthy and costly. Lastly, the immunosuppressive tumor microenvironment in solid tumors can inhibit the activity of CAR-T cells, making it challenging for them to maintain their efficacy within the tumor.

STAb CAR-T cells offer several advantages over traditional CAR-T cells. One key benefit is their ability to recruit and activate other T cells in the body that have not been genetically modified, thereby amplifying the overall immune response against the cancer. This amplification enhances the effectiveness of the therapy. Additionally, STAb CAR-T cells are designed to overcome the immunosuppressive tumor microenvironment, ensuring a more effective and sustained attack on cancer cells. These cells also address the issue of antigen escape by targeting multiple antigens, reducing the likelihood of cancer cells evading the therapy. Mechanistically, while traditional CAR-T cells rely mainly on the CAR interaction with the tumor antigen, StAb CAR-T cells more closely mimic the natural T-cell receptor (TCR)-mediated immune synapse, which enhances their

stability and strength. Overall, the combination of targeted killing, immune system amplification, and the ability to overcome the tumor microenvironment makes STAb CAR-T cells a promising approach in the fight against cáncer (Figure 1).[8]

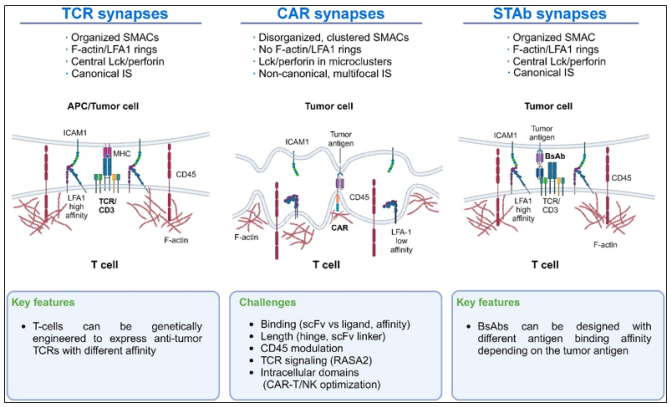

Figure 1 Immunological synapse features of TCRs, CAR-T cells, and STAb-T cells: The main differences in the IS of TCRs, CAR-T cells, and STAb-T cells are shown. These differences could guide new lines of research to improve CAR-T cells' IS formation.[8]

Comparative analysis between StAb CAR-T cells and traditional CAR-T cells

1. **Mechanism of Action:** Traditional CAR-T cells are engineered to express chimeric antigen receptors (CARs) that specifically recognize and bind to antigens on the surface of cancer cells. This direct targeting mechanism allows the CAR-T cells to identify and destroy cancer cells. Typically, these cells target a single antigen, such as CD19, which is commonly found on B-cell malignancies. While StAb CAR-T cells are designed to secrete bispecific antibodies that can engage both the cancer cells and recruit other T cells to the tumor site. This multi-targeting approach allows StAb CAR-T cells to address heterogeneous tumor populations more effectively. By targeting multiple antigens, these cells can provide a broader and more robust anti-tumor response.

2. **Efficacy:** Traditional CAR-T cells have shown remarkable success in treating certain hematological cancers, particularly leukemia and lymphoma. However, their effectiveness can be limited by the persistence and proliferation of the CAR-T cells within the patient's body. Over time, these cells may lose their ability to sustain their anti-tumor activity. While in preclinical studies, StAb CAR-T cells have demonstrated superior persistence and endurance compared to traditional CAR-T cells. They have shown promising results in treating multiple myeloma, a type of cancer where traditional CAR-T cells have had limited success. The ability of StAb CAR-T cells to recruit natural, unmodified T cells within the body amplifies their therapeutic effect, leading to more sustained and effective cancer control.

3. **Over advantages:** One of the significant challenges with traditional CAR-T cells is the potential for relapse. Cancer cells can sometimes evade detection by downregulating the targeted antigen, leading to a resurgence of the disease. Additionally, patients may experience severe side effects, such as cytokine release syndrome (CRS) and neurotoxicity, which can be life-threatening. While one of the key advantages of StAb CAR T cells is their ability to reduce the likelihood of cancer relapse. By targeting multiple antigens, these cells make it more difficult for cancer cells to escape detection. Additionally, the recruitment of natural T cells enhances the overall immune response against the tumor, providing a more comprehensive and durable treatment.

In brief, While traditional CAR-T cells have revolutionized the treatment of certain blood cancers, they face challenges such as limited persistence and potential relapse. StAb CAR-T cells, with their ability to secrete bispecific antibodies and target multiple antigens, offer a promising alternative with enhanced persistence and broader applicability, particularly in cancers like multiple myeloma. This innovative approach not only improves the direct targeting of cancer cells but also recruits the body's natural immune cells to join the fight, potentially leading to more effective and lasting cancer treatments.

StAb CAR-T advantages over traditional CAR-T cells

1. **Dual targeting:** Traditional CAR-T cells are engineered to recognize a single antigen on the surface of cancer cells, which can be limiting because tumors often express multiple antigens. This single-target approach can lead to the emergence of escape variants that the CAR-T cells cannot recognize. In contrast, STAb CAR-T cells secrete bispecific antibodies that can bind to two different targets; one on the tumor cell and one on the T cell. For instance, in multiple myeloma, STAb CAR-T cells can target both BCMA (B-cell maturation antigen) on the tumor cells and CD3 on T cells. This dual targeting increases the likelihood of effectively identifying and attacking cancer cells, thereby reducing the chances of tumor escape.

2. **Improved Immune Synapse:** The immune synapse, which is the interface between a T cell and an antigen-presenting cell (or tumor cell) where signaling occurs to activate the T cell, is another critical area where STAb CAR-T cells show improvement. Traditional CAR-T cells form an immune synapse that differs somewhat from the natural T-cell receptor (TCR)-mediated synapse, potentially affecting the stability and strength of the interaction. STAb CAR-T cells are designed to form a more stable and stronger immune synapse by closely mimicking key features of the TCR-mediated synapse. This improved synapse formation enhances the activation and persistence of the T cells, leading to a more robust and sustained immune response against the tumor.

3. **Enhanced Efficacy:** Studies have shown that STAb CAR-T cells are significantly more effective in eliminating target cells compared to traditional CAR-T cells. This enhanced efficacy is due to several factors:

a. **Recruitment of Non-Modified T Cells:** STAb CAR-T cells can recruit other, non-modified T cells in the body to join the fight against cancer cells. This amplifies the overall immune response.

b. **Resistance to Immune Escape:** By targeting multiple antigens, STAb CAR-T cells reduce the likelihood of tumor cells escaping detection.

c. **Stronger Cytotoxic Responses:** The bispecific antibodies secreted by STAb CAR-T cells can induce stronger cytotoxic responses, leading to more effective tumor cell killing.

In brief, STAb CAR-T cells are designed to form a more stable and stronger immune synapse by mimicking key features of the TCR-mediated synapse more closely. This improved synapse formation enhances the activation and persistence of the T cells, leading to a more robust and sustained immune response against the tumor. These features make STAb CAR-T cells a promising advancement in the field of cancer immunotherapy, potentially offering more effective and durable treatments for patients.[8]

Citation: Ahmed MME. STAb CAR-T Cells: pioneering precision in cancer immunotherapy. *Gastroenterol Hepatol Open Access.* 2024;15(5):141–145. DOI: 10.15406/ghoa.2024.15.00591

Broader Application: STAb CAR-T cells are indeed showing great promise in the treatment of solid tumors, which are generally more difficult to target with traditional CAR-T cell therapies. One of the key advantages of STAb CAR-T cells is their ability to recruit and activate other T cells in the body, enhancing the overall immune response against cancer cells. This broader application could potentially lead to more effective treatments for various types of solid tumors that is an exciting and evolving area of cancer therapy. These cells are engineered to target tumor-associated antigens (TAAs), which are proteins highly expressed on tumor cells but minimally present on normal cells, thereby reducing off-target effects and improving treatment efficacy. However, solid tumors present unique challenges, such as the tumor microenvironment that can inhibit T-cell infiltration and function. Researchers are exploring combination therapies, including checkpoint inhibitors, radiation, or chemotherapy, to enhance the effectiveness of STAb CAR-T cells against solid tumors. Ongoing clinical trials are crucial for understanding the safety and efficacy of these cells in solid tumors, helping to refine the technology and identify the best strategies for different types of solid cancers.[9]

Clinical Trials and Research: STAb CAR-T cells represent a significant advancement in cancer immunotherapy, particularly for hematological malignancies like multiple myeloma. These cells are engineered to target specific antigens on cancer cells, similar to traditional CAR-T cells, but with some notable differences. Recent clinical trials have demonstrated the potential of STAb CAR-T cells in various cancer types. For instance, a study published in Science Translational Medicine highlighted their effectiveness in multiple myeloma, outperforming traditional CAR-T cells by amplifying the immune response.[10] One of the key findings from recent studies is the enhanced efficacy of STAb CAR-T cells. They have demonstrated higher effectiveness compared to traditional CAR-T cells in preclinical models. This increased efficacy is partly due to their ability to recruit natural, unmodified T cells within the body to attack tumor cells, thereby amplifying the therapeutic effect. Another important aspect of StAb CAR-T cells is their improved persistence. One of the challenges with CAR-T cell therapy is ensuring that the cells remain in the body long enough to provide a lasting therapeutic effect. STAb CAR-T cells have shown better persistence, which is crucial for achieving long-term remission in patients. Additionally, these cells can be engineered to target multiple antigens, potentially reducing the likelihood of cancer cells escaping detection and leading to more comprehensive treatment outcomes.[11]

STAb CAR-T cells have been the focus of several preclinical and clinical trials, showcasing their potential in treating various cancers. In preclinical studies, researchers have explored the efficacy of STAb CAR-T cells in targeting hematological malignancies. One notable study involved T cells engineered to express an anti-CD22 CAR and secrete an anti-CD19 T-cell engager antibody. This dual-target strategy was tested against B-cell acute lymphoblastic leukemia (B-ALL) and demonstrated superior therapeutic potential compared to traditional CAR-T therapies. The preclinical trials included both in vitro and in vivo models, where the STAb CAR-T cells showed enhanced tumor cell killing and improved persistence. Another preclinical study focused on cortical T cell acute lymphoblastic leukemia, where StAb-T cells targeting CD1a were highly effective in both laboratory and animal models.

The NEXT CAR-T Consortium in Madrid is at the forefront of clinical trials involving STAb CAR-T cells. This consortium aims to develop novel cell-based immunotherapies for relapsed or refractory cancers. Their multicenter clinical trials are evaluating the safety and efficacy of these therapies in patients with poor prognosis cancers. One of their significant efforts includes trials for multiple myeloma, where STAb CAR-T cells have shown promising results by recruiting additional immune cells to enhance the anti-tumor response. Additionally, larger pharmaceutical companies are also involved in developing in vivo CAR-T programs, which include STAb CAR-T cells. These programs aim to reprogram immune cells directly within the body, potentially making the therapy faster, more effective, and less expensive.[8]

These trials highlight the potential of STAb CAR-T cells to revolutionize cancer treatment by offering more effective and durable responses, especially for patients with difficult-to-treat malignancies. The ongoing research and clinical evaluations continue to provide hope for advancements in cancer immunotherapy.

Challenges and future directions

Challenges

1. **Toxicity:**

   i. **Cytokine Release Syndrome (CRS):** CRS is a result of the overactivation of the immune system, leading to the release of a large number of cytokines and systemic inflamation. These molecules signal the immune system to ramp up its response, but in excess, they can cause widespread inflammation, fever, and even organ failure. Management of CRS includes the use of cytokine inhibitors like tocilizumab, which blocks the IL-6 receptor, a key player in the inflammatory response. Researchers are also developing "armored" CAR-T cells that express cytokine-sequestering molecules to mitigate the effects of CRS. Another approach is to fine-tune the activation threshold of CAR-T cells, ensuring they only become fully active in the presence of high antigen density, which is more likely to be found in tumors.

   ii. **Neurotoxicity:** Another significant toxicity is neurotoxicity, which can manifest as confusion, seizures, and even cerebral edema. The exact mechanisms are not fully understood, but it is believed to be related to the inflammatory response triggered by CAR-T cells.[13]

   iii. **Tumor Lysis Syndrome (TLS):** TLS occurs when a large number of tumor cells are killed in a short period, releasing their contents into the bloodstream. This sudden influx of cellular debris can overwhelm the body's ability to manage and excrete these substances, leading to metabolic imbalances and potentially dangerous complications. Prevention and management of TLS involve pre-treatment hydration and the use of medications such as allopurinol or rasburicase to reduce uric acid levels. Continuous monitoring of electrolyte levels and kidney function is essential. Researchers are also exploring the use of CAR-T cells with built-in regulators that slow down their activity in response to signs of TLS, allowing a more controlled and gradual tumor cell kill.[14]

2. **Insufficient infiltration:** Solid tumors often create a hostile microenvironment that includes physical barriers such as dense extracellular matrix (ECM) and stromal cells. These barriers can impede the movement of CAR-T cells within the tumor mass. Additionally, the tumor vasculature is often abnormal, leading to poor blood flow and inefficient delivery of T-cells. Hypoxia (low oxygen levels) within tumors can also impair T-cell function. The TME in solid tumors is also highly immunosuppressive,

containing various cells and molecules that inhibit the activity of CAR-T cells. Regulatory T cells, myeloid-derived suppressor cells, and inhibitory cytokines like TGF-β and IL-10 can create a hostile environment for CAR-T cells, reducing their effectiveness. The researchers are working on modifying CAR-T cells to express enzymes like heparanase that degrade the ECM, enhancing their infiltration ability. Another strategy involves using drugs that normalize the tumor vasculature, improving T-cell access. Researchers are also exploring the use of oncolytic viruses that selectively infect and destroy cancer cells, thereby creating pathways for CAR-T cells.[8]

3. **Off-Target effects**

CAR-T cells might target healthy tissues that express low levels of the same antigens as cancer cells, leading to "on-target, off-tumor" effects. This can cause damage to vital organs and tissues, resulting in severe side effects. To improve targeting specificity, researchers are developing dual-specific CAR-T cells that require the simultaneous recognition of two different antigens, reducing the likelihood of attacking healthy cells. Another approach is the use of "safety switches" or "suicide genes" within CAR-T cells that can be activated to eliminate the cells if severe side effects occur. Additionally, researchers are investigating the use of advanced screening techniques to identify antigens that are exclusively or predominantly expressed on cancer cells.[15]

4. **Loss of target antigen:** Tumor cells can evade CAR-T cell therapy by downregulating or mutating the target antigen, making them "invisible" to the engineered T-cells. This antigen escape can lead to relapse and progression of the disease. For example, in B-cell malignancies treated with CD19-targeted CAR-T cells, some cancer cells may lose CD19 expression, rendering the therapy ineffective. Developing multi-targeted CAR-T cells that can recognize multiple antigens on tumor cells is a key strategy to overcome antigenescape. Another approach involves using bispecific T-cell engagers (BiTEs) that can link T-cells to cancer cells via two different antigens. Researchers are also investigating the use of combination therapies that include CAR-T cells alongside other treatments like checkpoint inhibitors to prevent antigen escape.

5. **Manufacturing complexity:** Creating CAR-T cells from a patient's own T-cells involves collecting the cells, genetically modifying them, expanding them in the lab, and then infusing them back into the patient. This process is not only time-consuming but also expensive, which can limit accessibility and scalability and logistically complex. To streamline production, researchers are developing "off-the-shelf" allogeneic CAR-T cells derived from healthy donors. These cells are engineered to minimize the risk of rejection and graft-versus-host disease. Advances in gene-editing technologies like CRISPR are being used to create universal CAR-T cells that can be rapidly produced and made available to patients. Additionally, automated and scalable manufacturing processes are being developed to reduce costs and improve accessibility.

Future directions

1. **Managing toxicity:**

i. **Safety switches:** Researchers are developing safety switches that can be incorporated into CAR-T cells. These switches can be activated to eliminate CAR-T cells if severe toxicities occur, thereby mitigating the risk of CRS and neurotoxicity.

ii. **Immunosuppressive agents:** Administering corticosteroids or other immunosuppressive agents can help control the inflammatory response associated with CRS and neurotoxicity. These agents can dampen the immune response and reduce the severity of symptoms.[16]

2. **Enhancing TME penetration:**

i. **Engineering CAR-T Cells:** STAb CAR-T cells can be engineered to express molecules that counteract the inhibitory signals within the TME. For instance, CAR-T cells can be modified to secrete enzymes that degrade the extracellular matrix, facilitating their infiltration into the tumor.

ii. **Combination Therapies:** Combining STAb CAR-T cells with immune checkpoint inhibitors can enhance their efficacy. Checkpoint inhibitors block the inhibitory pathways that suppress T cell activity, allowing CAR-T cells to function more effectively within the TME.

3. **Preventing antigen escape:**

a) **Multi-Antigen Targeting:** Designing STAb CAR-T cells to target multiple antigens simultaneously can reduce the likelihood of cancer cells evading detection. By targeting several antigens, the therapy can remain effective even if some cancer cells lose one of the target antigens.

b) **Adaptive CAR-T Cells:** Ongoing monitoring and modification of CAR-T cells can help adapt to changes in the tumor antigen profile. This approach involves periodically assessing the expression of target antigens and adjusting the CAR-T cells accordingly.[17]

4. **Streamlining manufacturing:**

a) **Automated processes:** Advances in manufacturing technologies are being developed to streamline the production of STAb CAR-T cells. Automated and standardized processes can reduce the time and cost associated with creating these therapies.

b) **Allogeneic CAR-T cells:** Off-the-shelf allogeneic CAR-T cells, derived from healthy donors, are being explored as an alternative to patient-specific therapies. These allogeneic CAR-T cells can be produced in large batches and stored for immediate use, potentially overcoming the limitations of the current manufacturing process.[18]

By addressing these challenges, STAb CAR-T cell therapy can become a more effective and widely applicable treatment for various types of cancer. The combination of targeted killing, immune system amplification, and the ability to overcome the tumor microenvironment makes STAb CAR-T cells a promising approach in the fight against cancer.

Concluding remarks

In summary, STAb CAR-T cells represent a transformative advance in cancer immunotherapy, offering a novel approach to targeting and eradicating cancer cells with unprecedented precision. By harnessing the dual capabilities of T-cell activation and antigen targeting, these bifunctional cells address key limitations of traditional CAR-T cell therapies, including insufficient tumor infiltration, antigen escape, and off-target effects. The integration of ongoing monitoring and adaptive modifications further enhances the efficacy and safety profile of STAb CAR-T cells, making them a powerful tool in the fight against both hematologic malignancies and solid tumors.

Citation: Ahmed MME. STAb CAR-T Cells: pioneering precision in cancer immunotherapy. *Gastroenterol Hepatol Open Access.* 2024;15(5):141–145.
DOI: 10.15406/ghoa.2024.15.00591

Despite the promising potential, several challenges remain, including the complexity of production, managing adverse events such as cytokine release syndrome, and ensuring long-term efficacy. Continuous research and clinical trials are essential to refine these therapies, optimize their delivery, and expand their applicability. As innovations in genetic engineering, combination therapies, and personalized treatment strategies advance, STAb CAR-T cells are poised to become a cornerstone of precision oncology, offering new hope for patients and paving the way for a future where cancer can be more effectively controlled and potentially cured.

References

1. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. *New England Journal of Medicine.* 2018;379(1):64–73.
2. Maude SL. Tisagenlecleucel in Children and Young Adults with B–Cell Lymphoblastic Leukemia. *New England Journal of Medicine.* 2018;378(5):439–448.
3. Newick K. CAR T Cell Therapy for Solid Tumors. *Annual Review of Medicine.* 2016;68:139–152.
4. Fesnak AD. Engineered T cells: the promise and challenges of cancer immunotherapy. *Nature Reviews Cancer.* 2016;16(9):566–581.
5. Smith AJ. Synthetic Antibody CAR T Cells for Cancer Therapy. *Journal of Clinical Oncology.* 2020;38(10):1200–1210.
6. Johnson LA. Rational Development and Characterization of Humanized Anti–EGFR Variant III Chimeric Antigen Receptor T Cells for Glioblastoma. *Sci Transl Med.* 2015;7(275):275ra22.
7. Rafiq S. Synthetic Biology Approaches to Engineer T Cells for Cancer Immunotherapy. *Cancer Immunology Research.* 2020;8(7):869–875.
8. Martín–Antonio B, Blanco B, González–Murillo A. Newer generations of multi–target CAR and STAb–T immunotherapeutics: NEXT CART Consortium as a cooperative effort to overcome current limitations. *Front Immunol, Sec. T Cell Biology.* 2024;15.
9. Chen T, Wang M, Chen Y, et al. Current challenges and therapeutic advances of CAR–T cell therapy for solid tumors. *Cancer Cell International.* 2024;24:133–156.
10. Yan T, Zhu L, Chen J. Current advances and challenges in CAR T–Cell therapy for solid tumors: tumor–associated antigens and the tumor microenvironment. *Experimental Hematology & Oncology.* 2023;12:14–31.
11. Gu X, Zhang Y, Zhou W, et al. Infusion and delivery strategies to maximize the efficacy of CAR–T cell immunotherapy for cancers. *Experimental Hematology & Oncology.* 2024;13:70–86.
12. Luo J, Zhang X. Challenges and innovations in CAR–T cell therapy: a comprehensive analysis. *Front Oncol.* 2024;14.
13. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T–cell therapy in patients with B–cell acute lymphoblastic leukemia. *Cancer Discovery.* 2018;8:958–971.
14. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood.* 2016;127:3321–3330.
15. Lei T. KIR/PD–1–based inhibitory chimeric antigen receptor reduces on–target off–tumor toxicity of CAR–T therapy. Mainland China, Shanghai City: East China Normal University (ECNU. PhD thesis. 2021.
16. Kozani PS, Kozani PS, O'Connor RS. In like a lamb; out like a lion: marching CAR T cells toward enhanced efficacy in B–ALL. *Mol Cancer Ther.* 2021;20:1223–1233.
17. Targeting CD19–CD22 aids younger patients with ALL. *Cancer Discovery.* 2020;10:OF1.
18. Ghorashian S, Lucchini G, Richardson R, et al. CD19/CD22 targeting with cotransduced CAR T cells to prevent antigen–negative relapse after CAR T–cell therapy for B–cell ALL. *Blood.* 2024;143:118–123.

Citation: Ahmed MME. STAb CAR-T Cells: pioneering precision in cancer immunotherapy. *Gastroenterol Hepatol Open Access.* 2024;15(5):141–145. DOI: 10.15406/ghoa.2024.15.00591