Journal of Academic Inquiry and Knowledge Volume 2024 (4) 40-53
ISBN 979-8-9888908-2-9

CAR-T Cell Therapy: An Immunotherapy with Promises and Pitfalls

Sean Kim

Los Angeles, CA, USA

CAR-T Cell Therapy: An Immunotherapy with Promises and Pitfalls

Chimeric antigen receptor (CAR)-T cell therapy is a leading-edge adoptive cell therapy (ACT) (Golubovskaya, 2017; Almåsbak et al., 2016). ACT is a category of immunotherapy that separates immunocompetent cells from cancer patients and transfers these cells to patients after CARs are engineered into adoptive cells (modified cells with a specific Chimeric Antigen Receptor to focus on cancer cells) that eliminate cancers directly or support stimulation of the body's immune response to fight cancerous cells (Zhang et al., 2020; Raeke, 2023). Immunotherapy is part of a new generation of antitumor weapons targeting human immune systems rather than directly targeting tumor cells (Almåsbak et al., 2016; Surjit et al., 2022). Immunotherapy kills and resists tumor cells after activating the patient's immune system defenses (Almåsbak et al., 2016; Zhang et al., 2020). Traditional cancer therapies, such as clinical operations, chemotherapy, and radiotherapy, have short-term side effects that lower a cancer patient's quality of life. Immunotherapy, particularly CAR-T cell therapy, offers an innovative approach by genetically enhancing the immune system to fight certain cancers (Zhang et al., 2020; Dagar et al., 2023). CAR-T therapy is the most prominent immunotherapy in clinical trials (Raeke, 2023; Akhoundi et al., 2021). This paper examines the limitations and progress of

CAR-T cell therapy, highlighting its transformative potential and current challenges in the landscape of cancer immunotherapy treatment.

Background

The concept of genetic cytotoxic T-lymphocyte redirection to target tumor cells was first demonstrated three decades ago by Gideon Gross and colleagues (Almåsbak et al., 2016; Dagar et al., 2023). Cytotoxic T-lymphocytes, or T-cells, are white blood cells and lymphocytes that kill certain malignant cells (Surjit et al., 2022; De Marco et al., 2023). CAR-T cell therapy genetically modifies a patient's T-cells by re-engineering a CAR-T to fight a tumor antigen, followed by ex vivo cell expansion and T cell infusing back into the patient (Miliotou & Papadopoulou, 2018; Dagar et al., 2023). By enhancing the human immune system rather than directly targeting tumors, T cells can resist and kill tumor cells by activating patient defenses after genetic engineering (Dagar et al., 2023; Zhang et al., 2020). (See appendix A and B)

Despite the many versions of CAR-T cell therapies, the FDA has approved the clinical use of six therapies, which entailed four generations of CAR-T cell development (Golubovskaya & Mok, 2017; Pérez-Amill et al., 2018). In the first of the four generations, the CAR-T cell mechanism was active during examination, but T cells did not increase in vivo (multiply in the body). The failure to recognize a robust cytokine response after recognizing a tumor cell led researchers to question efficacy (Zhang et al., 2020; Pérez-Amill et al., 2018).

Nevertheless, second and third-generation CAR-T cells showed an increase in vivo CAR-T cell proliferation compared to first-generation CAR-T cells (Pérez-Amill et al., 2018; Dagar et al., 2023). Finally, fourth-generation CAR-T cells, TRUCKs, cause a protein, cytokines, to be secreted when fighting cancer (Dagar et al., 2023; Pérez-Amill et al., 2018). Cytokines have many beneficial qualities, including attracting greater quantities of immune cells to tumor sites,

strengthening CAR-T cells' mechanisms, and modifying the tumor environment for more effective therapy (De Marco et al., 2023; Zhang et al., 2020). CARs may incorporate an effective peptide to recognize and bind to its ligand in the cancerous cells and interact with other immune cells, such as dendritic cells (Surjit et al., 2022; Pérez-Amill et al., 2018). Peptides are the modified door keys on the CARs to fit into the keyhole on tumor cells (i.e., ligands). Recent and successful clinical trials, especially hematological malignancies, have led to further FDA approval of certain therapies and further studies into glioblastoma, breast cancer, and other cancerous diseases (Almåsbak et al., 2016; Zhang et al., 2020). However, clinical roadblocks such as cytokine release syndrome (CRS), off-tumor toxicity, and neurotoxicity limit CAR-T cell therapy's further use against other cancers (Abreu et al., 2020; Pérez-Amill et al., 2018).

Guiding Questions

1. What has the data from clinical trials emphasized are the common side effects of CAR T therapy?
2. What has been done in recent years, and what will be done in the future to overcome challenges regarding efficacy and side effects?

Pitfalls

When administering CAR-T cell therapy, variables such as dosage, patient-specific factors, and category of disease can induce severe toxicities, such as cytokine release syndrome (CRS), macrophage activation syndrome (MAS), neurotoxicity, and tumor lysis syndrome (TLS) (Dagar et al., 2023; Almåsbak et al., 2016). CRS and neurotoxicity remain the most prevalent but are treatable (Miliotou & Papadopoulou, 2018; Almåsbak et al., 2016). Effectiveness against certain solid tumors also remains a barrier to further applications in treatment plans (Zhang et al., 2020; Yan et al., 2023). Solid tumors hold characteristics, including the tumor microenvironment

(TME) and antigen heterogeneity, that have led to unsuccessful clinical trials compared to hematological cancers (Yan et al., 2023; Zhang et al., 2020).

Cytokine Release Syndrome

When high doses of T-cells are infused, the flooding of cytokine proteins supports high efficacy rates, yet high doses of cytokines can also cause a systemic inflammatory response (Zhang et al., 2020; Abreu et al., 2020). *Cytokines* are the proteins that strengthen CAR-T cell mechanisms and alter the tumor environment for more effective therapy (Landazuri, 2024; Yan et al., 2023). However, these proteins activate immune cells, including monocytes and macrophages, leading to the inflammatory response and the symptoms of CRS (Dagar et al., 2023; Albarrán et al., 2024). Consequently, CRS can lead to reversible organ dysfunction after the inflammatory response (Brudno & Kochenderfer, 2016; Dagar et al., 2023). Other mild symptoms of CRS include fever, fatigue, headache, rash, joint pain, and myalgia (Abreu et al., 2020; Zhang et al., 2020).

Neurological Toxicity

Neurologic toxicity, causing neurological symptoms, is most common when treating leukemia patients (Pérez-Amill et al., 2018; Abreu et al., 2020). The pathogenesis is unknown despite its prevalence in CD-19-specific CAR-T cell trials (Brudno & Kochenderfer, 2016; Zhang et al., 2020). Resolvable symptoms vary from paralysis, speech disorders, movement disorders, autism, and seizures (Rodriguez et al., 2021; Brudno & Kochenderfer, 2016). Unfortunately, CD-19-specific therapies can lead to death due to neurological toxicities (Tang et al., 2022; Zhang et al., 2020).

On-target/Off-tumor

Off-tumor toxicity or On-target/off-tumor (OTOT) toxicity is another concern of CAR-T

therapy (Pérez-Amill et al., 2018; Zhang et al., 2020). Off-tumor toxicity occurs when targeted antigen cells express the same properties as normal tissue cells. Further, these properties confuse modified T cells leading to attacks against normal tissues and organs (Landazuri, 2024; Abreu et al., 2020). OTOT toxicity is more likely to occur in solid tumors than other malignancies (Albarrán et al., 2024; Golubovskaya & Mok, 2017).

Promises

To overcome the challenges of CAR-T cell monotherapy, scientists have researched combining CAR-T cells with chemotherapy to decrease the side effects of the disease, enhance tumor antigen recognition, and increase the effectiveness and longevity of CAR-T cells (Liu et al., 2024; Pérez-Amill et al., 2018). Combinations of CAR-T cells with radiotherapy may also improve the transport and infiltration of T cells to tumor cells, enhance the display of tumor markers, and increase the resilience of CAR-T cells against obstacles such as the tumor microenvironment (TME) (Yan et al., 2023; Zhang et al., 2020). The complex microenvironment surrounding the tumor includes various extracellular matrices (ECMs), stromal cells, inflammatory cells, and abnormal blood vessels that can hinder certain therapies (Abreu et al., 2020; Yan et al., 2023).

One of the viable reasons for the unsatisfactory effect of CAR-T cells in solid tumors is that T cells cannot penetrate these physical and metabolic barriers formed by the TME (Melssen et al., 2023; Abreu et al., 2020). Furthermore, the TME can recruit immunosuppressive cells to weaken the efficacy of T-cells (Zhang et al., 2020; Melssen et al., 2023). Still, TME can be altered to enhance the effectiveness against CAR-T cells in solid tumors (Yan et al., 2023; Abreu et al., 2020). Using chemotherapy with cyclophosphamide, either alone or with fludarabine, facilitates T-cell implantation and reduces the quantity of inhibitory immune cells in TME

(Melssen et al., 2023; Zhang et al., 2020).

Toxicities including CRS and neurotoxicity can be treated with monthly immunoglobulin replacement (Hill et al., 2019; Almåsbak et al., 2016). Other treatments, including corticosteroids, have been used to combat neurologic toxicities due to norms of elevated cytokines that affect the central nervous system (Abreu et al., 2020; Zhang et al., 2020). Double-antigen-reporting CAR-T cells best avoid off-tumor or OTOT toxicity (Landazuri, 2024; Zhang et al., 2020). First, CAR-T cells recognize tumor cell antigen A and activate the expression of intracellular CAR encoding sequences (Zoine et al., 2024; Zhang et al., 2020). After CAR expression, the surface single-chain antibody recognizes antigen B, thereby preventing CAR-T cells from killing healthy cells (Korell et al., 2022; Zhang et al., 2020). Another way to reduce the dangers of OTOT is to reduce the receptor affinity (Landazuri, 2024; Korell et al., 2022). Receptor affinity is the strength to which CAR-T cells bind to the target antigen receptor on cancer cells (Surjit et al., 2022; Pérez-Amill et al., 2018). A strong receptor affinity leads to stronger binding onto cancer cells and to stronger binding on healthy tissue; thus, reducing affinity can balance the potency and side effects to balance the outcomes of therapy (Pérez-Amill et al., 2018; Korell et al., 2022).

Novel safety devices are emerging to fine-tune CAR-T cell therapy for greater efficacy against solid tumors, reduce side effects, including toxicities, and expand therapy to combat other forms of cancer (Yan et al., 2023; Abreu et al., 2020). Clinical trials reveal CAR-T cell therapy's most promising results in hematological malignancies, including Leukemia, Lymphomas, and Myeloma (Myers et al., 2023; Surjit et al., 2022).

Discussion

In a clinical trial, end-stage patients showed full recovery of up to 92 percent in acute

lymphocytic leukemia (DuVall et al., 2022; Miliotou & Papadopoulou, 2018). People with B-cell acute and chronic lymphocytic leukemia have shown high success rates in killing cancer cells with CD-19 CAR-T cell therapy. Scientists strive to combine CAR-T cell therapy with other treatments to improve effectiveness (Myers et al., 2023; Zhang et al., 2020). With anti-CD29 autologous CAR-T cells demonstrating significant antitumor activity against CD19-positive B-cell leukemias and lymphomas, further research shows encouraging results in early phase 1 trials in solid tumors, including neuroblastomas, tumors overexpressing mesothelin, HER2, and EGFR (Albelda, 2024; Golubovskaya & Mok, 2017). Further, CD47-CAR-T has shown efficacy against ovarian, pancreatic, and hepatocellular carcinoma, lung cancer, and melanoma (Golubovskaya & Mok, 2017; Albelda, 2024). For example, in a phase, I trial with 37 gastrointestinal malignancies in patients, a second-generation claudin18.2-specific CAR-T cell had an overall response rate of 48.6% and a disease control rate of 73.0%, with 44.8% of responses lasting ≥6 months (Qi et al., 2022; Albelda et al., 2024). The high overall response rate (ORR) and disease control rate (DCR) are revolutionary compared to conventional strategies such as chemotherapy (Ryan, 2024; Qi et al., 2022). For example, chemotherapy against colorectal cancer - the third most common cancer in the world - has an overall response rate of only 10-20% and a disease control rate of roughly 40% (Hoang et al., 2022; Ryan, 2024).

Conclusion

Adoptive cell transfer (ACT) therapy has become popularized in recent years due to greater precision in targeting cancerous cells, reductions in long-term side effects, and more personalized treatment plans than traditional therapies including chemotherapy and radiotherapy. However, roadblocks such as CRS and reduced efficacy rates throughout solid tumor clinical trials have led to skepticism about its overall efficacy (Pérez-Amill et al., 2018). Research into

CAR-T cell therapy and other immunotherapies still holds many unknown possibilities. The first trial of chronic lymphocytic leukemia treatment with CAR-T therapy was administered in 2010 (Pérez-Amill et al., 2018). After the FDA's clearance of the first official therapies in 2017, over 30,000 patients have been treated with CAR-T cell therapy. Scientists continue to research solutions by combining CAR-T therapy with other conventional treatments, incorporating safety switches if side effects from toxicities occur, and specializing the patient's T-cells to overcome the complex tumor microenvironment (Yan et al., 2023; Zhang et al., 2020). Further trials in liver cancer, breast cancer, neuroblastomas, pancreatic cancer, and glioblastomas hold an optimistic future for this novel therapy as research continues to expand.

References

Abreu, T. R., Miller, J. F. A. P., Topp, M. S., Kochenderfer, J. N., Lim, W. A., Jamnani, F. R., Srivastava, S., Zhao, Z., Milone, M. C., Zhong, X. S., Pegram, H. J., Garlanda, C., Hu, B., Avanzi, M. P., ... & Sadelain, M. (2019, December 30). Current challenges and emerging opportunities of CAR-T cell therapies. *Journal of Controlled Release*.

Albarrán, V., San Román, M., Pozas, J., Chamorro, J., Rosero, D. I., Guerrero, P., Calvo, J. C., González, C., Moreno, J., Cortés, A., & Soria, A. (2024). Adoptive T cell therapy for solid tumors: Current landscape and future challenges. *Frontiers in Immunology*, 15, 1352805. https://doi.org/10.3389/fimmu.2024.1352805

Albelda, S. M. (2024). CAR-T cell therapy for patients with solid tumors: Key lessons to learn and unlearn. *Nature Reviews Clinical Oncology*, 21, 47–66. https://doi.org/10.1038/s41571-023-00832-4

Almasbak, H., Aarvak, T., & Vemuri, M. C. (2016, May 19). CAR T cell therapy: A novel immunotherapy. *Wiley Online Library*. https://onlinelibrary.wiley.com/

Brudno, J. N., & Kochenderfer, J. N. (2016). Toxicities of chimeric antigen receptor T cells: Recognition and management. *Blood*, 127(26), 3321–3330. https://doi.org/10.1182/blood-2016-04-703751

Chen, L., & Ahmed, S. (2023). Real-world experience of CAR T-cell therapy in older patients with relapsed/refractory diffuse large B-cell lymphoma. *Blood*, 142(12), 1047–1055. https://doi.org/10.1182/blood.2023020197

Chihara, D., Liao, L., Tkacz, J., Franco, A., Lewing, B., Kilgore, K. M., Nastoupil, L. J., Dagar, G., Gupta, A., Masoodi, T., Nisar, S., Merhi, M., Hashem, S., Chauhan, R., Dagar, M., Mirza, S., Bagga, P., Kumar, R., Akil, A. S. A.-S., Macha, M. A., Haris, M., Uddin, S.,

Singh, M., & Bhat, A. A. (2023, August 25). Harnessing the potential of CAR-T cell therapy: Progress, challenges, and future directions in hematological and solid tumor treatments. *Journal of Translational Medicine*. https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-023-04292-3

De Marco, R. C., Monzo, H. J., & Ojala, P. M. (2023, March 27). CAR T cell therapy: A versatile living drug. *MDPI*. https://www.mdpi.com/1422-0067/24/7/6300 DuVall, A. S., et al. (2022). Updates in the management of relapsed and refractory acute lymphoblastic leukemia: An urgent plea for new treatments is being answered! *JCO Oncology Practice*, 18, 479-487. https://doi.org/10.1200/OP.21.00843

Golubovskaya, V. (2017, October 31). CAR-T cell therapy: From the bench to the bedside. *MDPI*. https://www.mdpi.com/2072-6694/9/11/150

Hill, J. A., Giralt, S., Torgerson, T. R., & Lazarus, H. M. (2019). CAR-T – and a side order of IgG, to go? – Immunoglobulin replacement in patients receiving CAR-T cell therapy. *Blood Reviews*, 38, 100596. https://doi.org/10.1016/j.blre.2019.100596

Hoang, T., Sohn, D. K., Kim, B. C., Cha, Y., & Kim, J. (2022). Efficacy and safety of systemic treatments among colorectal cancer patients: A network meta-analysis of randomized controlled trials. *Frontiers in Oncology*, 11, 756214. https://doi.org/10.3389/fonc.2021.756214

Korell, F., Berger, T. R., & Maus, M. V. (2022). Understanding CAR T cell-tumor interactions: Paving the way for successful clinical outcomes. *Med*, 3(8), 538–564. https://doi.org/10.1016/j.medj.2022.05.001

Landazuri, J. (2024, March 20). When it comes to low-affinity HER2 CAR T cells, less is more. *Fred Hutchinson Cancer Center*.

https://www.fredhutch.org/en/news/spotlight/2024/03/cogs-riddell-immuno.html

Liu, J., Jiao, X., Ma, D., Fang, Y., & Gao, Q. (2024). CAR-T therapy and targeted treatments: Emerging combination strategies in solid tumors. *Med*, 5(6), 530–549. https://doi.org/10.1016/j.medj.2024.03.001

Miliotou, A. N., & Papadopoulou, L. C. (n.d.). CAR T-cell therapy: A new era in cancer immunotherapy. *Eurekaselect*. https://www.eurekaselect.com/article/89803 Myers, R. M., Shah, N. N., & Pulsipher, M. A. (2023). How I use risk factors for success or failure of CD19 CAR T cells to guide management of children and AYA with B-cell ALL. *Blood*, 141(11), 1251–1264. https://doi.org/10.1182/blood.2022016937 Nair, R., & Westin, J. (1970, January 1). CAR T-cells. *SpringerLink*. https://link.springer.com/chapter/10.1007/978-3-030-41008-7_10

Olatunji, B. A., et al. (2023). Update on emerging therapies for advanced colorectal cancer. *American Society of Clinical Oncology Educational Book*, 43, e389574. https://doi.org/10.1200/EDBK_389574

Pharmacology, D. of. (n.d.). Chimeric antigen receptor T cell: A cancer immunotherapy. *Indian Journal of Pharmacology*. LWW. https://journals.lww.com/iphr/fulltext/2022/54030/chimeric_antigen_receptor_t_cell__a_cancer.11.aspx

Qi, C., Gong, J., Li, J., Liu, D., Qin, Y., Ge, S., Zhang, M., Peng, Z., Zhou, J., Cao, Y., Zhang, X., Lu, Z., Lu, M., Yuan, J., Wang, Z., Wang, Y., Peng, X., Gao, H., Liu, Z., ... & Shen, L. (2022). Claudin18.2-specific CAR T cells in gastrointestinal cancers: Phase 1 trial interim results. *Nature Medicine*, 28(6), 1189-1198. https://doi.org/10.1038/s41591-022-01800-8

Raeke, M. (2023, August 22). *Carl June on the boundless potential of car T cell therapy*. Carl June on The Boundless Potential of CAR T Cell Therapy. https://www.pennmedicine.org/news/news-blog/2023/august/carl-june-on-the-boundless potential-of-car-t-cell-therapy

Rodriguez, Y., AlGaeed, M., Dolbec, K., & Pang, T. (2021). Teaching neuroimage: CAR-T–induced nonconvulsive status epilepticus. *Neurology*, 97(12). https://doi.org/10.1212/WNL.0000000000012182

Ruhlmann, C. H., Iversen, T. Z., Okera, M., Muhic, A., Kristensen, G., Feyer, P., Hansen, O., & Herrstedt, J. (2015). Multinational study exploring patients' perceptions of side-effects induced by chemo-radiotherapy. *Radiotherapy and Oncology*, 117(2), 333–337. https://doi.org/10.1016/j.radonc.2015.09.014

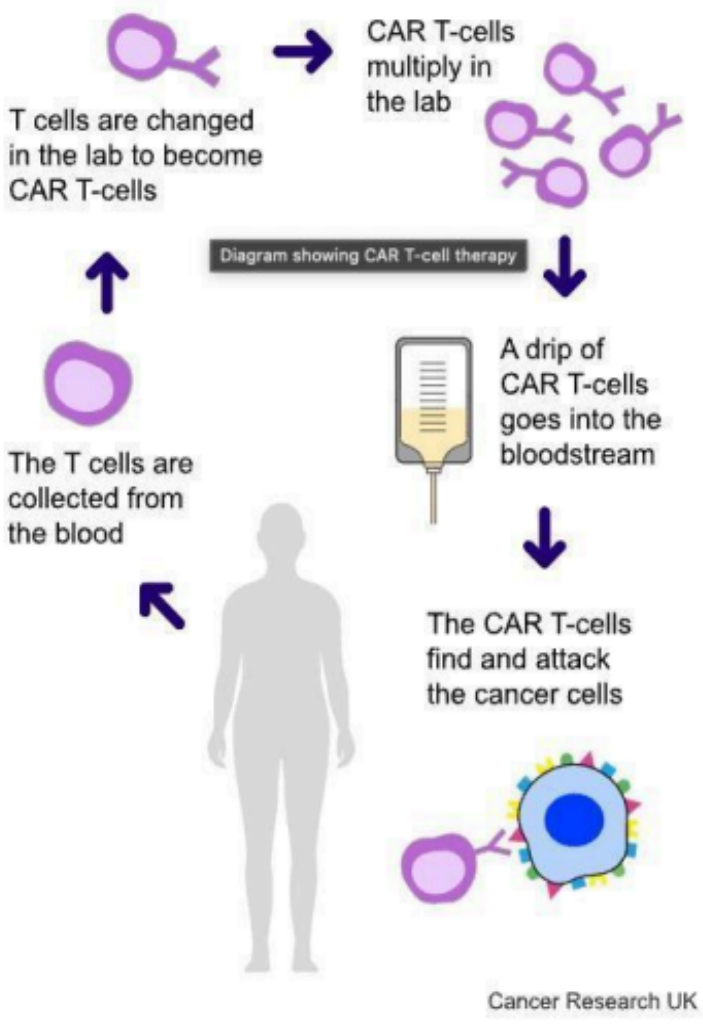
Ryan, C. (2024, July 1). Lunresertib plus FOLFIRI shows safety, elicits responses in CCNE1+ or FBXW7+ advanced GI tumors. *OncLive*. https://www.onclive.com/view/lunresertib-plus-folfiri-shows-safety-elicits-responses-in-ccne1-or-fbxw7-advanced-gi-tumors

Tang, K., Khwaja, R., Feng, L., Strati, P., Steiner, R. E., Nair, R., Flowers, C. R., Saini, N., Ramdial, J. L., Srour, S. A., Champlin, R. E., Rondon, G., Torres, J., Kebriaei, P., Nastoupil, L. J., Mistry, H., Shpall, E. J., Nieto, Y., Westin, J., ... & Ahmed, S. (2022). Comorbidities associated with early mortality after CD19 CAR-T cell therapy. *Blood*, 140(Supplement 1), 4684–4685. https://doi.org/10.1182/blood-2022-166267

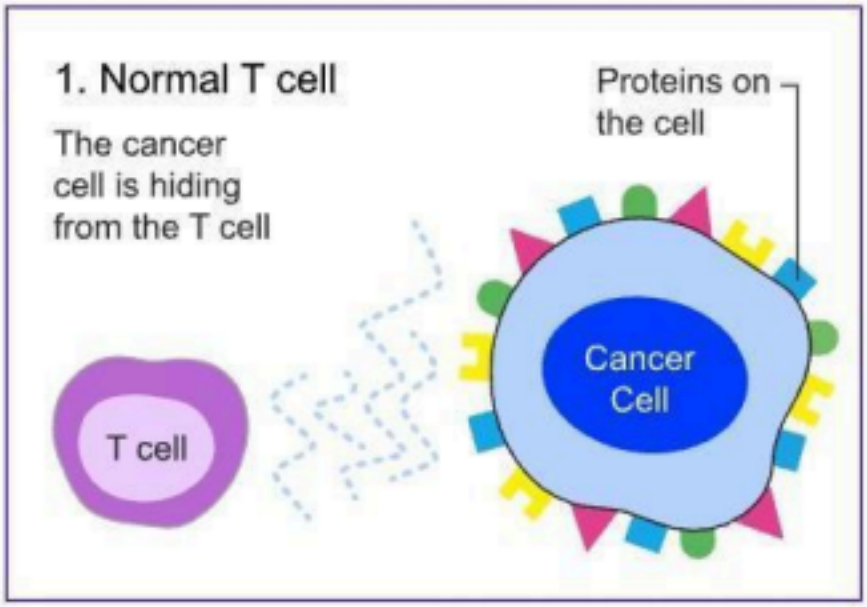
Yan, T., Zhu, L., & Chen, J. (2023). Current advances and challenges in CAR T-Cell therapy for solid tumors: Tumor-associated antigens and the tumor microenvironment. *Experimental Hematology & Oncology*, 12, 14. https://doi.org/10.1186/s40164-023-00373-7

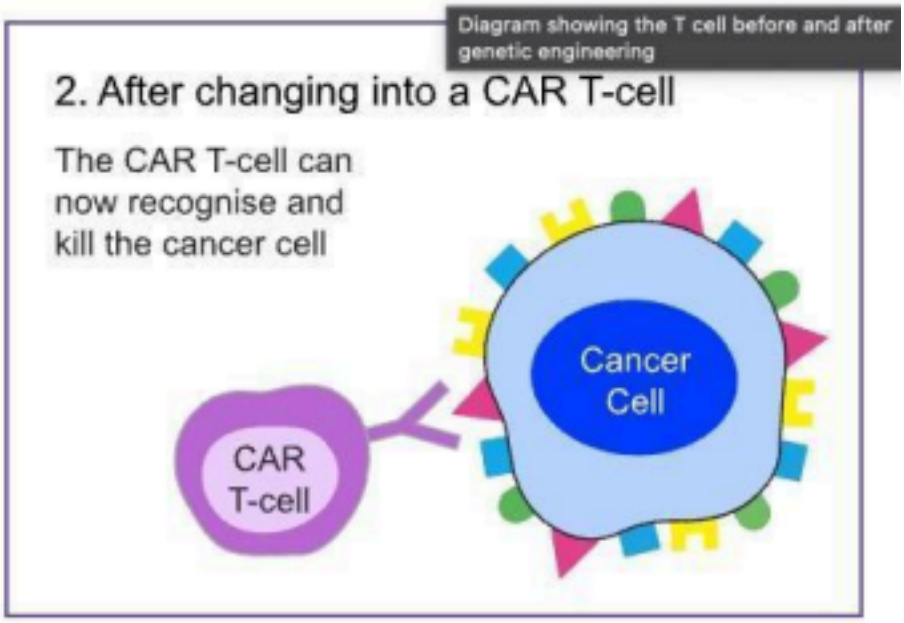
Zoine, J. T., Immadisetty, K., Ibanez-Vega, J., Moore, S. E., Nevitt, C., Thanekar, U., Tian, L., Karouni, A., Chockley, P. J., Arthur, B., Sheppard, H., Klco, J. M., Langfitt, D. M., Krenciute, G., Gottschalk, S., Babu, M. M., & Velasquez, M. P. (2024). Peptide-scfv antigen recognition domains effectively confer CAR T cell multiantigen specificity. *Cell Reports Medicine*, 5(2), 101422. https://doi.org/10.1016/j.xcrm.2024.101422

Appendix A



Appendix B





Cancer Research UK