Trends in Cancer

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Review

Future perspectives on engineered T cells for cancer

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Chimeric antigen receptor (CAR) T cell therapy has emerged as a revolutionary treatment for hematological malignancies, but its adaptation to solid tumors is impeded by multiple challenges, particularly T cell dysfunction and exhaustion. The heterogeneity and inhospitableness of the solid tumor microenvironment (TME) contribute to diminished CAR T cell efficacy exhibited by reduced cytotoxicity, proliferation, cytokine secretion, and the upregulation of inhibitory receptors, similar to the phenotype of tumor-infiltrating lymphocytes (TILs). In this review, we highlight recent advances in T cell therapy for solid tumors, particularly brain cancer. Innovative strategies, including locoregional delivery and 'armoring' CAR T cells with cytokines such as interleukin (IL)-18, are under investigation to improve efficacy and safety. We also highlight emerging issues with toxicity management of CAR T cell adverse events. This review discusses the obstacles associated with CAR T cell therapy in the context of solid tumors and outlines current and future strategies to overcome these challenges.

Highlights

The efficacy of chimeric antigen receptor (CAR) T cells targeting solid tumors is constrained by target heterogeneity, treatment-associated toxicities, and immunosuppressive factors in the tumor microenvironment, such as poor T cell infiltration, metabolic stress, and T cell exhaustion.

Toxicities associated with CAR T cell therapies can limit administration of therapeutic doses of CAR T cells.

Locoregional CAR T cell delivery can enhance CAR T cell efficacy and reduce on-target off-tumor toxicities.

Armoring CAR T cells with cytokines such as interleukin (IL)-12 and IL-18 can enhance CAR T cell potency and efficacy.

CAR T cells can be synthetically engineered to bypass normal T cell homeostasis and prolong antitumor cytotoxicity.

Cell therapies come of age

CAR T cell therapy represents a paradigm shift in the landscape of cancer treatment, harnessing the power of genetic engineering to reprogram the patient's own T cells to seek out and destroy cancer cells. The remarkable success of CAR T cell therapy in liquid tumors, such as certain leukemias, lymphomas, and myeloma, has paved the way for its exploration in solid tumors, although this has introduced a new set of complex challenges. The remarkable efficacy of CD19 and B cell maturation antigen (BCMA)-targeted CAR T cell therapies, approved by regulatory agencies for six different B cell and plasma cell malignancies, has set a benchmark for the potential of this modality. In 2024, TILs received US FDA approval for metastatic melanoma, representing the first T cell-based therapy approved for a solid tumor.

Recent advances in genetic editing have opened the door for multiplex gene manipulation of T cells, promising the development of turbocharged CAR T cells with improved survival, proliferation, and tumor-killing capabilities, as well as resistance to the hostile TME. The burgeoning field of synthetic biology also promises the creation of smart CAR T cells that respond to the cues within the TME or are regulated through exogenous molecules, offering a fine-tuned approach to cancer therapy. This review aims to dissect the challenges and solutions associated with CAR T cell therapy, particularly in solid tumors. By examining the progress and setbacks, we aim to outline a roadmap for the future of CAR T cell therapy, where it can become a mainstay not just for hematologic malignancies but also for the elusive and challenging realm of solid tumors.

CAR T-based therapies: challenges with T cell dysfunction and exhaustion

Loss of CAR T cell efficacy in the solid TME is a significant challenge in the field of CAR T cell therapy. This is believed, in part, to be caused by continuous antigen exposure (CAE) of T cells

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through the cognate antigen for the CAR [1]. To interrogate characteristics of CAR T cell exhaustion and associated changes in chromatin accessibility, groups have developed *in vitro* CAE assays to repeatedly stimulate CAR T cells with tumor cells over several weeks to months. These studies reveal that CAR T cells display hallmark features of T cell exhaustion, such as reduced cytotoxicity, proliferation, and cytokine secretion and upregulation of multiple inhibitory receptors, phenotypes comparable with TILs [2,3]. Additionally, such models uncovered additional characteristics of CAR T cell dysfunction, such as increased internalization of the CAR receptor, upregulation of natural killer (NK) cell receptors such as KLRB1, and signatures of CAR T cell dysfunction [2]. However, CAE assays fail to model the solid TME, where CAR T cells can encounter limitations to function, such as competition for metabolic fuels, physical barriers to CAR T cell infiltration, and immunosuppressive factors [4,5]. Interestingly, examination of T cell dysfunction in tumor-bearing syngeneic mouse models reveals that tumor-specific T cells become dysfunctional within hours instead of days of antigen stimulation [6].

The therapeutic CAR T cell response can be hindered by poor T cell fitness within the initial leukapheresis used for engineered cell manufacturing or acquired functional deficits throughout treatment, necessitating strategies to boost T cell function. To mitigate CAR T cell dysfunction, CRISPR screens have been conducted to systematically identify genes whose deletion or overexpression enhances T cell phenotypes, such as proliferation and persistence, memory, cytokine production, cytotoxicity, metabolism, mitochondrial function, and transcriptional and epigenetic regulators [7–24]. One gene identified in CRISPR screens conducted under immunosuppressive conditions was RASA2 [24]. RASA2 acts as a negative regulator of T cell proliferation and cytotoxicity, and RASA2 ablation counteracts mechanisms that suppress CAR and T cell receptor (TCR) antitumor activity in animal models. Building on these findings, there has been an effort to multiplex edits of driver genes to further improve T cell function [25–27]. The MEGA platform uses Cas13d to achieve knockdown of up to ten genes in primary T cells [28]. Using this technology, multiplex knockdown of genes involved in aerobic glycolysis augments CAR T cell metabolism and fitness. Additionally, strategies to bypass normal T cell homeostasis and maintain extended CAR T cell efficacy are under investigation. CRISPR/Cas9 deletion of both Regnase-1 and Roquin-1 increases T cell expansion, and antitumor function in xenograft solid tumor mouse models compared with either single edit and also causes a lymphoproliferative syndrome and toxicity in some mice [27]. The use of gene engineering can create synthetic CAR T cells that exhibit novel T cell states [29,30]. Repurposing IL-9R signaling using a chimeric orthogonal cytokine receptor engineers CAR T cells with increased central memory T cells (T_{CM}) and effector T cells (T_{EFF}) phenotypes and improves antitumor activity in solid tumor mouse models [31]. Furthermore, naturally occurring T cell mutations associated with T cell lymphomas are being appropriated to enhance engineered T cell therapies [32]. A gene fusion, *CARD11–PIK3R3*, found in a $CD4^+$ cutaneous T cell lymphoma augments NF-κB, AP-1, and MALT1 signaling and enhances the antitumor efficacy of CAR and TCR T cells [33].

Challenges with toxicities

Hyperactivation of CAR T cells and their inflammatory responses can enhance tumor clearance but also can drive hyperinflammatory toxicities associated with CAR T cell therapy, such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) (Box 1). These syndromes are characterized by sustained CAR T cell activation leading to tumor lysis, activation of monocytes/macrophages, and enhanced production of cytokines [34] and can cause life-threatening complications if higher doses of therapy are administered [35]. Neurotoxicity initially presents in patients with symptoms as word-finding difficulty, impaired motor skills, and mild disorientation [36–38]. This toxicity is associated with on-target off-tumor

Box 1. Toxicity syndromes with engineered T cell therapies

Cytokine release syndrome (CRS) is a systemic inflammatory response that can occur after certain immunotherapies, most notably CAR T therapy, as well as other therapies like such as bispecific T cell engagers (BiTEs). Clinically, CRS begins with fever, and, in severe cases, CRS can lead to life-threatening complications such as capillary leak syndrome, macrophage activation syndrome, disseminated intravascular coagulation, or organ failure. Cytokine blockade with tocilizumab, an IL-6 receptor antagonist, and anakinra, an IL-1 receptor antagonist, are effective in the management of CRS.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a neurological condition associated with diffusion of CAR T cells, endogenous T cells, macrophages, and cytokines into the cerebral spinal fluid and CNS, endothelial injury, and a compromised blood–brain barrier. This toxicity has been associated with CD19- and CD22-directed CAR T cell on-target off-tumor recognition of antigen in the brain and initially presents in patients with symptoms such as word-finding difficulty, impaired fine-motor skills, and mild disorientation.

Like ICANS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) often occurs in CAR T cell patients with severe CRS. However, the onset of IEC-HS is generally delayed compared with CRS and is characterized by macrophage activation like hemophagocytic lymphohistiocytosis (HLH), resulting in unrestrained cytokine-driven inflammation.

Recognition that CRS and IEC-HS are distinct processes allows optimized treatment recommendations. Administration of tocilizumab is a first-line therapy in CRS, whereas anakinra with or without systemic corticosteroids is a first-line treatment for IEC-HS. There may be a role for IL-18 blockade in ICANS and IEC-HS. Like CRS, both ICANS and IEC-HS are reversible in most patients; however, these toxicities can cause life-threatening complications of IEC therapy, especially if higher doses of the therapy are administered.

recognition of antigen in the brain by CD19- and CD22-directed CAR T cells [39,40]. Furthermore, the BCMA-directed CAR T cell therapy ciltacabtagene autoleucel, developed for the treatment of multiple myeloma, is reported to be linked with the onset of parkinsonism and is potentially associated with CAR T cell recognition of BCMA expressed on normal neurons and astrocytes in the brain [41]. Treatments for these toxicities include tocilizumab for CRS, anakinra with or without systemic corticosteroids for IEC-HS, and potentially IL-18 blockade for ICANS and IEC-HS [34,42].

A possible association between curative levels of CAR T cells and ensuing life-threatening levels of inflammatory toxicities was observed for patient nine in the Phase 1 clinical trial (NCT03089203) designed to evaluate the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) with prostate-specific membrane antigen (PSMA)-targeting transforming growth factor (TGF)-β-insensitive armored CAR T cells [43]. In this trial, the magnitude of peak peripheral CART-PSMA-TGFβ receptor dominant negative cell expansion and the grade of CRS generally increased with dose escalation and lymphodepletion (LD). Patient nine received the highest dose ($1–3 \times 10^8$ m^2) of CART-PSMA-TGFβRDN cells following LD and experienced a dramatic expansion of CART-PSMA-TGFβRDN cells; greater than 90% of peripheral blood $CD3^+$ T cells expressed the CAR. This correlated with a significant drop in serum TGF-β levels and a greater than 98% reduction in his serum PSA levels. The patient developed fever and hypotension, followed by increased levels of IL-6 and ferritin. Multiple immunosuppressive drugs were administered to reduce the high-grade CRS, but the patient died with grade 4 CRS and sepsis. Improved treatments to mitigate these toxicities may allow the safe administration of curative doses of CAR T cells.

Most CAR T cell targets for solid tumors are also expressed on both malignant and normal tissues [44], and this low level of target antigen expression on essential non-malignant tissues can also pose a significant barrier to safely administering a therapeutic CAR T cell dose to patients. For instance, low-level expression of several CAR-target antigens, mesothelin (MSLN) [45], CEACAM5 [46], and ERBB2 [47], on benign pulmonary epithelial cells has led to significant pulmonary toxicity in Phase 1 clinical trials designed to evaluate the safety of these products. Clinical data suggest an acceptable safety profile can be achieved with lower doses of anti-MSLN (NCT03054298) or

anti-HER2 CAR T cells, with evidence of clinical response for anti-HER2 CARs (NCT00902044) [48]. Additionally, intrapleural delivery of MSLN-directed CAR T cells followed by administration of pembrolizumab, an anti–PD-1 immune checkpoint inhibitor, proved safe and demonstrated evidence of antitumor activity for patients with malignant pleural mesothelioma cancer (NCT02414269) [49]. Local delivery of MSLN-directed CAR T cells is also under investigation in Phase 1 clinical trials designed to treat mesothelioma and ovarian cancer (NCT03054298) and pancreatic cancer (NCT03323944). In another example, administration of prostate stem cell antigen (PSCA)-directed CAR T cells in patients with mCRPC showed antitumor activity, but grade 3 cystitis was reported in some patients, presumably due to expression of PSCA on normal bladder (NCT03873805) [45,50]. In summary, low levels of expression of CAR T cell targets on normal tissues hinders the efficacy of CAR T cell therapy directed against solid tumors, and local delivery of CAR T cells to the tumor site may reduce CAR T cell associated toxicities and improve therapeutic efficacy.

Secondary malignancies after CAR T cell therapy

In 2023, the FDA announced that secondary T cell malignancies occurred in some patients who received treatment with CD19- or BCMA-targeted autologous CAR T cells [51] (Box 2). These events are rare; more than 34 000 patients have been treated with autologous CAR T cells [52]. A causal association with CAR T cells and secondary malignancies is possible; however, the associated prior alkylating chemotherapy administered to most patients is likely the largest risk factor for secondary malignancies. Furthermore, the underlying risks of second malignancies as revealed by 'immortal time bias' need to be determined [53], because patients can only develop secondary malignancies if they do not first die of their primary cancer. By contrast, two cases of T cell lymphoma expressing the CAR were reported in patients after treatment with allogeneic CD19 CAR T cells developed using non-viral engineering [54]. In these cases, the genetic insertion of the CAR at high vector copy numbers was likely involved in the development of a T cell lymphoma. In addition, in the steady state, T cell homeostasis and clonal abundance are controlled at the level of the TCR, unlike in B cells [55]. Thus, there is an inverse relationship between clonal frequency and T cell clonal survival due to intraclonal competition. This may explain, in part, why B cell malignancies are so much more common than T cell malignancies. In situations where the TCR has been deleted, resulting in abrogation of clonal competition, it is likely that the loss of this cell-intrinsic checkpoint could lead to an enhanced risk of T cell transformation. Therefore, the risk of transformation after allogeneic CAR T cell therapy is likely higher with allogeneic cells than with autologous T cells if the TCR has been deleted or in cases of severe lymphopenia where homeostatic expansion would overcome the effects of clonal competition. In addition, clonal hematopoiesis may be present in the patient lymphocytes used for CAR T cell manufacturing, and this can influence CAR T cell biology and clinical outcomes, but, in

Box 2. CAR T lymphoma

Secondary T cell malignancies, including lymphomas, have been reported in patients who received CAR T cell therapy. The US FDA Adverse Event Reporting System (FAERS) is a database that collects reports of adverse events, medication errors, and product quality issues related to drugs and therapeutic biologic products that are regulated by the FDA. As of December 2023, 22 cases of T cell malignancy were reported out of more than 12 000 cases in the FAERS database.

Cytogenetic and clonal abnormalities are frequently present in patients before receiving CAR T therapies, suggesting that a clonal evolution of existing treatment-related clonal hematopoiesis may be a risk factor for secondary cancer in CAR T patients. Viral integrations into key hematopoiesis regulatory genes, such as TET2 and CBL, have been reported, resulting in clonal expansion in two responding CAR T patients, with no malignant transformation reported to date.

The current evidence indicates that the risk of new T cell malignancies in CAR T recipients is very low. The benefits of CAR T therapy, particularly for patients with hematologic malignancies, outweigh the risks. Although caution and further research are warranted, the therapeutic advantages of CAR T therapy remain substantial.

contrast to autologous transplantation, clonal hematopoiesis was not associated with worse survival [56]. For now, the benefits of CAR T cells clearly outweigh the risks of secondary cancer after CAR T cell treatment in patients with advanced cancer. However, the risk versus benefit for the use of CAR T cells for autoimmunity and other indications outside of oncology remains to be determined.

Locoregional infusion

CAR T cells are delivered by the intravenous route of administration for all currently approved therapies. Recently, two groups reported the use of locoregional injections of CAR T cell therapy in mouse models treating unresectable adenocarcinoma and glioblastoma [57,58]. They found that encapsulating the CAR T cells in a fibrin gel was superior to direct injection of the cells or to intravenous administration. Encapsulating CAR T cells in a fibrin gel for delivery into the tumor resection cavity enhances their persistence and functionality, leading to improved antitumor activity compared with direct injection of the cells into the cavity. These findings suggest that the local application of CAR T cells within a fibrin gel matrix can potentially mitigate the risks associated with systemic CAR T cell therapies, including the reduction of on-target off-tumor toxicities. The regional delivery of CAR T cells in fibrin gel provided antitumor activity over an extended period after surgery without causing wound-healing complications, suggesting a reduction in the risk of on-target off-tumor toxicities. Together, these studies support the use of local application of CAR T cells as a surgical adjuvant therapy for solid tumors that cannot be completely excised.

Exciting new data from three clinical trials in patients with recurrent high-grade gliomas (rGBMs) demonstrate the therapeutic potential of postsurgical intracranial delivery of CAR T cells (Figure 1). Brown and colleagues targeted IL-13Rα2 in rGBM by using an E12Y-mutated IL-13

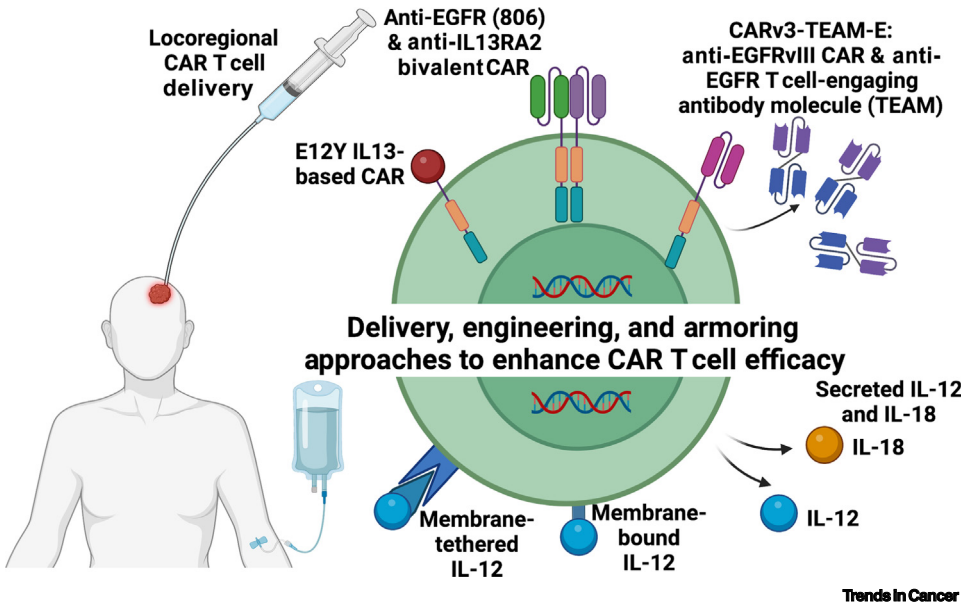

Figure 1. Advances in chimeric antigen receptor (CAR) T cell therapy of advanced glioblastoma were reported recently at three institutions. All three studies concluded that locoregional delivery of CAR T cells is superior to intravenous administration. One study used an E12Y-mutated interleukin (IL)-13 ligand to selectively target IL-13Rα2, and a second study used a bivalent CAR targeting mutated epidermal growth factor receptor (EGFR) and IL-13Rα2. The third study used a CAR targeting EGFRvIII that secreted a bispecific antibody targeting wild-type EGFR and CD3. All three studies reported evidence of tumor regression by imaging and severe neurotoxicity that was consistent with tumor inflammation-associated neurotoxicity (TIAN). Preclinical studies are testing various armoring strategies to deliver IL-12 and IL-13 to the tumor microenvironment (TME).

ligand as the targeting moiety, a strategy to increase selectivity for IL-13Rα2 and to 'detarget' from the ubiquitously expressed IL-13Rα1 [59]. In this nonrandomized trial, the overall survival was promising compared with previous trials, and pretreatment intratumoral T cell infiltration and increased interferon (FN)-γ signaling in the central nervous system (CNS) after cell infusion were positively associated with overall survival.

Choi and colleagues reported interim results from an ongoing clinical trial (NCT05660369) testing the intraventricular infusion of CARv3-TEAM (T cell engaging antibody molecule)-E T cells, which are anti-epidermal growth factor receptor (anti-EGFR)VIII CAR T cells designed to secrete an anti-EGFR T cell-engaging antibody molecule [60]. Bagley and colleagues reported interim results from an ongoing clinical trial (NCT05168423) testing the intrathecal delivery of bivalent CART-EGFR-IL13Ralpha2 cells targeting EGFR and IL13Rα2 [61]. Administration of the CAR T cells was associated with early-onset neurotoxicity, most consistent with ICANS and managed with high-dose dexamethasone and anakinra (anti-IL-1R). Both reports observed striking radiographic tumor regression that was dramatic and rapid, occurring within days after a single locoregional infusion.

Armored CAR T cells

Several engineering and combination strategies have been developed preclinically to enhance the efficacy of CAR and TCR T cell therapies in what is referred to as 'next-generation' or 'fourth-generation' cell therapies, and a few of these strategies are or have been under investigation in Phase 1 clinical trials. Armoring of CAR and TCR T cell therapies with engineered cell-intrinsic secretion of proinflammatory cytokines is one approach to enhance T cell antitumor efficacy. This approach is exemplified by the prolific iterations to integrate IL-12 stimulation into the engineered T cell (Figure 1). The earliest armoring of T cells with IL-12 demonstrated enhancement of antitumor activity in murine models of melanoma, sarcoma, colorectal adenocarcinoma, and leukemia [62–64]. In these models, constitutive secretion of IL-12 by TCR T cells demonstrated dose-limiting toxicities [63], which was improved by nuclear factor of activated T cells (NFAT)-inducible secretion of IL-12 from vascular endothelial growth factor receptor (VEGFR)2-specific CAR T cells [62]. In models of B cell leukemia, IL-12 armored CD19-specific CAR T cells induced B cell aplasia and tumor eradication in the absence of prior preconditioning, and no toxicity was observed despite constitutive secretion of IL-12, likely due to the lack of preconditioning [64].

In the first clinical study of armored T cell therapies, 33 patients with metastatic melanoma received autologous TILs transduced with a gamma-retrovirus vector expressing the IL-12 single chain under an NFAT-responsive promoter [65]. Ten of 16 patients exhibited objective responses when treated with 0.3–3 × 10^9 NFAT-IL-12 TIL doses, which were 10 to 100 times lower than TIL + IL-2 doses used in similar trials at that time. However, patients in every cohort experienced liver function toxicity, and most patients experienced fevers, which were more severe at higher cell doses. As TIL infusions contain broad specificities, the toxicities may be related to NFAT-driven IL-12 production from T cells with non-tumor reactivity, such as virus-specific T cells. These preclinical and clinical observations have inspired the innovation of more tumor-restricted IL-12 expression, including membrane-bound expression of IL-12 on the surface of CAR and TCR T cells [66,67], within the CAR ectodomain [68], on tumor cells [69], or in the TME [70].

In addition to IL-12, secretion of other proinflammatory cytokines enhances the efficacy of engineered T cells in preclinical models. For instance, expression of p40 by human GD2-specific CAR T cells and mouse B7H3-specific CAR T cells enhanced secretion of IL-23, which

was associated with an increase in granzyme B production, lower PD-1 expression, increased T cell persistence, and improved antitumor efficacy. IL-23–secreting CAR T cells outperformed IL-18– and IL-15–secreting CAR T cells in xenograft models of neuroblastoma and demonstrated a superior safety profile, as IL-18 and IL-15 secretion led to excessive body weight loss [71]. In other studies, IL-18 secretion by engineered immune cells led to enhancement of antitumor activity compared with other T cell groups. TCR T cells with NFAT-driven IL-18 secretion demonstrated enhanced anti-melanoma efficacy compared with NFAT-driven IL-12 or the combination of IL-12 and IL-18; additionally, IL-12 secretion led to significant weight loss and lethality that were not observed in groups treated with IL-18–producing T cells [72]. Three studies demonstrated IL-18-mediated enhancement of anti-leukemia activity by both human and murine CD19-specific CAR T cells due to autocrine signaling through IL-18R on the engineered T cell, which enhanced T cell persistence and activation of the antitumor functions of endogenous immune cells [72–74]. Phase 1 clinical trials (NCT04684563, NCT05989204, and NCT06287528) were initiated within the past 3 years to evaluate IL-18 secretion by anti-CD19 CAR T cells in patients with $CD19^+$ cancers. Early reports from the first trial reported complete responses in six of eight infused patients, including one patient who received 3×10^6 cells without LD [75].

Concluding remarks

Despite the profound successes in hematological malignancies, solid tumors present intricate challenges that necessitate innovative solutions (see Outstanding questions). Here, we have explored groundbreaking strategies aimed at circumventing the hostile TME, enhancing T cell fitness, and improving the specificity and safety of therapeutic approaches. In the drive to enhance efficacy, the field has witnessed the emergence of locoregional delivery methods and the development of armored CAR T cells secreting cytokines or possessing multiplex gene edits. These advancements strive not only to bolster the cancer-killing prowess of T cells within the solid tumor sanctuary but also to diminish systemic toxicities that have previously limited the scalability of such treatments. Simultaneously, the sobering implications of CAR T cell-associated severe toxicities and the rare yet concerning risk of secondary malignancies underscore the need for careful, balanced clinical translation.

As we look to the future, the continued integration of synthetic biology, gene editing, and innovative delivery methods will refine T cell therapies, potentially redefining them as the cornerstone of cancer treatment, even in the most challenging solid tumor settings. The rapid pace of discovery and translation in this field portends a new era in oncology, one where the full potential of CAR T cells can be harnessed to combat all cancers with an unprecedented precision.

Outstanding questions

How can locoregional delivery methods improve the efficacy and safety of CAR T cell therapy for solid tumors?

What are the challenges associated with T cell dysfunction and exhaustion in the tumor microenvironment in the context of engineered T cell therapy for cancer?

How does armoring CAR T cells with IL-12 and IL-18 enhance their function in targeting solid tumors, and what are the potential synergies of combining IL-12 and IL-18 therapy with other strategies in preclinical and clinical studies?

What is the long-term safety of highly engineered CAR T cells in patients with cancer, and will the safety profile be the same in patients with autoimmune disorders?

How do the overall benefits of CAR-T therapy compare with the risks associated with the development of secondary malignancies?

Author contributions

C.H.J. conceived the article. C.H.J., R.M.Y., and A.D.P. wrote the article, and A.D.P. prepared the figure and edited the manuscript. All authors approved the submitted version of the article.

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Declaration of interests

C.H.J. is an inventor of patents related to the CAR therapy product that is the subject of this review, as well as other CAR therapy products, and may be eligible to receive a select portion of royalties paid from Kite to the University of Pennsylvania. C.H.J. is a scientific cofounder and holds equity in Capstan Therapeutics, Dispatch Biotherapeutics, and Bluewhale Bio. C.H.J. serves on the board of AC Immune and is a scientific adviser to BluesphereBio, Cabaletta, Carisma, Cartography, Cellares, Cellcarta, Celldex, Danaher, Decheng, ImmuneSensor, Kite, Marble Therapeutics, Poseida, Verismo, Viracta, ViTToria, and WIRB-Copernicus group. C.H.J., A.D.P., and R.M.Y. are inventors on patents and/or patent applications licensed to Novartis Institutes of Biomedical Research and Kite and may receive license revenue from such licenses.

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