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Nanomaterials for T-cell cancer immunotherapy

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T-cell-based immunotherapies hold promise for the treatment of many types of cancer, with three approved products for B-cell malignancies and a large pipeline of treatments in clinical trials. However, there are several challenges to their broad implementation. These include insufficient expansion of adoptively transferred T cells, inefficient trafficking of T cells into solid tumours, decreased T-cell activity due to a hostile tumour microenvironment and the loss of target antigen expression. Together, these factors restrict the number of therapeutically active T cells engaging with tumours. Nanomaterials are uniquely suited to overcome these challenges, as they can be rationally designed to enhance T-cell expansion, navigate complex physical barriers and modulate tumour microenvironments. Here, we present an overview of nanomaterials that have been used to overcome clinical barriers to T-cell-based immunotherapies and provide our outlook of this emerging field at the interface of cancer immunotherapy and nanomaterial design.

The year 2017 witnessed a landmark in adoptive T-cell therapy (ACT) for the treatment of cancer, with the arrival of the first approved products. In August and October that year, the US Food and Drug Administration (FDA) approved tisagenlecleucel (Kymriah)[1] and axicabtagene ciloleucel (Yescarta)[2] for treating certain B-cell leukaemias and lymphomas, respectively. Both medicines are examples of chimeric antigen receptor (CAR) T-cell therapies targeting the CD19 antigen present on B cells. While these first two CAR T-cell therapies have continued to gain approvals for additional disease indications, age groups and regulatory jurisdictions, a large pipeline of additional T-cell therapies is also advancing. Indeed, in July 2020, the third CAR T-cell therapy, brexucabtagene autoleucel (TECARTUS) was approved for Mantle Cell Lymphoma[3]. The pipeline also includes a variety of classes of therapeutic T cells, including CAR T and T-cell receptor engineered-T-cell (TCR-T) therapies against numerous antigens, tumour infiltrating lymphocyte (TIL) therapies derived from a patient's own surgically resected tumour tissue, and cytotoxic T lymphocytes (CTL) such as those targeting Epstein–Barr virus antigens for use in treating Epstein–Barr-virus-positive lymphomas[4]. Each class of T-cell therapy has its unique properties (Fig. 1 and Table 1) that make it more or less advantageous for use in specific diseases, patients and therapeutic settings. Of the four types of T-cell therapy, only CD19-directed CAR T cells have been approved for restricted types of B-cell-related haematological cancers[1–3]. However, it is widely anticipated that CAR T-cell therapies targeting B-cell maturation antigen will soon be approved for treating multiple myeloma[5–7]. Moreover, progress is also being made in solid tumour applications, where TIL therapies for cervical cancer[8,9] and a TCR-T therapy for sarcoma[10] have both commenced pivotal trials after showing promising data in initial studies. If these trials are successful, the TIL and TCR-T therapy classes may also have an approved treatment as an exemplar. Antiviral CTLs for virus-driven cancers are perhaps a little further behind in development, but they have demonstrated clinical benefits in lymphoma[4] and nasopharyngeal carcinoma[11,12]. In general, T-cell-based cancer immunotherapies are emerging as powerful tools for cancer therapy in the clinic[13,14].

Despite these important advances, many hurdles remain to the wide implementation of ACT for cancer. Based on the results of approved and investigational T-cell therapy products, as well as findings in preclinical tumour models, the key challenges include: (1) failure of therapeutic T cells to expand in vivo to yield sufficient numbers of effector cells due to insufficient stimulatory signals[15]; (2) inefficient trafficking of T cells to the tumour site due to both physical barriers[16,17] and immune-suppressive environments[18]; (3) therapeutic T-cell exhaustion and death due to hostile tumour microenvironments[19–22]; and (4) loss of target antigen expression due to genetic mutations[23–25]. Of these challenges, the use of nanomaterials may be especially advantageous in addressing insufficient T-cell trafficking and overcoming the suppressive tumour microenvironment. In the following sections, we will briefly introduce the application of nanomaterials in cancer treatment, and then discuss specific examples of nanomaterials designed to improve T-cell expansion in vivo, overcome the physical barriers and immune-suppressive environment to enhance T-cell penetration of solid tumours, and re-direct T-cell function for cancer immunotherapy. We will also provide our future outlook on these emerging areas, including a discussion of potential applications at the interface of nanomaterials and in vivo T-cell immunotherapy.

Nanomaterials for T-cell cancer immunotherapy

Nanomaterials — materials with one or more external dimensions in the range of 1–100 nm — have been intensively investigated for cancer treatment in the past few decades[26]. For example, nanomaterials can enhance drug dispersion or stability, alter drug biodistribution, or improve drug accumulation in tumour sites, and some formulations have been approved for cancer treatment in the clinic[27–29]. These nanomaterials benefit from the enhanced permeability and retention effect, allowing them to passively target tumours[30], and they have demonstrated improved outcomes in clinical trials[31–33]. For example, liposomal doxorubicin (Doxil and Myocet) was shown to improve pharmacokinetics and biodistribution and reduce cardiotoxicity compared with free drug[34]. Additionally, liposomal cytarabine–daunorubicin (also known as

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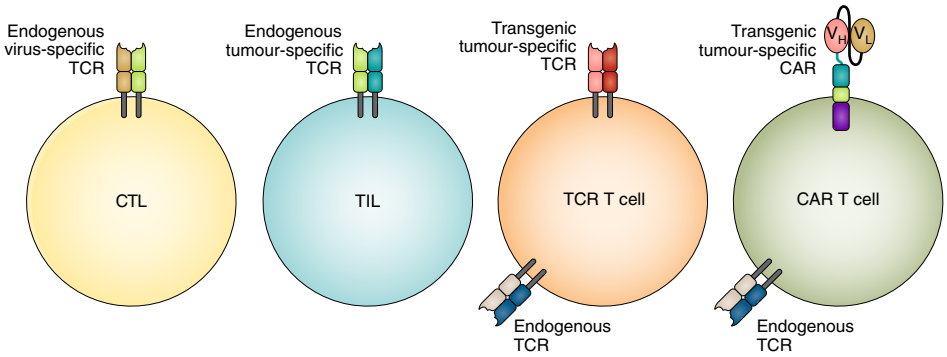

Fig. 1 | Classes of T cells deployed in ACT. Adoptive T-cell therapy makes use of either naturally occurring or redirected T cells. The naturally occurring T cells include CTLs against viral antigens for virus-induced cancers, or TILs for solid tumours. The redirected T cells are generated by the addition of a gene encoding a tumour-antigen-specific TCR or CAR. The antigen specificity of TILs is often not characterized but, where delineated, typically consists of a mix of populations targeting tumour-associated antigens, which are upregulated self-antigens found at lower levels in healthy tissues, cancer germline antigens, which are normally only expressed in the gonads or during foetal development, and neoepitopes, which are cancer-specific mutations. While TIL therapy can achieve excellent clinical responses, the TILs must be isolated from surgically resected tumour biopsies, which is not feasible in many indications. When bulk T cells from the peripheral blood or cord blood, or derived from induced pluripotent stem cells are redirected by addition of a transgenic receptor, the endogenous TCR may be deleted using gene editing tools if doing so enhances the activity of the T-cell product or improves the safety profile. Therapeutic T cells encoding both a tumour-antigen-specific TCR and a CAR have been reported. V_H, variable domain of heavy chain; V_L, variable domain of light chain.

CPX-351) — compared with the standard cytarabine and daunorubicin treatment in patients with high-risk acute myeloid leukaemia — showed improved overall survival[26]. Moreover, nanomaterial albumin-bound paclitaxel (Abraxane) was shown to be superior to free paclitaxel in terms of response rate and disease progression for patients with breast cancer[35]. To further enhance therapeutic outcomes, second-generation nanomaterials that build on the existing benefits of nanomaterials by adding new functions, such as active targeting[36,37], stimuli-responsive drug release[38,39] or the co-delivery of multiple drugs[40,41], are currently in clinical trials or preclinical studies for cancer therapy. Additional research is focused on nanomaterials that modulate the immune system as well as materials that can overcome physical barriers and immune-suppressive environments[42–45]. The development of these nanomaterial-based cancer therapies has greatly benefited from the modifiable features of nanomaterials, such as their variable surface characteristics (Fig. 2a)[46,47], physicochemical properties (Fig. 2b)[48–50] and controllable cargo encapsulation and release (Fig. 2c)[51,52]. Recently, these unique properties of nanomaterials have also been used to overcome the challenges faced by T-cell therapies (Fig. 2d)[44,53,54]. For example, nanomaterials can be used for in vivo T-cell engineering, targeted T-cell delivery[55], stimuli-responsive drug release[56] and nanovaccine-boosted T-cell expansion strategies[57]. Moreover, nanomaterial-based bispecific T-cell engagers (NBiTEs; nanomaterials functionalized with antibodies that bridge T cells and tumour cells) have been used to redirect CTL functions for applications in T-cell immunotherapies[58]. In addition, nanomaterials can help T cells overcome physical barriers and immune-suppressive environments to achieve solid tumour delivery. Specific investigations include tumour extracellular matrix (ECM)-targeting nanomaterials to enhance T-cell penetration[59], nanomaterial-based scaffolds to locally deliver T cells to solid tumours[60] and nanomaterial delivery systems to co-deliver biomolecules to circumvent the immune-suppressive environment[61] in solid tumours. These recent studies successfully incorporating nanomaterials into T-cell-based cancer immunotherapies to enhance their efficacy illustrate the immense potential for nanomaterials to more broadly improve the clinical efficacy of T-cell therapies. We will discuss specific examples of nanomaterials designed to improve T-cell immunotherapy in the sections below.

Nanomaterials to enhance T-cell expansion in vivo

While ACT can be an effective cancer treatment, ex vivo manufactured T cells may fail to persist or become exhausted after infusion[62]. To combat these limitations, this section will discuss the potential of nanomaterial fabrication to enhance in vivo T-cell expansion through T-cell targeted delivery, backpacking nanomaterials and nanomaterial-based vaccines.

T-cell-targeted delivery to enhance expansion. In vivo T-cell expansion can be achieved through T-cell-targeted nanomaterials (Fig. 3(i)) delivering genes, cytokines, antibodies and small molecules. To illustrate the efficacy of this approach, one study[63] developed a polymeric nanomaterial to specifically co-deliver plasmids encoding a 194-1BBz CAR and a piggyBac transposase to T cells in vivo, inducing CAR expression and expansion. This nanomaterial was designed to actively target $CD3^+$ cells using anti-CD3e F(ab′)2 fragments conjugated to its surface. Further, to enhance gene transfer, nuclear localization and microtubule-associated sequences were co-loaded alongside the DNA cargo to promote nuclear entry. In combination, these design elements allowed for the efficient delivery of piggyBac transposase in vivo, resulting in CAR T-cell generation and expansion in a mouse model of leukaemia[63]. This in vivo T-cell engineering approach to CAR T-cell production has the potential to become an alternative to current ex vivo procedures, as it may be more time- and cost-effective than current ex vivo practices. Though this polymeric nanomaterial was also found in approximately 5.9% of non-T blood cells after intravenous injection in mice[63], which leads to concern over the risks of 'off-target' toxicity[64], this study is a proof of concept that CAR T-cell therapy can be administered via traditional drug treatment methods. Nanomaterials are also relatively easier to scale up than traditional CAR T-cell therapy using living cells, and could be a transformative technology for in vivo CAR or TCR transgene delivery for broader implementation of cancer immunotherapy. This nanomaterial-based approach to deliver CARs in vivo is now moving into clinical testing (Table 2)[63].

In addition to gene delivery, investigations have explored the use of cytokine delivery to modulate T-cell behaviour in vivo, as these molecules are known to play an important role in T-cell activity[65]. Numerous cytokines have been tested in clinical trials as

Table 1 | Characteristics of the T cells used for ACT

	CTL	TIL	TCR-T	CAR T
Source	Isolated from healthy donors sharing relevant MHC alleles.	Isolated from patient's own tumour.	Manufactured from autologous or allogeneic peripheral blood T cells, cord blood T cells or iPSC-derived T cells.	
Specificity	EBV, CMV or HPV antigens.	Mixed population with various specificities.	Single tumour antigen.	Single or multiple tumour antigens depending on design.
Target type	TCR binds peptide from target antigen presented in complex with self MHC molecule.			CAR binds antigen directly.
Target location	Antigen can be expressed in any subcellular location since the antigen presentation pathway will result in surface-expressed peptide–MHC complexes.			Cell surface or secreted targets only.
Pros	Safety	Safety, efficacy	Evidence for activity in solid cancers.	HLA independence
Cons	Virus-driven tumours only.	Difficult to manufacture. Not feasible for many tumours.	Few patients express both antigen and correct HLA allele.	Few responses in solid cancers thus far.

EBV, Epstein–Barr virus; CMV, cytomegalovirus; HPV, human papillomavirus; HLA, human leukocyte antigen.

anticancer agents, but they were largely unsuccessful — causing harsh side effects, offering narrow therapeutic windows and providing only modest benefits in select settings[66]. Despite these limitations, in the 1990s, recombinant tumour necrosis factor (TNF; tasonermin)[67] and interleukin-2 (IL-2; aldesleukin)[68] were approved in certain countries for the treatment of unresectable soft tissue sarcomas of the limbs or metastatic renal clear cell carcinoma and melanoma, respectively[67,69]. For recombinant TNF-α, toxicity was such an issue that its use was restricted to isolated limb perfusion to minimize systemic exposure[67]. With the advent of ACT, IL-2 was initially administered alongside these therapies in an attempt to improve the expansion and persistence of the infused T cells, but the combination contributed to severe toxicity, including capillary leak syndrome[70], leading investigators to pursue ACT approaches without the addition of cytokines[71,72]. Apart from IL-2 and TNF, a number of cytokines including IL-12, IL-7 and IL-15 were explored to enhance the efficacy of T-cell therapies[73]. However, despite the potential benefits of cytokine treatments, they faced limitations due to systemic toxicity resulting from the non-specific uptake of free cytokines across cell types expressing the appropriate receptor[74,75]. To mitigate these negative effects, cytokine conjugation to poly(ethylene glycol) (PEG) was explored and has become a well-established strategy to prolong blood circulation and reduce toxicity, leading to several PEGylated cytokines approved for clinical use including interferon and granulocyte colony-stimulating factor[76] as well as several others currently in clinical trials[77]. Moreover, a number of alternative polymers have been used to increase the safety and efficacy of cytokines[78], while nanomaterials have been explored as a means to target cytokine delivery to specific cell types[55,79,80]. Results from these investigations demonstrate that nanomaterial-based targeting of cytokines can enhance T-cell immunotherapies with limited toxicity. One study[55], utilizing an IL-2–Fc fusion-protein-modified liposome nanomaterial in a mouse model of melanoma, found that intravenously injected liposomes were successfully delivered to the surface of over 95% of the adoptively transferred T cells, inducing enhanced T-cell proliferation in tumour-bearing mice. Further, repeated injections allowed for multi-wave in vivo proliferation of T cells with limited toxicity. These results demonstrate the potential for nanomaterials to enable cytokine-based strategies, but future studies must address the remaining challenges to cytokine treatments. These include ways to enhance the targeting of desired cell types over the total population of cytokine receptor-expressing cells, the potential burst release of cytokines in the bloodstream, as well as the impact of nanomaterial biodegradability on clearance, delivery and toxicity.

In addition to cytokine delivery, nanomaterials-based delivery systems that target the exhaustion pathways[81] have also been shown to enhance T-cell expansion in vivo[82–85]. For example, one study designed a liposome modified with anti-CD90 antibodies to target T cells and deliver the transforming growth factor-β (TGF-β) inhibitor compound SB525334, resulting in notable inhibition of tumour growth compared with untargeted liposomes in a mouse model of melanoma[82]. Another study designed a poly(lactic-co-glycolic acid) (PLGA) and PEG (PLGA–PEG) nanomaterial modified with antibody for programmed cell death protein 1 (anti-PD-1) to target exhausted T cells[83]. This nanomaterial was loaded with the TGF-β receptor inhibitor compound SD-208 and successfully reversed the exhausted state of T cells in vivo[83]. Beyond TGF-β inhibition, small-molecule delivery for STAT3/STAT5 pathway inhibition could be utilized to decrease levels of T-cell exhaustion, as activation of the transcription factor STAT3/STAT5 following TCR/CD28 co-stimulation is a precursor for expression of the T-cell exhaustion marker FOXP3 (ref. [86]). A recent study[84] employed this strategy in a mouse model of melanoma and delivered a regulatory T-cell-targeted hybrid nanomaterial that inhibited the STAT3/STAT5 pathway using imatinib, resulting in enhanced $CD8^+$ T-cell infiltration in tumour tissue and superior tumour growth inhibition compared with freely administered imatinib. The results of these investigations support the continued exploration of inhibiting immunosuppressive pathways to overcome T-cell exhaustion and enhance the therapeutic efficacy of T-cell immunotherapy.

Given the separate successes of using cytokines to stimulate immune responses and inhibitors to prevent immune suppression, many investigations have sought to combine these strategies and utilize nanomaterials for the co-delivery of immune stimulatory signals and immune suppression inhibitors[85,87]. One study[85] synthesized 100 nm iron nanomaterials modified with antibodies for CD137 (anti-CD137) and programmed death-ligand 1 (anti-PD-L1) — referred to as 'immunoswitches'. Anti-CD137 provided co-stimulation signalling to enhance T-cell proliferation, while anti-PD-L1 blocked PD-L1–PD-1 interactions and thus prevented PD-1-mediated T-cell exhaustion. The investigation used these immunoswitches in a mouse model of melanoma, demonstrating greatly enhanced $CD8^+$ T-cell counts in both tumour tissue and tumour-draining lymph nodes, as well as inhibited tumour growth. Notably, this technology effectively expanded T cells in vivo without inducing exhaustion. Another study[87] showed that combined delivery of both an immune stimulatory signal (IL-2) and a TGF-β inhibitor (SB505124) via liposome-coated polymeric gels also increased T-cell infiltration and prolonged survival in a

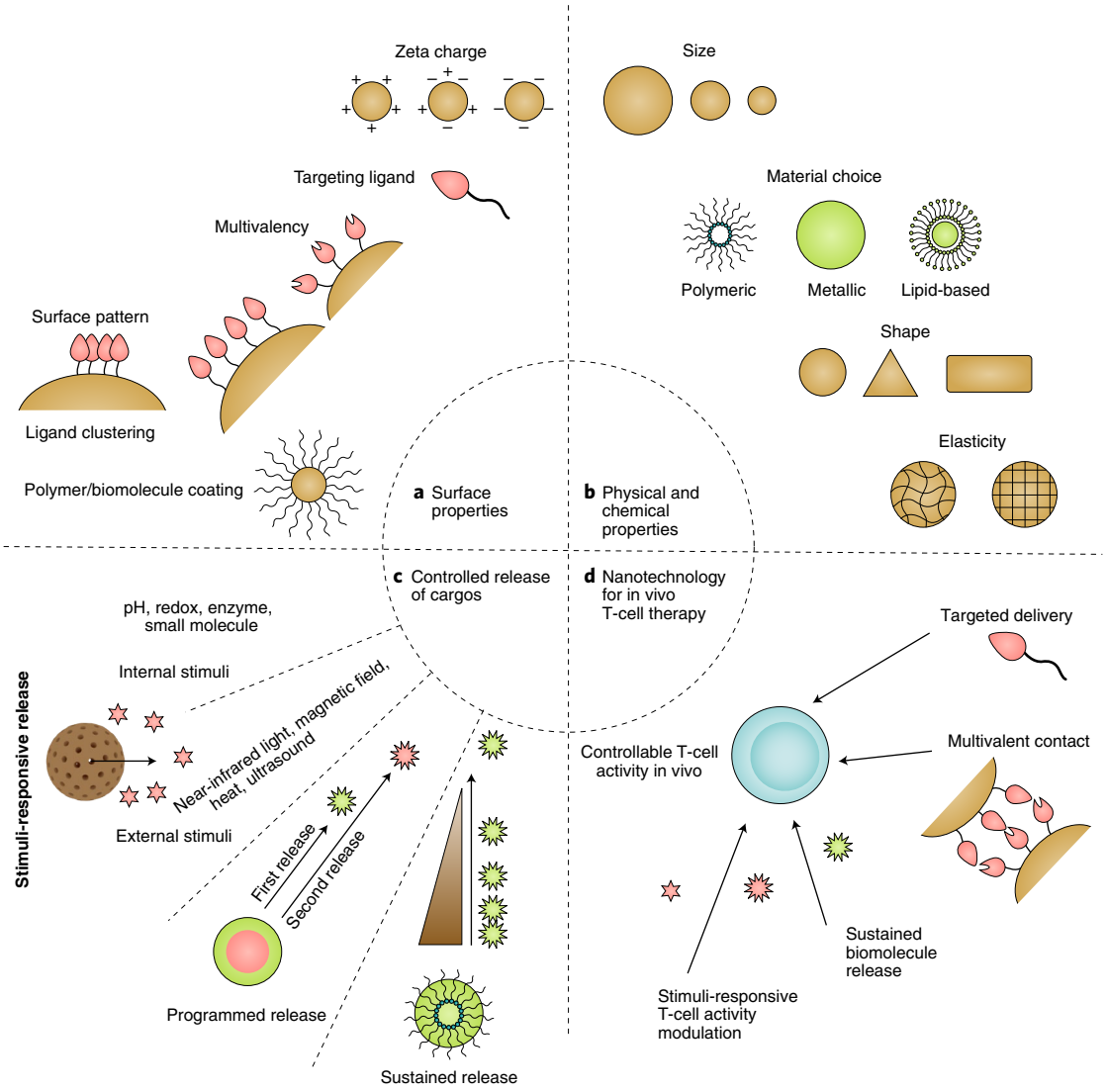

Fig. 2 | The current nanomaterial toolbox can be applied to in vivo T-cell therapies. a–c, Current strategies for expanding the functionalities of nanotechnologies include surface characteristics (**a**), physicochemical properties (**b**) and encapsulation and release features (**c**) of nanomaterials. **d**, Nanomaterials with optimized features could greatly benefit future T-cell cancer immunotherapies in vivo.

mouse model of melanoma[87]. In all, these results demonstrate the ability of nanomaterial-based systems to modulate T-cell behaviour in vivo, illustrating their potential to impact future cancer immunotherapy applications.

Backpacking nanomaterials for in vivo T-cell expansion. As an alternative to the separate delivery of nanomaterials and T cells, nanomaterials can be attached to T cells in a strategy known as 'backpacking' to achieve in vivo T-cell expansion (Fig. 3(ii)). In this method, nanomaterials are conjugated to the T cell, such that their contents are delivered primarily to the T cell in a pseudo-autocrine pattern[88]. Since this backpacking strategy conjugates nanomaterials only to the target cell population — the therapeutic T cells — it results in higher delivery specificity and decreased in vivo toxicity[89]. A recent study from the same group developed a nanogel incorporating IL-15 superagonist complexes (IL-15Sa) via the crosslinking of disulfide bonds that, when backpacked onto CAR T cells, was able to control T-cell expansion in a stimuli-responsive manner[56]. When the CAR T-cell–nanogel system was infused into a mouse model of melanoma, it recognized and bound cancer cells, and the antigen-specific recognition increased the reduction potential on the T-cell surface, allowing for the cleavage of disulfide bonds to release IL-15Sa from the nanogel. IL-15Sa then induced expansion of CAR T cells, and this controlled-release strategy led to a 16-fold increase in T-cell expansion compared with freely administered IL-15Sa. Moreover, this nanogel backpacking system showed limited systemic toxicity in vivo, while systemic injection of free cytokines for T-cell expansion is associated with severe toxicity[89,90]. Most importantly, the nanogel-modified CAR T cells showed enhanced therapeutic efficacy and prolonged survival in vivo[56]. This approach of backpacking T cells with cytokines has recently entered clinical trials for treating a variety of solid tumours and lymphomas (Table 2)[43,56]. In addition to using these strategies to enhance T-cell expansion in vivo, several studies also demonstrated that backpacking nanomaterials encapsulating therapeutic small molecules can synergistically inhibit tumour cell growth and improve mouse survival[91–94]. The success of these studies supports the continued investigation of this backpacking nanomaterial strategy, as it has the potential to deliver a variety of other compounds that have been too toxic or non-specific in previous systemic delivery strategies.

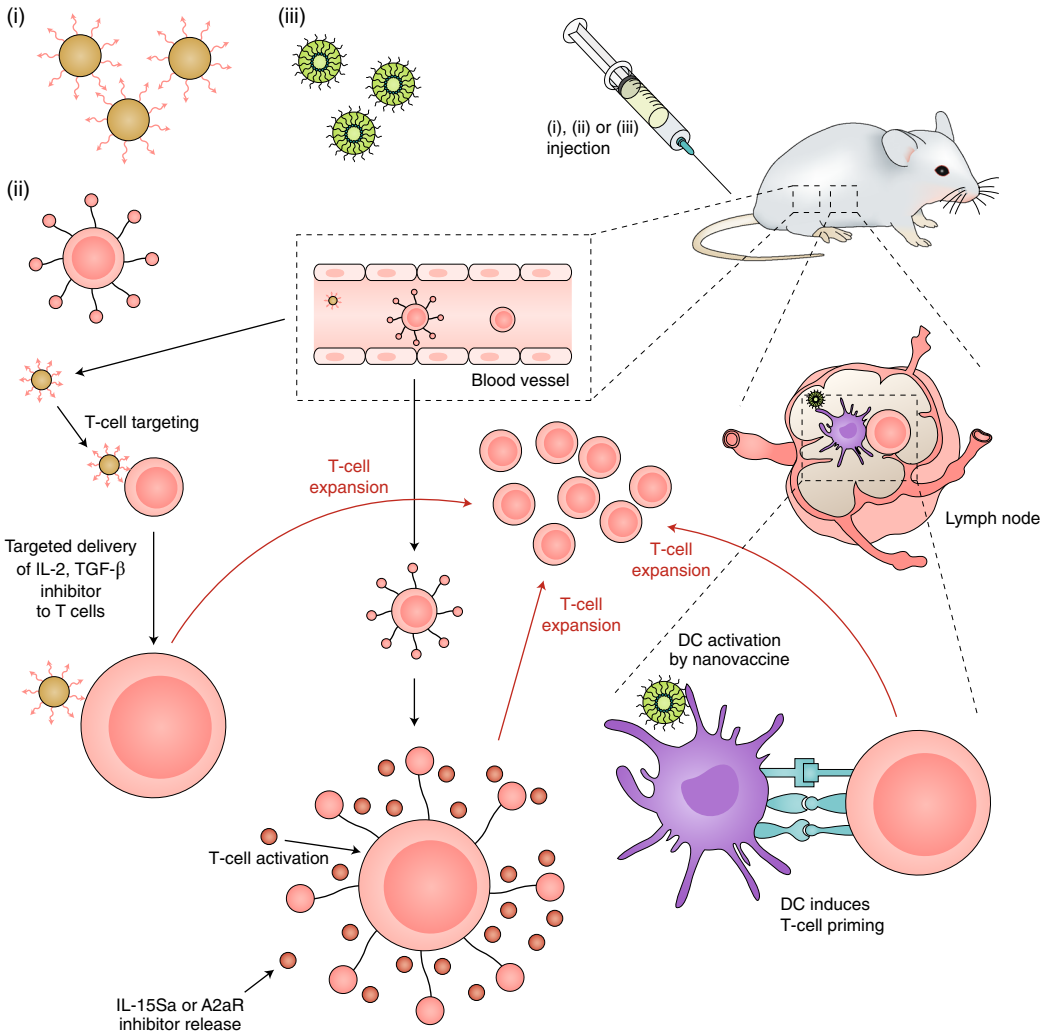

Fig. 3 | Nanomaterials for in vivo T-cell expansion. Nanomaterials can be designed for targeted delivery to T cells and induce T-cell activation and expansion in vivo (i). Backpacking nanoparticles are attached to the T-cell surface and release their cargo of stimulatory cues in response to environmental or applied stimuli, leading to precise control over the expansion of T cells in vivo (ii). Vaccine nanoparticles that target antigen-presenting cells, such as DCs, can activate these cells and induce T-cell expansion in vivo (iii).

Further, future studies may improve on these backpacking nanomaterials to incorporate systems that monitor T-cell activity or involve more intelligent controlled-release strategies to enhance in vivo efficacy while decreasing systemic toxicity.

Nanomaterials-based vaccines for in vivo T-cell expansion. Engineered T cells can also be expanded in vivo by utilizing nanomaterials-based vaccination strategies (Fig. 3(iii))[95]. Different from the expansion induced by targeted nanomaterials and backpacking nanomaterials, the expansion of T cells mediated by nanomaterials-based vaccines mimic the physiological process that T cells undergo upon antigen-specific priming and boosting. Many studies have demonstrated the controllable expansion of CAR T cells by designing a CAR with an additional antigen receptor specific for an exogenous antigen, leading to in vivo CAR T-cell expansion reliant on subsequent vaccination with the exogenous antigen[96,97]. A recent study[98] took this concept a step further by developing a vaccine strategy to expand CAR T cells directly within the lymph node microenvironment. They designed amphiphile CAR T-cell ligands (amph-ligands) that bound endogenous albumin following injection, allowing them to be trafficked to lymph nodes and preferentially anchored to the surface of dendritic cells (DCs)[99,100]. The DCs then provide co-stimulatory signals to boost the expansion of CAR T cells in vivo. The therapeutic efficacy of this approach was investigated using a mutant epidermal growth factor receptor (EGFRvIII)-specific CAR and an amph-ligand of PEG–distearoylphosphatidylethanolamine (PEG–DSPE) conjugated to the EGFRvIII peptide pepvIII in a mouse model of EGFRvIII$^+$ glioma[98]. The EGFRvIII-specific CAR T cells and pepvIII treatment was shown to substantially expand CAR T cells in vivo with improved CAR T-cell infiltration in tumours as well as delayed tumour growth and prolonged survival compared with an EGFRvIII-specific CAR T-cell treatment alone. Other studies have demonstrated the 'secondary antigen' strategy to induce T-cell expansion, including a recent study[57] that developed a lipid nanomaterial-based mRNA vaccine (CARVac) to circumvent the low persistence of CAR T cells in vivo. This investigation featured CAR T cells targeting the tight junction protein claudin 6 (CLDN6) combined with the CARVac, a lipid nanomaterial encapsulating mRNA encoding CLDN6. Following adoptive transfer of the CLDN6-CAR T cells, the CARVac was intravenously injected, leading to the expression of CLDN6 on the surface of antigen-presenting cells and the release of co-stimulatory signals for effective CAR T-cell priming. The CARVac injection greatly enhanced CAR T-cell numbers, peaking

Table 2 | Preclinical and clinical studies of nanomaterials-based T-cell cancer immunotherapies

Nanomaterials		Cargo molecules	Model/indication	Stage	Reference
Nanomaterials for T-cell expansion in vivo	**T-cell-targeted delivery**				
	Poly(beta-amino ester)-based nanomaterial	Plasmids encoding a 194-1BBz CAR and a piggyBac transposase	TBD	Phase 1 projected 2020–2021	63
	Liposome	IL-2–Fc fusion protein	Mouse melanoma	Preclinical	55
	Liposome	TGF-β inhibitor (SB525334)	Mouse melanoma	Preclinical	82
	PLGA–PEG nanomaterial	TGF-β receptor inhibitor (SD-208)	Mouse colon cancer	Preclinical	83
	T-cell (Treg)-targeted hybrid nanomaterial	STAT3/STAT5 pathway inhibitor (imatinib)	Mouse melanoma	Preclinical	84
	Iron nanomaterial	Anti-CD137 and anti-PD-L1	Mouse melanoma	Preclinical	85
	Liposome-coated polymeric gel	Mouse IL-2 and a TGF-β inhibitor (SB505124)	Mouse melanoma	Preclinical	87
	Backpacking nanomaterials				
	IL-15 superagonist complex nanogel	IL-15 superagonist complex	Various solid tumours and lymphomas	Phase 1	56
	Multilamellar liposomal vesicles	A2a adenosine receptor inhibitor (SCH-58261)	Mouse model of human ovarian cancer	Preclinical	93
	Nanomaterials-based vaccines				
	Amphiphile ligands (EGFRvIII peptide-conjugated DSPE–PEG)	NA	Mouse glioma expressing EGFRvIII$^+$	Preclinical	98
	Lipid nanomaterial	mRNA encoding the tight junction protein claudin 6 (CLDN6)	Mouse melanoma expressing CLDN6	Preclinical	57
Nanomaterials overcome physical barriers and hostile tumour microenvironments	**Nanomaterials that target physical barriers**				
	PLGA nanomaterial	Photothermal agent indocyanine green	Mouse melanoma	Preclinical	104
	Calcium phosphate nanomaterials with lipid bilayer coating	An antifibrotic compound α-mangostin and a plasmid encoding the stimulatory cytokine LIGHT	Mouse pancreatic cancer	Preclinical	59
	Nanomaterials that reverse the immune-suppressive environment				
	Lipid nanomaterial	A PI3K inhibitor (PI-3065) and a T-cell stimulator (7DW8-5)	Mouse breast cancer	Preclinical	61
	Multilamellar liposomal vesicles	A2a adenosine receptor inhibitor (SCH-58261)	Mouse model of human ovarian cancer	Preclinical	93
	Nanomaterials for local T-cell delivery				
	Macroporous alginate scaffolds	IL-15 superagonists, antibodies for CD3, CD28 and CD137	Mouse breast cancer, mouse ovarian cancer	Preclinical	60
	Nickel–titanium alloys	Antibodies for CD3, CD28, CD137	Mouse model of human pancreatic cancer expressing receptor tyrosine kinase-like orphan receptor (ROR1)	Preclinical	111
Nanomaterials as NBiTEs	Liposome	Human epidermal growth factor receptor 2 (HER2) and CD20 antibodies	Mouse breast cancer	Preclinical	131
	Polystyrene nanomaterial	Antibodies for HER2 and calreticulin protein	Mouse breast cancer	Preclinical	132
	Exosome	Exosome expressing antibodies for CD3 and epidermal growth factor receptor (EGFR)	Mouse breast cancer	Preclinical	58

TBD, to be determined; NA, not applicable; LIGHT, tumour necrosis factor superfamily 14.

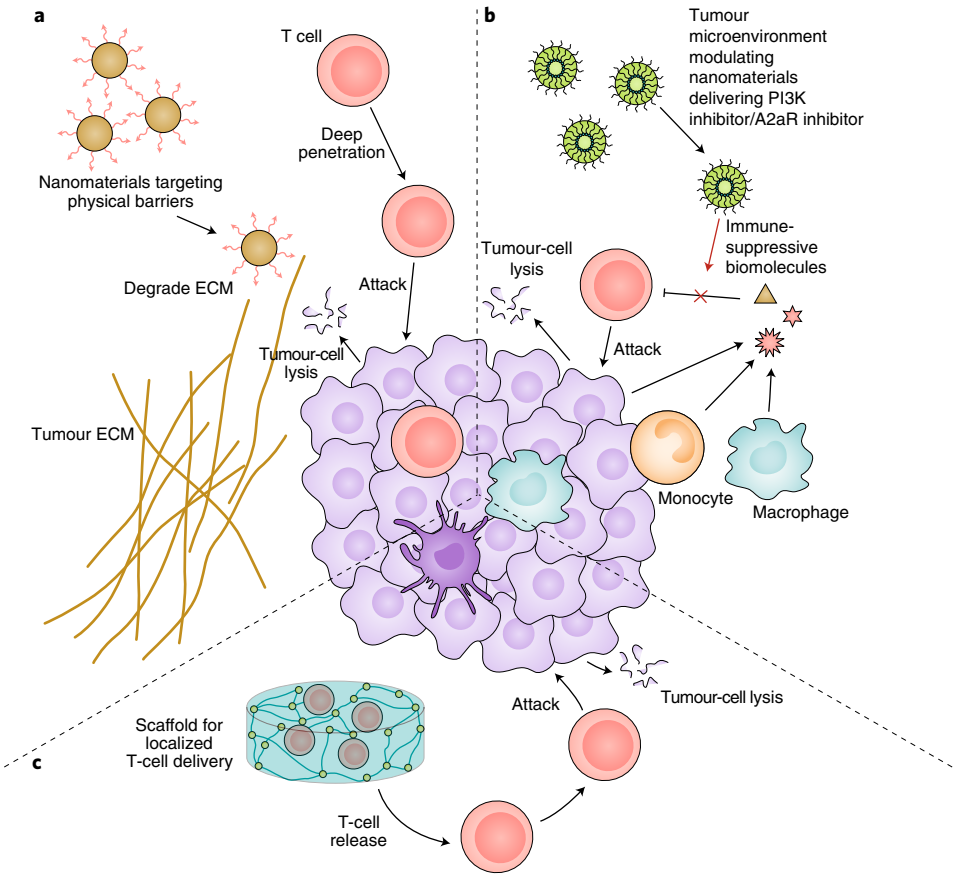

Fig. 4 | Nanomaterials overcome physical barriers and immune-suppressive environments for T-cell therapy. a, Nanomaterials can be designed to target the ECM and degrade the physical barriers inhibiting T-cell penetration and tumour cell targeting. **b**, Nanomaterials targeting the tumour microenvironment can deliver stimulatory cues to the tumour tissue and reverse the suppressive tumour microenvironment (immunological barrier), thus activating T-cell activity. **c**, Nanomaterials can locally deliver T cells directly to the tumour tissue with sustained release, which enhances tumour cell killing.

3–4 days after vaccination in mice. The in vivo experiments showed that a sub-therapeutic CLDN6-CAR T-cell dose combined with a single injection of the CARVac completely inhibited tumour growth in lymphodepleted mice. Further, one investigation demonstrated that vaccines targeting cross-presenting DCs ($BATf3^{+}CD103^{+}CD8^{+}$ in mice and $CD141^{+}$ in humans) induced potent antigen-specific T-cell proliferation[101], indicating that future studies should consider targeting this DC subtype for enhanced in vivo T-cell expansion. In all, these results highlight the potential of designing nanomaterials to effectively expand engineered T cells in vivo and enhance their performance.

Nanomaterials to improve T-cell engagement with solid tumours

ACT has been used in the clinic for the treatment of many cancer types[102]. However, current therapies are approved for blood cancers such as B-cell lymphoma[14,103]. Solid tumour treatment using T cells is limited by both physical barriers[16,17] and immune-suppressive environments. Considering these obstacles, this section will discuss the potential of nanomaterials to overcome the immune-suppressive environment and physical barriers to T-cell therapy, and describe how nanomaterial design can be used to enhance T-cell penetration, enable localized T-cell delivery and help modulate the suppressive tumour microenvironment.

Nanomaterials enhance T-cell penetration in solid tumours. One method for enhancing T-cell penetration in solid tumours involves the use of nanomaterials designed to remove the inhibitive ECM barrier (Fig. 4a). For example, one study[104] utilized a PLGA nanomaterial encapsulating the photothermal agent indocyanine green. Briefly, in a mouse model of melanoma, the nanomaterial was injected intratumorally, and subsequent near-infrared light irradiation allowed for the killing of tumour cells and the disruption of the ECM before CAR T-cell administration. This treatment led to reduced interstitial fluid pressure, improved CAR T-cell penetration in the tumour tissue and increased antitumour efficacy compared with CAR T cells alone. Instead of nanomaterial-based photothermal therapy to remove the fibrotic ECM of solid tumours, some investigations have explored the use of nanomaterials delivering an anti-fibrotic drug[59]. In a recent study[59], a core–shell calcium phosphate liposome nanomaterial (Nano-sapper) was developed to enhance CTL infiltration in an immune-excluded tumour (in which T cells are restricted to a peritumoral zone rich in fibroblasts, with few lymphocytes within the epithelial tumour mass itself)[105,106] in a mouse model of pancreatic cancer[59,107]. As α-mangostin has been shown to effectively reduce liver fibrosis levels in mice[108], this molecule was loaded into the Nano-sapper to reduce the physical barriers of the solid tumour. Additionally, a plasmid encoding the stimulatory cytokine LIGHT (tumour necrosis factor superfamily 14, TNFSF14, CD258) was co-delivered in the Nano-sapper to recruit CTLs to the immune-excluded tumour, and the ECM glycoprotein-targeting peptide FHK was conjugated to the nanomaterial surface. The Nano-sapper effectively reversed the overactivation of fibroblasts and generated lymphocyte-recruiting chemoattractants in situ in the tumour tissue, thus enabling CTL infiltration. Further, the Nano-sapper was shown to enhance checkpoint blockade therapy

against the immune-excluded solid tumour, indicating the potential for ECM removal to enhance cancer immunotherapy.

Nanomaterials reverse the immune-suppressive environment in solid tumours. Beyond an enriched ECM, aggressive solid tumours typically have a suppressive tumour microenvironment wherein immune cells and cytokines interact with tumour cells to mediate immune tolerance in tumour tissue, which affects clinical immunotherapy outcomes[109]. This tumour microenvironment can lead to exhaustion or even death of adoptively transferred T cells[110]. Thus, blocking the effects of an immune-suppressive tumour microenvironment could improve T-cell therapy in solid tumours (Fig. 4b). For example, one study[61] utilized a lipid-based nanomaterial containing both a PI3K inhibitor (PI-3065) and a T-cell stimulator (7DW8-5), which inhibited suppressor cells and simultaneously activated T cells in the tumour microenvironment. In a mouse model of breast cancer, this combination of treatments provided a two-week window for CAR T-cell therapy to effectively treat solid tumours[61]. In another study, CD19-specific CAR T cells were modified with multilamellar liposomal vesicles conjugated to their surface[93]. The multilamellar liposomal vesicles were loaded with a small molecule A2a adenosine receptor antagonist (SCH-58261) that can inhibit interactions between the A2a receptor on the T-cell surface and adenosine, thus preventing T-cell inactivation[93]. This therapeutic strategy was used in a mouse model of ovarian cancer where the tumour cells were engineered to overexpress CD19, and it enhanced accumulation of T cells in tumour sites and a successful reversal of the immune-suppressive tumour microenvironment, leading to increased CAR T-cell therapeutic efficacy[93].

Nanomaterials for local T-cell delivery to solid tumours. In addition to altering physical barriers and the immune-suppressive environment to enhance CAR T-cell penetration and therapeutic efficacy, nanomaterials can also be combined with polymeric scaffolds as a means to locally deliver T cells to tumour tissue[60,111,112] (Fig. 4c). One study developed a porous scaffold from polymerized alginate that contained mesoporous silica particles encapsulating IL-15 superagonists, coated with lipid bilayers and featuring antibodies for CD3, CD28 and CD137 conjugated to their surface. The scaffold also had T cells bound to its surface via a synthetic collagen-mimetic peptide[60]. Thus, sustained release of the soluble IL-15 superagonist complex, combined with antibody surface modifications, allowed the particles to keep the delivered T cells in an activated and proliferative state. The study investigated the in vivo antitumour effects of this T-cell-functionalized scaffold in a post-resection model of breast cancer, which showed that none of the tumours in mice receiving the T-cell scaffold system relapsed while mice in other treatment groups — including intravenously injected T cells, locally administered T cells, and locally administered T cells with IL-15 superagonist and antibodies — all experienced tumour relapse and death. Moreover, T cells delivered via the scaffold showed increased survival time in an unresected mouse model of ovarian cancer. However, while the polymer-based scaffolds could effectively expand T cells and enhance the therapy in vivo, they have a random or semi-random pore network, which may result in unpredictable cell loading and release kinetics that can impact T-cell therapeutic efficiency[111]. A more recent study[111] showed that nickel–titanium alloys in thin films with precisely defined micropatterned mesh structures (abbreviated as TFN) can load antigen-specific CAR T cells for improved T-cell therapy. The TFN networks show well-organized loading of CAR T cells on the surface with a narrow distribution of T-cell counts. In a mouse model of ovarian cancer, this localized delivery method greatly enhanced the central memory and effector T-cell populations in tumour tissue without inducing CAR T-cell exhaustion. Compared with intravenous or intratumoral T-cell delivery, CAR T cells delivered by the TFNs were more efficacious and suppressed solid tumour growth in several mouse models. Though the scaffolds described here enhanced CAR T-cell performance, T cells delivered in close proximity to tumours still face the obstacle of inefficient penetration[60], and future studies should focus on enhancing the penetration of locally delivered T cells into tumour tissues.

Nanomaterials to prevent target antigen loss

T-cell-mediated killing of tumour cells is dependent on the interaction between surface receptors on T-cells and the antigens present on cancer cells[113]. Thus, tumour cells may escape T-cell killing by manipulating these interactions via decreasing or eliminating the expression of major histocompatibility complex (MHC) class I/antigen, co-stimulatory molecules, and other markers on their cell surface, leading to low therapeutic efficiency or even resistance[114]. To overcome this, studies have developed 'universal' CARs where the targeting domain of the CAR is provided separately in a 'plug-and-play' fashion, enabling antigen swapping during treatment[115,116]. Another potential solution for antigen escape/loss is the development of bispecific T-cell engagers (BiTEs). BiTEs have been developed to bridge T cells and tumour cells, thus redirecting T cells to tumour cells and providing a promising strategy for cancer immunotherapy[117–119]. BiTE-induced tumour cell killing is a MHC I-independent process, as no antigen presentation or ex vivo engineering of T-cell receptors is needed[120,121], making BiTEs an effective strategy for generating antigen-specific T-cell immune responses towards tumours with low MHC I/antigen expression. Studies demonstrate that patients with B-lineage acute lymphoblastic leukemia treated with blinatumomab (an FDA-approved BiTE) show substantially prolonged survival compared with patients receiving traditional chemotherapy[122]. However, as BiTEs have short blood circulation times[117], effective therapy outcomes rely on constant administration, which may lead to patient discomfort[123]. Further limitations involve the binding affinity between each BiTE and the T-cell surface. The binding force maintained by a single BiTE may not be enough to firmly conjugate T cells to tumour cells[124], and many BiTEs may be needed to establish each pair[125]. In all, these problems restrict the broad clinical application of the BiTEs for cancer immunotherapy.

The development of nanomaterial-based BiTEs (NBiTEs) provides a great opportunity for improving BiTE therapy (Fig. 5). First, nanomaterials can have a three-dimensional structure and controllable morphology, as well as flexible surface-modification properties that provide diverse surface topologies[126]. Certain surface patterns of antibody-modified nanomaterials induce multivalent contact between antibodies and cells[125], which could enhance the binding affinity between T cells, tumour cells and BiTEs. Another benefit of the NBiTEs is prolonged circulation time[127], as nanomaterial surface coatings can decrease clearance to prolong circulation time in the blood[128,129]. This means that a long-term therapeutic effect may be achievable with NBiTEs, allowing them to avoid the limitation of frequent administration. Moreover, it is possible to design NBiTEs that encapsulate stimulatory molecules, such as IL-2, which can be released over time to sustain T-cell activation and enhance antitumour efficacy[130]. Several successful NBiTEs have been reported, including in mouse models of breast cancer. For example, one study[131] conjugated both human epidermal growth factor receptor 2 (HER2) and CD20 antibodies to the surface of liposomes and demonstrated a 25-fold increase in antibody potency using a cell viability assay. Moreover, enhanced tumour growth inhibition was observed in the NBiTE-treated mice compared with free antibodies, illustrating the benefit of multivalent contact between the liposome and cells. Another study[132] designed a 30 nm polystyrene-based NBiTE with antibodies for HER2 and calreticulin protein on its surface. The NBiTEs showed remarkably lower dissociation constants (K_d) compared with free anti-HER2 antibody because of their

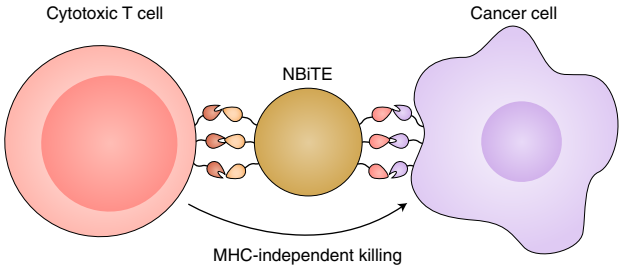

Fig. 5 | NBiTEs for cancer immunotherapy. A typical NBiTE is developed by adding two scFvs on the nanoparticle surface, with one scFv targeting a T-cell-specific antigen while the other targets a tumour-specific antigen. The multivalent contact at the nanomaterial/cell interfaces makes NBiTEs bridge T cells and tumour cells more effectively than traditional BiTEs and induces potent tumour cell killing.

multivalent contact with HER2 (ref. [132]). This NBiTE not only showed HER2-specific cancer cell killing but also induced enhanced antigen uptake by antigen-presenting cells and a durable tumour-specific immune response. Recently, in order to enhance the circulation time of NBiTEs, one group[58] engineered a HEK293 cell that overexpresses single-chain variable fragments (scFVs) for both CD3 and epidermal growth factor receptor (EGFR) to target T cells and EGFR-positive triple-negative breast cancer cells, respectively. Exosomes secreted by the cell line were collected using centrifugation, and they demonstrated effective conjugation to both T cells and breast cancer cells, showing potent antitumour immunity. In all, these studies demonstrate that NBiTEs are promising agents for re-directing T-cell functions for cancer immunotherapy. Since the NBiTE-induced tumour cell killing is a MHC I-independent process, this novel immunotherapy strategy has great potential to solve the problem of antigen loss during T-cell therapy.

Future directions and outlook

Substantial advances have been made in the development of nanomaterials to enhance T-cell therapy, including nanomaterial designs that enhance T-cell expansion, redirect T-cell functions and overcome the physical and biological barriers of solid tumours. However, formidable challenges remain for the clinical application of nanomaterials in T-cell immunotherapy, as discussed below.

To start, further investigations are needed to establish strategies for the rational design of nanomaterials for their desired applications in cancer immunotherapy. Many fundamental questions about the effects of nanomaterial composition, size, shape, elasticity and surface charge on T-cell function must be answered for applying nanomaterials to T-cell therapies. When considering surface modifications, effective targeting methods — such as multi-ligand modifications[133] — must be developed and validated to reduce non-specific uptake and prevent toxicity. Further, the patterns and density of these modifications, as well as general nanomaterial surface topology, must be evaluated to optimize nanomaterial designs for T-cell binding and activation, as an understanding of this relationship could enhance nanomaterial–T-cell interactions for strategies such as NBiTEs[134]. In terms of cargo, nanomaterials serve as a highly versatile delivery platform with the ability to traffic small molecules, genes, antibodies, and even combinations of these therapeutics, but the optimized cargo to work synergistically with current T-cell therapies has yet to be established. Further, the controlled release of cargo from these nanomaterials via stimuli-responsive drug delivery has been extensively investigated in cancer nanomedicine[51], and these same advancements should be incorporated into nanomaterial applications in T-cell therapies as diverse cargos are investigated. As future work begins to address all of these areas of interest and continues vetting nanomaterials for applications in cancer immunotherapy, it is also important to consider the biodegradability, toxicity and long-term safety of the nanomaterials themselves as they are developed.

Another consideration for future development is the manufacturing of nanomaterials on a clinical scale. As of 2017, of all the submissions to the US FDA for drug products utilizing nanomaterials, liposomes were the most prevalent category (33% of drug products) followed by drug products containing nanocrystals (23%), with one reason for their widespread use being the simplicity of manufacturing these structures[27]. However, in the context of nanomaterials for T-cell therapy, many studies utilize complex nanomaterial designs. With increasing design complexity, manufacturing costs and regulatory procedures to demonstrate safety and efficacy increase as well. Thus, researchers should keep the final goal of the nanomaterial — widespread clinical application — in mind when engineering nanomaterial solutions. Specifically, we suggest that researchers in this field keep in mind the cost, good manufacturing practice (GMP)-grade scale up and quality control of their nanomaterial in future studies.

Further, while nanomaterial-based strategies have been developed for different facets of T-cell therapy, such as in vivo T-cell expansion, T-cell re-direction and overcoming physical barriers and immune-suppressive environments, there are several unaddressed obstacles that nanomaterials have the potential to overcome. One major limitation to adoptively transferred T cells is a lack of control over their in vivo behaviour. Recent investigations are seeking to develop strategies to remotely control in vivo T-cell activity[135,136], and synthetically engineered T cells have been developed to undergo expansion, cancer-specific killing or death when exposed to specific small molecules[137], antibodies[103] or light[136]. As shown in Fig. 2, the cancer nanomedicine field includes many remotely controlled drug release systems to provide on-demand release of cargo with both internal and external stimuli[51], but these technologies need to be employed in cancer immunotherapy to precisely control T-cell activity in vivo. However, to investigate the impact of nanomaterials on T-cell activity, in vivo tracking and visualization tools with spatiotemporal resolution are urgently needed to study how infused T cells engage target cells, expand, exhaust and die. As nanomaterials have been extensively investigated as contrast agents to enhance many kinds of imaging modality[138–141], T cells labelled with nanomaterial-based contrast agents should be explored to visualize activity in real time in vivo[141]. As this work would allow for a more fundamental understanding of adoptively transferred T cells, a focus should also be placed on investigating the uncontrolled T-cell expansion and abnormal monocyte interactions that may induce severe cytokine release syndrome and even patient death[142,143], and effective cytokine release syndrome management methods must be explored. Beyond utilizing nanomaterials to study in vivo T-cell behaviour, nanomaterial solutions should be more broadly incorporated into ACTs. Several nanomaterial studies focus on modulating CAR T-cell therapy, but only a few investigate TIL, CTL and TCR-T therapies[144,145] even though these therapies could benefit from nanomaterials that increase their potency and in vivo expansion while reducing toxicity. Further, nanomaterials developed for T-cell-based immunotherapies could likely be used to modulate other immune cells, such as macrophages[146,147] and natural killer cells[148], and B-cell therapies[149] for other types of immunotherapy.

In all, nanomaterials are being widely explored to improve T-cell cancer immunotherapies, and they have demonstrated success for in vivo T-cell expansion, altering T-cell activity and overcoming barriers to solid tumour delivery. These promising nanotechnologies that can regulate T-cell function have the potential for more widespread use in both fundamental immunology research and clinical applications for cancer immunotherapy. With their

continued optimization, nanomaterials could ultimately expand the benefits of current T-cell-based cancer treatments and lead to the development of more advanced cancer immunotherapies.

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References

1. O'Leary, M. C. et al. FDA approval summary: tisagenlecleucel for treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. *Clin. Cancer Res.* **25**, 1142–1146 (2019).
2. Bouchkouj, N. et al. FDA approval summary: axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma. *Clin. Cancer Res.* **25**, 1702–1708 (2019).
3. Wang, M. et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N. Engl. J. Med.* **382**, 1331–1342 (2020).
4. Bollard, C. M. et al. Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. *J. Clin. Oncol.* **32**, 798–808 (2014).
5. Xu, J. et al. Exploratory trial of a biepitopic CAR T-targeting B cell maturation antigen in relapsed/refractory multiple myeloma. *Proc. Natl Acad. Sci. USA* **116**, 9543–9551 (2019).
6. Cohen, A. D. et al. B cell maturation antigen–specific CAR T cells are clinically active in multiple myeloma. *J. Clin. Invest.* **129**, 2210–2221 (2019).
7. Raje, N. et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **380**, 1726–1737 (2019).
8. Stevanović, S. et al. A phase II study of tumor-infiltrating lymphocyte therapy for human papillomavirus-associated epithelial cancers. *Clin. Cancer Res.* **25**, 1486–1493 (2019).
9. Jazaeri, A. A. et al. Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma. *J. Clin. Oncol.* **37**, 2538 (2019).
10. Hong, D. S. et al. Phase I dose escalation and expansion trial to assess the safety and efficacy of ADP-A2M4 SPEAR T cells in advanced solid tumors. *J. Clin. Oncol.* **38**, 102 (2020).
11. Louis, C. U. et al. Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. *J. Immunother.* **33**, 983–990 (2010).
12. Huang, J. et al. Epstein-Barr virus-specific adoptive immunotherapy for recurrent, metastatic nasopharyngeal carcinoma. *Cancer* **123**, 2642–2650 (2017).
13. Guedan, S., Ruella, M. & June, C. H. Emerging cellular therapies for cancer. *Annu. Rev. Immunol.* **37**, 145–171 (2019).
14. June, C. H., O'Connor, R. S., Kawalekar, O. U., Ghassemi, S. & Milone, M. C. CAR T cell immunotherapy for human cancer. *Science* **359**, 1361–1365 (2018).
15. Gilham, D. E., Debets, R., Pule, M., Hawkins, R. E. & Abken, H. CAR-T cells and solid tumors: tuning T cells to challenge an inveterate foe. *Trends Mol. Med.* **18**, 377–384 (2012).
16. Caruana, I. et al. Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes. *Nat. Med.* **21**, 524–529 (2015).
17. Buckanovich, R. J. et al. Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy. *Nat. Med.* **14**, 28–36 (2008).
18. Motz, G. T. et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nat. Med.* **20**, 607–615 (2014).
19. Ren, J. et al. Multiplex genome editing to generate universal CAR T cells resistant to PD1 inhibition. *Clin. Cancer Res.* **23**, 2255–2266 (2017).
20. Bollard, C. M. et al. Tumor-specific T-cells engineered to overcome tumor immune evasion induce clinical responses in patients with relapsed Hodgkin lymphoma. *J. Clin. Oncol.* **36**, 1128–1139 (2018).
21. Chang, C.-H. et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* **162**, 1229–1241 (2015).
22. Lukashev, D. et al. Cutting edge: hypoxia-inducible factor 1α and its activation-inducible short isoform I.1 negatively regulate functions of $CD4^+$ and $CD8^+$ T lymphocytes. *J. Immunol.* **177**, 4962–4965 (2006).
23. Sotillo, E. et al. Convergence of acquired mutations and alternative splicing of CD19 enables resistance to CART-19 immunotherapy. *Cancer Discov.* **5**, 1282–1295 (2015).
24. O'Rourke, D. M. et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci. Transl. Med.* **9**, eaaa0984 (2017).
25. Hamieh, M. et al. CAR T cell trogocytosis and cooperative killing regulate tumour antigen escape. *Nature* **568**, 112–116 (2019).
26. Shi, J., Kantoff, P. W., Wooster, R. & Farokhzad, O. C. Cancer nanomedicine: progress, challenges and opportunities. *Nat. Rev. Cancer* **17**, 20–37 (2017).
27. D'Mello, S. R. et al. The evolving landscape of drug products containing nanomaterials in the United States. *Nat. Nanotechnol.* **12**, 523–529 (2017).
28. Jones, A.-A. D. III, Mi, G. & Webster, T. J. A status report on FDA approval of medical devices containing nanostructured materials. *Trend. Biotechnol.* **37**, 117–120 (2019).
29. Anselmo, A. C. & Mitragotri, S. Nanoparticles in the clinic: an update. *Bioeng. Transl. Med.* **4**, e10143 (2019).
30. Maeda, H., Wu, J., Sawa, T., Matsumura, Y. & Hori, K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J. Control. Release* **65**, 271–284 (2000).
31. Barenholz, Y. C. Doxil®—the first FDA-approved nano-drug: lessons learned. *J. Control. Release* **160**, 117–134 (2012).
32. Miele, E., Spinelli, G. P., Miele, E., Tomao, F. & Tomao, S. Albumin-bound formulation of paclitaxel (Abraxane® ABI-007) in the treatment of breast cancer. *Int. J. Nanomed.* **4**, 99–105 (2009).
33. Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J. & Corrie, S. R. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm. Res.* **33**, 2373–2387 (2016).
34. Petersen, G. H., Alzghari, S. K., Chee, W., Sankari, S. S. & La-Beck, N. M. Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional non-liposomal doxorubicin. *J. Control. Release* **232**, 255–264 (2016).
35. Gradishar, W. J. et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J. Clin. Oncol.* **23**, 7794–7803 (2005).
36. Bertrand, N., Wu, J., Xu, X., Kamaly, N. & Farokhzad, O. C. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Adv. Drug Del. Rev.* **66**, 2–25 (2014).
37. Bazak, R., Houri, M., El Achy, S., Kamel, S. & Refaat, T. Cancer active targeting by nanoparticles: a comprehensive review of literature. *J. Cancer Res. Clin. Oncol.* **141**, 769–784 (2015).
38. Lu, Y., Aimetti, A. A., Langer, R. & Gu, Z. Bioresponsive materials. *Nat. Rev. Mater.* **2**, 16075 (2016).
39. Airan, R. D. et al. Noninvasive targeted transcranial neuromodulation via focused ultrasound gated drug release from nanoemulsions. *Nano Lett.* **17**, 652–659 (2017).
40. Kemp, J. A., Shim, M. S., Heo, C. Y. & Kwon, Y. J. "Combo" nanomedicine: co-delivery of multi-modal therapeutics for efficient, targeted, and safe cancer therapy. *Adv. Drug Del. Rev.* **98**, 3–18 (2016).
41. Vaughan, H. J., Green, J. J. & Tzeng, S. Y. Cancer-targeting nanoparticles for combinatorial nucleic acid delivery. *Adv. Mater.* **32**, 1901081 (2020).
42. Wang, H. & Mooney, D. J. Biomaterial-assisted targeted modulation of immune cells in cancer treatment. *Nat. Mater.* **17**, 761–772 (2018).
43. Irvine, D. J. & Dane, E. L. Enhancing cancer immunotherapy with nanomedicine. *Nat. Rev. Immunol.* **20**, 321–334 (2020).
44. Dellacherie, M. O., Seo, B. R. & Mooney, D. J. Macroscale biomaterials strategies for local immunomodulation. *Nat. Rev. Mater.* **4**, 379–397 (2019).
45. Goldberg, M. S. Improving cancer immunotherapy through nanotechnology. *Nat. Rev. Cancer* **19**, 587–602 (2019).
46. Xia, Y., Tian, J. & Chen, X. Effect of surface properties on liposomal siRNA delivery. *Biomaterials* **79**, 56–68 (2016).
47. Banerjee, A., Qi, J., Gogoi, R., Wong, J. & Mitragotri, S. Role of nanoparticle size, shape and surface chemistry in oral drug delivery. *J. Control. Release* **238**, 176–185 (2016).
48. Zhao, Z., Ukidve, A., Krishnan, V. & Mitragotri, S. Effect of physicochemical and surface properties on in vivo fate of drug nanocarriers. *Adv. Drug Del. Rev.* **143**, 3–21 (2019).
49. Zhu, M. et al. Physicochemical properties determine nanomaterial cellular uptake, transport, and fate. *Acc. Chem. Res.* **46**, 622–631 (2013).
50. Duan, X. & Li, Y. Physicochemical characteristics of nanoparticles affect circulation, biodistribution, cellular internalization, and trafficking. *Small* **9**, 1521–1532 (2013).
51. Mura, S., Nicolas, J. & Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. *Nat. Mater.* **12**, 991–1003 (2013).
52. Kamaly, N., Yameen, B., Wu, J. & Farokhzad, O. C. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. *Chem. Rev.* **116**, 2602–2663 (2016).
53. Chen, Q. et al. In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment. *Nat. Nanotechnol.* **14**, 89–97 (2019).
54. Riley, R. S., June, C. H., Langer, R. & Mitchell, M. J. Delivery technologies for cancer immunotherapy. *Nat. Rev. Drug Discov.* **18**, 175–196 (2019).
55. Zheng, Y. et al. In vivo targeting of adoptively transferred T-cells with antibody- and cytokine-conjugated liposomes. *J. Control. Release* **172**, 426–435 (2013).
56. Tang, L. et al. Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery. *Nat. Biotechnol.* **36**, 707–716 (2018).

This study describes a strategy that facilitates in vivo T-cell expansion via a stimuli-responsive cytokine release nanotechnology.
57. Reinhard, K. et al. An RNA vaccine drives expansion and efficacy of claudin-CAR-T cells against solid tumors. *Science* **367**, 446–453 (2020). **In this paper, a lipid nanomaterial-based mRNA vaccine (CARVac) was designed to enhance CAR T-cell expansion in vivo.**
58. Cheng, Q. et al. Reprogramming exosomes as nanoscale controllers of cellular immunity. *J. Am. Chem. Soc.* **140**, 16413–16417 (2018). **In this study, an exosome-based NBiTE that can re-direct T-cell functions for cancer immunotherapy was developed.**
59. Huang, Y. et al. Dual-mechanism based CTLs infiltration enhancement initiated by Nano-sapper potentiates immunotherapy against immune-excluded tumors. *Nat. Commun.* **11**, 622 (2020). **This study developed a core–shell calcium phosphate liposome nanomaterial to enhance CTL infiltration in an immune-excluded tumour.**
60. Stephan, S. B. et al. Biopolymer implants enhance the efficacy of adoptive T-cell therapy. *Nat. Biotechnol.* **33**, 97–101 (2015). **This paper describes nanomaterial-based scaffolds to locally deliver T cells to solid tumours.**
61. Zhang, F. et al. Nanoparticles that reshape the tumor milieu create a therapeutic window for effective T-cell therapy in solid malignancies. *Cancer Res.* **78**, 3718–3730 (2018).
62. Sockolosky, J. T. et al. Selective targeting of engineered T cells using orthogonal IL-2 cytokine-receptor complexes. *Science* **359**, 1037–1042 (2018).
63. Smith, T. T. et al. In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers. *Nat. Nanotechnol.* **12**, 813–820 (2017). **This study developed a polymeric nanomaterial to specifically deliver CAR-encoding genes to T cells in vivo, inducing CAR expression and expansion in vivo**.
64. Schmidts, A. & Maus, M. V. Making CAR T cells a solid option for solid tumors. *Front. Immunol.* **9**, 2593 (2018).
65. Landskron, G., De la Fuente, M., Thuwajit, P., Thuwajit, C. & Hermoso, M. A. Chronic inflammation and cytokines in the tumor microenvironment. *J. Immunol. Res.* **2014**, 149185 (2014).
66. Eklund, J. W. & Kuzel, T. M. A review of recent findings involving interleukin-2-based cancer therapy. *Curr. Opin. Oncol.* **16**, 542–546 (2004).
67. Balkwill, F. Tumour necrosis factor and cancer. *Nat. Rev. Cancer* **9**, 361–371 (2009).
68. McDermott, D. F. et al. The high-dose aldesleukin "select" trial: a trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. *Clin. Cancer Res.* **21**, 561–568 (2015).
69. Weigent, D. A., Huff, T. L., Peterson, J. W., Stanton, G. J. & Baron, S. Role of interferon in streptococcal infection in the mouse. *Microb. Pathog.* **1**, 399–407 (1986).
70. Tartour, E., Mathiot, C. & Fridman, W. Current status of interleukin-2 therapy in cancer. *Biomed. Pharmacother.* **46**, 473–484 (1992).
71. Porter, D. L., Levine, B. L., Kalos, M., Bagg, A. & June, C. H. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N. Engl. J. Med.* **365**, 725–733 (2011).
72. D'Angelo, S. P. et al. Antitumor activity associated with prolonged persistence of adoptively transferred NY-ESO-1 ^{c259}T cells in synovial sarcoma. *Cancer Discov.* **8**, 944–957 (2018).
73. Parmiani, G., Rivoltini, L., Andreola, G. & Carrabba, M. Cytokines in cancer therapy. *Immunol. Lett.* **74**, 41–44 (2000).
74. Lotze, M. T. et al. In vivo administration of purified human interleukin 2. II. Half life, immunologic effects, and expansion of peripheral lymphoid cells in vivo with recombinant IL 2. *J. Immunol.* **135**, 2865–2875 (1985).
75. Atkins, M. B. et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J. Clin. Oncol.* **17**, 2105 (1999).
76. Mishra, P., Nayak, B. & Dey, R. PEGylation in anti-cancer therapy: an overview. *Asian J. Pharm. Sci.* **11**, 337–348 (2016).
77. Garber, K. Cytokine resurrection: engineered IL-2 ramps up immuno-oncology responses. *Nat. Biotechnol.* **36**, 378–379 (2018).
78. Xie, Y. Q., Wei, L. & Tang, L. Immunoengineering with biomaterials for enhanced cancer immunotherapy. *WIREs Nanomed. Nanobiotechnol.* **10**, e1506 (2018).
79. McHugh, M. D. et al. Paracrine co-delivery of TGF-β and IL-2 using CD4-targeted nanoparticles for induction and maintenance of regulatory T cells. *Biomaterials* **59**, 172–181 (2015).
80. Yao, H. et al. Effective melanoma immunotherapy with interleukin-2 delivered by a novel polymeric nanoparticle. *Mol. Cancer Ther.* **10**, 1082–1092 (2011).
81. Wherry, E. J. & Kurachi, M. Molecular and cellular insights into T cell exhaustion. *Nat. Rev. Immunol.* **15**, 486–499 (2015).
82. Zheng, Y., Tang, L., Mabardi, L., Kumari, S. & Irvine, D. J. Enhancing adoptive cell therapy of cancer through targeted delivery of small-molecule immunomodulators to internalizing or noninternalizing receptors. *ACS Nano* **11**, 3089–3100 (2017).
83. Schmid, D. et al. T cell-targeting nanoparticles focus delivery of immunotherapy to improve antitumor immunity. *Nat. Commun.* **8**, 1747 (2017).
84. Ou, W. et al. Regulatory T cell-targeted hybrid nanoparticles combined with immuno-checkpoint blockage for cancer immunotherapy. *J. Control. Release* **281**, 84–96 (2018).
85. Kosmides, A. K., Sidhom, J.-W., Fraser, A., Bessell, C. A. & Schneck, J. P. Dual targeting nanoparticle stimulates the immune system to inhibit tumor growth. *ACS Nano* **11**, 5417–5429 (2017).
86. Pallandre, J.-R. et al. Role of STAT3 in $CD4^+CD25^+FOXP3^+$ regulatory lymphocyte generation: implications in graft-versus-host disease and antitumor immunity. *J. Immunol.* **179**, 7593–7604 (2007).
87. Park, J. et al. Combination delivery of TGF-β inhibitor and IL-2 by nanoscale liposomal polymeric gels enhances tumour immunotherapy. *Nat. Mater.* **11**, 895–905 (2012).
88. Xie, Y.-Q. et al. Redox-responsive interleukin-2 nanogel specifically and safely promotes the proliferation and memory precursor differentiation of tumor-reactive T-cells. *Biomater. Sci.* **7**, 1345–1357 (2019).
89. Berger, C. et al. Safety and immunologic effects of IL-15 administration in nonhuman primates. *Blood* **114**, 2417–2426 (2009).
90. Robinson, T. O. & Schluns, K. S. The potential and promise of IL-15 in immuno-oncogenic therapies. *Immunol. Lett.* **190**, 159–168 (2017).
91. Huang, B. et al. Active targeting of chemotherapy to disseminated tumors using nanoparticle-carrying T cells. *Sci. Transl. Med.* **7**, 291ra94 (2015).
92. Jones, R. B. et al. Antigen recognition-triggered drug delivery mediated by nanocapsule-functionalized cytotoxic T-cells. *Biomaterials* **117**, 44–53 (2017).
93. Siriwon, N. et al. CAR-T cells surface-engineered with drug-encapsulated nanoparticles can ameliorate intratumoral T cell hypofunction. *Cancer Immunol. Res.* **6**, 812–824 (2018).
94. Siegler, E. L. et al. Combination cancer therapy using chimeric antigen receptor-engineered natural killer cells as drug carriers. *Mol. Ther.* **25**, 2607–2619 (2017).
95. Martin, J. D., Cabral, H., Stylianopoulos, T. & Jain, R. K. Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges. *Nat. Rev. Clin. Oncol.* **17**, 251–266 (2020).
96. Slaney, C. Y. et al. Dual-specific chimeric antigen receptor T cells and an indirect vaccine eradicate a variety of large solid tumors in an immunocompetent, self-antigen setting. *Clin. Cancer Res.* **23**, 2478–2490 (2017).
97. Tanaka, M. et al. Vaccination targeting native receptors to enhance the function and proliferation of chimeric antigen receptor (CAR)-modified T cells. *Clin. Cancer Res.* **23**, 3499–3509 (2017).
98. Ma, L. et al. Enhanced CAR-T cell activity against solid tumors by vaccine boosting through the chimeric receptor. *Science* **365**, 162–168 (2019). **In this study, amphiphile CAR T ligands that can preferentially be anchored to the dendritic cell surface to boost in vivo CAR T-cell expansion were developed**.
99. Tsopelas, C. & Sutton, R. Why certain dyes are useful for localizing the sentinel lymph node. *J. Nucl. Med.* **43**, 1377–1382 (2002).
100. Liu, H. et al. Structure-based programming of lymph-node targeting in molecular vaccines. *Nature* **507**, 519–522 (2014).
101. Zeng, B. et al. Self-adjuvanting nanoemulsion targeting dendritic cell receptor Clec9A enables antigen-specific immunotherapy. *J. Clin. Invest.* **128**, 1971–1984 (2018).
102. Shah, N. N. & Fry, T. J. Mechanisms of resistance to CAR T cell therapy. *Nat. Rev. Clin. Oncol.* **16**, 372–385 (2019).
103. Rafiq, S., Hackett, C. S. & Brentjens, R. J. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. *Nat. Rev. Clin. Oncol.* **17**, 147–167 (2020).
104. Chen, Q. et al. Photothermal therapy promotes tumor infiltration and antitumor activity of CAR T cells. *Adv. Mater.* **31**, 1900192 (2019). **This study developed a photothermal agent-encapsulated PLGA nanomaterial to disrupt tumour ECM to enhance CAR T-cell penetration in solid tumour.**
105. Ganesh, K. & Massagué, J. TGF-β inhibition and immunotherapy: checkmate. *Immunity* **48**, 626–628 (2018).
106. Bommareddy, P. K., Shettigar, M. & Kaufman, H. L. Integrating oncolytic viruses in combination cancer immunotherapy. *Nat. Rev. Immunol.* **18**, 498–513 (2018).
107. Vitiello, G. A., Cohen, D. J. & Miller, G. Harnessing the microbiome for pancreatic cancer immunotherapy. *Trend. Cancer* **5**, 670–676 (2019).
108. Rahmaniah, R. et al. Alpha mangostin inhibits hepatic stellate cells activation through TGF-β/Smad and Akt signaling pathways: an in vitro study in LX2. *Drug Res.* **68**, 153–158 (2018).
109. Gajewski, T. F. et al. Cancer immunotherapy strategies based on overcoming barriers within the tumor microenvironment. *Curr. Opin. Immunol.* **25**, 268–276 (2013).

110. Pitt, J. et al. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. *Ann. Oncol.* **27**, 1482–1492 (2016).
111. Coon, M. E., Stephan, S. B., Gupta, V., Kealey, C. P. & Stephan, M. T. Nitinol thin films functionalized with CAR-T cells for the treatment of solid tumours. *Nat. Biomed. Eng.* **4**, 195–206 (2020).
This study developed nickel–titanium alloys with precisely defined micropatterned mesh structures for improved CAR T-cell delivery in solid tumour.
112. Smith, T. T. et al. Biopolymers codelivering engineered T cells and STING agonists can eliminate heterogeneous tumors. *J. Clin. Invest.* **127**, 2176–2191 (2017).
113. Ribas, A. & Wolchok, J. D. Cancer immunotherapy using checkpoint blockade. *Science* **359**, 1350–1355 (2018).
114. Sharma, P., Hu-Lieskovan, S., Wargo, J. A. & Ribas, A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell* **168**, 707–723 (2017).
115. Hyrenius-Wittsten, A. & Roybal, K. T. Paving new roads for CARs. *Trend. Cancer* **5**, 583–592 (2019).
116. Hughes-Parry, H. E., Cross, R. S. & Jenkins, M. R. The evolving protein engineering in the design of chimeric antigen receptor T cells. *Int. J. Mol. Sci.* **21**, 204 (2020).
117. Goebeler, M.-E. et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. *J. Clin. Oncol.* **34**, 1104–1111 (2016).
118. Baeuerle, P. A. & Reinhardt, C. Bispecific T-cell engaging antibodies for cancer therapy. *Cancer Res.* **69**, 4941–4944 (2009).
119. Choi, B. D. et al. CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity. *Nat. Biotechnol.* **37**, 1049–1058 (2019).
120. Zhukovsky, E. A., Morse, R. J. & Maus, M. V. Bispecific antibodies and CARs: generalized immunotherapeutics harnessing T cell redirection. *Curr. Opin. Immunol.* **40**, 24–35 (2016).
121. Huehls, A. M., Coupet, T. A. & Sentman, C. L. Bispecific T-cell engagers for cancer immunotherapy. *Immunol. Cell Biol.* **93**, 290–296 (2015).
122. Kantarjian, H. et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N. Engl. J. Med.* **376**, 836–847 (2017).
123. Topp, M. S. et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* **16**, 57–66 (2015).
124. Brischwein, K. et al. Strictly target cell-dependent activation of T cells by bispecific single-chain antibody constructs of the BiTE class. *J. Immunother.* **30**, 798–807 (2007).
125. Song, W., Das, M. & Chen, X. Nanotherapeutics for immuno-oncology: a crossroad for new paradigms. *Trend. Cancer* **6**, 288–298 (2020).
126. Montet, X., Funovics, M., Montet-Abou, K., Weissleder, R. & Josephson, L. Multivalent effects of RGD peptides obtained by nanoparticle display. *J. Med. Chem.* **49**, 6087–6093 (2006).
127. Lipka, J. et al. Biodistribution of PEG-modified gold nanoparticles following intratracheal instillation and intravenous injection. *Biomaterials* **31**, 6574–6581 (2010).
128. Liu, X. et al. Mixed-charge nanoparticles for long circulation, low reticuloendothelial system clearance, and high tumor accumulation. *Adv. Healthc. Mater.* **3**, 1439–1447 (2014).
129. Romberg, B., Hennink, W. E. & Storm, G. Sheddable coatings for long-circulating nanoparticles. *Pharm. Res.* **25**, 55–71 (2008).
130. Sun, Z. et al. A next-generation tumor-targeting IL-2 preferentially promotes tumor-infiltrating $CD8^+$ T-cell response and effective tumor control. *Nat. Commun.* **10**, 3874 (2019).
131. Chiu, G. N. et al. Modulation of cancer cell survival pathways using multivalent liposomal therapeutic antibody constructs. *Mol. Cancer Ther.* **6**, 844–855 (2007).
132. Yuan, H. et al. Multivalent bi-specific nanobioconjugate engager for targeted cancer immunotherapy. *Nat. Nanotechnol.* **12**, 763–769 (2017).
133. Peiris, P. M. et al. Precise targeting of cancer metastasis using multi-ligand nanoparticles incorporating four different ligands. *Nanoscale* **10**, 6861–6871 (2018).
134. Cai, H. et al. Full control of ligand positioning reveals spatial thresholds for T cell receptor triggering. *Nat. Nanotechnol.* **13**, 610–617 (2018).
135. Qi, J. et al. Chemically programmable and switchable CAR-T therapy. *Angew. Chem. Int. Ed.* **59**, 12178–12185 (2020).
136. Huang, Z. et al. Engineering light-controllable CAR T cells for cancer immunotherapy. *Sci. Adv.* **6**, eaay9209 (2020).
137. Wu, C.-Y., Roybal, K. T., Puchner, E. M., Onuffer, J. & Lim, W. A. Remote control of therapeutic T cells through a small molecule-gated chimeric receptor. *Science* **350**, aab4077 (2015).
138. Chen, Y.-S., Zhao, Y., Yoon, S. J., Gambhir, S. S. & Emelianov, S. Miniature gold nanorods for photoacoustic molecular imaging in the second near-infrared optical window. *Nat. Nanotechnol.* **14**, 465–472 (2019).
139. Zhong, Y. et al. Boosting the down-shifting luminescence of rare-earth nanocrystals for biological imaging beyond 1500 nm. *Nat. Commun.* **8**, 737 (2017).
140. Xing, Z. et al. The fabrication of novel nanobubble ultrasound contrast agent for potential tumor imaging. *Nanotechnology* **21**, 145607 (2010).
141. Meir, R. et al. Nanomedicine for cancer immunotherapy: tracking cancer-specific T-cells in vivo with gold nanoparticles and CT imaging. *ACS Nano* **9**, 6363–6372 (2015).
142. Giavridis, T. et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat. Med.* **24**, 731–738 (2018).
143. Norelli, M. et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat. Med.* **24**, 739–748 (2018).
144. Wu, Y., Gu, W., Li, J., Chen, C. & Xu, Z. P. Silencing PD-1 and PD-L1 with nanoparticle-delivered small interfering RNA increases cytotoxicity of tumor-infiltrating lymphocytes. *Nanomedicine* **14**, 955–967 (2019).
145. Chen, M., Ouyang, H., Zhou, S., Li, J. & Ye, Y. PLGA-nanoparticle mediated delivery of anti-OX40 monoclonal antibody enhances anti-tumor cytotoxic T cell responses. *Cell. Immunol.* **287**, 91–99 (2014).
146. Klichinsky, M. et al. Human chimeric antigen receptor macrophages for cancer immunotherapy. *Nat. Biotechnol.* **38**, 947–953 (2020).
147. Shields, C. W. et al. Cellular backpacks for macrophage immunotherapy. *Sci. Adv.* **6**, eaaz6579 (2020).
148. Kim, K.-S. et al. Multifunctional nanoparticles for genetic engineering and bioimaging of natural killer (NK) cell therapeutics. *Biomaterials* **221**, 119418 (2019).
149. Wennhold, K., Shimabukuro-Vornhagen, A. & von Bergwelt-Baildon, M. B cell-based cancer immunotherapy. *Transfus. Med. Hemoth.* **46**, 36–46 (2019).

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Competing interests

C.H.J. works under a research collaboration involving the University of Pennsylvania and the Novartis Institutes of Biomedical Research, Inc. C.H.J. is an inventor of intellectual property licensed by the University of Pennsylvania to Novartis. C.H.J. has sponsored research and equity from Tmunity Therapeutics. C.H.J. is a consultant for Immune Design, Viracta and Carisma. N.C.S. holds shares in Tmunity Therapeutics and Fate Therapeutics.

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