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Recent advances in biomaterial designs for assisting CAR-T cell therapy towards potential solid tumor treatment

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Chimeric antigen receptor T (CAR-T) cells have shown promising outcomes in the treatment of hematologic malignancies. However, CAR-T cell therapy in solid tumor treatment has been significantly hindered, due to the complex manufacturing process, difficulties in proliferation and infiltration, lack of precision, or poor visualization ability. Fortunately, recent reports have shown that functional biomaterial designs such as nanoparticles, polymers, hydrogels, or implantable scaffolds might have potential to address the above challenges. In this review, we aim to summarize the recent advances in the designs of functional biomaterials for assisting CAR-T cell therapy for potential solid tumor treatments. Firstly, by enabling efficient CAR gene delivery *in vivo* and *in vitro*, functional biomaterials can streamline the difficult process of CAR-T cell therapy manufacturing. Secondly, they might also serve as carriers for drugs and bioactive molecules, promoting the proliferation and infiltration of CAR-T cells. Furthermore, a number of functional biomaterial designs with immunomodulatory properties might modulate the tumor microenvironment, which could provide a platform for combination therapies or improve the efficacy of CAR-T cell therapy through synergistic therapeutic effects. Last but not least, the current challenges with biomaterials-based CAR-T therapies will also be discussed, which might be helpful for the future design of CAR-T therapy in solid tumor treatment.

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1. Introduction

In recent decades, immunotherapy, which relies on the body's immune system to target and destroy cancer cells by activating

the immune response, has been successful in increasing cure rates and reducing side effects.¹ As an important approach of immunotherapy, chimeric antigen receptor T (CAR-T) cell therapy involves collecting, modifying, and re-injecting a patient's T-cells to enhance the immune system's ability to attack cancer cells. Although CAR-T cell therapy has achieved remarkable efficacy in the treatment of hematological tumors,^{2–5} there are still limitations for solid tumor treatments, such as high cost, uncontrolled safety, lack of precision, and poor infiltration or visualization ability.⁶ In particular, the

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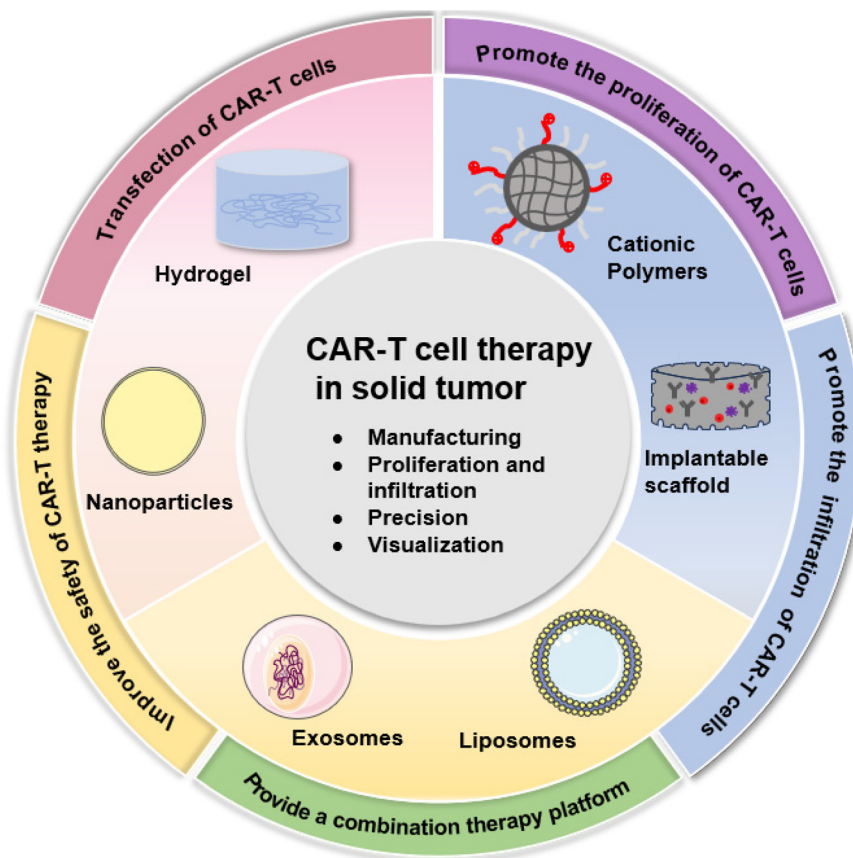


Fig. 1 The application of biomaterial designs (in terms of liposomes, exosomes, nanoparticles, hydrogel, cationic polymers, or implantable scaffold) in assisting CAR-T cell therapy towards solid tumor treatment.

complex tumor microenvironment (TME) in solid tumors affects the proliferation and infiltration of CAR-T cells.⁷ Fortunately, recent reports have shown that biomaterial vectors are widely used in CAR-T therapy to address these challenges. They can enhance the immunomodulatory effects of CAR-T therapy, deliver targeted treatments, and provide early warning of toxic side effects. For CAR gene delivery vectors, non-viral gene delivery vectors such as liposomes and polymers are popular biomaterial designs and have low toxicity or immuno-

genicity.⁸ In the case of overcoming the complex TME, biomaterial designs can be loaded with cytokines to induce CAR-T cell proliferation⁹ and biomaterial scaffolds loaded with cytokines can provide a three-dimensional microenvironment for CAR-T cell proliferation and survival.¹⁰ Furthermore, functional biomaterial designs can promote CAR-T cell infiltration by modulating the TME, and provide a platform for CAR-T cell therapy in combination with other therapies such as radiotherapy, chemotherapy, photothermal therapy (PTT), immune checkpoint inhibitor therapy and sonodynamic therapy (SDT).¹¹⁻¹⁴ Last but not least, biomaterials with environmentally responsive design might also improve the precision of delivering CAR-T cells and reduce toxic side effects.¹⁵ In short, this review aims to summarize the current challenges of CAR-T cell therapy in solid tumors, with focus on the role of functional biomaterials in addressing these issues, as well as possible strategies to promote the solid tumor treatment efficacy of CAR-T cell therapy (Fig. 1).



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2. Challenges of CAR-T cell therapy in solid tumor treatment

So far, the FDA has approved six CAR-T products, based on the outstanding success of CAR-T cell therapies in patients with



hematologic cancers.^{16–18} However, CAR-T cell therapy still faces several limitations or challenges in solid tumor treatments (Fig. 2). Firstly, CAR-T cell therapy involves four stages: T cell isolation and enrichment, activation, genetic engineering and expansion.¹⁹ The complex process and the individualization for patients usually lead to high cost,²⁰ limiting the advancement and accessibility of the product towards clinical trials. Currently, lentiviral vectors (LVs) and retroviral vectors (RVs) are frequently utilized in CAR-T products.^{17,21–24} But these viral vectors are hindered by immunogenicity, cytotoxic and low capacity issues.²⁵ Furthermore, T cell culture^{26,27} and virus purification^{25,28,29} are time-consuming, which contributes to the high cost of CAR-T treatments. Secondly, the complex tumor microenvironment (TME) in a solid tumor provides physical and biological impediments, in cases of abnormal vascular distribution,³⁰ hypoxia,⁷ or acidic microenvironment³¹ within tumor tissues.³² It also limits the proliferation and infiltration of CAR-T cells, resulting in poor outcomes in the treatment of solid tumors.^{9,33} The TME also contains a variety of cells with immunosuppressive capacity, such as regulatory T cells and tumor-associated macrophage (TAM). Their overexpression of cytokines with immunosuppressive capacity such as transforming growth factor β (TGF β), interleukin-10 (IL-10), interleukin-8 (IL-8)^{7,34} creates a molecular biology barrier. These factors constitute an immunosuppressive environment that can significantly reduce the efficacy of CAR-T cells.⁹ Thirdly, CAR-T cell therapy for cancer has con-

cerns on undesired off-target effects.³⁵ Another problem posed by the lack of precision in CAR-T therapy is the cytokine storm. CAR-T cells are transfused back into the patient's body, the body will release a large amount of cytokine, resulting in toxic side effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).^{36–38} Studies have shown that the critical factors, determining the incidence and severity of CRS or ICANS, are the design of the CAR, the specific target, and the tumor type.³⁹ Last but not least, monitoring the efficacy and safety of CAR-T cell therapy is challenging.^{40,41} Due to the uncertainty of CAR-T therapy and possible side effects accompanying the entire process, *in vivo* assays are needed to understand its efficacy and pharmacodynamics.⁴² Imaging techniques such as computerized tomography (CT) and magnetic resonance imaging (MRI) fail to detect the spatial distribution of CAR-T cells in solid tumors.⁴³ Thus, the incapacity to monitor the accumulation of CAR-T cells in tumors using clinical imaging modalities is a key obstacle in CAR-T cell therapy for solid tumors. In short, the above issues, including high cost connected with the complex manufacturing process, complex tumor microenvironment, lack of precision, and poor visualization ability, are significant endeavors that should be resolved for CAR-T therapies towards potential solid tumor treatments.

Recent studies have shown that combining functional biomaterials with CAR-T cell therapy is a promising strategy.⁴⁴ In

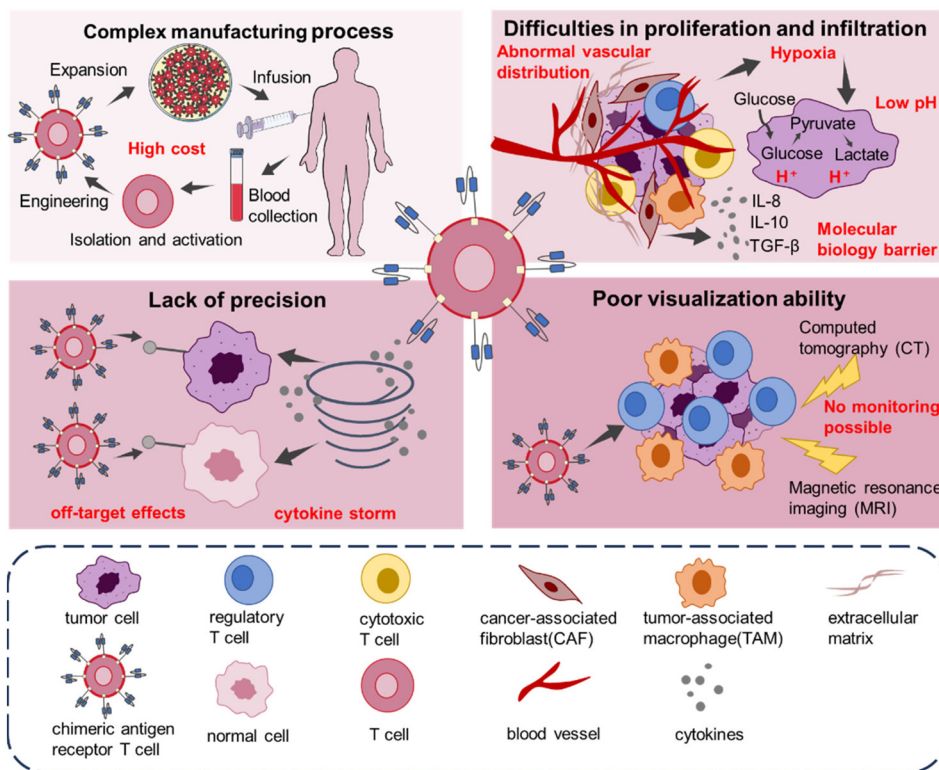


Fig. 2 Schematic of the complex manufacturing process, difficulty in proliferation and infiltration, lack of precision, and poor visualization ability in CAR-T cell therapy towards solid tumor treatment.



the treatment of solid tumors, functional biomaterials have shown vitality in drug delivery and imaging therapy.^{45,46} Functional biomaterials allow the development of novel transfection reagents. Biomaterials, in terms of liposomes or cell vesicles, possess low immunogenicity and biocompatible or cost-effective advantages, making them ideal inert carriers for CAR gene transfection.^{47,48} Furthermore, T-cell transfection *in situ* is made possible by introducing functional biomaterials. It can streamline the preparation procedure and make CAR-T cell therapy significantly less expensive. There are also functional biomaterials that have undergone modifications to exhibit immunomodulatory characteristics. These materials can respond to and regulate the TME, enhancing the efficacy of CAR-T cell therapy.⁴⁹ When loaded with cytokines, biomaterials can even further enhance T cell proliferation and differentiation *in situ*.⁵⁰ Furthermore, functional biomaterials can be employed as carriers to enclose CAR-T cells and deliver them to the tumor location by controlled release. It can improve the targeting of CAR-T cell therapy and reduce off-target effects. While developing CAR-T therapies, it is also necessary to develop corresponding diagnostic technologies to monitor CAR-T concentration and therapeutic efficacy in real time, as well as to monitor treatment-related side effects. It is possible to reflect T cell activation and functional status by targeting cell surface markers or key substances in metabolic pathways.^{51,52} Therefore, the application of functional biomaterials in assisting CAR-T cell therapy might be with promising future.

3. Functional biomaterials enhance the efficacy of CAR-T cell immunotherapy

The process of CAR-T therapy for treating solid tumors involves the use of functional biomaterials such as nanoparticles, polymers, liposomes, and exosomes⁵³ (Table 1). Firstly, functional biomaterials can improve the manufacturing of CAR-T cells. Biomaterial-based non-viral genetic vectors with low cytotoxicity, low immunogenicity and high safety provide new ideas for the transfection of CAR-T cells. Gene delivery vectors based on functional biomaterials are safer and with less cytotoxic effects, in comparison with traditional viral vectors. It can improve the manufacturing process of CAR-T cells in a more cost-effective mass production manner. Secondly, the application of various functional biomaterials can remodel TME to promote the proliferation and infiltration of CAR-T cells, and improve the effect of tumor immunotherapy. In addition, functional biomaterials can provide a combination therapy platform for CAR-T cell therapy, which can also improve the targeting of CAR-plasmids and CAR-T cells, and mitigate the off-target effect of solid tumors. Moreover, it enables the integration of diagnosis and treatment to avoid the toxic side effects of CAR-T therapy. The following section

will explore the application of functional biomaterials in CAR cell therapy from the above perspective.

3.1. Transfection of CAR-T cells

Gene delivery vectors can be optimized for different types of T cells to achieve higher efficiency and selectivity, an important aspect of CAR-T cell manufacturing. Currently, most CAR-T therapies use LVs or RVs to introduce genes into the precursor or stem cell genomes *in vitro*.^{67–71} Although viral vectors have high gene delivery efficiency, they can cause immune responses and uncertainty in gene insertion.⁷² Yu *et al.* constructed epidermal growth factor receptor variant III CAR expression plasmid vectors for third-generation intracellular expression of CAR-targeting EGFR variant III. It was found that self-assembled nanoparticles (pEGFRvIII-CAR@SNPs) could exhibit high efficiency and reduced cytotoxicity in gene transfection of Jurkat cells, which has considerable potential for T cell transient CAR modification.⁷³ With the wide use of mRNA coronavirus vaccines, non-viral vectors have attracted more and more attention.⁷⁴ Compared to viral vectors, non-viral vectors are less cytotoxic, less immunogenic and less mutagenic, and the target gene is not integrated into the host genome after transfection using non-viral vectors.⁷⁵ Chen *et al.* successfully transfected CAR into primary T cells with the help of vertically aligned silicon nanotubes (Fig. 3A). It has higher delivery efficiency and CAR expression efficiency than electroporation.⁶² Inoo *et al.* found that electroporating mRNA into T cells to create anti-VEGFR2 CAR-T cells has similar anti-tumor effects as single retroviral vector-modified CAR-T cells.⁷⁶ In addition, non-viral vectors for CAR-T cell therapy products are simpler to manufacture, leading directly to lower costs and easier quality control. Bozza *et al.* developed non-integrated DNA nanocarrier nano-S/MARt vectors that can generate active CAR-T cells. This platform is advantageous because it does not contain viral components, making it non-immunogenic, simple, and versatile. It is capable of extrachromosomal replication in the nucleus of dividing cells and provides sustained transgene expression in human T cells without compromising their behavioral and molecular integrity.⁷⁷ Billingsley *et al.* screened a sequential library of ionizable lipid nanoparticle (LNP) formulations with different excipient components, and the prepared B10 LNPs of formulation increased mRNA delivery by 3-fold. It also reduced cytotoxicity and showed potent cancer cell killing power, and the prepared B10 LNPs provided new ideas for an effective mRNA delivery platform for iMPIT cell engineering.⁷⁸ But both transduction *in vitro* and electroporation processes carry significant costs and risks.

Therefore, researchers have turned their attention to generating CAR-T cells *in vivo*. Since the process of producing CAR-T cells *in vitro* is not required, the cost of T-cell culture can be reduced, resulting in a substantial reduction in the price of CAR-T cell therapy with this strategy. Furthermore, it does not require the use of initial cells and there are no immune problems. Compared with *in vitro* CAR-T cells, *in vivo* CAR-T cells have better performance and self-renewal ability. Agarwal *et al.* used LV targeting CD8⁺ cells to induce CAR-T cells *in situ* in





Table 1 Functional biomaterial designs in CAR-T cell therapy

Types	Strategies	Functions	Ref.	Advantages	Disadvantages
Liposomes	Engineering lipid nanoparticles of CD19 CAR	Non-viral gene vectors	54	Delivery of drugs or genes through fusion with cell membranes, good biocompatibility, low cytotoxicity, high drug stability	Low encapsulation rate and prone to leakage
Polymers	To add SCH-58261 to lipids, encapsulate the A2aR antagonist SCH-58261 into lipid nanoparticles, and embellish to CAR-T cells	To promote infiltration of CAR-T cells	49		
	mRNA core coalesced with poly(β -amino) ester with anti-CD3/CD8-modified poly (glutamic acid) as shell	Non-viral gene vectors	55		
	Preparation of hyaluronic acid-based hydrogels to load CAR-T cells targeting human chondroitin sulfate proteoglycan 4	Implantable stents	56		
	Mixing CAR-T cells, cytokines and light curable gelatin methacrylate hydrogel PMN-mediated CAR-T cells	Partial delivery of CAR-T cells	10		
Exosomes	Poly(lactic-glycolic) acid (PLGA) nanoparticle loaded with indocyanine green	To promote infiltration of CAR-T cells	57	Higher stability and drug retention efficiency with different polymers for multiple drug delivery modes	Controllability and biocompatibility of drug release kinetics in polymer delivery systems need to be improved
	Interleukin-15 and an injectable hydrogel	Photothermal therapy	58		
	IL-6-specific antibody conjugated to a thermo-sensitive hydrogel poly(<i>N</i> -isopropylacrylamide- <i>co</i> -methacrylic acid)	To improve targeting	59		
	Loading specific mRNA into exosomes using phage shell protein MS2	Suppress CAR-T-cell-induced cytokine storm	60		
	Transfection of CARs into primary T cells <i>via</i> vertically aligned silicon nanotube arrays	Non-viral gene vectors	61	Good stability in blood, natural targeting ability, low immunogenicity	Difficulty in purifying exosomes and obtaining high yields of pure exosomes
	Loading of IL 12 in human serum albumin nanoparticles and incorporation into CAR-T cells to prepare redox-responsive protein nanopreparations	Non-viral gene vectors	62	Good biocompatibility and tunability, low toxicity, self-degradable	Preparation of stable structures is more difficult to achieve
Nanoparticles	Nanoparticles loaded with antigen	Partial delivery of CAR-T cells	63	High stability, low cost, wide range of applications	Complex preparation process and poor batch-to-batch reproducibility
	PNP-nanoparticle-based hydrogels	To improve targeting	64		
	Lipid nanoparticle system with a surface modified by CD3 antibody was constructed containing IL-6 shRNA and CD19-CAR	Enhanced expansion of CAR-T cells Transfection of CAR-T cells	65 66		

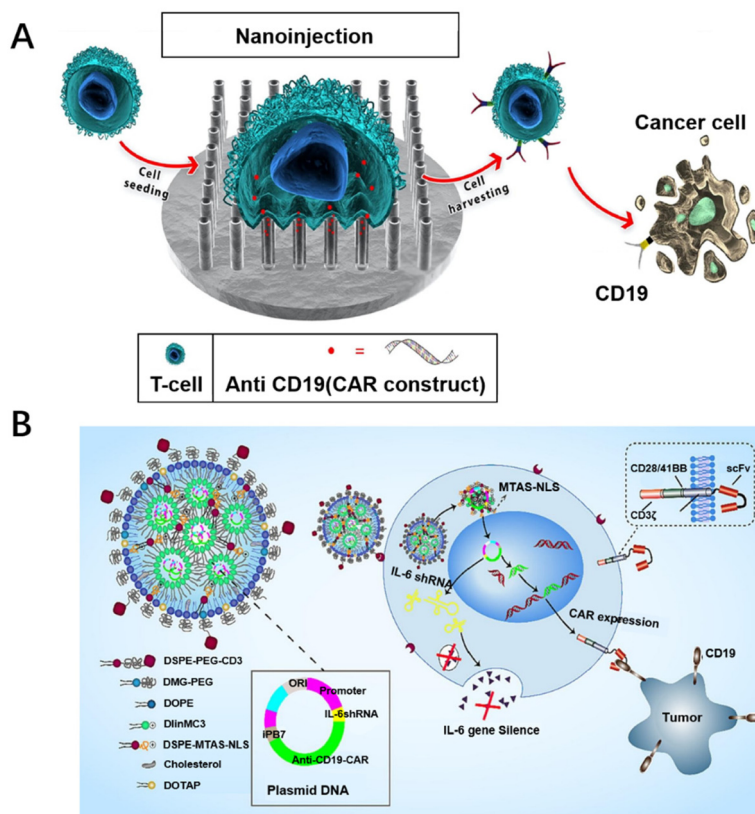


Fig. 3 Biomaterial designs for promoting the transfection of CAR-T cells. (A) Vertically aligned silicon nanotube arrays successfully transfect CAR into primary T cells. Reproduced with permission.⁶² Copyright 2023, Elsevier. (B) A lipid nanoparticle system with a surface modified with CD3 antibodies was constructed containing plasmids of interleukin 6 short hairpin RNA (IL-6 shRNA) and CD19-CAR (antiCD3-LNP/CAR19⁺ shIL6) combination genes to stably transfect T cells. Reproduced with permission.⁶⁶ Copyright 2022, Elsevier.

immune-deficient NOD-scid-IL2Rc null mice.⁷⁹ However, in their study, CAR-positive NK and NKT cells would also be detected, which might be due to the non-specificity of the lentiviral vector. To improve the non-specificity of lentiviral vectors, non-viral vectors modified with biomaterials have been reported. As a typical example, Zhou *et al.* constructed a CD3 antibody-modified LNP (antiCD3-LNP/CAR19⁺ sh-IL6) wrapped in a plasmid system, mediated by CD3 antibodies to target T cells, stably transfecting T cells *in vivo* with the nuclear localization peptide MTAS-NLS, which produced IL-6 hypersecretory CAR-T cells directly *in vivo* to kill CD19-high expressing leukemia tumor cells (Fig. 3B).⁶⁶ Recently, Zhu *et al.* achieved *in situ* manufacture of CAR-T cells in mice by self-assembling mPEG-PCL-PEI with T-cell-targeted anti-CD3ε f(ab')₂ fragment and α-cyclodextrin, loading plasmid CAR, and realizing the effective aggregation of CAR-T cells at tumor sites.⁸⁰ Biomaterial designs can be used to deliver CAR-expressing genes directly to circulating T cells *in vivo*, enabling the *in situ* generation of CAR-T cells, simplifying the process of CAR-T cell preparation, making it simple and economical to prepare, and providing a new idea for CAR-T cell therapy.

In short, functional biomaterial designs have become a popular choice for gene delivery due to their low cost, good biocompatibility, low toxicity and low immunogenicity.

Different biomaterials such as liposomes,⁸¹ polymers⁸² and exosomes^{83,84} as vectors can overcome the insecurity of viral vectors and electroporation methods, providing new opportunities for the widespread use of CAR-T therapies for solid tumors (Table 2). CAR-T cells can be generated *in vivo* by using different biomaterials as gene delivery vectors, simplifying the CAR-T cell preparation process and reducing costs, with a similar therapeutic effect.

3.2. Promotion of the proliferation of CAR-T cells

Providing appropriate growth factors and cell culture conditions can promote the proliferation of CAR-T cells and afford sufficient numbers of CAR-T cells. Consequently, cytokines loaded on biomaterials can induce T cell proliferation and differentiation *in situ*. This approach has been shown to enhance the efficacy and safety of preclinical models.⁴⁴ For example, Liu *et al.* used integrated mesoporous silica nanoparticles as carriers loaded with IL-2 and transforming growth factor-β (TGF-β) to achieve the combined release of IL-2/TGF-β, promoting the proliferation and differentiation of terminal effector T cells through the up-regulation of perforin, granzyme B and interferon-γ (Fig. 4A).⁹⁰ By regulating the immune microenvironment, inducing vascular normalization, recruiting cytotoxic T cells and inducing T cell proliferation and



Table 2 Biomaterial designs for CAR-T cell generation

Gene vectors	Types	Genes	Models	<i>In vivo/vitro</i>	Ref.
Viral vectors	<i>Lentiviral vectors</i>	—	B Cellular tumors	<i>In vivo</i>	85
	SINV-LV				
Non-viral vectors	<i>Retroviral vectors</i>	—	Cell ablation	<i>In vivo</i>	86
	Bicistronic retroviral vector encoding				
Non-viral vectors	<i>Lipid nanoparticles</i>	shRNA	Leukemia	<i>In vivo</i>	66
	AntiCD3-LNP/CAR19 ⁺ shIL6				
	CAR mRNA/9322-O16B LNP	mRNA	Leukaemia	<i>In vitro</i>	87
	<i>Cationic polymers</i>	DNA	T lymphocytes	<i>In vitro</i>	88
	Polymeric nanomicelles carrier for piggyBac				
	pDNA@SNPsx/y	pDNA	Jurkat T cells	<i>in vitro</i>	73
	PBAE 447 polymer-microtubule-associated nuclear localization peptide	DNA	Leukaemia	<i>In vivo</i>	89
	CD3-targeted polymeric nanoparticles carrying Cy5-labeled mRNA	mRNA	T lymphocytes	<i>In vitro</i>	55
	<i>Exosomes</i>	mRNA	T lymphocytes	<i>In vitro</i>	61
	Exosome delivery platform				

differentiation, it can effectively improve the efficacy of CAR-T cell therapy.⁹¹ Meanwhile, the implantable scaffold provides a platform technology for the programming of CAR-T cells that may stimulate novel therapeutic approaches. Implantable scaffolds are scaffold structures that can be implanted in the body and are usually made of biodegradable materials. They provide a three-dimensional microenvironment in which CAR-T cells can grow and differentiate, thereby enhancing their viability and aggressiveness.⁹² Agarwalla *et al.* have developed a multifunctional alginate scaffold (MASTER) for T cell programming and release, which is modified with antibodies and encapsulates cytokines to promote cell proliferation. Mice treated with MASTER CAR-T cells showed better anti-tumor effects and greater persistence (Fig. 4B).⁵⁰ Therefore, specific cytokines can be delivered by using biomaterial designs to promote CAR-T cell proliferation.

3.3. Promotion of the infiltration of CAR-T cells

Biomaterial-based delivery systems have been developed to modify and improve TME by addressing abnormal vascular distribution, hypoxia, acidity, and heterogeneity. They also promote the infiltration of various immune cells and enhance the activity of anti-tumor immune cells, resulting in improved efficacy of immunotherapies.⁹³ For example, Deng *et al.* have developed a nanomedicine called F3-low molecular weight heparin-hydrazone-gambogic acid (FLG) that can repair abnormal tumor vasculature by inhibiting the VEGF/VEGFR2 pathway. They also designed another nanomedicine, MAR/MPA, by loading maraviroc (MAR) loaded with methoxypoly(ethylene glycol)-poly(lactic acid) (mPEG-PLA, MPP) nanoparticles modified with benzamide lipid derivatives (MPA), which can selectively inhibit the C-C motif chemokine ligand 5 (CCL5)/C-C chemokine receptor type 5 (CCR5)-related pathway in the tumor tissues. The nanosystem with the combination of FLG and MAR/MPA directly regulates vascular endothelial cells, induces vascular normalization, promotes recovery of the vascular system, remodels the TME, and improves therapeutic efficacy.⁹⁴ Luo *et al.* used alginate microspheres loaded with interleukin-15 (IL-15) to fabricate an injectable

immuno-microchip (i-G/MC) system. They also used marine extracellular hemoglobin as an oxygen carrier, which continuously released oxygen after injection to remodel the TME, contributing to the infiltration of CAR-T cells.⁹⁵ For example, Yang *et al.* modified a biodegradable hollow manganese dioxide (H-MnO₂) nanopatform with poly(ethylene glycol) (PEG). The photosensitizer chlorine e6 (Ce6) and the anticancer drug doxorubicin can be co-loaded in this hollow H-MnO₂-PEG nanopatform with high loading capacity (HMnO₂-PEG/C&D). The obtained H-MnO₂-PEG/C&D dissociates at acidic pH to release the loaded drug while triggering the decomposition of the tumor's endogenous H₂O₂ to produce oxygen, thus alleviating hypoxia.⁹⁶ Adequate oxygen in the TME can downregulate the expression of hypoxia inducible factor 1 α (HIF-1 α) and facilitate the infiltration of CAR-T cells. In another case, Jie *et al.* designed a self-assembling peptide-based scaffold for mimicking cellular matrices, and local delivery of CAR-T cells by the scaffold resulted in long-term retention and increased CAR-T cell infiltration.⁹⁷ More interestingly, Li *et al.* prepared porous microneedle (PMN) patches made of poly(lactic-glycolic) acid (PLGA). PMN patch-assisted delivery enables dispersed inoculation of CAR-T cells in solid tumors. This patch disrupts the physical barrier formed by the extracellular matrix and facilitates the infiltration of CAR-T cells (Fig. 5A).⁹⁸ Furthermore, Li *et al.* developed a genetically programmable cell vesicle (D@aPD-L1 NVs) containing an anti-programmed death ligand 1 single-chain variable fragment (anti-PD-L1 scFv) and a glutamine antagonist. Using D@aPD-L1 NVs, it is possible to distribute glutamine antagonists specifically to the tumor location, lower the proportion of immunosuppressive cells, encourage the recruitment of inflammatory cells and the release of inflammatory cytokines in tumor tissues, and enhance the ability of CAR-T cells to infiltrate the tumor (Fig. 5B).⁹⁹ Therefore, in order to facilitate the entry of CAR-T cells into solid tumors, unique biomaterials can be designed to improve the therapeutic effect of CAR-T cells. These biomaterial designs have shown promising applications in improving the therapeutic effect of CAR-T cells by overcoming the TME and might be expected to be an important adjunct to CAR-T cell therapy in future.



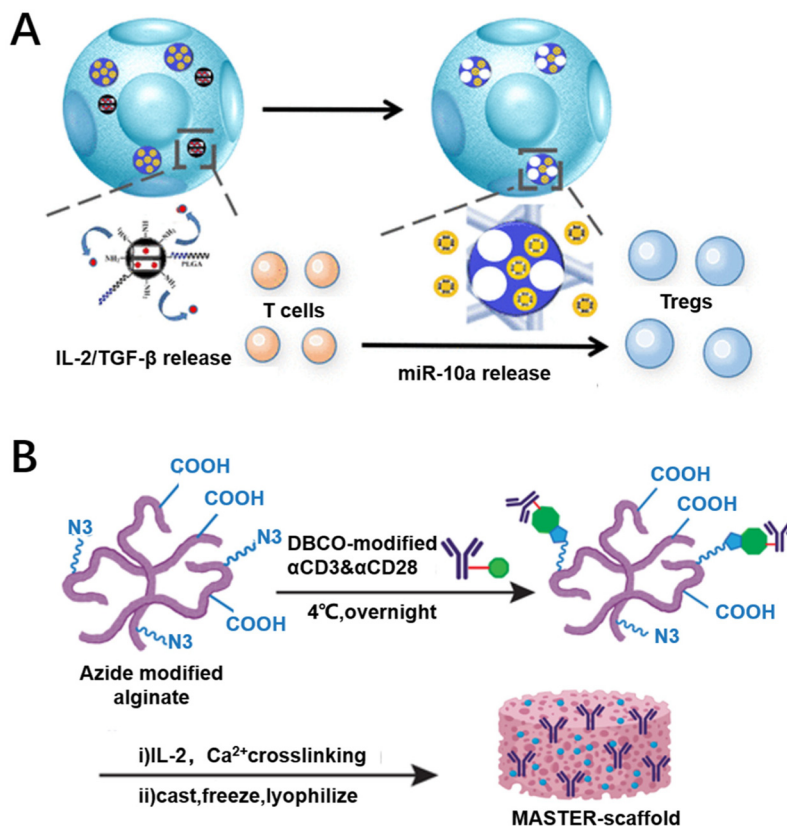


Fig. 4 Biomaterial designs for promoting the proliferation of CAR-T cells. (A) Mesoporous silica nanoparticles (MSNs) loaded with IL-2 and TGF- β release IL-2 and TGF- β to promote CAR-T cell proliferation. Reproduced with permission.⁹⁰ Copyright 2018, American Chemical Society. (B) Multifunctional alginate scaffold (MASTER) encapsulating cytokines that promote CAR-T cell proliferation. Reproduced with permission.⁵⁰ Copyright 2022, Springer Nature.

3.4. Providing a combination therapy platform for CAR-T cell therapy

In short, previous studies have shown that CAR-T cell therapy alone is not effective at treating solid tumors. In recent years, it has been found that combining CAR-T cell therapy with chemotherapy, radiotherapy, photothermal and other therapies through functional biomaterials might be a good option to improve the efficacy of CAR-T therapy and to reduce side effects. Furthermore, the unique properties of biomaterial designs (*e.g.*, liposomes or polymers) might further enhance the effect of combination therapy and might be beneficial for improving the safety or efficacy of immunotherapy.

3.4.1. Combination with chemotherapy. Chemotherapy pretreatment can improve TME immunosuppressive characteristics and boost CAR-T cell immunological activity.¹⁰⁰ Chemotherapy is the most common method of treating cancers by employing chemical medications, although it has drawbacks such as non-specificity, severe systemic side effects, multidrug resistance, and poor targeting capacity. A number of chemotherapeutic drugs, including doxorubicin, cyclophosphamide and oxaliplatin, can play an immunomodulatory role when administered at low doses, promoting dendritic cell activation and tumor antigen presentation to CAR-T cells,

increasing the persistence of CAR-T cells, and making tumor cells sensitive to CAR-T cells.¹⁰¹ As a result, combining chemotherapeutic drugs and CAR-T cell therapy for solid tumor treatment has attracted more and more attention. To investigate the mechanism of combined chemotherapy and CAR-T cell therapy, Ramakrishnan *et al.* found that chemotherapy causes an increase in the number of mannose-6-phosphate receptors on the surface of tumor cells, which accumulate and render tumor cells more susceptible to lysis by CTL *in vivo*.¹⁰² Chao *et al.* designed a lyophilized alginate hydrogel scaffold co-delivering CAR-T cells and metformin, which inhibits cancer cell oxidation, modulates the TME, promotes CAR-T cell proliferation and infiltration, and contributes to an improved anti-tumor response.¹⁰³ Zhang *et al.* used oxidized sodium alginate OSA-modified tumor cell membrane vesicles (O-TMV) as a gelling agent, encapsulating Acitretin in the lipid bilayer of O-TMV, 4-1BB antibody and PF-06446846 nanoparticles in the cavity of the hydrogel. O-TMV hydrogel has good sustained release properties and drug retention capacity for continuous therapy, while regulating T cell dissipation and major histocompatibility complex I (MHC I) expression, expanding tumor immunotherapy.¹⁰⁴ Furthermore, the negligible hemolytic ability of the O-TMV vector and O-TMV@ABP hydrogel further indicates their good biocompatibility in the



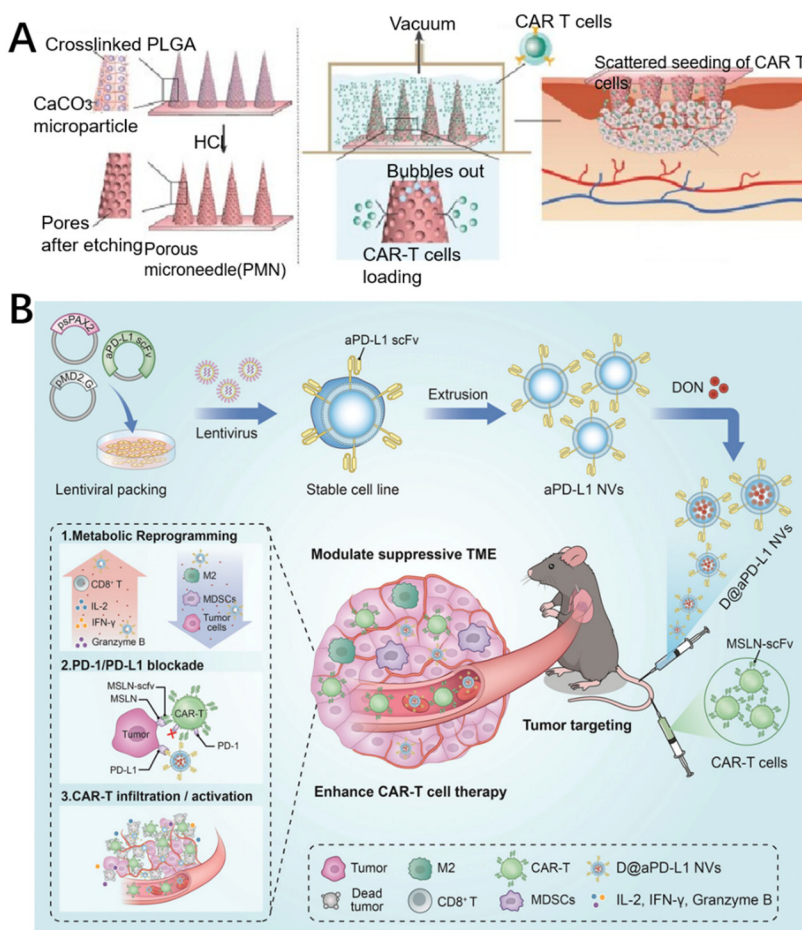


Fig. 5 Biomaterial designs to promote CAR-T cell infiltration. (A) The delivery of CAR-T cells by porous microneedles (PMN) patches made of PLGA can evenly disperse CAR-T cells into solid tumors and promote their proliferation and infiltration. Reproduced with permission.⁹⁸ Copyright 2022, Oxford University Press. (B) The cellular nanovesicles (NVs) that express high-affinity anti-murine PD-L1 single chain variable fragment (aPD-L1 scFv) are loaded with glutamine antagonists (D@aPD-L1 NVs) to improve the infiltration of CAR-T cells. Reproduced with permission.⁹⁹ Copyright 2023, John Wiley and Sons.

treatment of cancer. Therefore, the combination of chemotherapy and CAR-T cell therapy has a positive effect on the body's anti-tumor immune response, promoting the regeneration of CAR-T cells and enhancing the efficacy of CAR-T therapy. Compared with the combination therapy alone, the biomaterial platform with its combination has potential versatility to control the systemic release rate of drugs and to improve biocompatibility.

3.4.2. Combination with radiotherapy. Radiation therapy can directly cause apoptosis and necrosis of tumor cells, induce dendritic cell maturation and activation, and promote tumor antigen presentation. Following radiation, damage-associated molecular patterns and INF- γ are released, which can enhance CAR-T cell trafficking and infiltration, leading to a synergistic anti-tumor effect when combined with CAR-T cell therapy.¹⁰⁵ Radiotherapy damages tumor DNA through high-energy radiation, preventing appropriate replication and eventually causing necrosis. This method is beneficial for treating various cancers, but it has limited effects in inhibiting tumor

cell spread.¹⁰⁶ Previous studies have shown that local delivery of CAR-T cells can overcome therapeutic barriers in solid tumors, effectively promote the infiltration and spread of CAR-T cells, stimulate sustained systemic immune function, establish circulating immune memory, and effectively prevent tumor recurrence. Radiotherapy can enhance the immune response by inducing the partial release of chemokines to increase T-cell trafficking, promote cytotoxic T-cell recruitment, increase the expression of adhesion molecules associated with promoting T-cell infiltration, and release tumor antigens.¹⁰⁷ When used in combination with CAR-T cell therapy, radiotherapy has promising applications in cancer treatment. In clinical trials, radiotherapy administered prior to CAR-T cell infusion has been shown to be effective at reducing the number of primary tumor cells and improving T cell trafficking. Compared to patients who did not receive radiotherapy, CRS was milder and less neurotoxic.¹⁰⁸ Radiation therapy has been demonstrated to sensitize antigen-negative tumor cells to CAR-T cell-mediated apoptosis *via* tumor necrosis factor-



related apoptosis-inducing ligand receptor 1 (TRAIL-R1).¹⁰⁹ Liang *et al.* developed a liposome-delivered radioisotope therapy that improved immunotherapy by enhancing tumor vascular permeability, tumor retention duration and intra-tumor permeability.¹¹⁰ Liang's experiments demonstrated that radiotherapy can normalize tumor vascular function, which can increase the expression of chemokines in tumors, and then promote the local infiltration of CAR-T cells into the tumor. Therefore, radiation therapy can directly cause apoptosis of tumor cells, promote the release of tumor-associated antigens and damage-related molecular patterns. It can also increase the local expression of multiple cytokines, and attract lymphocytes including CAR-T, thereby stimulating tumor-specific immune responses to treat solid tumors. The development of related functional biomaterials may also provide assistance for the combined treatment strategy to further promote the efficacy of CAR-T cell therapy.

3.4.3. Combination with photothermal therapy (PTT). The combination of photothermal therapy with CAR-T therapy introduces external stimulation to achieve controllability of CAR expression, allowing T cells at the tumor site to be selectively programmed. PTT kills tumor cells by turning light energy into heat energy when exposed to near-infrared light. PTT has distinct advantages over traditional cancer therapies, including good selectivity, low systemic toxicity, and repeatability.¹¹¹ Chen *et al.* found that mild heating of tumors causes changes in the physicochemical properties and physiology of tumors, leading to increased infiltration and accumulation of CAR-T cells, and PTT releases tumor-associated antigens and activates the immune system, promoting CAR-T lymphocyte aggregation at tumor sites.¹¹¹ Zhu *et al.* synthesized tumor-specific HA@Cu₂-xS-PEG (PHCN) nanoenzymes by combining nanoenzymes with dual photo-thermal-nanocatalytic properties with CAR-T cells. The nano-enzyme-mediated photothermal effect could destroy the extra-tumor stroma, which increased the infiltration of B7-H3 CAR-T cells,¹¹² potentially improving CAR-T cell therapeutic barriers against solid tumors. Ma *et al.* prepared a novel nanomaterial by coating CAR-T cell membrane containing recognized GPC3⁺ HCC cells onto mesoporous silica containing IR780 nanoparticles.¹¹³ IR780 can produce fluorescence and heat under laser irradiation and can be used for PTT, the nanoparticle has good targeting ability and photothermal antitumor ability which provides a new idea for enhancing the efficacy of CAR-T cells. Chen *et al.* designed CAR-T biohybrids (CT-INP) that not only retain the original activity and function of CAR-T cells, but also have fluorescent tracer and microenvironmental remodeling ability to induce an immune favorable TME, triggered by a photothermal effect that disrupts the physical and immune barriers of solid tumors and greatly enhances CAR-T immunotherapy.⁵⁸ The photothermal effect can disrupt the barrier of solid tumors and promote CAR expression, which can kill tumor cells, as well as disrupt the extracellular stroma of tumors, dilate blood vessels to promote blood flow, recruit CAR-T cells, and improve the efficacy of CAR-T cell therapy. Not only that, with the modification of functional biomaterials

(*e.g.*, nanoparticles), they can also improve their targeting ability and reshape the TME.

3.4.4. Combination with an immune checkpoint blockade inhibitor. Tumor cells experience immunological escape *via* immune checkpoint effects when treated with CAR-T cells alone. Immune checkpoint inhibitors can reorganize the TME, reactivating T cells that have lost their effector function to play an aggressive role.¹¹⁴ Immune checkpoint inhibitors like Nivolumab and Pembrolizumab can help to re-activate T cells that have lost their effector function, making them more aggressive.¹¹⁵ Low doses of programmed death-1 (PD-1) blockers have been found to improve the effectiveness of CAR-T treatment while reducing adverse effects.¹¹⁶ However, as a biomolecule, monoclonal antibodies lack targeting *in vivo* and are difficult to enrich in tumor tissues after entry. Zhao and colleagues created a fusion protein made up of scFv and amphiphilic immunological tolerance elastin-like polypeptide (iTEP). It self-assembled with PD-1 antibodies to form nanoparticles capable of blocking PD-1 immune checkpoints, providing a PD-1 antibody-targeted immune cell delivery system.¹¹⁷ Su *et al.* created a microfluidic nanovesicle for the delivery of CD47/PD-L1 antibodies that promoted TAM polarization toward M1 and immune cell infiltration with better therapeutic effects than free antibodies, offering a new idea for improving immunotherapy with immune checkpoint inhibitors.¹¹⁸ Hu *et al.* loaded CAR-T cell targeting CSPG4 antigens, anti-PD-L1 blocking antibody-conjugated human platelets (P-aPDL1) and cytokine IL-15 into a hydrogel using a methacrylate-hyaluronic acid (HAMA) hydrogel as a vehicle to release CAR-T cells and platelets conjugated with checkpoint inhibitors, which could inhibit local tumor recurrence in mice and the growth of distant tumors.⁵⁶ One of the main reasons for ineffective or weak efficacy of CAR-T cell therapy is insufficient T cell expansion and poor T cell persistence. The combination of CAR-T therapies with immune checkpoint inhibitors has shown encouraging results to enhance the proliferation, persistence and therapeutic efficacy of CAR-T cells.

3.4.5. Combination with sonodynamic therapy (SDT). Combining sonodynamic therapy with CAR-T cell therapy, when ultrasound (US) is applied to a localized tumor activates CAR to initiate the killing of tumor cells. Only the tumor exposed to ultrasound is attacked, while other tissues in the body are left undisturbed. SDT uses US to excite sonosensitizers to produce reactive oxygen species (ROS) at the tumor site for therapeutic purposes.¹¹⁹ Abundant ROS accumulation can directly kill tumor cells, release antigens, and activate systemic immune responses in amplified CAR-T cells. By combining SDT with focused ultrasound (FUS), which can cause local heating of biological tissues, researchers have been able to ablate tumors and control drug release, vasodilation, neuromodulation, and transgene expression.¹²⁰ Based on the above basis, some investigators combined SDT and CAR-T cell therapy for synergistic treatment to enhance the efficacy of CAR-T therapy. Wu *et al.* developed a class of inducible CAR-T cells. FUS can activate CAR-T cells at a specific time and site, and CAR-T therapies synergized with FUS are safer. Significantly lower cytotoxicity outside the targeted



tumor and inhibition of tumor growth *in vivo* can reduce damage to normal tissues.¹²¹ The anticancer effect of SDT is usually compromised by a complex TME that can deplete ROS and support tumorigenesis and progression. To improve the therapeutic efficacy of acoustic sensitizers, the development of biomaterial-based nanoacoustic sensitizers has become a major strategy.¹¹⁹ Yang *et al.* prepared fluorinated covalent conjugated polymers (COPs) using the acoustic sensitizer porphyrin (THPP) and perfluorodecanedioic acid (PFSEA) as cross-linkers in combination to produce PECE@THPP_{pF}-COPs. It not only alleviated tumor hypoxia and improved TME, but also synergistically inhibited tumor growth by inducing immunogenic cell death in cancer cells under ultrasound irradiation.¹²² This multifunctional nanoacoustic sensitizer addresses the hypoxic environment present in CAR-T cell therapy for solid tumors, improves TME, and eliminates immunosuppression. Wang *et al.* constructed fluorine-containing oscillatory mesoporous organic silica nanoparticles with intraparticle secondary scattering properties to remodel immunosuppressive TME and vascular homeostasis. It promotes vascular normalization, generates more ROS during ICG-mediated sonodynamic therapy, activates systemic immune responses, promotes the proliferation of CAR-T cells, and facilitates their entry into solid tumors to exert anti-tumor effects.¹²³ Nanoparticles as a carrier opened the infiltration barrier, and promoted CAR-T or effector T cell infiltration. In summary, SDT can address the bottleneck of CAR-T therapy, and the combination of SDT and CAR-T cell therapy is expected to be an effective strategy for immunotherapy of solid tumor.

3.5. Improvement of the safety of CAR-T therapy

When using CAR-T therapies for solid tumors, there are concerns about their safety due to off-target effects and cytokine storms. Currently, researchers are addressing the safety of CAR-T therapy by improving targeting and diagnostic techniques. Targeting systems by using functional biomaterial designs, such as nanoparticles or peptides, have been carried out to enhance the targeting of CAR-plasmids or CAR-T cells and reduce off-target effects. Furthermore, a platform has been created based on these materials to monitor the effectiveness of CAR-T cell treatment *in vivo* and to detect possible toxic side effects, which might be beneficial for the application of CAR-T therapy in solid tumors.

3.5.1. Prevention of undesired off-target effects. The key to CAR-T cell therapy is using gene editing technology to deliver CAR genes into T cells, giving them the ability to recognize and attack tumor cells. The *in vitro*-expanded CAR-T cells are infused back into the patient to seek out and recognize tumor cells that match their surface CAR structure, and then release cytotoxins to kill these tumor cells. Since the correlated antigens commonly recognized by CAR-T cells are not unique to tumor cells, it cannot distinguish between tumor cells expressing the corresponding antigens and normal cells, which might cause off-target effects. Therefore, improving precision is an important design strategy for the application of CAR-T cell therapy in solid tumors.

As one strategy for enhancing the precision of CAR-plasmids transported to T cells, Rurik *et al.* developed a therapeutic approach to generate transient CAR-T cells. The designed CAR-plasmid was packaged in CD5-targeted liposome nanoparticles to transduce mRNA into T cells *in vivo*. The lipid nanoparticles can specifically bind T cells and enter inside them through cytotocytosis to produce transient, effective CAR-T cells *in vivo*.¹²⁴ In another case, Siriwon *et al.* cross-linked CAR-T with multilayer liposome vesicles (cMLVs) containing the small molecule antagonist SCH-5826. The cMLV nanoparticles could be anchored to the surface of CAR-T cells. And cMLV-anchored CAR-T cells were able to target the spleen, lymph nodes, and lungs, more effectively lymphoid organs and tumors.⁴⁹ Wang's team divided the intracellular activation

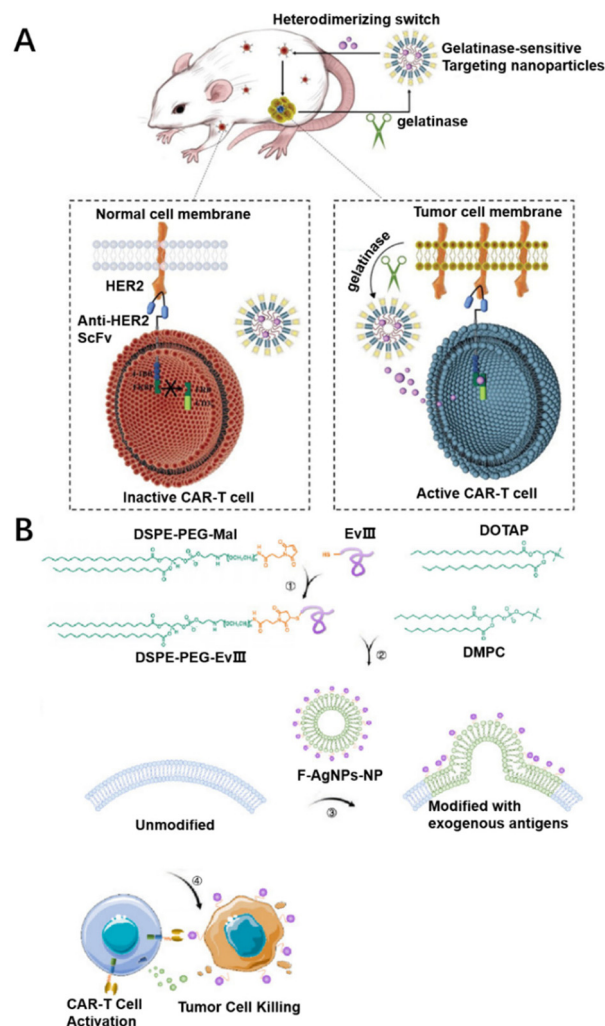


Fig. 6 Biomaterial designs for improved targeting. (A) Primitive gelatinase-responsive nanoparticles were used to selectively deliver heterodimerization switches that CAR-T cells consistently and precisely activate only on tumors. Reproduced with permission.¹²⁵ Copyright 2023, John Wiley and Sons. (B) The F-AgNP modified exogenous antigens onto the tumor cell membranes, which provided sufficient targets for CAR-T cell recognition, enabling CAR-T cell to exert antitumor effects independent of tumor inherent antigen profiles. Reproduced with permission.⁶⁴ Copyright 2022, Springer Nature.



domain of CAR into two parts, inserted a heterodimer between the two parts, and loaded the switchable molecule with gelatinase-targeted nanoparticles. The switchable molecule is specifically delivered to the tumor to achieve CAR-T localization-specific activation in the tumor. The switchable CAR-T delivery composite system was found to improve the targeting of CAR-T cells and achieve tumor-specific killing, effectively solving the problem of the off-target effect of CAR-T cell therapy for solid tumors (Fig. 6A).¹²⁵ Sun *et al.* found that it is possible to load exogenous antigens onto nanoparticles (F-AgNPs). The F-AgNPs modify exogenous antigens to tumor cell membranes *via* membrane fusion. The modification of the tumor cell membrane *in situ* provides sufficient targets for subsequent CAR-T cell recognition, allowing CAR-T cells to redirect to tumors without corresponding targets (Fig. 6B).⁶⁴

Furthermore, the targeting ability of CAR-T cells can be improved by the assistance of the unique responsiveness of biomaterials. Miller *et al.* added a heat shock protein transcription start sequence upstream of the CAR structural gene to enable engineered T cells to express CAR only in high-temperature environments. Upon irradiation with near-infrared light, polyethylene glycol (PEG)-coated plasmonic gold nanorods (AuNRs) aggregated in tumor tissues *in vivo* generating heat, which promotes the expression of engineered T-cells in the vicinity of the tumor tissues to be converted into CAR-T and thus enhances the targeting of CAR-T.¹²⁶ Nguyen *et al.* separated the functional structural domains of the CAR structure and added a light-responsive module to the separated functional structural domains of the CAR under the action of specific wavelengths emitted by the converted nanomaterials, thus enabling the targeted generation of CAR-T within tumor tissues.¹²⁷

3.5.2. Integration of diagnosis and treatment. The effectiveness of CAR-T cell therapies in treating solid tumors can be

monitored through visualization of the CAR-T cell expansion and distribution in patients. This can also serve as an early warning of toxicity progression. To expand the application of CAR-T cell therapies, it is essential to develop dynamic imaging platforms for efficacy monitoring and toxicity assessment. In a study by Kiru *et al.*, CAR-T cells were labeled with iron oxide nanoparticles, enabling non-invasive detection of iron-labeled T cells using MRI, photoacoustic imaging, and magnetic particle imaging.¹²⁸ This method allows real-time monitoring of the accumulation and distribution of CAR-T cells in solid tumors, providing an effective means to investigate the use of CAR-T cells for the treatment of solid tumors. Furthermore, Shi *et al.* developed a novel multifunctional nanoprobe (FA-Gd-GERTs@Ibrutinib) for tri-modal CT/MRI/SERS bioimaging and tri-modal CAR-T cell/chemotherapy/PTT. The photothermal effect of the nanoprobe promotes angiogenesis in lymphoma tissue, disrupts the extracellular matrix, loosens dense tissue, and stimulates chemokine secretion, effectively enhancing the infiltrative capacity of non-Hodgkin's lymphoma and greatly improving the anti-tumor efficacy.¹²⁹ In conclusion, the combination of bioimaging and multiple therapeutic approaches through functional biomaterials to achieve diagnostic and therapeutic integration can greatly promote the efficacy of CAR-T therapy and provide a new strategy for CAR-T therapy for solid tumors.

3.5.3. Others. During the clinical translation of CAR-T therapies for the treatment of solid tumors, the most problematic issue is CRS. As a typical example, monoclonal antibodies currently used for the treatment of CAR-T-induced CRS still face a number of serious problems, such as systemic toxicity and short time to exert effects. Interestingly, by using functional biomaterials, CRS in CAR-T cell therapy might be inhibited (Fig. 7). As a typical example, Li *et al.* developed a hydrogel material with the ability to adsorb interleukin-6. They

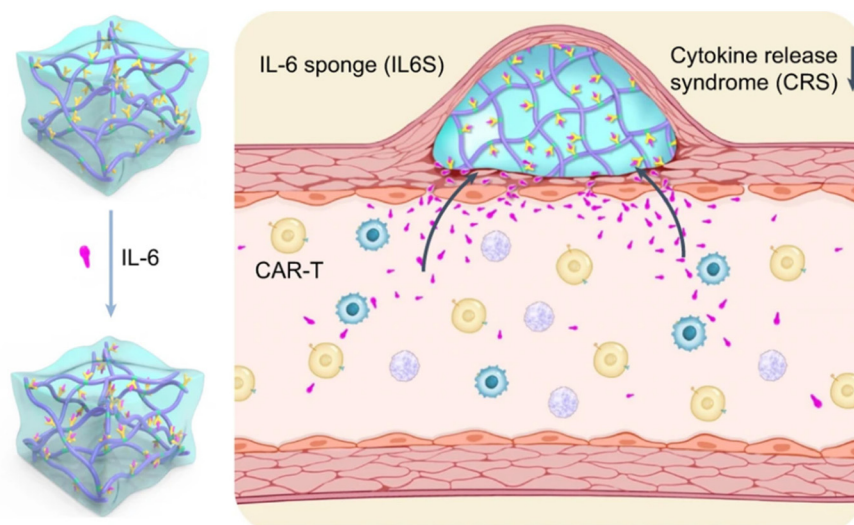


Fig. 7 Biomaterial designs inhibit cytokine release syndrome. A temperature-sensitive hydrogel functionalized with antibodies targeting the pro-inflammatory cytokine interleukin-6 (IL-6) in mitigating cytokine release syndrome during CAR-T-cell therapy. Reproduced with permission.⁶⁰ Copyright 2023, Springer Nature.



created an IL-6 sponge (IL-6S) by chemically coupling a thermosensitive hydrogel poly(*N*-isopropylacrylamide-*co*-methacrylic acid) with an IL-6-specific antibody. Excess IL-6 can be absorbed and neutralized *in vivo via* subcutaneous injection of this hydrogel, lowering the development of CRS.⁶⁰ This technique has the potential to significantly lower the severity of CRS while also improving the safety and tolerability of CAR-T cell therapy. It takes an innovative approach to deal with the side effects in CAR-T cell therapy.

4. Conclusion and perspectives

In summary, CAR-T cell therapy has shown great success in the treatment of hematological tumors, and researchers are now focusing on improving its efficacy in the treatment of solid tumors. The biomaterial-based strategy promises to change the manufacturing methods of CAR-T cells, regulate the TME, improve the safety and enhance the efficacy of CAR-T cells for the treatment of solid tumors. However, there are several challenges that need to be addressed to achieve this goal. Firstly, non-viral gene vectors based on biomaterial designs suffer from low transfection efficiency compared to viral vectors. It requires the extraction of more cells from patients and a longer time for expanding the CAR-T cells. Therefore, future research requires a more in-depth study of non-viral gene vectors, developing novel gene delivery vectors in gene loading and T-cell gene modification. In addition, generating CAR-T cells *in vivo* simplifies the manufacturing process of CAR-T cells and reduces costs. But it may be transduced in other cells, leading to off-target transduction.¹³⁰ Fortunately, recent reports have shown that using a switching technique enhances the safety and effectiveness of CAR-T cells. Based on functional biomaterial designs, the method has various designs and is expected to achieve the distinction between T cells and normal cells. Furthermore, recent reports have shown that biomaterial designs can also provide a platform for CAR-T cell therapy as a combination therapy. However, clinical data on combination therapies are limited, and the optimal dosing regimen for combination therapy still needs to be explored. Last but not least, biomaterial designs are often used in therapeutic applications in the form of nanomaterials,¹³¹ which are difficult to industrialize and have poor inter-batch reproducibility due to the complexity of the nanomaterial preparation process.^{132,133} Simplicity should be considered when designing biomaterials to simplify the manufacturing process of CAR-T cells for industrial production. It is also important to emphasize that the long-term compatibility, degradation characteristics and safety of implantable scaffolds still need to be explored. Polymeric materials implanted in the human body may release degradation products that may be toxic to humans.^{134–136} It needs optimization of the design of biomaterial systems based on their own physicochemical properties, biocompatibility, targeting and other characteristics to achieve effective modulation of the TME and sustained intratumor immune activation. Gong *et al.* used materials alone to

modulate cell–cell interactions for disease treatment and reduce CRS and neurotoxicity by constructing *in situ* PEGylation of CAR-T cells.¹³⁷ It provides a safer strategy and direction for biomaterial-based CAR-T cell therapy. There remains a significant market opportunity for CAR-T clinical therapy, particularly in the treatment of solid tumors. Allogeneic CAR-T cells are one of the future directions, but they can produce host-*versus*-graft reactions and graft-*versus*-host disease problems.^{138,139} It can be designed together with special functional biomaterials to improve the biocompatibility and durability of allogeneic CAR-T cells, paving the way for breakthroughs in the treatment of solid tumors. In short, these insights will provide important guidelines for the development of safe and inexpensive biomaterial designs to enhance the efficacy of CAR-T cell therapy. As functional biomaterials continue to advance, this strategy might show great potential for creating a promising therapeutic approach towards solid tumor treatment.

Author contributions

Literature review and writing—original draft preparation, Y. L. and writing—review and editing and supervision, Y. C., Z. L. and Y.-L. W. All authors have read and agreed to the current version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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