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RESEARCH ARTICLE

CAR-T Cells: Novel Designs and Emerging Therapeutics for B-Cell Malignancies

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ABSTRACT: Chimeric antigen receptor (CAR)-T cell therapy is a novel approach to treating hematologic cancers such as leukemia. This review paper focuses on optimization strategies for CAR-T cell engineering to improve therapeutic durability and reduce relapse rates. Key methods discussed include advances in dual antigen targeting to mitigate antigen escape alongside signal enhancements in the costimulatory domain to enhance T cell persistence. Next-generation CAR-T cells will be discussed and further address challenges like tumour microenvironments. By incorporating these advancements in dual antigen targeting, combined with innovations in CAR cell body design and development processes, CAR-T cell therapy has the potential to significantly improve therapeutic efficacy, reduce complications, and increase accessibility for leukemia patients.

KEYWORDS: Cellular and Molecular Biology, Genetics, Chimeric Antigen Receptor (CAR), CAR-T Cell Therapy, B-Cell Malignancies, Leukemia, CD19, CD22, CD37.

Introduction

Cancer is a life-changing topic and an obstacle to many families worldwide. Cancer, with its complex nature in biology making it challenging to treat effectively, is one of the leading causes of mortality and morbidity globally: in 112 out of 183 countries, estimates from the WHO in 2019 rank cancer as the first or second leading cause of death.[1] Cancer cases are expected to be 28.4 million in 2040, a 47% rise from 2020, which has been a burden on developing countries due to demographic changes.[1] A seemingly death-bound disease has caused concern over an improved treatment or cure.[2] Modern cancer treatment approaches have had varying degrees of success but are frequently associated with a variety of side effects, like targeting other cells that are not cancer cells, harming the patient. [3] Radiotherapy, one of the most common cancer treatments, could result in radio-resistance;[4] hadron therapy, a new alternative involving protons and light nuclei, has no insight to its long term impacts;[5] chemotherapy, based on cytotoxic drugs, often results in a impaired quality of life and severe side effects;4 surgery, effective but invasive; and other treatments all have led to certain negative downsides.[6] Individualized therapy offers a promising solution by leveraging a patient's immune system to eliminate cancer cells with high specificity to reduce off-target effects and to provide more personalized and potentially less harmful treatment options.[7] Despite all this, recently, a viable and new approach to cancer has been revealed, chimeric antigen receptor (CAR)-T cell therapy.

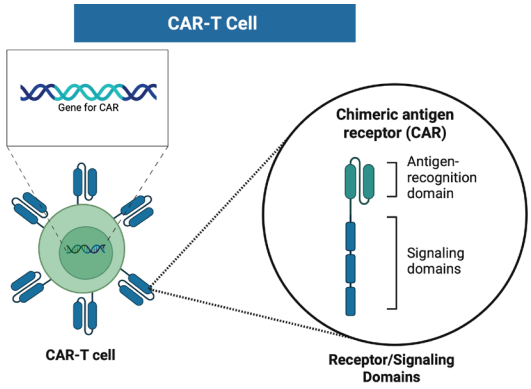

Figure 1: Diagram of a CAR-T cell. Illustrates how the gene for a chimeric antigen receptor (CAR) enables the expression of a synthetic receptor that combines antigen recognition and intracellular signalling domains. (Created with Biorender)

As a personalized treatment, CAR-T cells are engineered lymphocytes, immune cells, that are altered to specifically express certain receptors and target singular cancer cells that display a specific antigen.[3,8] This approach is much more advantageous than regular T cells that rely on a normal major histocompatibility complex (MHC), a group of genes that help the immune system recognize foreign substances, and expression that restrains the immune response.[8] The CAR protein on the external surface of engineered T cells helps recognize cancer antigens, which then activates the CAR-T cell to order the cancer cell to undergo apoptosis (Figure 1).[9] From all this, CAR-T cell therapy has become a very important factor in fighting B-cell malignancies (BCMs) like leukemia.[10] B-cell malignancies are a diverse group of hematologic cancers that have a spectrum that includes aggressive forms like dif-

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fuse large B-cell lymphoma to indolent variants like follicular lymphoma.[11] These malignancies are characterized by uncontrolled proliferation of malignant B-cells that typically retain surface expression of markers.[11] Malignant B-cells consistently express surface markers, which serve as ideal targets for engineered T-cells.[11,12] For example, acute lymphoblastic leukemia (ALL) expresses CD19, a pan-B-cell maker, making it an ideal target for CAR-T cells.[13] CAR-T cells, therefore, are engineered to target CD19 with high specificity as they bind to the CD19 antigen and trigger cytotoxic responses that eliminate both malignant and normal B cells.[13] However, CAR-T cell therapy faces many obstacles, like patient tolerance and specific antigen selection.[14] Tumour cells that lack specific antigens can impair antigen selectivity of CAR-T cells and can even develop resistance through the downregulation of antigen expression by increasing the activity of immune inhibitory factors from CAR-T cell cytotoxicity.[15,16] In this review, by summarizing the most recent literature on CAR T-cells, the review article will provide the latest research on CAR-T cell therapies in terms of their structure and mechanism, dual antigen targeting advances, optimization strategies for CAR-T cell design, and the limitations and future directions of CAR- T cell therapy research.

Discussion

CAR T Cell Structure and Mechanism:

Chimeric antigen receptor (CAR)-T cell therapy is an innovative immunotherapy and a highly personalized treatment that relies on artificial receptor engineering on T cells to target specific antigens on cancer cells.[17,18] The modular CAR protein is composed of two key components: an external domain for antigen recognition and an internal signalling region for T cell activation. The external region usually consists of a single-chain variable fragment (scFv) derived from antibodies that bind specific antigens on the cancer cell surface through high-affinity binding (Figure 2).[9,19] Unlike traditional T cell receptors (TCRs), this novel design removes the dependency on the MHC, overcoming a major limitation in the internal signalling domain of TCRs. [20,21]

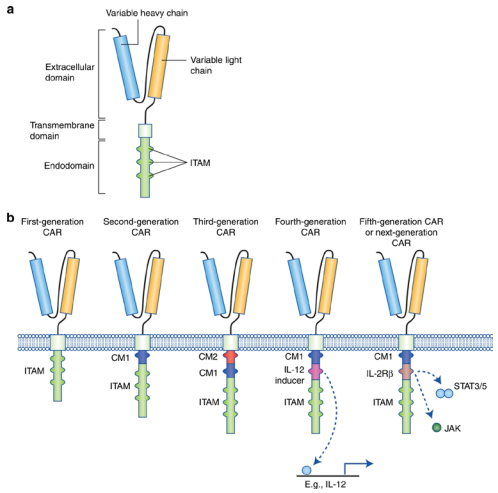

Figure 2: [9] Structure of CAR generations. A. The modular structure of a CAR protein consists of an extracellular domain that includes a single-chain variable fragment (scFv) derived from antibodies, which is responsible for antigen recognition. The transmembrane domain anchors the receptor to the cell membrane and ensures structural stability, and the endodomain contains the intracellular signalling motifs such as immunoreceptor tyrosine-based activation motifs (ITAMs), which mediate downstream T cell activation. B. Demonstrates the progressive development across five generations of CAR-T cells. (Reprints with Permission from Tokarew *et al.*)

Internally, CAR proteins rely on signalling domains for effective T cell activation. The primary activation signal originates from the CD3ξ chain in the intracellular domain, which contains immunoreceptor tyrosine–based activation motifs (ITAMs).[22,23] Additional "boost" signals come from costimulatory domains, like CD28, which help T cells multiply and strengthen their response.[24,25] When fully activated, CAR-T cells release cytotoxic granules that contain perforin and granzymes, which induce apoptosis, self-destruction, in target cells.[26]

Generations of CAR-T cells have had progressive improvements to the overall CAR design. CAR development began with the first-generation CARs. First-generation CARs were comparatively simple in design. It consisted of three main components: an extracellular antigen recognition domain, like a molecular "search radar" to find cancer cells; a transmembrane domain for structural integrity; and an intracellular domain for signalling that activates the T cell (Figure 2b).[9] Single-chain variable fragments (scFvs), which were built for the antigen recognition domain, are engineered antibody fragments composed of a variable heavy chain (VH) and a variable light chain (VL) connected by a flexible peptide linker (Figure 2a).[27] Each scFv is a specialized search tool made by stitching together the two chains from antibodies. The scFvs helped provide high specificity for tumour-associated antigens like CD19 in BCMs like leukemia, for example. This surface protein acts like a cellular "ID card" that is consistently expressed on over 90% of B-cell cancers while being nearly absent from other cell types, minimizing off-target effects.[28,29] Despite the targeted antigen recognition, first-generation CARs relied simply on the CD3ξ signalling domain in the intracellular region, housing the immunoreceptor tyrosine-based activation motifs (ITAMs).[9,30] The ITAMs are responsible for T cell activation upon antigen reception, but were limited due to their signalling capacity. With a lack of co-stimulatory signals to improve capacity, first-generation CARs resulted in poor T cell persistence, reduced cytokine secretion, and limited therapeutic efficacy for first-generation CARs.

Second-generation CARs incorporated co-stimulatory domains such as CD28 to enhance T cell survivability and anti-tumour activity (Figure 2b).[9,31] Alongside CD3ξco-stimulatory signalling domains address many of the limitations of first-generation CARs. CD3ξ chain is the primary signalling domain that contains the ITAM, initiating the costimulatory domain, a secondary signalling domain, obtained from native co-stimulatory molecules like CD28 and 4-1BB, that enhances T cell activation.[32] The extracellular and transmembrane regions remained largely untouched, with their scFvs ensuring targeted binding to tumour antigens like CD19. Most importantly, second-generation CARs became the backbone of FDA-approved CAR-T cell therapies (Table 1).[33]

Third-generation CARs represent a significant advancement in CAR technology through incorporating multiple

costimulatory domains to improve cytokine secretion and overall efficacy (Figure 2b).[9,19] These CARs usually combine two distinct co-stimulatory signals in tandem with CD3ξ. For example, combination domains such as CD28 and 4-1BB are used to provide synergistic signalling: CD28 enhances immediate T cell activation and cytokine release, and 4-1BB promotes T cell survival and memory formation.[34,35] This multi-signal approach has shown improved efficacy, particularly in solid tumours where the TME is highly immunosuppressive. Third-generation CARs, however, are still under investigation.

Fourth-generation CARs, "armoured CARs", are engineered to produce immune-stimulatory cytokines like interleukin-12 (IL-12) to counter immunosuppressive tumour microenvironments (Figure 2b).[9,36] IL-12 is a potent immunomodulatory cytokine that enhances T cell and natural killer cell activity, promotes the recruitment and activation of other immune cells, and reprograms the TME to be more immunogenic to overcome tumour-induced immunosuppression.[37–39] In addition to cytokine secretion, armoured CARs may also express checkpoint inhibitors like PD-1 blockers to prevent T cell exhaustion.[40,41] Enzymes that degrade immunosuppressive factors in the TME, like adenosine or TGF β, are also expressed.[42] These modifications from third-generation CARs make fourth-generation CARs more promising for treating solid tumours, specifically with the degradation of the TME, a major barrier to effective immunotherapy.

Lastly, fifth-generation CARs integrated cytokine receptor signalling to enhance T cell function, representing the cutting edge of CAR-T cell technology (Figure 2b).[9,43] These CARs are designed to mimic the signalling of cytokine receptors like the IL-2 receptor to further enhance T cell activation and persistence. The key innovation in fifth-generation CARs is the inclusion of a cytokine receptor signalling domain alongside the traditional CD3ξ and multiple co-stimulatory domains. This allows the CAR-T cells to respond to endogenous cytokines in the TME, providing an additional layer of activation.

Table 1: FDA Approved CAR-T Cell Therapies.

Name	Brand Name	Target Antigen	Targeted Disease	Reference
Idecabtagene vicleucel	Abecma	anti-BCMA*	Relapsed or Refractory Multiple Myeloma	Munshi NC, Anderson LD Jr, Shah N, *et al. N Engl J Med*. 2021;384(8):705-716. [44]
Lisocabtagene maraleucel	Breyanzi	anti-CD19	Relapsed or Refractory Large B-cell Lymphoma	Sehgal A, Hoda D, Riedell PA, *et al. Lancet Oncol*. 2022;23(8):1066-1077. [45]
Ciltacabtagene autoleucel	Carvykti	anti-BCMA*	Relapsed or Refractory Multiple Myeloma	Berdeja JG, Madduri D, Usmani SZ, *et al. Lancet*. 2021;398(10297):314-324. [46]
Tisagenlecleucel	Kymriah	anti-CD19	B-Cell Lymphoblastic Leukemia	Maude SL, Laetsch TW, Buechner J, *et al. N Engl J Med*. 2018;378(5):439-448. [47]
Brexucabtagene autoleucel	Tecartus	anti-CD19	Mantle Cell Lymphoma	Deshpande A, Wang Y, Munoz J, Jain P. *Drugs Today (Barc)*. 2022;58(6):283-298. [48]
Axicabtagene ciloleucel	Yescarta	anti-CD19	Refractory Large B-Cell Lymphoma	Neelapu SS, Locke FL, Bartlett NL, *et al. N Engl J Med*. 2017;377(26):2531-2544. [49]

*BCMA: B-cell Maturation Antigen

The table highlights six FDA-approved CAR-T cell therapies, each targeting either CD19 or BCMA antigens in various B-cell malignancies. The diversity of targeted diseases underscores the clinical success and expanding role of CAR-T therapy in treating relapsed or refractory hematologic cancers.

CD19-specific CAR T cell therapy, widely used for treating BCMs like leukemia and lymphoma, specifically shows the success of this approach.[12] CD19 is a pan-B-cell marker that ensures selective targeting of malignant cells while sparing most of the healthy tissues.[50] This CD-19 specific approach has demonstrated significant efficacy. In a meta-analysis encompassing 448 patients, 82% had an incidence rate of complete remission (CR).[51] Furthermore, clinical studies report CR rates exceeding 80% in many cases with patients with ALL.[52]

Not only have CD-19-specific strategies seen promising results, but an antibody-drug conjugate targeting CD22, inotuzumab ozogamicin, has shown encouraging results. Antibody-drug conjugates (ADCs), a similar yet different approach to hematologic malignancies, leverage unique molecular characteristics of each patient's tumours through targeting specific antigens like CD19 or CD22.53 ADCs are monoclonal antibodies conjugated to cytotoxic drugs that deliver the drug directly to the tumour and kill the cancer cell internally.[54] Through the selective expression of target antigens on cancer cells, ADCs represent a highly individualized treatment strategy. Inotuzumab ozogamicin in a phase 3 trial demonstrated improved response rates and overall survival compared with conventional methods like chemotherapy in patients with refractory or relapsed B-ALL (Table 2).[55] Blinatumomab is a bispecific T-cell engager (BiTE) antibody that targets the CD3 on T cells and CD19 on B cells. It has significantly improved efficacy in treating relapsed B-cell acute lymphoblastic leukemia (B-ALL) by its mechanism of redirecting T cells to eliminate malignant B cells, leading to improved remission rates.[56] These findings emphasize the efficacy of CD19 and CD22-specific CAR-T cell therapy in treating BCMs, providing substantial benefits as an individualized therapy to patients.

Individualization and Non-Invasive Nature:

Paradigm shifts toward highly individualized cancer treatments have revolutionized health care. CAR-T cell therapy exemplifies this approach. This therapy begins with the collection of the patient's T cells through apheresis, a non-invasive process that separates blood components, minimizing risk to the patient by avoiding the need for invasive surgical intervention.[57] Apheresis collects blood components and returns the rest into the patient, which is essential in minimizing impact (Figure 3). These collected T cells then get genetically engineered to express CARs, designed to recognize tumour antigens on specific tumour cells.[58] Lentiviruses are essential in the addition of CAR genes to the T cells with high efficiency. These viral vectors carry the CAR construct, which includes the intracellular signalling regions and the antigen-recognition domain that are integrated into the host genome ex vivo, ensuring stable expression.[59] Lentiviral vectors are advantageous due to their low immunogenicity and ability to transduce both dividing and nondividing cells.[60,61] The personalized engineering allows a highly specific targeting of malignant cells through uniquely tailoring each CAR-T cell therapy to the patient's cancer profile.[50] With such precision, CAR-T cell therapy reduces the risk of off-target effects, a common issue with conventional treatments like radiation therapy, which often lead to toxicities and significant side effects.

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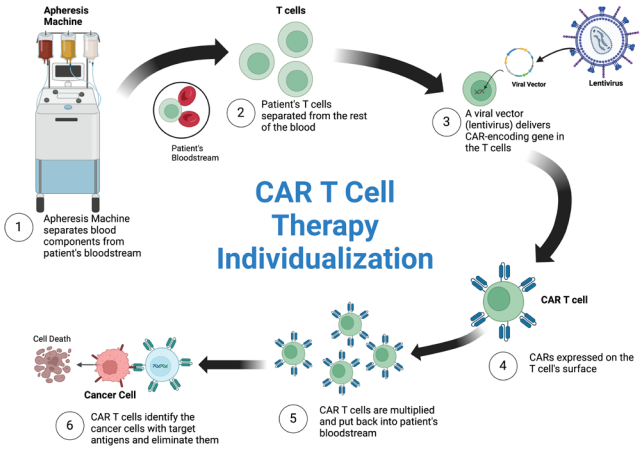

Figure 3: Cycle of the Individualization of CAR-T Cell Therapies. 1. & 2. Isolation of a patient's T cells via apheresis. 3. Genetic modification using a viral vector to express chimeric antigen receptors 4. Receptors are expressed on the T cell's surface 5. Engineered T cells are expanded, multiplied, and reinfused into the patient. 6. CAR T cells eliminate cancer cells with high specificity. This personalized approach enables the targeted recognition and elimination of cancer cells. (Created with Biorender)

The non-invasive nature of CAR-T cell therapy involves only intravenous infusions for cell reinfusion following T cell modification *ex vivo*. Minimizing physical trauma to the patient most often results in shorter recovery times and improved quality of life.[62] Furthermore, CAR-T therapy's ability to minimize residual disease while achieving deep remissions has been highlighted in numerous clinical trials, particularly in hematological malignancies like B-ALL.[63] The individualization of CAR-T cell therapy allows it to address immune evasion and tumour heterogeneity more effectively.[64] CD19-specific CAR-T therapies, for example, target a pan-B-cell marker that is widely expressed in multiple BCMs, which ensures efficacy and reduces the likelihood of tumour escape.[65] Additionally, patients who may not be candidates for aggressive treatments due to age and other complications significantly benefited from CAR-T's non-invasive nature.[66]

Table 2: Clinical Trials on Certain Antibody-Drug Conjugates.

Antibody-Drug Conjugate (ADC)	Target Antigen	Indication	Results	Reference
Blinatumomab	CD19	Relapsed/Refractory B-Cell ALL	34% CR* with full hematological recovery, 44% full, partial, or incomplete hematologic recovery	Kantarjian H, Stein A, Gökbuget N, *et al. N Engl J Med.* 2017;376(9):836-847.[67]
Inotuzumab Ozogamicin	CD22	Relapsed/Refractory B-cell Acute Lymphoblastic Leukemia (B-ALL)	80.7% CR Duration of remission of 4.6 months	Kantarjian HM, DeAngelo DJ, Stelljes M, *et al. N Engl J Med.* 2016;375(8):740-753.[68]
Polatuzumba Vedotin	CD79b	Relapsed/Refractory Diffuse Large B-Cell Lymphoma	77% CR	Tilly H, Morschhauser F, Sehn LH, *et al. N Engl J Med.* 2022;386(4):351-363. [69]
Vadastuximab Talirine	CD33	Acute Myeloid Leukemia (AML)	70% CR and CR with incomplete blood count recovery	Fathi AT, Erba HP, Lancet JE, *et al. Blood.* 2018;132(11):1125-1133. [70]
Loncastuximab Tesirine	CD19	Relapsed/Refractory B-Cell Lymphomas	48.3% ORR** 24.1% CR	Caimi PF, Ai W, Alderuccio JP, *et al. Lancet Oncol.* 2021;22(6):790-800. [71]
Brentuximab Vedotin	CD30	B-cell Lymphomas (Hodgkin Lymphoma)	85% ORR*** 67% CR	Advani RH, Moskowitz AJ, Bartlett NL, *et al. Blood.* 2021;138(6):427-438. [72]

*CR: Complete Response
**ORR: Overall Response Rate
***ORR: Objective Response Rate
The table summarizes the efficacy of various antibody-drug conjugates (ADCs) targeting surface antigens in treating relapsed or refractory hematologic malignancies. The reported high complete response and overall response rates across multiple trials highlight the therapeutic potential of ADCs.

Next-generation CAR-T cell therapies are becoming even more refined as research continues. Through features such as dual antigen targeting, CAR-T cell therapy can enhance patient outcomes and can be featured as the cornerstone of personalized and non-invasive cancer care, potentially inspiring more effective and patient-centred approaches to oncology.

Next-Generation CARs & Optimization Strategies for CAR-T Cell Design

Armoured CARs:

Armoured CAR-T cells, a fourth-generation CAR design, symbolize novel approaches to enhancing the efficacy of CAR-T cell therapy, especially in immunosuppressive tumours.[9] Armoured CARs are engineered to secrete cytokines and other therapeutic molecules like antibodies or enzymes that degrade physical barriers within the tumour microenvironment (TME).[73] The TME is one of the main barriers to CAR-T cell efficacy as it includes extracellular matrix components that hinder CAR-T activation. Through secreting extracellular matrix-degrading enzymes like metalloproteinases, armoured CARs can enhance the persistence and efficient penetration of CAR-T cells in tumours.[74] A study by Suarez *et al.* demonstrates that armoured second-generation CAR-T cells engineered to secrete human anti-programmed death ligand 1 (PD-L1) have effectively blocked PD-1/PD-L1 interaction within the TME of clear cell renal cell carcinoma (ccRCC).[75] Furthermore, a study by Harrasser *et al.* explored the use of armoured CAR-T cells using anti-PD-L1 scFvs for localized delivery within the TME, enhancing the anti-tumour efficacy while minimizing systemic toxicity by blockading the PD-1/PD-L1 pathway.[76] Collectively, these studies indicate the potential of optimizing anti-PD-L1 antibody secretion into next-generation armoured CAR-T cells to enhance their anti-tumour activity by overcoming the immune checkpoint-mediated suppression in the TME.[73,75,76]

Universal CARs:

Driven by the challenge of obtaining autologous T cells from patients for CAR-T cell therapy, researchers have begun to develop universal CAR-T cells. Universal CAR-T cells are allogenic T cells, derived from healthy donors, engineered to target tumour-specific antigens.[77] The key advantage of universal CAR-T cells is the potential of their "universal" use, making CAR-T cell therapy more accessible and scalable.[78] Alternative processes like nanoparticle-mediated in situ manufacturing, for example, can lower the manufacturing procedure, ultimately shortening administration time.[79] This eliminates the logistical challenges and delays associated with autologous CAR-T therapies, like the time required for T-cell engineering. The crucial challenge with allogeneic CAR-T cells is the risk of graft-versus-host disease (GVHD), where the donor T cells attack the patient's tissues. "Off-the-shelf" CAR-T cells, enabled through genetic modification, are engineered to avoid GVHD and prevent immune rejection.[80] This is achieved by removing the TCR in donor T cells, preventing the recognition of patient-specific antigens.[80] Recent trials from Lin *et al*. have shown promising results for universal CAR-T cells, demonstrating that donor-derived CAR-T cells were able to achieve comparable remission rates to autologous CAR-T cells in patients with leukemia.[78]

Advances in Dual Antigen Targeting:

Dual antigen targeting is another key strategy that addresses issues of immune escape and relapse, further benefiting CAR-T therapies in BCMs. Immune escape occurs when cancer cells downregulate or lose their target antigen expression, making CAR T cells effectively useless.[81] This phenomenon is a major player in relapse with patients undergoing CD19 CAR-T cell therapy, relapse due to antigen expression loss.[82,83] BCMs like leukemia and lymphoma often experience relapses due to the loss of CD19 expression, a key target in CAR-T cell therapy.[84] Dual antigen targeting approaches aim to overcome this limitation by developing CAR-T cells that simultaneously target two antigens, such as CD19 and CD37 (Figure 4). This strategy reduces the likelihood of immune escape by ensuring that even if one antigen is lost, the cancer cell would still be susceptible to the CAR-T cell attack. In pre-clinical trials by Scarfò *et al*., anti-CD37 CARs were combined with anti-CD19 CARs to create dual-specific CAR T cells to recognize them alone or in combination, overcoming potential antigen escape.[85] In addition, dual antigen targeting also addresses concerns about heterogeneity within tumour populations. Many BCMs exhibit heterogeneous antigen expression, where many subpopulations of cells lack the primary target antigen.[86] Through dual targeting, dual CAR-T cells ensure coverage across diverse tumour populations, reducing chances of survival or antigen-negative clones.[87] Overall, the durability of the therapeutic response is enhanced even in patients with heterogeneous tumours.

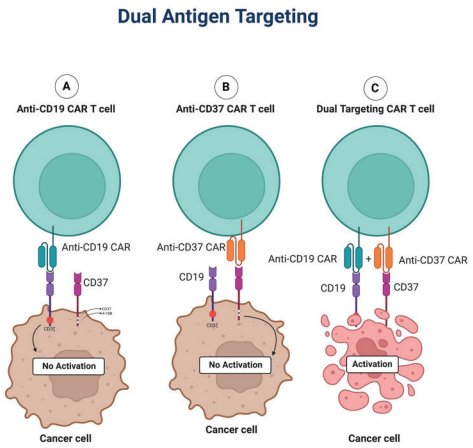

Figure 4: Demonstration of Dual Antigen Targeting CARs. A. Shows the binding of the CD19 antigen to the anti-CD19 CAR. It indicates the activation of only the CD3ξ. B. Shows the binding of the CD37 antigen to the anti-CD37 CAR. It indicates the activation of only the CD37 antigen. C. Shows the binding of both the CD19 and CD37 antigens, resulting in the activation of apoptosis factors in the cancer cell. (Created with Biorender).

Refining dual antigen targeting to improve safety and reduce toxicities is underway. Off-target effects and excessive immune activation can cause adverse effects like cytokine release syndrome (CRS) or neurotoxicity.[88] Researchers are developing strategies like split-signal CARs, requiring simultaneous engagement of both target antigens to activate the CAR-T cells, lowering the risk of off-target activations.[89]

Dual antigen targeting is a promising advancement in CAR-T cell therapy, especially for BCMs prone to antigen loss or heterogeneity. This approach offers a more robust defence against immune escape by targeting multiple antigens, addressing multiple limitations of the current single-antigen CAR-T design. Continued research and trials will further optimize this strategy, potentially making it a significant part of next-generation CAR-T cell therapies.

Controlling CAR-T Cell Activity:

Tightly regulating CAR-T cell activity is crucial to ensuring the safety of this promising approach. Safety switches, engineered mechanisms that enable the deactivation of CAR-T cells in the event of severe adverse effects, are among the many advancements in this field.[90] An example is the inducible suicide gene system, commonly utilizing iCaspase-9, which involves the expression of a caspase protein that gets activated when exposed to a small molecule, which induces apoptosis in the CAR-T cells like AP1903.[91,92] iCaspase-9 has shown rapid means to mitigate life-threatening toxicities like CRS. Clinicians can control CAR-T survivability by activating suicide gene responses to small molecules, which maintains patient safety while preserving the therapeutic benefits of CAR technology.[93]

Regulatable CAR systems allow for the modulation of CAR-T cell activity, which is advantageous in managing toxicity and ensuring that CAR-T therapy is only active when needed.[94] ON-switch CAR, an example of regulatable CAR systems, involves the incorporation of a receptor that can only be activated through the addition of a small molecule.[95] ON-switch CAR designs optimize this strategy through offering

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an external trigger function, which gives CAR-T flexibility in control. This ability to "turn on" CAR-T cells minimizes off-target effects and reduces the chance of CRS, as the immune cells are only activated by a signal.[96] OFF-switch CARs, relying on molecules to bind to the CAR receptor to deactivate the cells, is a complementary strategy to regulate T cells.[95] This ability to "turn off" CAR-T cells prevents excessive activation and from being overstimulated, which can lead to further toxicity.

Split CAR technology divides the CAR cell into separate components, separating the intracellular signalling domain from the antigen-receptor binding domain.[97] This design requires two molecules to simultaneously bring the components together to activate the CAR-T cells. These designs have improved the treatment of BCMs through targeting CD19.[98] This adds another layer of control to clinicians to manage the availability of the separate components, ensuring the activation only under desired conditions.

Challenges, Limitations, and Future Directions:

Although CAR-T cell therapy has shown success in many clinical trials, there are challenges and limitations that hinder its advancements. So far in the discussion, key limitations are antigen escape, toxicities, and limited efficacies in solid tumours. However, two additional prominent challenges are high cost and safety risks. In patients with severe CRS, it has been estimated to cost up to $500,000 for CAR-T cell therapy.[99] These high prices are constituted of the complex manufacturing process, hospital care, and long-term monitoring, with only specific locations having these therapies.[100] Furthermore, CAR-T cell therapy is linked with severe, life-threatening side effects like cytokine release syndrome.[101] Cytokine release syndrome occurs when massively activated CAR-T cells trigger hyperinflammatory cascades through the excessive release of IL-6, for example.[102] When CAR-T cells become highly activated, they flood the body with inflammatory proteins like IL-6. This "cytokine storm" can damage multiple organs by causing inflammation, seeping blood vessels, and poor oxygen delivery.[103] The heart and blood vessels are often affected, leading to low blood pressure and irregular heartbeats.[103] CRS also frequently impacts the brain, causing confusion, seizures, or even coma in what's called ICANS (immune effector cell-associated neurotoxicity syndrome).[104,105] Treatments include immune-suppressing drugs like tocilizumab and steroids, but severe cases still carry significant risks. Off-target attacks can also lead to severe damage if the target antigen is present in healthy tissues.[106] However, all in all, CAR-T cells' potential is immense and will be vital in future applications. These serious safety concerns, combined with the therapy's high costs, remain major hurdles for CAR-T cell treatment.

Conclusion

In summary, CAR-T cell therapy represents a significant advancement in the treatment of BCMs like leukemia through a highly personalized approach by harnessing the patient's immune system to eliminate cancer cells. Optimization strategies of CAR-T cell design have shown promising success in therapeutic efficacy by reducing relapse and immune escape rates. Advances in the structural engineering of CAR-T cells, like the costimulatory domain incorporation as well as the next-generation CAR design, have improved their ability to overcome the immunosuppressive TME. Universal CAR-T cells advancements have promised better accessibility and minimize adverse effects for a more patient-centred approach. Furthermore, dual antigen targeting strategies have significantly mitigated challenges associated with antigen escape by optimizing the ability to simultaneously recognize multiple tumour-associated antigens. By minimizing relapse, it ensures a more sustained response in leukemia patients. Other safety measures like safety switches and inducible CAR systems have given clinicians more control over CAR-T activity, addressing possible concerns like CRS. Several challenges, like off-target effects and high manufacturing costs, have been logistical hurdles that limit accessibility, which necessitates innovative steps like universal CARs. More research is needed to overcome these hurdles. Future advancements in synthetic biology, like CRISPR and combinatorial therapeutic approaches, may further enhance the benefits of CAR-T cell research. In conclusion, CAR-T cell therapy has demonstrated exponential potential as a transformative immunotherapy for leukemia, with ongoing innovations to improve efficiency. The future of CAR-T cell therapy is bright, paving the way for broader applications in oncology and beyond.

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References

1. Sung, H.; Ferlay, J.; Siegel, R. L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA. Cancer J. Clin*. **2021**, *71* (3), 209–249. https://doi.org/10.3322/caac.21660.
2. Slob, J.; van Houwelingen, T.; Kort, H. S. M. Health Care Work ers' Expectations of the Mercury Advance SMARTcare Solution to Prevent Pressure Injuries: Individual and Focus Group Interview Study. *JMIR Nurs.* **2024**, *7*, e47992. https://doi.org/10.2196/47992.
3. Sun, D.; Shi, X.; Li, S.; Wang, X.; Yang, X.; Wan, M. CAR-T Cell Therapy: A Breakthrough in Traditional Cancer Treatment Strategies (Review). *Mol. Med. Rep.* **2024**, *29* (3), 47. https://doi.org/10.3892/mmr.2024.13171.
4. Chen, H. H. W.; Kuo, M. T. Improving Radiotherapy in Cancer Treatment: Promises and Challenges. *Oncotarget* **2017**, *8* (37), 62742–62758. https://doi.org/10.18632/oncotarget.18409.
5. Paganetti, H.; Beltran, C.; Both, S.; Dong, L.; Flanz, J.; Furutani, K.; Grassberger, C.; Grosshans, D. R.; Knopf, A.-C.; Langendijk, J. A.; Nystrom, H.; Parodi, K.; Raaymakers, B. W.; Richter, C.; Sawakuchi, G. O.; Schippers, M.; Shaitelman, S. F.; Teo, B. K. K.; Unkelbach, J.; Wohlfahrt, P.; Lomax, T. Roadmap: Proton Therapy Physics and Biology. Phys. *Med. Biol.* **2021**, *66* (5). https://doi.org/10.1088/1361-6560/abcd16.
6. Adjiri, A. Identifying and Targeting the Cause of Cancer Is Need ed to Cure Cancer. *Oncol. Ther.* **2016**, *4* (1), 17–33. https://doi.org/10.1007/s40487-015-0015-6.
7. Sterner, R. C.; Sterner, R. M. CAR-T Cell Therapy: Current Limitations and Potential Strategies. *Blood Cancer J.* **2021**, *11* (4), 69. https://doi.org/10.1038/s41408-021-00459-7.
8. De Marco, R. C.; Monzo, H. J.; Ojala, P. M. CAR T Cell Therapy:

A Versatile Living Drug. *Int. J. Mol. Sci.* **2023**, *24* (7), 6300. https://doi.org/10.3390/ijms24076300.
9. Tokarew, N.; Ogonek, J.; Endres, S.; Von Bergwelt-Baildon, M.; Kobold, S. Teaching an Old Dog New Tricks: Next-Generation CAR T Cells. *Br. J. Cancer* **2019,** *120* (1), 26–37. https://doi.org/10.1038/s41416-018-0325-1.
10. Ayala Ceja, M.; Khericha, M.; Harris, C. M.; Puig-Saus, C.; Chen, Y. Y. CAR-T Cell Manufacturing: Major Process Parameters and next-Generation Strategies. *J. Exp. Med.* **2024**, *221* (2), e20230903. https://doi.org/10.1084/jem.20230903.
11. Cuenca, M.; Peperzak, V. Advances and Perspectives in the Treatment of B-Cell Malignancies. *Cancers* **2021**, *13* (9), 2266. https://doi.org/10.3390/cancers13092266.
12. Park, J. H.; Rivière, I.; Gonen, M.; Wang, X.; Sénéchal, B.; Curran, K. J.; Sauter, C.; Wang, Y.; Santomasso, B.; Mead, E.; Roshal, M.; Maslak, P.; Davila, M.; Brentjens, R. J.; Sadelain, M. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **2018**, *378* (5), 449–459. https://doi.org/10.1056/NEJMoa1709919.
13. Maude, S. L.; Laetsch, T. W.; Buechner, J.; Rives, S.; Boyer, M.; Bittencourt, H.; Bader, P.; Verneris, M. R.; Stefanski, H. E.; Myers, G. D.; Qayed, M.; De Moerloose, B.; Hiramatsu, H.; Schlis, K.; Davis, K. L.; Martin, P. L.; Nemecek, E. R.; Yanik, G. A.; Peters, C.; Baruchel, A.; Boissel, N.; Mechinaud, F.; Balduzzi, A.; Krueger, J.; June, C. H.; Levine, B. L.; Wood, P.; Taran, T.; Leung, M.; Mueller, K. T.; Zhang, Y.; Sen, K.; Lebwohl, D.; Pulsipher, M. A.; Grupp, S. A. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N. Engl. J. Med.* **2018**, *378* (5), 439–448. https://doi.org/10.1056/NEJMoa1709866.
14. Ahmad, A. CAR-T Cell Therapy. *Int. J. Mol. Sci.* **2020**, *21* (12), 4303. https://doi.org/10.3390/ijms21124303.
15. Majzner, R. G.; Mackall, C. L. Tumor Antigen Escape from CAR T-Cell Therapy. *Cancer Discov.* **2018**, *8* (10), 1219–1226. https://doi.org/10.1158/2159-8290.CD-18-0442.
16. Abreu, T. R.; Fonseca, N. A.; Gonçalves, N.; Moreira, J. N. Current Challenges and Emerging Opportunities of CAR-T Cell Therapies. *J. Control. Release Off. J. Control. Release Soc.* **2020**, *319*, 246–261. https://doi.org/10.1016/j.jconrel.2019.12.047.
17. Porter, D. L.; Levine, B. L.; Kalos, M.; Bagg, A.; June, C. H. Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia. *N. Engl. J. Med.* **2011**, *365* (8), 725–733. https://doi.org/10.1056/NEJMoa1103849.
18. June, C. H.; O'Connor, R. S.; Kawalekar, O. U.; Ghassemi, S.; Milone, M. C. CAR T Cell Immunotherapy for Human Cancer. *Science* **2018,** *359* (6382), 1361–1365. https://doi.org/10.1126/science.aar6711.
19. Sadelain, M.; Brentjens, R.; Rivière, I. The Basic Principles of Chimeric Antigen Receptor Design. *Cancer Discov.* **2013**, *3* (4), 388–398. https://doi.org/10.1158/2159-8290.CD-12-0548.
20. Jackson, H. J.; Rafiq, S.; Brentjens, R. J. Driving CAR T-Cells Forward. *Nat. Rev. Clin. Oncol.* **2016**, *13* (6), 370–383. https://doi.org/10.1038/nrclinonc.2016.36.
21. Maude, S. L.; Frey, N.; Shaw, P. A.; Aplenc, R.; Barrett, D. M.; Bunin, N. J.; Chew, A.; Gonzalez, V. E.; Zheng, Z.; Lacey, S. F.; Mahnke, Y. D.; Melenhorst, J. J.; Rheingold, S. R.; Shen, A.; Teachey, D. T.; Levine, B. L.; June, C. H.; Porter, D. L.; Grupp, S. A. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. *N. Engl. J. Med.* **2014**, *371* (16), 1507–1517. https://doi.org/10.1056/NEJMoa1407222.
22. Kalos, M.; Levine, B. L.; Porter, D. L.; Katz, S.; Grupp, S. A.; Bagg, A.; June, C. H. T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia. Sci. *Transl. Med.* **2011**, *3* (95), 95ra73. https://doi.org/10.1126/scitranslmed.3002842.
23. Zhang, X.; Zhu, L.; Zhang, H.; Chen, S.; Xiao, Y. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. *Front. Immunol.* **2022**, *13*, 927153. https://doi.org/10.3389/fimmu.2022.927153.
24. Kochenderfer, J. N.; Dudley, M. E.; Kassim, S. H.; Somerville, R. P. T.; Carpenter, R. O.; Stetler-Stevenson, M.; Yang, J. C.; Phan, G. Q.; Hughes, M. S.; Sherry, R. M.; Raffeld, M.; Feldman, S.; Lu, L.; Li, Y. F.; Ngo, L. T.; Goy, A.; Feldman, T.; Spaner, D. E.; Wang, M. L.; Chen, C. C.; Kranick, S. M.; Nath, A.; Nathan, D.-A. N.; Morton, K. E.; Toomey, M. A.; Rosenberg, S. A. Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated with Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor. J. Clin. Oncol. Off. *J. Am. Soc. Clin. Oncol.* **2015**, *33* (6), 540–549. https://doi.org/10.1200/JCO.2014.56.2025.
25. Abramson, J. S.; McGree, B.; Noyes, S.; Plummer, S.; Wong, C.; Chen, Y.-B.; Palmer, E.; Albertson, T.; Ferry, J. A.; Arrillaga-Romany, I. C. Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma. *N. Engl. J. Med.* **2017**, *377* (8), 783–784. https://doi.org/10.1056/NEJMc1704610.
26. Montalvo, M. J.; Bandey, I. N.; Rezvan, A.; Wu, K.-L.; Saeedi, A.; Kulkarni, R.; Li, Y.; An, X.; Sefat, K. M. S. R.; Varadarajan, N. Decoding the Mechanisms of Chimeric Antigen Receptor (CAR) T Cell-Mediated Killing of Tumors: Insights from Granzyme and Fas Inhibition. *Cell Death Dis.* **2024**, *15* (2), 109. https://doi.org/10.1038/s41419-024-06461-8.
27. Huehls, A. M.; Coupet, T. A.; Sentman, C. L. Bispecific T-Cell Engagers for Cancer Immunotherapy. *Immunol. Cell Biol.* **2015**, *93* (3), 290–296. https://doi.org/10.1038/icb.2014.93.
28. Rousselot, P.; Coudé, M. M.; Gokbuget, N.; Gambacorti Passerini, C.; Hayette, S.; Cayuela, J.-M.; Huguet, F.; Leguay, T.; Chevallier, P.; Salanoubat, C.; Bonmati, C.; Alexis, M.; Hunault, M.; Glaisner, S.; Agape, P.; Berthou, C.; Jourdan, E.; Fernandes, J.; Sutton, L.; Banos, A.; Reman, O.; Lioure, B.; Thomas, X.; Ifrah, N.; Lafage-Pochitaloff, M.; Bornand, A.; Morisset, L.; Robin, V.; Pfeifer, H.; Delannoy, A.; Ribera, J.; Bassan, R.; Delord, M.; Hoelzer, D.; Dombret, H.; Ottmann, O. G.; European Working Group on Adult ALL (EWALL) group. Dasatinib and Low-Intensity Chemotherapy in Elderly Patients with Philadelphia Chromosome-Positive ALL. *Blood* **2016**, *128* (6), 774–782. https://doi.org/10.1182/blood-2016-02-700153.
29. Schuster, S. J.; Bishop, M. R.; Tam, C. S.; Waller, E. K.; Borchmann, P.; McGuirk, J. P.; Jäger, U.; Jaglowski, S.; Andreadis, C.; Westin, J. R.; Fleury, I.; Bachanova, V.; Foley, S. R.; Ho, P. J.; Mielke, S.; Magenau, J. M.; Holte, H.; Pantano, S.; Pacaud, L. B.; Awasthi, R.; Chu, J.; Anak, Ö.; Salles, G.; Maziarz, R. T.; JULIET Investigators. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N. Engl. J. Med.* **2019**, *380* (1), 45–56. https://doi.org/10.1056/NEJMoa1804980.
30. Smith-Garvin, J. E.; Koretzky, G. A.; Jordan, M. S. T Cell Activation. *Annu. Rev. Immunol.* **2009**, *27*, 591–619. https://doi.org/10.1146/annurev.immunol.021908.132706.
31. Schuster, S. J.; Svoboda, J.; Chong, E. A.; Nasta, S. D.; Mato, A. R.; Anak, Ö.; Brogdon, J. L.; Pruteanu-Malinici, I.; Bhoj, V.; Landsburg, D.; Wasik, M.; Levine, B. L.; Lacey, S. F.; Melenhorst, J. J.; Porter, D. L.; June, C. H. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N. Engl. J. Med. 2017, 377 (26), 2545–2554. https://doi.org/10.1056/NEJMoa1708566.
32. Jayaraman, J.; Mellody, M. P.; Hou, A. J.; Desai, R. P.; Fung, A. W.; Pham, A. H. T.; Chen, Y. Y.; Zhao, W. CAR-T Design: Elements and Their Synergistic Function. *EBioMedicine* **2020**, *58*, 102931. https://doi.org/10.1016/j.ebiom.2020.102931.
33. Chen, Y.-J.; Abila, B.; Mostafa Kamel, Y. CAR-T: What Is Next?

DOI: 10.36838/v7i10.1

Cancers **2023**, *15* (3), 663. https://doi.org/10.3390/cancers15030663.

34. Zhao, Z.; Condomines, M.; van der Stegen, S. J. C.; Perna, F.; Kloss, C. C.; Gunset, G.; Plotkin, J.; Sadelain, M. Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells. *Cancer Cell* **2015**, *28* (4), 415–428. https://doi.org/10.1016/j.ccell.2015.09.004.
35. Roselli, E.; Boucher, J. C.; Li, G.; Kotani, H.; Spitler, K.; Reid, K.; Cervantes, E. V.; Bulliard, Y.; Tu, N.; Lee, S. B.; Yu, B.; Locke, F. L.; Davila, M. L. 4-1BB and Optimized CD28 Co-Stimulation Enhances Function of Human Mono-Specific and Bi-Specific Third-Generation CAR T Cells. J. Immunother. *Cancer* **2021**, *9* (10), e003354. https://doi.org/10.1136/jitc-2021-003354.
36. Koneru, M.; Purdon, T. J.; Spriggs, D.; Koneru, S.; Brentjens, R. J. IL-12 Secreting Tumor-Targeted Chimeric Antigen Receptor T Cells Eradicate Ovarian Tumors in Vivo. *Oncoimmunology* **2015**, *4* (3), e994446. https://doi.org/10.4161/2162402X.2014.994446.
37. Pegram, H. J.; Lee, J. C.; Hayman, E. G.; Imperato, G. H.; Ted der, T. F.; Sadelain, M.; Brentjens, R. J. Tumor-Targeted T Cells Modified to Secrete IL-12 Eradicate Systemic Tumors without Need for Prior Conditioning. *Blood* **2012**, *119* (18), 4133–4141. https://doi.org/10.1182/blood-2011-12-400044.
38. Landoni, E.; Woodcock, M. G.; Barragan, G.; Casirati, G.; Cinella, V.; Stucchi, S.; Flick, L. M.; Withers, T. A.; Hudson, H.; Casorati, G.; Dellabona, P.; Genovese, P.; Savoldo, B.; Metelitsa, L. S.; Dotti, G. IL-12 Reprograms CAR-Expressing Natural Killer T Cells to Long-Lived Th1-Polarized Cells with Potent Antitumor Activity. *Nat. Commun.* **2024**, *15* (1), 89. https://doi.org/10.1038/s41467-023-44310-y.
39. Chmielewski, M.; Abken, H. TRUCKs: The Fourth Generation of CARs. *Expert Opin. Biol. Ther.* **2015**, *15* (8), 1145–1154. https://doi.org/10.1517/14712598.2015.1046430.
40. Pang, K.; Shi, Z.-D.; Wei, L.-Y.; Dong, Y.; Ma, Y.-Y.; Wang, W.; Wang, G.-Y.; Cao, M.-Y.; Dong, J.-J.; Chen, Y.-A.; Zhang, P.; Hao, L.; Xu, H.; Pan, D.; Chen, Z.-S.; Han, C.-H. Research Progress of Therapeutic Effects and Drug Resistance of Immunotherapy Based on PD-1/PD-L1 Blockade. Drug Resist. Updat. Rev. Comment. Antimicrob. *Anticancer Chemother.* **2023**, *66*, 100907. https://doi.org/10.1016/j.drup.2022.100907.
41. Rotte, A. Combination of CTLA-4 and PD-1 Blockers for Treatment of Cancer. *J. Exp. Clin. Cancer Res. CR* **2019**, *38* (1), 255. https://doi.org/10.1186/s13046-019-1259-z.
42. Chen, W. TGF-β Regulation of T Cells. *Annu. Rev. Immunol.* **2023**, *41*, 483–512. https://doi.org/10.1146/annurev-immunol-101921-045939.
43. Eyquem, J.; Mansilla-Soto, J.; Giavridis, T.; van der Stegen, S. J. C.; Hamieh, M.; Cunanan, K. M.; Odak, A.; Gönen, M.; Sadelain, M. Targeting a CAR to the TRAC Locus with CRISPR/Cas9 Enhances Tumour Rejection. *Nature* **2017**, *543* (7643), 113–117. https://doi.org/10.1038/nature21405.
44. Munshi, N. C.; Anderson, L. D.; Shah, N.; Madduri, D.; Berdeja, J.; Lonial, S.; Raje, N.; Lin, Y.; Siegel, D.; Oriol, A.; Moreau, P.; Yakoub-Agha, I.; Delforge, M.; Cavo, M.; Einsele, H.; Goldschmidt, H.; Weisel, K.; Rambaldi, A.; Reece, D.; Petrocca, F.; Massaro, M.; Connarn, J. N.; Kaiser, S.; Patel, P.; Huang, L.; Campbell, T. B.; Hege, K.; San-Miguel, J. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N. Engl. J. Med.* **2021**, *384* (8), 705–716. https://doi.org/10.1056/NEJMoa2024850.
45. Sehgal, A.; Hoda, D.; Riedell, P. A.; Ghosh, N.; Hamadani, M.; Hildebrandt, G. C.; Godwin, J. E.; Reagan, P. M.; Wagner-Johnston, N.; Essell, J.; Nath, R.; Solomon, S. R.; Champion, R.; Licitra, E.; Fanning, S.; Gupta, N.; Dubowy, R.; D'Andrea, A.; Wang, L.; Ogasawara, K.; Thorpe, J.; Gordon, L. I. Lisocabtagene Maraleucel as Second-Line Therapy in Adults with Relapsed or Refractory Large B-Cell Lymphoma Who Were Not Intended for Haematopoietic Stem Cell Transplantation (PILOT): An Open-Label, Phase 2 Study. *Lancet Oncol.* **2022**, *23* (8), 1066–1077. https://doi.org/10.1016/S1470-2045(22)00339-4.
46. Berdeja, J. G.; Madduri, D.; Usmani, S. Z.; Jakubowiak, A.; Agha, M.; Cohen, A. D.; Stewart, A. K.; Hari, P.; Htut, M.; Lesokhin, A.; Deol, A.; Munshi, N. C.; O'Donnell, E.; Avigan, D.; Singh, I.; Zudaire, E.; Yeh, T.-M.; Allred, A. J.; Olyslager, Y.; Banerjee, A.; Jackson, C. C.; Goldberg, J. D.; Schecter, J. M.; Deraedt, W.; Zhuang, S. H.; Infante, J.; Geng, D.; Wu, X.; Carrasco-Alfonso, M. J.; Akram, M.; Hossain, F.; Rizvi, S.; Fan, F.; Lin, Y.; Martin, T.; Jagannath, S. Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T-Cell Therapy in Patients with Relapsed or Refractory Multiple Myeloma (CARTITUDE-1): A Phase 1b/2 Open-Label Study. *Lancet Lond. Engl.* **2021**, *398* (10297), 314–324. https://doi.org/10.1016/S0140-6736(21)00933-8.
47. Maude, S. L.; Laetsch, T. W.; Buechner, J.; Rives, S.; Boyer, M.; Bittencourt, H.; Bader, P.; Verneris, M. R.; Stefanski, H. E.; Myers, G. D.; Qayed, M.; De Moerloose, B.; Hiramatsu, H.; Schlis, K.; Davis, K. L.; Martin, P. L.; Nemecek, E. R.; Yanik, G. A.; Peters, C.; Baruchel, A.; Boissel, N.; Mechinaud, F.; Balduzzi, A.; Krueger, J.; June, C. H.; Levine, B. L.; Wood, P.; Taran, T.; Leung, M.; Mueller, K. T.; Zhang, Y.; Sen, K.; Lebwohl, D.; Pulsipher, M. A.; Grupp, S. A. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N. Engl. J. Med.* **2018**, *378* (5), 439–448. https://doi.org/10.1056/NEJMoa1709866.
48. Deshpande, A.; Wang, Y.; Munoz, J.; Jain, P. Brexucabtagene Autoleucel: A Breakthrough in the Treatment of Mantle Cell Lymphoma. *Drugs Today* **2022**, *58* (6), 283–298. https://doi.org/10.1358/dot.2022.58.6.3378055.
49. Neelapu, S. S.; Locke, F. L.; Bartlett, N. L.; Lekakis, L. J.; Miklos, D. B.; Jacobson, C. A.; Braunschweig, I.; Oluwole, O. O.; Siddiqi, T.; Lin, Y.; Timmerman, J. M.; Stiff, P. J.; Friedberg, J. W.; Flinn, I. W.; Goy, A.; Hill, B. T.; Smith, M. R.; Deol, A.; Farooq, U.; McSweeney, P.; Munoz, J.; Avivi, I.; Castro, J. E.; Westin, J. R.; Chavez, J. C.; Ghobadi, A.; Komanduri, K. V.; Levy, R.; Jacobsen, E. D.; Witzig, T. E.; Reagan, P.; Bot, A.; Rossi, J.; Navale, L.; Jiang, Y.; Aycock, J.; Elias, M.; Chang, D.; Wiezorek, J.; Go, W. Y. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N. Engl. J. Med.* **2017,** *377* (26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447.
50. Neelapu, S. S.; Tummala, S.; Kebriaei, P.; Wierda, W.; Gutierez, C.; Locke, F. L.; Komanduri, K. V.; Lin, Y.; Jain, N.; Daver, N.; Westin, J.; Gulbis, A. M.; Loghin, M. E.; de Groot, J. F.; Adkins, S.; Davis, S. E.; Rezvani, K.; Hwu, P.; Shpall, E. J. Chimeric Antigen Receptor T-Cell Therapy - Assessment and Management of Toxicities. *Nat. Rev. Clin. Oncol.* **2018**, *15* (1), 47–62. https://doi.org/10.1038/nrclinonc.2017.148.
51. Aamir, S.; Anwar, M. Y.; Khalid, F.; Khan, S. I.; Ali, M. A.; Khattak, Z. E. Systematic Review and Meta-Analysis of CD19-Specific CAR-T Cell Therapy in Relapsed/Refractory Acute Lymphoblastic Leukemia in the Pediatric and Young Adult Population: Safety and Efficacy Outcomes. Clin. *Lymphoma Myeloma Leuk.* **2021**, *21* (4), e334–e347. https://doi.org/10.1016/j.clml.2020.12.010.
52. Cappell, K. M.; Kochenderfer, J. N. Long-Term Outcomes Following CAR T Cell Therapy: What We Know So Far. *Nat. Rev. Clin. Oncol.* **2023**, *20* (6), 359–371. https://doi.org/10.1038/s41571-023-00754-1.
53. Riccardi, F.; Dal Bo, M.; Macor, P.; Toffoli, G. A Comprehensive

Overview on Antibody-Drug Conjugates: From the Conceptualization to Cancer Therapy. *Front. Pharmacol.* **2023**, *14*, 1274088. https://doi.org/10.3389/fphar.2023.1274088.
54. Dumontet, C.; Reichert, J. M.; Senter, P. D.; Lambert, J. M.; Beck, A. Antibody-Drug Conjugates Come of Age in Oncology. Nat. Rev. *Drug Discov.* **2023**, *22* (8), 641–661. https://doi.org/10.1038/s41573-023-00709-2.
55. Kantarjian, H. M.; DeAngelo, D. J.; Stelljes, M.; Martinelli, G.; Liedtke, M.; Stock, W.; Gökbuget, N.; O'Brien, S.; Wang, K.; Wang, T.; Paccagnella, M. L.; Sleight, B.; Vandendries, E.; Advani, A. S. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **2016**, *375* (8), 740–753. https://doi.org/10.1056/NEJMoa1509277.
56. Burt, R.; Warcel, D.; Fielding, A. K. Blinatumomab, a Bispecific B-Cell and T-Cell Engaging Antibody, in the Treatment of B-Cell Malignancies. Hum. *Vaccines Immunother.* **2019**, *15* (3), 594–602. https://doi.org/10.1080/21645515.2018.1540828.
57. Bear, A. S.; Fraietta, J. A.; Narayan, V. K.; O'Hara, M.; Haas, N. B. Adoptive Cellular Therapy for Solid Tumors. *Am. Soc. Clin. Oncol. Educ. Book* **2021**, No. 41, 57–65. https://doi.org/10.1200/EDBK_321115.
58. Albinger, N.; Hartmann, J.; Ullrich, E. Current Status and Perspective of CAR-T and CAR-NK Cell Therapy Trials in Germany. *Gene Ther.* **2021**, *28* (9), 513–527. https://doi.org/10.1038/s41434-021-00246-w.
59. Prommersberger, S.; Hudecek, M.; Nerreter, T. Antibody-Based CAR T Cells Produced by Lentiviral Transduction. *Curr. Protoc. Immunol.* **2020**, *128* (1), e93. https://doi.org/10.1002/cpim.93.
60. Labbé, R. P.; Vessillier, S.; Rafiq, Q. A. Lentiviral Vectors for T Cell Engineering: Clinical Applications, Bioprocessing and Future Perspectives. *Viruses* **2021**, *13* (8), 1528. https://doi.org/10.3390/v13081528.
61. Lana, M. G.; Strauss, B. E. Production of Lentivirus for the Es tablishment of CAR-T Cells. *Methods Mol. Biol. Clifton NJ* **2020**, *2086*, 61–67. https://doi.org/10.1007/978-1-0716-0146-4_4.
62. Perthus, A.; Colin, F.; Charton, E.; Anota, A.; Guibert, S. D.; Ysebaert, L.; Daufresne, P.; Lhomme, F.; Manson, G.; Bellec, A.; Bars, L. L.; Chapelle, T. L. D. L.; Houot, R.; Moignet, A. P1687: LIFE AFTER CAR T-CELLS: DO PATIENTS RECOVER A NORMAL LIFE? *HemaSphere* **2023**, *7* (S3), e725933e. https://doi.org/10.1097/01.HS9.0000973620.72593.3e.
63. Maude, S. L.; Frey, N.; Shaw, P. A.; Aplenc, R.; Barrett, D. M.; Bunin, N. J.; Chew, A.; Gonzalez, V. E.; Zheng, Z.; Lacey, S. F.; Mahnke, Y. D.; Melenhorst, J. J.; Rheingold, S. R.; Shen, A.; Teachey, D. T.; Levine, B. L.; June, C. H.; Porter, D. L.; Grupp, S. A. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. *N. Engl. J. Med.* **2014**, *371* (16), 1507–1517. https://doi.org/10.1056/NEJMoa1407222.
64. Alviano, A. M.; Biondi, M.; Grassenis, E.; Biondi, A.; Serafini, M.; Tettamanti, S. Fully Equipped CARs to Address Tumor Heterogeneity, Enhance Safety, and Improve the Functionality of Cellular Immunotherapies. *Front. Immunol.* **2024**, *15*, 1407992. https://doi.org/10.3389/fimmu.2024.1407992.
65. Milone, M. C.; Xu, J.; Chen, S.-J.; Collins, M. A.; Zhou, J.; Powell, D. J.; Melenhorst, J. J. Engineering Enhanced CAR T-Cells for Improved Cancer Therapy. *Nat. Cancer* **2021**, *2* (8), 780–793. https://doi.org/10.1038/s43018-021-00241-5.
66. Chihara, D.; Liao, L.; Tkacz, J.; Franco, A.; Lewing, B.; Kilgore, K. M.; Nastoupil, L. J.; Chen, L. Real-World Experience of CAR T-Cell Therapy in Older Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma. *Blood* **2023**, *142* (12), 1047–1055. https://doi.org/10.1182/blood.2023020197.
67. Kantarjian, H.; Stein, A.; Gökbuget, N.; Fielding, A. K.; Schuh, A. C.; Ribera, J.-M.; Wei, A.; Dombret, H.; Foà, R.; Bassan, R.; Arslan, Ö.; Sanz, M. A.; Bergeron, J.; Demirkan, F.; Lech-Maranda, E.; Rambaldi, A.; Thomas, X.; Horst, H.-A.; Brüggemann, M.; Klapper, W.; Wood, B. L.; Fleishman, A.; Nagorsen, D.; Holland, C.; Zimmerman, Z.; Topp, M. S. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **2017**, *376* (9), 836–847. https://doi.org/10.1056/NEJMoa1609783.
68. Kantarjian, H. M.; DeAngelo, D. J.; Stelljes, M.; Martinelli, G.; Liedtke, M.; Stock, W.; Gökbuget, N.; O'Brien, S.; Wang, K.; Wang, T.; Paccagnella, M. L.; Sleight, B.; Vandendries, E.; Advani, A. S. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **2016**, *375* (8), 740–753. https://doi.org/10.1056/NEJMoa1509277.
69. Tilly, H.; Morschhauser, F.; Sehn, L. H.; Friedberg, J. W.; Trněný, M.; Sharman, J. P.; Herbaux, C.; Burke, J. M.; Matasar, M.; Rai, S.; Izutsu, K.; Mehta-Shah, N.; Oberic, L.; Chauchet, A.; Jurczak, W.; Song, Y.; Greil, R.; Mykhalska, L.; Bergua-Burgués, J. M.; Cheung, M. C.; Pinto, A.; Shin, H.-J.; Hapgood, G.; Munhoz, E.; Abrisqueta, P.; Gau, J.-P.; Hirata, J.; Jiang, Y.; Yan, M.; Lee, C.; Flowers, C. R.; Salles, G. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *N. Engl. J. Med.* **2022**, *386* (4), 351–363. https://doi.org/10.1056/NEJMoa2115304.
70. Fathi, A. T.; Erba, H. P.; Lancet, J. E.; Stein, E. M.; Ravandi, F.; Faderl, S.; Walter, R. B.; Advani, A. S.; DeAngelo, D. J.; Kovacsovics, T. J.; Jillella, A.; Bixby, D.; Levy, M. Y.; O'Meara, M. M.; Ho, P. A.; Voellinger, J.; Stein, A. S. A Phase 1 Trial of Vadastuximab Talirine Combined with Hypomethylating Agents in Patients with CD33-Positive AML. *Blood* **2018**, *132* (11), 1125–1133. https://doi.org/10.1182/blood-2018-03-841171.
71. Caimi, P. F.; Ai, W.; Alderuccio, J. P.; Ardeshna, K. M.; Hamadani, M.; Hess, B.; Kahl, B. S.; Radford, J.; Solh, M.; Stathis, A.; Zinzani, P. L.; Havenith, K.; Feingold, J.; He, S.; Qin, Y.; Ungar, D.; Zhang, X.; Carlo-Stella, C. Loncastuximab Tesirine in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS-2): A Multicentre, Open-Label, Single-Arm, Phase 2 Trial. *Lancet Oncol.* **2021**, *22* (6), 790–800. https://doi.org/10.1016/S1470-2045(21)00139-X.
72. Advani, R. H.; Moskowitz, A. J.; Bartlett, N. L.; Vose, J. M.; Ramchandren, R.; Feldman, T. A.; LaCasce, A. S.; Christian, B. A.; Ansell, S. M.; Moskowitz, C. H.; Brown, L.; Zhang, C.; Taft, D.; Ansari, S.; Sacchi, M.; Ho, L.; Herrera, A. F. Brentuximab Vedotin in Combination with Nivolumab in Relapsed or Refractory Hodgkin Lymphoma: 3-Year Study Results. *Blood* **2021**, *138* (6), 427–438. https://doi.org/10.1182/blood.2020009178.
73. Yeku, O. O.; Purdon, T. J.; Koneru, M.; Spriggs, D.; Brentjens, R. J. Armored CAR T Cells Enhance Antitumor Efficacy and Overcome the Tumor Microenvironment. *Sci. Rep.* **2017**, *7* (1), 10541. https://doi.org/10.1038/s41598-017-10940-8.
74. Mehana, E.-S. E.; Khafaga, A. F.; El-Blehi, S. S. The Role of Matrix Metalloproteinases in Osteoarthritis Pathogenesis: An Updated Review. *Life Sci.* **2019**, *234*, 116786. https://doi.org/10.1016/j.lfs.2019.116786.
75. Suarez, E. R.; Chang, D. K.; Sun, J.; Sui, J.; Freeman, G. J.; Signoretti, S.; Zhu, Q.; Marasco, W. A. Chimeric Antigen Receptor T Cells Secreting Anti-PD-L1 Antibodies More Effectively Regress Renal Cell Carcinoma in a Humanized Mouse Model. *Oncotarget* **2016**, *7* (23), 34341–34355. https://doi.org/10.18632/oncotarget.9114.
76. Harrasser, M.; Gohil, S. H.; Lau, H.; Della Peruta, M.; Muczynski, V.; Patel, D.; Miranda, E.; Grigoriadis, K.; Grigoriadis, A.; Granger, D.; Evans, R.; Nathwani, A. C. Inducible Localized Delivery of an Anti-PD-1 scFv Enhances Anti-Tumor Activity of

DOI: 10.36838/v7i10.1

ROR1 CAR-T Cells in TNBC. *Breast Cancer Res.* **2022**, *24* (1), 39. https://doi.org/10.1186/s13058-022-01531-1.
77. Qasim, W. Allogeneic CAR T Cell Therapies for Leukemia. *Am. J. Hematol. 2019*, *94* (S1). https://doi.org/10.1002/ajh.25399.
78. Lin, H.; Cheng, J.; Mu, W.; Zhou, J.; Zhu, L. Advances in Universal CAR-T Cell Therapy. *Front. Immunol.* **2021**, *12*, 744823. https://doi.org/10.3389/fimmu.2021.744823.
79. Fan, M.; Zheng, J.; Huang, Y.; Lu, M.; Shang, Z.; Du, M. Nanoparticle-Mediated Universal CAR-T Therapy. *Int. J. Pharm.* **2024**, *666*, 124779. https://doi.org/10.1016/j.ijpharm.2024.124779.
80. Chen, S.; Van Den Brink, M. R. M. Allogeneic "Off-the-Shelf" CAR T Cells: Challenges and Advances. *Best Pract. Res. Clin. Haematol.* **2024**, *37* (3), 101566. https://doi.org/10.1016/j.beha.2024.101566.
81. Vago, L.; Gojo, I. Immune Escape and Immunotherapy of Acute Myeloid Leukemia. *J. Clin. Invest.* **2020**, *130* (4), 1552–1564. https://doi.org/10.1172/JCI129204.
82. Blass, E.; Ott, P. A. Advances in the Development of Personalized Neoantigen-Based Therapeutic Cancer Vaccines. *Nat. Rev. Clin. Oncol.* **2021**, *18* (4), 215–229. https://doi.org/10.1038/s41571-020-00460-2.
83. Mishra, A.; Maiti, R.; Mohan, P.; Gupta, P. Antigen Loss Following CAR-T Cell Therapy: Mechanisms, Implications, and Potential Solutions. *Eur. J. Haematol.* **2024**, *112* (2), 211–222. https://doi.org/10.1111/ejh.14101.
84. Shalabi, H.; Kraft, I. L.; Wang, H.-W.; Yuan, C. M.; Yates, B.; Delbrook, C.; Zimbelman, J. D.; Giller, R.; Stetler-Stevenson, M.; Jaffe, E. S.; Lee, D. W.; Shern, J. F.; Fry, T. J.; Shah, N. N. Sequential Loss of Tumor Surface Antigens Following Chimeric Antigen Receptor T-Cell Therapies in Diffuse Large B-Cell Lymphoma. *Haematologica* **2018**, *103* (5), e215–e218. https://doi.org/10.3324/haematol.2017.183459.
85. Scarfò, I.; Ormhøj, M.; Frigault, M. J.; Castano, A. P.; Lorrey, S.; Bouffard, A. A.; van Scoyk, A.; Rodig, S. J.; Shay, A. J.; Aster, J. C.; Preffer, F. I.; Weinstock, D. M.; Maus, M. V. Anti-CD37 Chimeric Antigen Receptor T Cells Are Active against B- and T-Cell Lymphomas. *Blood* **2018**, *132* (14), 1495–1506. https://doi.org/10.1182/blood-2018-04-842708.
86. Frigault, M. J.; Maus, M. V. State of the Art in CAR T Cell Therapy for CD19+ B Cell Malignancies. *J. Clin. Invest.* **2020**, *130* (4), 1586–1594. https://doi.org/10.1172/JCI129208.
87. Johnson, D. B.; Nebhan, C. A.; Moslehi, J. J.; Balko, J. M. Immune-Checkpoint Inhibitors: Long-Term Implications of Toxicity. *Nat. Rev. Clin. Oncol.* **2022**, *19* (4), 254–267. https://doi.org/10.1038/s41571-022-00600-w.
88. Hayden, P. J.; Roddie, C.; Bader, P.; Basak, G. W.; Bonig, H.; Bonini, C.; Chabannon, C.; Ciceri, F.; Corbacioglu, S.; Ellard, R.; Sanchez-Guijo, F.; Jäger, U.; Hildebrandt, M.; Hudecek, M.; Kersten, M. J.; Köhl, U.; Kuball, J.; Mielke, S.; Mohty, M.; Murray, J.; Nagler, A.; Rees, J.; Rioufol, C.; Saccardi, R.; Snowden, J. A.; Styczynski, J.; Subklewe, M.; Thieblemont, C.; Topp, M.; Ispizua, Á. U.; Chen, D.; Vrhovac, R.; Gribben, J. G.; Kröger, N.; Einsele, H.; Yakoub-Agha, I. Management of Adults and Children Receiving CAR T-Cell Therapy: 2021 Best Practice Recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2022**, *33* (3), 259–275. https://doi.org/10.1016/j.annonc.2021.12.003.
89. King-Peoples, T. R.; Posey, A. D. Splitting Signals Drives CARs Further. *Nat. Cancer* **2021**, *2* (9), 873–875. https://doi.org/10.1038/s43018-021-00257-x.
90. Lu, L.; Xie, M.; Yang, B.; Zhao, W.-B.; Cao, J. Enhancing the Safety of CAR-T Cell Therapy: Synthetic Genetic Switch for Spatiotemporal Control. *Sci. Adv.* **2024**, *10* (8), eadj6251. https://doi.org/10.1126/sciadv.adj6251.
91. Guercio, M.; Manni, S.; Boffa, I.; Caruso, S.; Di Cecca, S.; Sinibaldi, M.; Abbaszadeh, Z.; Camera, A.; Ciccone, R.; Polito, V. A.; Ferrandino, F.; Reddel, S.; Catanoso, M. L.; Bocceri, E.; Del Bufalo, F.; Algeri, M.; De Angelis, B.; Quintarelli, C.; Locatelli, F. Inclusion of the Inducible Caspase 9 Suicide Gene in CAR Construct Increases Safety of CAR.CD19 T Cell Therapy in B-Cell Malignancies. *Front. Immunol.* **2021**, *12*, 755639. https://doi.org/10.3389/fimmu.2021.755639.
92. Zhou, X.; Di Stasi, A.; Brenner, M. K. iCaspase 9 Suicide Gene System. Methods Mol. Biol. *Clifton NJ* **2015**, *1317*, 87–105. https://doi.org/10.1007/978-1-4939-2727-2_6.
93. Stock, S.; Klüver, A.-K.; Fertig, L.; Menkhoff, V. D.; Subklewe, M.; Endres, S.; Kobold, S. Mechanisms and Strategies for Safe Chimeric Antigen Receptor T-Cell Activity Control. *Int. J. Cancer* **2023**, *153* (10), 1706–1725. https://doi.org/10.1002/ijc.34635.
94. Labanieh, L.; Majzner, R. G.; Klysz, D.; Sotillo, E.; Fisher, C. J.; Vilches-Moure, J. G.; Pacheco, K. Z. B.; Malipatlolla, M.; Xu, P.; Hui, J. H.; Murty, T.; Theruvath, J.; Mehta, N.; Yamada-Hunter, S. A.; Weber, E. W.; Heitzeneder, S.; Parker, K. R.; Satpathy, A. T.; Chang, H. Y.; Lin, M. Z.; Cochran, J. R.; Mackall, C. L. Enhanced Safety and Efficacy of Protease-Regulated CAR-T Cell Receptors. *Cell* **2022**, *185* (10), 1745-1763.e22. https://doi.org/10.1016/j.cell.2022.03.041.
95. Zhang, J.; Du, B.; Liu, M. Let's Turn the CAR-T Cells ON and OFF Precisely. *Cancer Cell* **2022**, *40* (11), 1264–1266. https://doi.org/10.1016/j.ccell.2022.10.019.
96. Jan, M.; Scarfò, I.; Larson, R. C.; Walker, A.; Schmidts, A.; Guirguis, A. A.; Gasser, J. A.; Słabicki, M.; Bouffard, A. A.; Castano, A. P.; Kann, M. C.; Cabral, M. L.; Tepper, A.; Grinshpun, D. E.; Sperling, A. S.; Kyung, T.; Sievers, Q. L.; Birnbaum, M. E.; Maus, M. V.; Ebert, B. L. Reversible ON- and OFF-Switch Chimeric Antigen Receptors Controlled by Lenalidomide. *Sci. Transl. Med.* **2021**, *13* (575), eabb6295. https://doi.org/10.1126/scitranslmed.abb6295.
97. Li, S.; Shi, L.; Zhao, L.; Guo, Q.; Li, J.; Liu, Z.; Guo, Z.; Cao, Y. J. Split-Design Approach Enhances the Therapeutic Efficacy of Ligand-Based CAR-T Cells against Multiple B-Cell Malignancies. *Nat. Commun.* **2024**, *15* (1), 9751. https://doi.org/10.1038/s41467-024-54150-z.
98. He, X.; Feng, Z.; Ma, J.; Ling, S.; Cao, Y.; Gurung, B.; Wu, Y.; Katona, B. W.; O'Dwyer, K. P.; Siegel, D. L.; June, C. H.; Hua, X. Bispecific and Split CAR T Cells Targeting CD13 and TIM3 Eradicate Acute Myeloid Leukemia. *Blood* **2020**, *135* (10), 713–723. https://doi.org/10.1182/blood.2019002779.
99. Choi, G.; Shin, G.; Bae, S. Price and Prejudice? The Value of Chimeric Antigen Receptor (CAR) T-Cell Therapy. Int. J. Environ. Res. *Public. Health* **2022**, *19* (19), 12366. https://doi.org/10.3390/ijerph191912366.
100. Cliff, E. R. S.; Kelkar, A. H.; Russler-Germain, D. A.; Tessema, F. A.; Raymakers, A. J. N.; Feldman, W. B.; Kesselheim, A. S. High Cost of Chimeric Antigen Receptor T-Cells: Challenges and Solutions. *Am. Soc. Clin. Oncol. Educ. Book* **2023**, No. 43, e397912. https://doi.org/10.1200/EDBK_397912.
101. Frey, N.; Porter, D. Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. Biol. Blood Marrow Transplant. J. Am. Soc. *Blood Marrow Transplant.* **2019**, *25* (4), e123–e127. https://doi.org/10.1016/j.bbmt.2018.12.756.
102. Chen, P.; Tang, Y.; He, W.; Yang, R.; Lan, Z.; Chen, R.; Zhang, P. Potential Pathophysiological Mechanisms Underlying Multiple Organ Dysfunction in Cytokine Release

Syndrome. *Mediators Inflamm.* **2022**, *2022*, 7137900. https://doi.org/10.1155/2022/7137900.
103. Müller, F.; Taubmann, J.; Bucci, L.; Wilhelm, A.; Bergmann, C.; Völkl, S.; Aigner, M.; Rothe, T.; Minopoulou, I.; Tur, C.; Knitza, J.; Kharboutli, S.; Kretschmann, S.; Vasova, I.; Spoerl, S.; Reimann, H.; Munoz, L.; Gerlach, R. G.; Schäfer, S.; Grieshaber-Bouyer, R.; Korganow, A.-S.; Farge-Bancel, D.; Mougiakakos, D.; Bozec, A.; Winkler, T.; Krönke, G.; Mackensen, A.; Schett, G. CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-Up. *N. Engl. J. Med.* **2024**, *390* (8), 687–700. https://doi.org/10.1056/NEJMoa2308917.
104. Freyer, C. W.; Porter, D. L. Cytokine Release Syndrome and Neurotoxicity Following CAR T-Cell Therapy for Hematologic Malignancies. *J. Allergy Clin. Immunol.* **2020**, *146* (5), 940–948. https://doi.org/10.1016/j.jaci.2020.07.025.
105. Gazeau, N.; Liang, E. C.; Wu, Q. V.; Voutsinas, J. M.; Barba, P.; Iacoboni, G.; Kwon, M.; Ortega, J. L. R.; López-Corral, L.; Hernani, R.; Ortiz-Maldonado, V.; Martínez-Cibrian, N.; Martinez, A. P.; Maziarz, R. T.; Williamson, S.; Nemecek, E. R.; Shadman, M.; Cowan, A. J.; Green, D. J.; Kimble, E.; Hirayama, A. V.; Maloney, D. G.; Turtle, C. J.; Gauthier, J. Anakinra for Refractory Cytokine Release Syndrome or Immune Effector Cell-Associated Neurotoxicity Syndrome after Chimeric Antigen Receptor T Cell Therapy. *Transplant. Cell. Ther.* **2023**, *29* (7), 430–437. https://doi.org/10.1016/j.jtct.2023.04.001.
106. Flugel, C. L.; Majzner, R. G.; Krenciute, G.; Dotti, G.; Riddell, S. R.; Wagner, D. L.; Abou-El-Enein, M. Overcoming On-Target, off-Tumour Toxicity of CAR T Cell Therapy for Solid Tumours. *Nat. Rev. Clin. Oncol.* **2023**, *20* (1), 49–62. https://doi.org/10.1038/s41571-022-00704-3.

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