

Review

Recent Advances in the Exploitation of Cell Surface Receptors for Targeted Cell Therapies

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Abstract

The past decade has witnessed significant expansion in both preclinical and approved receptor-targeted therapeutic cell modalities. These include immune cells engineered to express chimeric antigen receptors (CARs), and bispecific immune cell engagers developed for the treatment of cancer, autoimmune disorders, infectious diseases, and metabolic disorders. Although these approaches have produced remarkable clinical outcomes, cell therapy-associated off-target toxicities continue to present significant safety challenges. This review provides a framework for the rational design of optimized cell therapies aimed at enhancing therapeutic efficacy while minimizing adverse side effects. With the state-of-the-art advances in genomic profiling, artificial intelligence-driven design tools, and scalable manufacturing technologies, the outlook for next-generation receptor-targeted cell therapies is highly promising.

Keywords: receptor; targeted therapy; immunotherapy; chimeric antigen receptor; CAR; bispecific antibody; BiTE; hapten

1. Introduction

The use of synthetic molecules for the treatment of disease has been well established for many decades. However, inspired by the pioneering work of Dr. William B. Coley in the 1890s on the role of host defense mechanism by the immune system against tumors [1], the exploitation of immune cells as living drugs (i.e., cellular therapy) to treat a pathology has become an attractive approach. Because the defense response by immune cells can be very potent, the specificity of cellular therapy to the target pathology is very critical to avoid toxicity to healthy tissue. One of the effective ways to achieve this specificity is to direct these immune cells selectively to the pathologic cells using the latter's cell-specific receptors. Such receptor-targeted cell therapies (RTCTs) capable of activating and/or engaging the host immune system have demonstrated their potential as highly targeted and adaptable treatment strategies for a wide range of human diseases, including hematological and solid malignancies, viral infections, autoimmune and fibrotic cardiovascular disorders. Indeed, publications on RTCTs indexed in the PubMed database per year have increased dramatically, rising from fewer than five in the year 2000 to approximately 500 in 2025 (Figure 1). It is to be noted that there is an associated increase in the publications related to clinical studies demonstrating the translative potential of RTCTs. This is not surprising given that several RTCTs including idecabtagene vicleucel and ciltacabtagene autoleucel have been approved for the treatment of multiple myeloma [2,3], and lisocabtagene maraleucel for B-cell lymphoma [4]. In this review, we outline strategies for designing highly specific and



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durable RTCTs, highlight different types of RTCTs with a focus on engineered chimeric antigen receptors (CARs) cells and the readily available off-the-shelf modalities such as the Bispecific T-cell engagers (BiTEs) and immunostimulatory haptens, thereby highlighting opportunities to enhance clinical effectiveness and expand therapeutic applications of cell therapies.

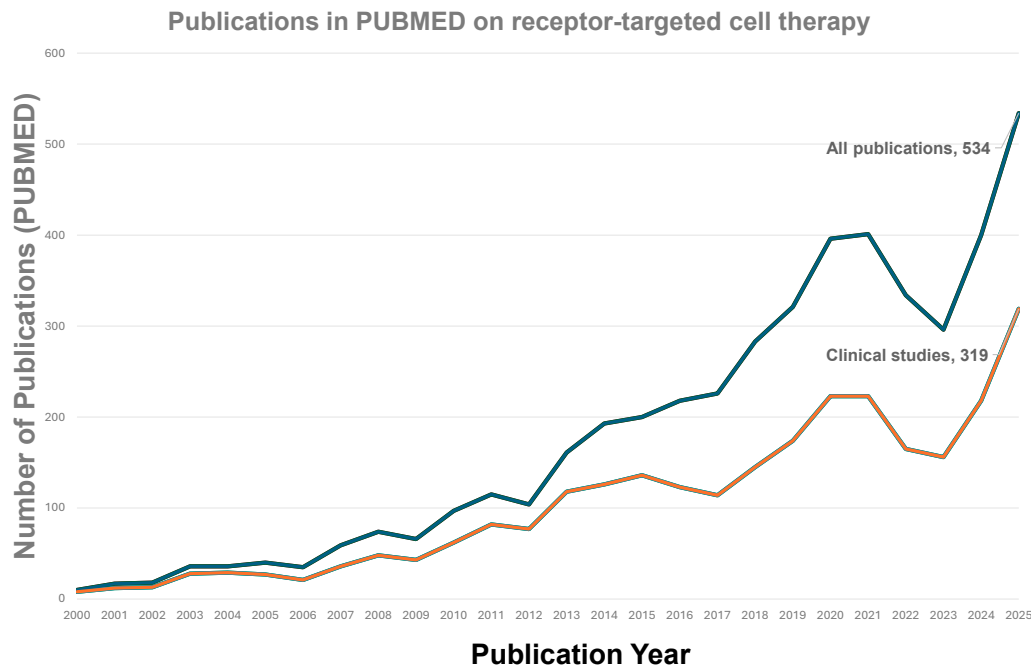


Figure 1. Increasing trend in publications on receptor-targeted cell therapy. The search was performed in PUBMED with the search term “receptor targeted cell therapy.” The search was further limited to years 2000–2025 and article types including case reports, clinical studies, and letters. Reviews and news articles were not included.

2. Design of RTCTs

The design of RTCTs involves several critical steps including (i) choice of immune effector cell, (ii) identification of appropriate cell surface receptor on the pathologic cell and a ligand that can bind to the target cell surface receptor, (iii) design of an immune cell engager that can recruit the immune cells by binding to an immune cell surface receptor, and (iv) design of a bispecific tether that connects the ligand to the immune cell engager (Figure 2). In this section, we outline each of these steps in greater detail.

Choice of immune effector cell

Engineered T cells are the most explored immune cell type that has shown clinical success. CAR-T cells provide highly specific, antigen-driven cytotoxicity along with robust in vivo expansion and the capacity to form long-lived memory populations, enabling durable responses, particularly in hematologic malignancies. Despite these advantages, CAR-T therapies are frequently associated with toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, and their effectiveness in solid tumors remains limited due to factors like T cell exhaustion, antigen heterogeneity, and the immunosuppressive tumor microenvironment [5,6]. To overcome these challenges, alternative natural killer (NK) cells and macrophages are being explored as effector cells. CAR-NK cells offer important advantages, including a lower risk of graft-versus-host disease (unlike T cells, CAR-NK cells do not kill host non-hematopoietic cells) and a reduced propensity to trigger severe cytokine release syndrome, which supports the development of allogeneic, off-the-shelf therapies [7]. However, in vivo persistence of CAR-NK is generally

shorter than that of T cells [8,9]. In contrast, CAR-engineered macrophages (CAR-M) leverage their natural ability to infiltrate solid tumors and actively remodel the tumor microenvironment through phagocytosis and cytokine secretion [10]. This makes CAR-Ms particularly attractive for solid tumor applications, though challenges remain in efficient genetic engineering, phenotype control, and sustaining antitumor activity.

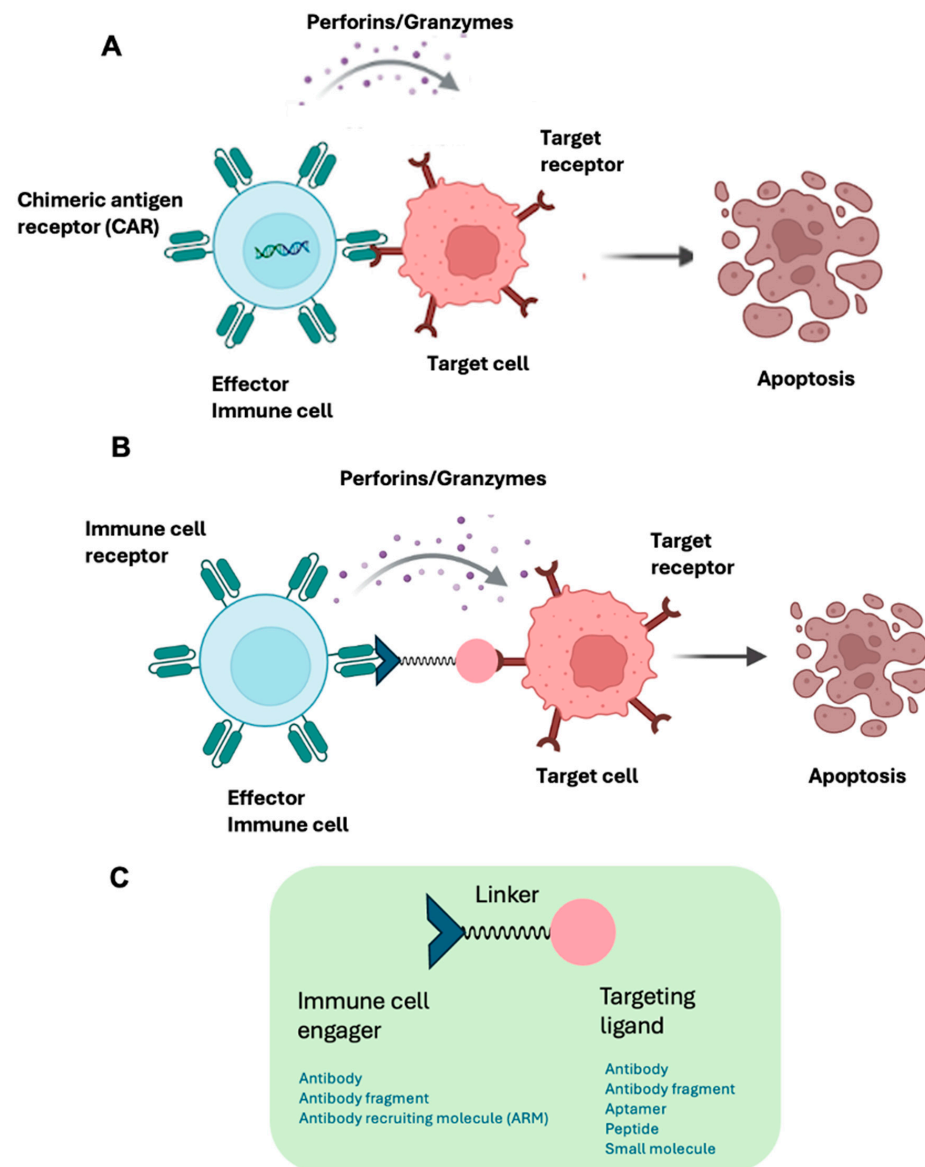


Figure 2. Schematic of receptor-targeted cell therapy: (A) The immune effector cell is tethered to the target pathologic cell either directly, as used in CAR T therapy, or (B) via a linker as employed in BiTEs or a bispecific tether in ligand–hapten conjugation. Upon target receptor recognition and binding, the effector cell releases cytotoxic agents such as perforins and granzyme, ultimately resulting in the apoptosis of the pathologic target cell. (C) The general construct of the bispecific tether consists of an immune cell engager, a linker and a targeting ligand.

Neutrophils are an emerging platform for CAR engineering, offering unique advantages including rapid recruitment to sites of inflammation and strong tumor infiltration capacity [11]. Their short lifespan and inherent plasticity, however, present significant challenges for therapeutic application, including limited persistence and the potential for protumor polarization under certain conditions [12–14]. Overall, T cells, NK cells, macrophages, and neutrophils each present distinct functional profiles and trade-offs, and

the optimal effector cell choice depends on the disease context, tumor biology, and desired therapeutic balance between efficacy, safety, and scalability. Similar pros and cons exist for non-engineered endogenous T cell and NK cell engagers.

Identification of cell surface receptors and targeting ligands

The disease-specific cell surface receptor of choice should be expressed at significantly higher levels relative to the normal surrounding tissue. One major hindrance to the widespread use of RTCTs is their associated off-target effects resulting from the ligand binding to normal tissue [15]. The Human Epidermal Growth Factor Receptor 2 (HER2), a tyrosine kinase involved in cellular proliferation, is an example of a surface receptor that is highly expressed on diseased cells but also present in normal tissue [16]. Even though HER/ErbB-targeted CAR-based modalities have been developed [17], their associated off-target side effects in the lungs have resulted in adverse toxicity effects, including severe cytokine production and death [18]. Unwanted off-target effects have also been reported in CAR T therapies targeting the Cluster of Differentiation 19 (CD19), a B cell-specific surface receptor for the elimination of B lymphoblastic leukemia cells [19]. The most successful RTCTs will therefore rely on their ability to distinguish diseased cells from healthy cells. Recent developments in the generation and availability of datasets from single-cell technologies, such as transcriptomics and proteomics [20–23] have enabled the identification of disease-specific surface receptor targets. Neoantigens, which are novel genes emerging from disease-specific cellular programs including mutagenesis, alternative-splicing events, virally derived tumor antigens, and changes in chromatin post-translational modifications that result in activation of otherwise silenced genes, also present an attractive opportunity for identifying disease-specific receptor targets for RTCT therapy [24–26].

Further, antigen density is another factor influencing the effectiveness of RTCTs. The efficiency of RTCT is often directly proportional to the number of antigen receptors presented on the target cell [27]. This is critical as it allows for the use of minimum effective dose regimens that may offer significant efficacy while showing minimal off-target toxicity [28]. Antigen loss or downregulation by cancer cells negatively impacts the efficacy of antigen-targeted cell therapies [29]. In cases where the antigen densities are low, RTCTs can be designed to target more than one receptor antigen on the target diseased cell. For example, multiple CARs that co-target CD19 and CD22 provide a concerted strong toxicity on CD19+/CD22+ leukemia cells relative to normal cells expressing either of these single antigens [30,31].

Persistence of the target receptor on the diseased cell surface is also a critical component of RTCT efficacy. Cell surface receptors involved in cellular transport and signaling hold a principal role in receptor-dependent intracellular delivery of therapeutic cytotoxic drugs as exemplified by the use of a Folic acid Receptor (FR) for the treatment of ovarian and lung cancer [32], Prostate-Specific Membrane Antigen (PSMA) for prostate cancer [33], and Glucose Transporter 1 (GLUT1) for glioblastoma [34]. However, their natural internalization may make them less favorable for RTCT, which relies on the formation of stable synaptic interactions on the surface of the target cell and effector cell. Indeed, anti-FR [35,36] and anti-PSMA CAR T therapies [37] have also had mixed results that can be attributed to their intracellular translocation. Antigen escape, a phenomenon that results in the loss of target surface receptors via genetic mutations and alternative splicing have also been reported as impediments to BCMA, CD19 and HER2-targeted RTCTs [38,39]. Trogocytosis, a contact-dependent process where an effector cell rips off pieces of the membrane (typically the receptor) from a target cell, often leaving the target cell alive, has also emerged as a potent hinderance to effective RTCTs raised against BCMA-, CD20-, CD22-positive cancers [40–43]. In addition, those receptors with persistent surface presentation on the target cell should be able to cluster in order to induce efficient cell killing by the effector

immune cells [44]. For example, CD19 engagement with CAR T cells expressing anti-CD19 CAR leads to the microcluster formation and aggregation of CARs that results in T cell activation via tyrosine kinase ZAP70 inside the cell [45,46]. Together, these reports reinforce the need for careful and strict protocols required to qualify a target receptor for an effective RTCT program.

Like receptors, the ideal and appropriate small molecule targeting ligand should be identified based on several key characteristics, including binding affinity, specificity for the target receptor, chemical and metabolic stability, and availability of functional groups that can be used for conjugation chemistry. There are several comprehensive reviews that discuss these considerations in detail [15,47,48]. The integration of structural biology in drug discovery has enabled the development of ligands with both physical and chemical properties compatible with the target receptor 3D structure. Furthermore, machine learning and artificial intelligence (AI)-based tools have revolutionized the development of ligands that bind to target receptors with high affinity and specificity [49]. The affinity of the ligand for its target cell receptor is one of the critical parameters for developing potent RTCTs. Surprisingly, ligands with moderate affinity to their targeted receptors performed better than those with high affinity. It is hypothesized that moderate affinity ensures sufficient target cell killing signaling without immune cell exhaustion [50,51], which is key for RTCTs. In a recently reported study, low-affinity single-chain variable fragment (scFv)-based CAR-NK cells exhibited better antitumor effects compared to their high-affinity counterparts, although this is not consistently observed in other cases. A high-affinity interaction of BiTE for HER2 led to increased levels of cytokine release, causing toxicity, whereas moderate affinity led to moderate antitumor efficacy, albeit a better safety profile [52]. In addition, because T cells are known to be serial killers, a low or moderate affinity with fast off rates enables T cells to switch from one target cell to another more efficiently, resulting in better overall therapeutic benefit [50]. Moreover, low affinity CAR designs have been reported to limit target antigen trogocytosis by CAR cells, thereby preventing immune cell self-attack, while promoting CAR cell persistence, and overall efficacy [40,53]. The key is to strike a balance in affinity to achieve optimal efficacy and safety of an RTCTs.

Design of an immune cell engager

The immune cell engager is designed to bind to a specific cell-surface receptor on the immune cells (Figure 2). The desired immune cell receptor is often an activating receptor or costimulatory receptors such as CD3 or CD2 on T cells, and CD16 on NK cells and macrophages. An effective RTCT cell displays an immune cell surface receptor profile that balances potent antitumor activity with persistence and safety. For example, an ideal CAR-T cell retains a quiescent but intact TCR/CD3 complex and appropriately tuned costimulatory signaling, enabling activation without chronic tonic signaling or premature exhaustion [54,55]. Bisppecific ScFv-based molecules are the most common immune cell engagers (e.g., in BiTEs) that bind the activating receptors on effector immune cells with high affinity. They are preferred over antibodies due to their small size, ease of synthesis, increased tumor penetration, and lower immunogenicity. While a high affinity of T cell engager for the T cell surface receptor is generally desired for achieving high therapeutic benefit, a recent study showed that a lower affinity BiTE can provide an optimal therapeutic window [56].

Design of the linker

The optimal linker plays a crucial role in altering the binding affinities and pharmacokinetics. Generally, the linker connecting the targeting ligand and the immune cell engager is carefully chosen to ensure the binding affinities of these two components to their target receptors on the diseased cell and immune effector cells are not affected. The

length of the linker should also be adjusted to ensure that a proper immune cell–target cell synapse is established. For instance, a flexible SGGGG repeat linker used to connect the two scFvs in bispecific antibody constructs. The number and length of repeats are chosen for the desired flexibility of the two scFvs [57]. Linker design in ligand–hapten conjugates is a central determinant of immune recruitment efficacy because it controls the spatial presentation and accessibility of the hapten relative to the targeting ligand. When a ligand is a small molecule such as a folate or short peptide, the linker must be long and flexible enough to avoid steric interference with receptor binding while ensuring that haptens such as dinitrophenyl (DNP), rhamnose or fluorescein remain solvent-exposed for productive antibody engagement. This principle has been clearly demonstrated in folate–hapten conjugates, where variations in linker length and composition significantly altered antibody recruitment and downstream antitumor activity despite similar folate receptor binding affinities. Poly(ethylene glycol) (PEG)-based linkers (e.g., PEG6) are commonly employed because they provide hydrophilicity and conformational flexibility, improving hapten exposure and reducing nonspecific interactions [58]. Such PEG-conjugated ligands have been used in several patents such as WO2025085675A1/(conjugates, compositions and methods for treating rsv infection).

3. Types of RTCTs

CAR-T cell therapies are popular types of RTCTs that require engineering of T cells either in vitro or in vivo [59,60]. Alternatively, RTCTs such as BiTEs, which are synthetic antibodies or their fragments with dual target specificity (i.e., one end binds to the disease cell target and the other end binds to effector immune cells), do not require engineered cells. They function in vivo by physically tethering host immune cells to target cells, thereby inducing cytotoxicity [57,61,62]. Similarly, immunostimulatory haptens, small immune-activating molecules recognized by pre-existing host antibodies, can be chemically linked to disease-specific receptor-targeting ligands (Figure 3). Upon binding to the diseased cell surface receptor, these constructs get recognized and bound by the endogenous antibodies and recruit immune cells, leading to antibody-dependent and/or complement-dependent cytotoxic elimination of target cells [63]. In this section, we examine the key design considerations and therapeutic trade-offs associated with CAR-T, BiTEs, and hapten-based immunotherapies, highlighting their respective clinical successes, limitations, and emerging engineering strategies aimed at improving therapeutic specificity, durability, and overall efficacy.

Chimeric antigen receptor (CAR)-based RTCTs

CARs are synthetic, modular surface receptors engineered as fusion proteins composed of three primary domains: (i) an extracellular antigen-recognition domain, most commonly a scFv derived from an antibody; (ii) a transmembrane domain; and (iii) an intracellular signaling domain designed for immune cell activation and effector function. The first-generation CAR contained scFv, a hydrophobic alpha helix transmembrane domain, and an intracellular domain based on the CD3ζ (zeta) chain of the T-cell receptor (TCR) complex. The CD3ζ would further host three immunoreceptor tyrosine-based activation motifs (ITAMs), which upon antigen interaction, are phosphorylated by lymphocyte-specific protein tyrosine kinase (Lck) and zeta-chain-associated protein kinase (Zap70) and thereby resulting in T cell activation and elimination of the target cell [59,64]. This simple CAR design was initially explored as a therapeutic for HIV and some cancers, although it offered insufficient CAR T cell activation and poor antitumor effects [65]. Subsequent CAR generations utilized additional and multiple costimulatory ITAMs derived from CD28 and CD137, thereby improving CAR T cell proliferation, in vivo persistence, and greater antitumor efficacy. The highly potent second-, third-, fourth-, and fifth-generation CARs

have since been developed and resulted in FDA-approved programs for the treatment of several hematologic malignancies [66]. Regardless of the CAR construct, CAR-T cells were designed to have their CARs engage with target pathologic cell via direct binding of the CAR to the target cell surface receptor (the traditional CAR cell therapy, Figure 3A). Alternatively, bifunctional “adapter” bridges were used to connect the target cell receptors with CARs (Figure 3B). This modular design offered the ability to control the dose and dosing frequency, thereby providing a convenient way for preventing any potential “cytokine storm” [67,68].

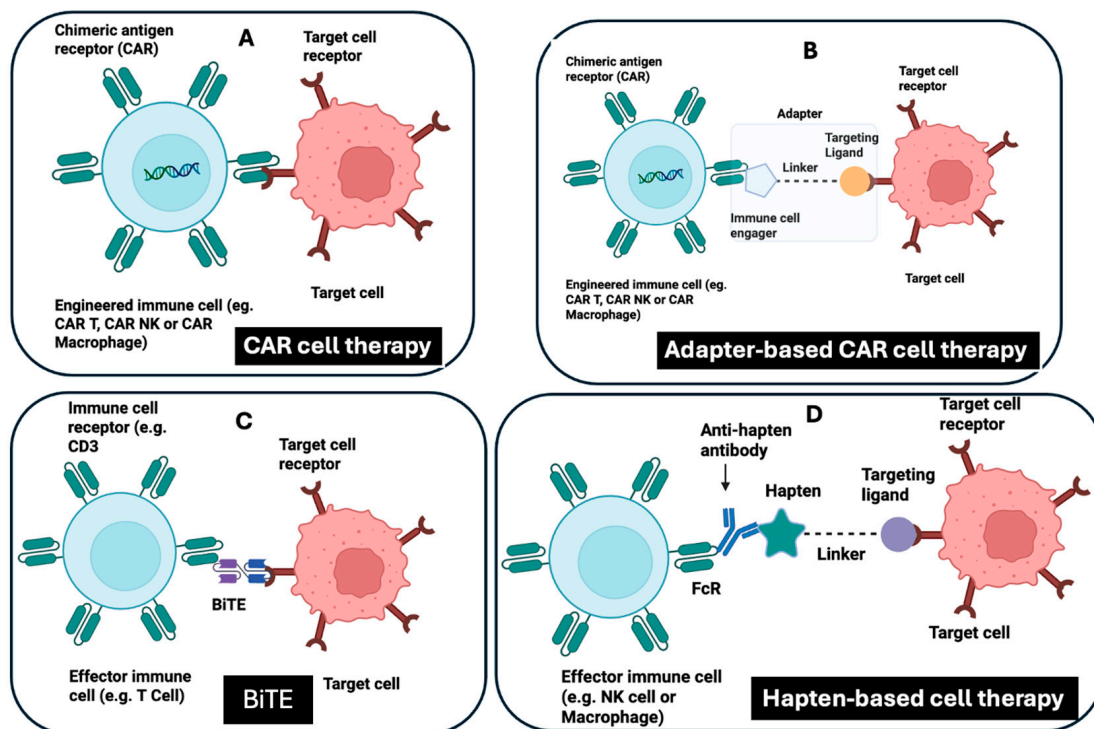


Figure 3. Common types of receptor-targeted cell therapies: (A) General CAR cell therapy involves direct binding of CAR to the targeted cell surface receptor. (B) Adapter-based CAR cell therapy that connects the CAR cell to target cell via a bispecific “adapter” bridge. (C) A common bispecific T cell engager construct that uses a bispecific scFv bridge to bring the target cell and the immune cell into proximity. (D) Hapten-based cell therapy that exploits small molecule “haptens” to stimulate immune response against target cells.

Traditional CAR T cell therapies involved isolating immune cells from the patient via leukapheresis, followed by ex vivo viral transduction to express CAR. These engineered cells were injected back into the patient in an autologous transfer. However, the high cost and time-consuming processing of ex vivo engineered cells set the stage for in vivo versions of CAR therapies. For example, FDA-approved ex vivo cell therapies, such as Tisagenlecleucel for B-ALL and Ciltacabtagene for multiple myeloma, cost around \$0.5 to 1.5 million to the patient [69,70], thus limiting access to treatment to just a few patients. In addition, the requirement for chemotherapy lymphodepletion pre-conditioning of patients and the long (~2–4 week) process of ex vivo cell engineering, and CAR cell expansion to clinically relevant levels can be obviated by in vivo CAR therapy. In vivo CAR cell engineering, in which lipid-based RNA nanoparticles and viral-based therapeutic gene cargos are delivered to selected target T and NK cells within the patient’s body, is an emerging, time- and cost-effective, platform for CAR engineering with the potential to address many of the inefficiencies of ex vivo CARs [71]. Such scalable and readily available

off-the-shelf receptor-targeted *in vivo* therapies hold great potential to improve survival chances of otherwise terminally ill patients.

An effective *in vivo* CAR seeks to achieve tissue-specific delivery and allay safety concerns associated with integrating lentiviral and retroviral vectors into unintended cells. In this view, the non-integrating and less mutagenic lipid-based RNA nanoparticles (LNPs) have also gained interest and achieved early preclinical success. In addition to the components of the *ex vivo* CAR, the *in vivo* CAR cargo will also contain a target immune cell receptor binder, such as CD7 and CD3, to promote T cell-specific tropism of therapeutic vectors upon injection into the patient. LNP-RNA cargos have also been pre-coated with immune cell receptor-targeted antibodies or ligands to promote binding, internalization and release of the therapeutic mRNA CAR. While there are presently no FDA-approved *in vivo* CARs, preclinical and clinical studies utilizing this newly emerged technology show great promise and future for *in vivo* cell therapy [60,71,72].

While CAR-T therapies have had clinical success, particularly in liquid cancers, their on-target off-site side effects, high manufacturing costs, and their dismal success against solid tumors arising from antigen heterogeneity and immunosuppressive tumor microenvironment (TME) have prompted growing interest in the exploration of natural killer (NK) cells and macrophages of the innate immune system. NK cells have intrinsic antitumor cytotoxicity and can rapidly respond and destroy stressed cancer cells via direct target cell delivery of perforins and granzymes [73,74]. In addition, NK cell-derived inflammatory cytokines promote mobilization and recruitment of other members of the host immune system, thereby exerting a concerted antitumor activity [75]. Intriguingly, unlike CAR-T, which is vulnerable to the negative effects of target antigen escape, NK-based CARs retain their intrinsic cytotoxicity against tumor cells even after target antigen loss. These intrinsic qualities make NK-based CARs superior alternatives to CAR-T, especially in complex heterogeneous TME of solid cancers. Consistently, CAR-NK modalities including those raised against HER2 [76,77] and Delta-like ligand 3 (DLL3) [78,79] for solid cancers have been explored in both preclinical and clinical settings. Macrophages expressing CARs (CAR-Ms) have also attracted attention in recent immunotherapy protocols resulting in considerable strides in the fight against solid cancers [80,81]. The high abundance of macrophages in solid tumors [82–84] make CAR-Ms attractive alternatives to circumvent the immunosuppressive tumor microenvironment and limited tumor infiltration ability observed in other effector immune cells. Recent preclinical and clinical evaluation of CAR-M for the treatment of Myeloid differentiation primary response 88 (MyD88)-positive gliomas and HER2-breast cancer have presented CAR-Ms as potentially effective immunotherapy strategies against solid cancers [85,86]. Nevertheless, CAR-Ms and CAR-NK continue to face engineering challenges due to poor *ex vivo* viral infectivity for CAR cell generation, high cost of manufacturing, and limited persistence following delivery into the recipient patient [9,87,88].

Several strategies to enhance the application of T-, M- and NK-based CARs have been proposed and range from the development of multi-target CARs to overcome antigen heterogeneity challenges [89,90], direct intratumoral delivery of CAR cells to promote accessibility to target antigens [91,92], as well as strategies combining pro-inflammatory adjuvants designed to outcompete the immunosuppressive tumor-derived cytokines [9,93,94]. Intriguingly, the versatile universal CAR designs based on T and NK cells have been explored and offer the ability to target more than one antigen receptor via the use of modular adapter molecules (Figure 3B). In this instance, CAR T and CAR NK cells engineered to target fluorescein have been developed to detect and bind bispecific adapter molecules containing fluorescein conjugated to folate, a natural ligand for folate receptor that is highly expressed on cancers [67,95–98], fluorescein conjugated to anti-B7-H3 antibody for osteosar-

coma [99], and fluorescein conjugated to HIV antibodies [100]. Other adapter bridges have replaced fluorescein with biotin, small peptides, among others [5,101]. While universal CARs are still in their exploratory stage, they represent a highly attractive avenue in the fight against therapy resistance arising from tumor heterogeneity and antigen escape while also providing off-the-shelf treatment options.

BiTEs

Another highly efficient but simple in vivo RTCT is to recruit the immune system using soluble molecules without the need for cell engineering. Such in vivo RTCTs have employed bispecific T cell engagers (aka BiTEs) consisting of an antibody fragment that binds to the T cell antigen (e.g., CD3) on one end and a disease cell surface receptor (e.g., BCMA on multiple myeloma cancer cells) on the other end (Figure 3C). Unlike adapter bridges utilized in universal CARs, these synthetic BiTEs target pre-existing effector and target cell surface receptors. Consequently, BiTEs, which utilize ligand-based linkers, bind and bring together the target and effector killer cells, thereby improving target specificity [102] without MHC restriction or the need for engineering of effector immune cells. Interestingly, secreted BiTEs have also been incorporated into engineered CAR T constructs such that CAR cell-derived circulating BiTEs recruit and engage bystander effector cells with potential to effect target cell death even after the loss of the CAR antigen. In this system, in addition to the components of a conventional CAR, bispecific scFv antibody fragments are cloned in tandem to target both effector cell receptor (e.g., CD3) and diseased cell receptor (e.g., EGFR or CD19). The incorporation of Immunoglobulin Kappa leader sequence upstream the BiTE then facilitates the cleavage and secretion of BiTEs that can bind and bring together target and effector cells in a manner similar to that of exogenous BiTEs [103–105]. In the clinic, BiTEs have shown effective tumor elimination, especially in hematological cancers. Their effectiveness is limited in solid tumors due to immunosuppressive TME [106].

Hapten-based RTCTs

Use of small molecule haptens that have pre-existing endogenous antibodies naturally present in humans has also been explored for RTCT [63]. Haptens such as, DNP, rhamnose, and alpha-Gal are connected to the targeting ligands to generate bifunctional bridges. When administered, these bispecific bridges bind to pathogenic cells via the ligand on one end and to circulating antibodies on the other (Figure 3D). These antibody-bound bridges bind to Fcγ receptors, thereby recruiting and activating the immune NK cells and macrophages to kill pathologic cells via antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and/or complement-dependent cytotoxicity (CDC) [107,108].

The early generation of hapten-based RTCT involved decorating cancer cells with folate-conjugated fluorescein for which antibodies were induced by vaccination in mice [109]. The folate-fluorescein bound to folate receptors on the cancer cells in mice carrying tumors induced an immune response to kill the cancer cells, leading to a reduction in tumor size. A similar approach was then used for eliminating folate receptor β-expressing macrophages for the treatment of rheumatoid arthritis [110]. Anti-rhamnose antibodies generated using rhamnose glycoconjugates were used to treat melanoma [111]. Recent work in hapten-based cancer immunotherapy has emphasized the role of hapten-based conjugates as enhancers of adaptive and innate antitumor responses [108]. Such hapten-based immunotherapy was also applied to treat infectious diseases. Recent work by Liu et al. showed that zanamivir–DNP conjugates effectively treated influenza infection in pre-vaccinated mice [112]. More recent work used a combination of two different haptens: DNP and rhamnose conjugated to the same zanamivir molecule [113]. The resulting dual hapten conjugate produced higher efficacy against the influenza infection. Finally, an alter-

nate approach is where an antibody's crystallizable fragment (Fc) can be used as a "hapten surrogate" as it can bind to Fc-receptors expressed on the surface of various immune cells, leading to antibody-dependent cellular cytotoxicity against viral infections [114].

4. Future Outlook

Conventionally, receptor-targeted therapies have employed small molecules, peptides, proteins, aptamers, and gene-targeting oligonucleotides. However, broader application of these strategies is often constrained by low specificity, high systemic toxicity, high cost, and reduced efficacy due to disease heterogeneity and adaptive resistance mechanisms [115–117]. Together, these limitations have fueled growing interest in receptor-targeted cell therapies capable of specifically recognizing, destroying, and dynamically responding to diseased cells.

By exploiting disease-specific surface receptor expression patterns, RTCTs enable the directed recruitment of cytotoxic host T cells, natural killer (NK) cells, macrophages and other effector cells toward pathological targets. Despite encouraging clinical successes, this emerging field continues to face challenges related to specificity, safety, and manufacturing costs that limit widespread application. However, advances in single-cell technological breakthroughs, such as transcriptomics and proteomics, have revealed a vast landscape of cell surface receptors, while engineering improvements in cell and viral vector manufacturing and processing have improved the overall cost and speed of the production of RTCTs. Altogether, the future looks very promising for the application of novel RTCTs for the treatment of various diseases.

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