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Review article

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Responsive biomaterials: optimizing control of cancer immunotherapy

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Abstract

Immunotherapy has emerged as an eminent and effective modality in the treatment of cancer. However, current cancer immunotherapies lack spatial and temporal control, resulting in systemic side effects and suboptimal patient outcomes. Responsive biomaterials have proven to be powerful tools for controlling cancer immunotherapies by providing precise control over the delivery and kinetics of immunotherapeutic cargoes. Here, we discuss biological barriers to cancer immunotherapy and how biomaterial-based strategies that respond to different stimuli — both internal and external — can be used to increase the therapeutic efficacy while reducing the toxicity of cancer immunotherapies. We examine the use of biomaterials that respond to physiological stimuli (pH, enzymes and redox potential) and exogenous energetic stimuli (light, magnetism and ultrasound) and expand upon the use of these strategies in propagating three key approaches in cancer immunotherapy: cancer vaccines, T cell-based therapy and therapies involving sustained delivery.

Sections

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Introduction

Cancer immunotherapy involves enhancing the native immunity of a patient and spans the use of several strategies, including engaging immunostimulatory cascades (such as stimulating interferon genes (STING))[1–3], repressing inhibitory agents (such as regulatory T cells)[4–6] or even directly reprogramming immune cells to specifically engage tumour targets (such as chimeric antigen receptor (CAR) T cells)[7–10]. Physicians and scientists have been developing these methods to combat cancer since the late nineteenth century[11–14]; however, groundbreaking discoveries in cancer immunotherapy since the early twenty-first century have resulted in clinical advances like never before, evidenced by the 2018 Nobel Prize in Medicine for immune checkpoint blockade (ICB) therapy[15–17] (Fig. 1a).

Unfortunately, off-target and on-target off-tumour toxicities still remain important unmet challenges in cancer immunotherapy[18–20]. Most current immunotherapies, including checkpoint antibodies and cell-based therapies, are administered without any auxiliary agents and result in a lack of pharmacological control. This non-specificity has implications for both efficacy and toxicity; because a large proportion of therapeutic agents do not reach the tumour, a larger initial dose must be used to achieve a therapeutic effect, which amplifies toxic side effects. Therefore, there is a need for strategies that optimize therapeutic responses and mitigate off-target and on-target off-tumour toxicities[20–22].

Biomaterial-based strategies are highly tunable and can enable the precise control of cancer immunotherapies to initiate antitumour responses[23–29] (Fig. 1b). Biomaterials allow for effective delivery of immunotherapies by overcoming major biological barriers of tumours and tumour microenvironments (TMEs) and can also be modified to safely navigate the immune landscape of the body (Box 1). Since 2005, several biomaterial-based therapies have entered clinical trials with moderate success; however, these therapies have yet to be approved by the FDA (Table 1). Novel, emerging approaches utilize engineered biomaterials that respond to specific endogenous cues (such as pH, redox potential and enzymatic activity) and exogenous cues (such as light, magnetic and acoustic energy), resulting in precise spatiotemporal control of immunotherapeutic activity[30–35].

In this Review, we discuss the current progress in biomaterial-based approaches for controlling both the spatial and temporal dynamics of cancer immunotherapies. We elaborate on various strategies being explored to tune and improve the therapeutic efficacy of biomaterial-based cancer immunotherapies while providing commentary on their potential limitations. We also provide a comprehensive future outlook on the preclinical and clinical translation of these approaches and expand on considerations to bring them from bench to bedside. Although combination cancer immunotherapy holds great promise, it is not the centre of this Review; therefore, we refer readers interested in current combination immunotherapy (such as chemo-immunotherapy, photodynamic immunotherapy, photothermal immunotherapy, sonodynamic immunotherapy and magnetic hyperthermia immunotherapy) to other published works[36–39].

Physiological stimuli to mediate cancer immunotherapy

The TME has become an important target for the treatment of cancer, exhibiting specific physiological properties including acidic pH, higher redox potentials, increased hypoxic status, overexpressed enzymes and increased metabolic activity[23,39–42]. These changes facilitate tumour angiogenesis and metastasis and also result in treatment resistance and failure. Thus, harnessing the unique properties of the TME and designing biomaterial platforms with TME-responsive capabilities have shown to be an effective strategy in cancer immunotherapeutics[23,43,44]. These platforms can respond to various endogenous stimuli (such as pH, redox potential and enzymes) and specifically target tumour sites, augmenting therapeutic efficacy while reducing systemic side effects (Fig. 2).

pH-induced immunotherapeutic delivery

Utilizing pH responsiveness as a therapeutic strategy to target tumours has been widely explored[22,45,46]. Compared with healthy tissues, tumours typically have acidic extracellular microenvironments, with pH ranging from 6.5 to 6.8 owing to deregulated metabolism, insufficient perfusion and build-up of lactic acid[40,42]. Additionally, it has been reported that after endocytosis by antigen-presenting cells (APCs), the pH reaches a range between 5.0 and 6.0 in endosomes and a range between 4.0 and 5.0 in lysosomes[42,46]. Thus, using smart biomaterials that are capable of physical changes, such as swelling and shrinking, and chemical changes, such as dissociation and degradation, to release their therapeutic cargo in response to changes in pH is advantageous[45–48].

Two primary strategies have been used to develop these biomaterials, the first being the use of polycations/polyanions that are capable of pH-dependent protonation/ionization[45,46]. These systems largely include various classes of nanomaterials, such as lipid nanoparticles (LNPs)[49], liposomes[50], amphiphilic polymer nanoparticles[51] and nanovaccines[52], as well as nanogels/microgels[53] that can encapsulate immunotherapeutic payloads. The second strategy is incorporating pH-cleavable acid-sensitive bonds into therapeutic materials[45,46]; examples include acid-labile polymers[53], peptide conjugates[54], metal–organic frameworks[55,56], hybrid nanoparticles[57] and crosslinked polymers[58,59].

One major drawback of pH-sensitive platforms is that they can be recognized by opsonin in plasma, resulting in phagocytosis and clearance by the reticuloendothelial system before achieving a therapeutic effect[46]. As a result, only a few pH-sensitive platforms have made it into clinical trials. A clinically viable pH-sensitive system must satisfy specific requirements in terms of efficient pH-triggered release, serum stability, bioavailability and batch-to-batch reproducibility.

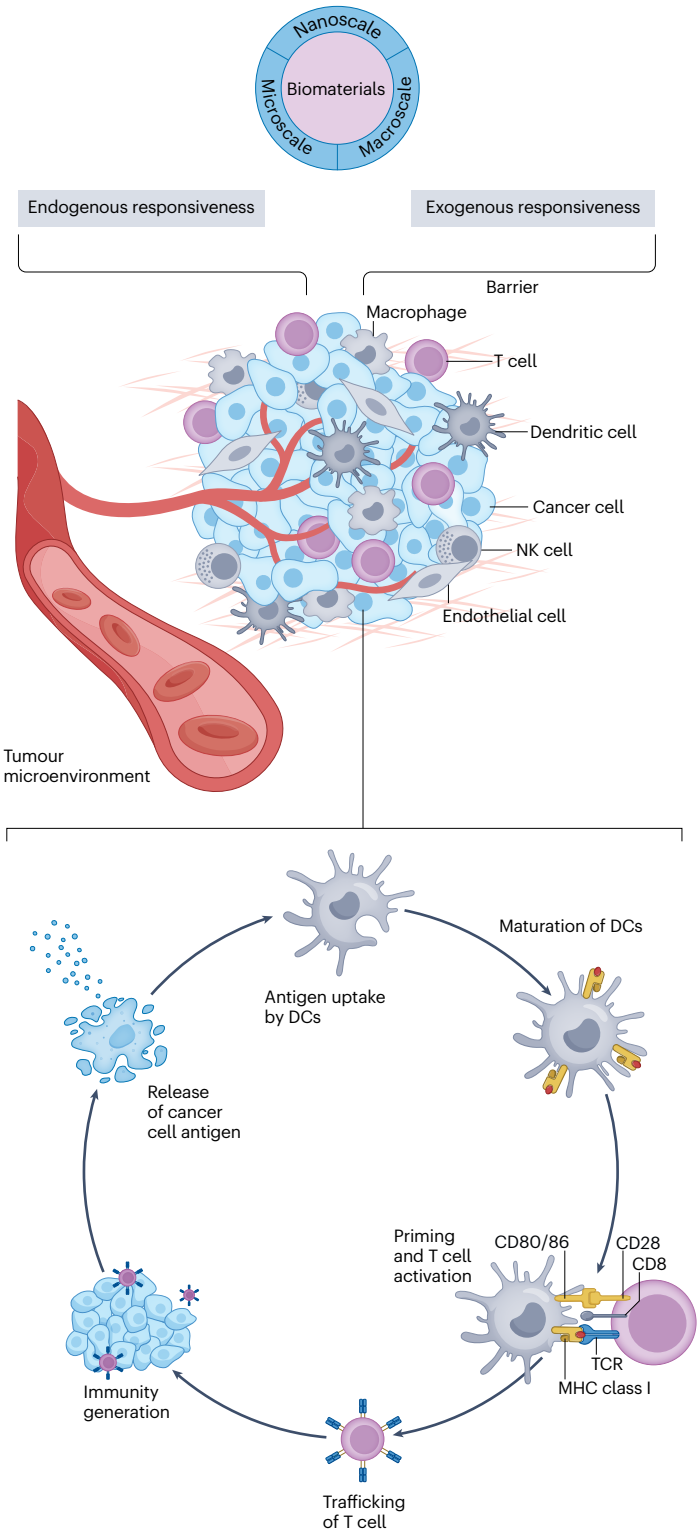
pH-mediated protonation/ionization. pH-responsive biomaterials generally possess amine and carboxyl groups that become charged in acidic environments and facilitate the desired therapeutic effect. For nanoparticle-based delivery systems, the ‘proton sponge’ effect — in which nanoparticle components become charged and cause an influx of water and counterions into late endosomes — can rupture the

Fig. 1 | Developments in cancer immunotherapy. a, Timeline highlighting landmark achievements in cancer immunotherapy. **b**, Overview of the application of nanoscale, microscale and macroscale biomaterials with endogenous and/or exogenous responsiveness to boost the efficacy of cancer immunotherapy. Responsive biomaterials can be used to regulate each step of the cellular mechanisms involved in cancer immunotherapy. The steps include: release of cancer antigens, antigen uptake by dendritic cells (DCs), maturation of and antigen presentation by DCs, priming and activation of T cells, trafficking of T cells to tumours and subsequent T cell-based immunity against tumour cells. The invoked T cell-based immunity causes a further release of cancer-associated antigens, resulting in a ‘cancer immunity cycle’. CAR, chimeric antigen receptor; MHC, major histocompatibility complex; NK, natural killer; TCR, T cell receptor.

a

- **1891:** Immune-modulating therapy for cancer
- **1893:** 'Coley's toxins' to treat cancer
- **1962:** Conducted groundbreaking studies leading to the development of monoclonal antibodies
- **1976:** Discovered IL-2 as T cell growth factor
- **1985:** IL-2 developed for effective cancer immunotherapy
- **1986:** 'α-Interferon' to treat cell leukaemia approved by the FDA
- **1988:** First chemokine discovered
- **1997:** **First monoclonal antibody for lymphoma approved by the FDA**
- **2000:** First antibody–drug conjugate approved by the FDA
- **2003:** Discovery of checkpoint inhibitors that suppress cancer
- **2006:** Gene therapy for human cancer
- **2008:** First cancer vaccine approved in Russia
- **2010:** IL-7 used for human cancer
- **2011:** **Anti-CTLA4 antibody approved by the FDA**
- **2014:** **Anti-PD1 antibody approved by the FDA**
- **2015:** IL-15 used in human cancer clinical trials
- **2017:** **CD19 CAR T cell therapy approved by the FDA**
- **2018:** **Nobel Prize awarded for immuno-oncology discoveries**
- **2019:** First regimen for breast cancer approved by the FDA
- **2021:** **First bispecific antibody approved by the FDA**
- **2023:** Paediatric brain cancer therapy approved by the FDA

b



endosomal membrane and release encapsulated therapeutic payloads into the cell cytoplasm[45,46]. For example, polymeric nanomaterials made from the pH-responsive polymer poly(dimethylaminoethyl methacrylate) mediate the efficient intracellular release of immunotherapeutic payloads such as STING agonists. Specifically, the tertiary amine groups in the poly(dimethylaminoethyl methacrylate) polymer

Box 1

Biological barriers to cancer immunotherapy

Despite remarkable advances in cancer immunotherapy, the broader clinical translation of these therapies remains encumbered by several constraints (Fig. 3). These include, but are not limited to: the immunosuppressive microenvironment and vascular barrier within tumours; the heterogeneity of tumours; the escape of nucleic acid-based therapies from endosomal compartments and the possible and unpredictable toxic side effects of immunotherapy[64,191,194,201–205]. Responsive biomaterials hold the potential to effectively overcome these barriers, thereby amplifying the potency of cancer immunotherapy.

Limited tumour penetration

Within the confined tumour lesion, rapid expansion of malignant cells causes a sharp decline in oxygen tension and nutrient availability[201,202] (Fig. 3a). This rapid expansion, in turn, aberrantly activates angiogenesis and results in the formation of irregular vasculature with abnormal architecture. The altered tumour vasculature contributes to diminished and erratic haemodynamic profiles, thereby impeding the efficient perfusion of immunotherapies into tumours[40]. Concurrently, the divergent vascular supply — abundant at the tumour periphery but attenuated at its core — necessitates substantial penetration by immunotherapies to access the tumour as a whole[206]. This spatial gradient in vascular nourishment elevates interstitial fluid pressure from the outer edges of the tumour towards its central core, creating a diffusion barrier and restricting the penetration of immunotherapeutic agents from the peripheral vasculature[207]. Additionally, the dense, dysregulated extracellular matrix in the tumour microenvironment (TME) further impedes the diffusion of immunotherapeutics[208]. These inherent biological barriers prevent effective transport and penetration of immunotherapeutic agents within the tumour. Responsive biomaterials endowed with finely tuned attributes, such as reversible charge modulation, size reduction and shape transition properties (Fig. 3a), have been developed to overcome these biological barriers. These biomaterials, which are capable of navigating the intricate TME landscape, can potentially improve therapeutic diffusion and penetration.

Poor activation of antitumour immunity

Although the initial iteration of immune checkpoint inhibitors yielded unparalleled therapeutic outcomes, the efficacy of these inhibitors remains confined to a small subset of patients owing to a series of key factors such as tumour heterogeneity, pre-existing immune response, secretion of immunosuppressive cytokines and downregulation of antigen presentation[192,193]. Nevertheless, the pursuit of activating antitumour responses in patients has led to the exploration of additional immunomodulatory mechanisms[203]. Various emerging therapeutics — encompassing elements pertaining to both co-inhibitory (such as CTLA4) and co-stimulatory (such as CD28) markers within the innate immune system — have shown preclinical efficacy and have transitioned into active clinical trials[137,203,209,210]. These emerging technologies are focused on targeting adaptive immune processes involving lymphocytes as well as innate immune processes involving macrophages and natural killer cells to intercept immune-inhibitory checkpoints or act as immunostimulatory agonists for an array of solid and haematopoietic malignancies[203,204] (Fig. 3b). Developing responsive biomaterials functionalized with immunomodulatory elements or delivering immunotherapeutic cargo to supplement natural antitumour mechanisms and activate necessary antitumour pathways will further improve cancer immunotherapies.

The endosomal system

Despite recent advances in immunotherapeutic drug delivery, therapeutic agent entrapment in endosomal compartments and degradation by hydrolytic enzymes remains a crucial hurdle. To address this challenge, diverse lipid-like materials have been used to facilitate the escape of immunotherapeutic agents from endosomal entrapment[64] (Fig. 3c). Examples include lipids, peptides or proteins with fusogenic attributes[69], lipids sensitive to pH fluctuations[49,70] and lipids amenable to charge alteration[65,211]. These approaches aim to overcome endosomal confinement for successful cytoplasmic delivery of immunotherapies.

Systemic toxicity

Each immunotherapeutic modality, with its underlying mechanism of action, can impart unique toxicity profiles[191,194] (Fig. 3d). Notably, cytokine-based interventions, exemplified by high doses of IL-2 impacting T cell and natural killer cell function, culminate in capillary leakage and a sepsis-like syndrome[191,205]. This cascade can trigger multiorgan failure and constrain the clinical applicability of cytokine therapies. Similarly, immune checkpoint blockade therapy not only enhances T cell antitumour function, but also induces organ-specific inflammatory side effects[192]. Furthermore, the implementation of CAR T cells can result in toxicity linked to their potent immune effector response, including cytokine release syndrome and neurotoxicity[205,212,213]. Additionally, antibody-mediated and T cell-based therapies for patients with solid tumours are impeded by the frequent co-expression of target antigens on non-malignant tissue, creating a substantial risk of on-target off-tumour toxicity[194]. Responsive biomaterials offer a promising avenue to address all these concerns by facilitating the localized retention of immunotherapeutic agents and blocking their spread into circulation. Thus, responsive biomaterials can augment the safety and efficacy of local immunotherapies, constituting a pivotal advancement in this field.

backbone protonate in response to decreased pH within endosomal compartments and trigger endosomal escape of the immunotherapeutic payload[60,61]. Similarly, nanoparticles fabricated from ultra-pH-sensitive materials such as PC7A, which activate the STING pathway themselves, can improve the surface presentation of tumour antigens upon delivery to APCs. Utilizing PC7A nanoparticles to deliver STING agonists elicits an even greater activation of the STING pathway, causing a strong cytotoxic T cell response[62,63]. Therefore, pH-responsive

Table 1 | Clinical translation of biomaterial-based cancer immunotherapies

Starting year	Sponsor	Concept	Carrier	Target cancer	Clinical stage	ClinicalTrials.gov identifiers
2005	Ludwig Institute for Cancer Research	NY-ESO-1 ISCOMATRIX in patients with high-risk, resected melanoma	Lipid nanoparticles	NY-ESO-1-expressing tumours	Phase II	NCT00199901
2006	National Institute of Health Clinical Center	TNF-bound colloidal gold in treating patients with advanced solid tumours	Colloidal gold nanoparticles	Solid tumour	Phase I	NCT00356980
2006	EMD Serono	Cancer vaccine study for non-small-cell lung cancer	Liposome	Non-small-cell lung cancer	Phase III	NCT00409188
2008	Cytos Biotechnology	Safety and immunogenicity of CYT-004 MelQbG10 vaccine in patients with advanced stage melanoma	Virus-like nanoparticles	Malignant melanoma	Phase II	NCT00651703
2009	ImmunoFrontier	Recombinant protein vaccine to treat oesophageal cancer	Nanogels	Oesophageal cancer	Phase I	NCT01003808
2009	Duke University	Cancer vaccine given in combination with lapatinib to patients with metastatic breast cancer	Liposome	Metastatic breast cancer	Phases I and II	NCT00952692
2010	Lipotek Pty	Liposomal vaccine to treat malignant melanoma	Liposome	Malignant melanoma	Phase I	NCT01052142
2010 and 2011	ImmunoVaccine Technologies (IMV)	Cancer vaccine to treat patients with advanced tumours	Liposome	Breast, ovarian, prostate, fallopian tube, peritoneal cancer	Phase I	NCT01095848 and NCT01416038
2014	XEME Biopharma	Oncoquest-L vaccine in patients with previously untreated follicular lymphoma	Proteo-liposome	Follicular lymphoma	Phase II	NCT02194751
2015	BioNTech RNA Pharmaceutical GmbH	Administration of a cancer vaccine in patients with advanced melanoma	Liposome	Stage IV melanoma	Phase I	NCT02410733
2017	ModernaTX	Lipid nanoparticle-mediated mRNA-2416 for intratumoural injection	Lipid nanoparticles	Relapsed or refractory solid tumour malignancies or lymphoma and ovarian cancer	Phases I and II	NCT03323398
2018	ModernaTX	Lipid nanoparticle-mediated mRNA-2752 for intratumoural injection	Lipid nanoparticles	Relapsed or refractory solid tumour malignancies or lymphoma	Phase I	NCT03739931
2018	Exicure	Intratumoural cavrotolimod combined with pembrolizumab or cemiplimab in patients	TLR9 agonist-functionalized nanoparticles	Various solid tumours	Phases I and II	NCT03684785
2019	Repertoire Immune Medicines	RPTR-147 in patients with selected solid tumours and lymphomas	Antigen-functionalized nanoparticles	Various solid tumours and lymphomas	Phase I	NT03815682
2019	ModernaTX	Adjuvant treatment with the personalized cancer vaccine mRNA-4157 and pembrolizumab in participants with high-risk melanoma	Lipid nanoparticles	Melanoma	Phase II	NCT03897881
2021	Radboud University	Immunomodulatory nanoparticles in treating patients with advanced solid tumours	PLGA-based nanoparticles	Solid tumours	Phase I	NCT04751786
2021	Radboud University Medical Center	Dose escalation study of immunomodulatory nanoparticles	PLGA-based nanoparticles	Advanced solid tumours	Phase I	NCT04751786
2021	Sahlgrenska University Hospital, Sweden	Study of premarking of axillary nodes before start of neoadjuvant chemotherapy	SPIO nanoparticles	Breast cancer	NA	NCT05625698
2022	Zhejiang Haichang Biotech	Safety, tolerability and pharmacokinetics of WGI-0301 in patients with advanced solid tumours	Lipid nanoparticles	Advanced solid tumours	Phase I	NCT05267899
2023	University of Florida	Novel RNA-nanoparticle vaccine for the treatment of early melanoma recurrence following adjuvant anti-PD1 antibody therapy	DOTAP liposome	Melanoma	Phase I	NCT05264974

DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; NA, not applicable; PLGA, poly(lactic-co-glycolic acid); SPIO, superparamagnetic iron oxide; TLR9, Toll-like receptor 9; TNF, tumour necrosis factor.

STING-activating nanovaccines offer a simple and robust strategy in boosting antitumour immunity for cancer immunotherapy. Membrane fusion is an alternative mechanism for enhancing endosomal escape, driven by a conformational transition in fusion lipids, peptides, polymers and proteins. These conformational changes trigger the fusion of these entities with the endosomal membrane, de-complexing them from the encapsulated cargo and releasing the cargo into the cytosol[64,65] (Fig. 3c). The propensity for such conformational changes frequently emerges because of specific cellular receptor interactions or pH alteration. For example, nanoparticles engineered with fusion proteins or pH-sensitive fusogenic polymers demonstrate efficient endosomal escape to facilitate the translocation of encapsulated antigens into cellular cytosol, thereby resulting in antigen presentation and the induction of antigen-specific cellular immunity[66,67]. Complementary to these mechanisms, other strategies for endosomal escape include membrane destabilization through pore formation and photochemical internalization through light-triggered reactive oxygen species (ROS) to rupture endosomal membranes with subsequent release of genetic cargoes into the cytosol[68] (Fig. 3c).

Perhaps, the most clinically successful of these pH-responsive nanoparticle-based systems are LNPs[69], which have been utilized to deliver various nucleic acids (DNA, small interfering RNA (siRNA), mRNA and single-guide RNA) to tumours and the TME. LNPs can deliver mRNA encoding for tumour-associated antigens (TAAs), co-stimulatory receptors, cytokines, tumour suppressors, Cas9 endonuclease and CAR or T cell receptor (TCR) for potent cancer immunotherapies[49,69–71]. Additionally, these delivery carriers have self-adjuvancy, which can boost cancer immunotherapy. For example, LNPs consisting of selected cationic lipid-like materials enhanced the antitumour efficacy of an mRNA cancer vaccine by activating the Toll-like receptor 4 (TLR4) signal pathway[72]. Similarly, heterocyclic lipids were able to elicit strong APC maturation via intracellular STING pathways for efficient

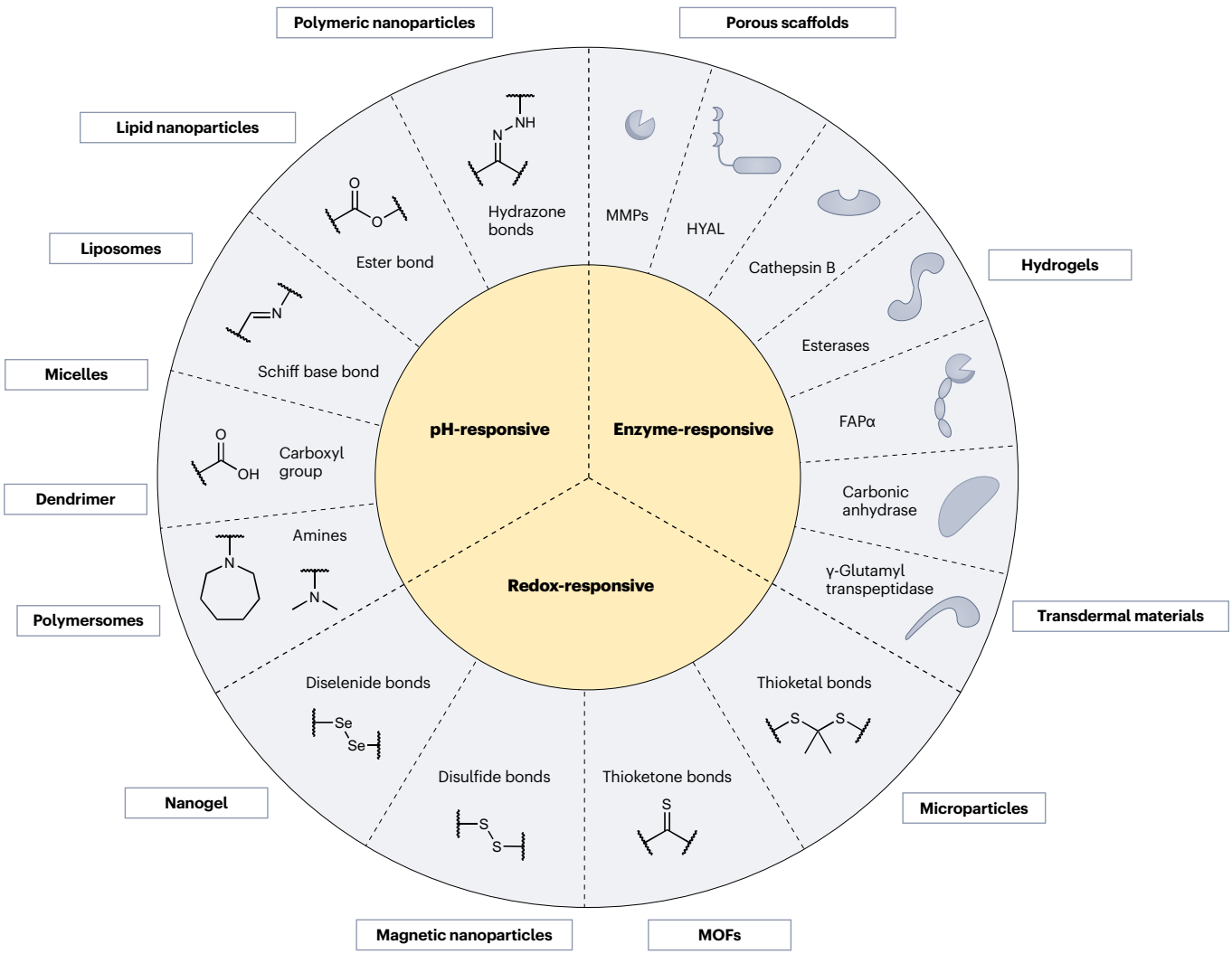


Fig. 2 | Biomaterials responsive to endogenous stimuli for cancer immunotherapy. Biomaterials with responsive moieties respond to endogenous cues, including pH, enzymes and redox potential. Representative pH-responsive and redox-responsive chemical bonds along with representative enzymes that are overexpressed in the tumour microenvironment are displayed. FAPα, fibroblast activation protein-α; HYAL, hyaluronidase; MMP, matrix metalloproteinase; MOF, metal–organic framework.

antigen-specific mRNA vaccines in a number of in vivo tumour models[73]. Moreover, a series of adjuvant-pulsed mRNA LNP vaccines were engineered by incorporating a TLR7/8 agonist into the lipid design, which activated a type I IFN response to increase antigen-specific $CD8^+$ T cell expansion, established antitumour memory immunity and suppressed tumour growth[74–76].

Furthermore, nanoparticle-based systems have been coupled with pH-responsive gels that actively modulate the pH of the TME to achieve a therapeutic effect. For example, a bioresponsive fibrin gel loaded with anti-CD47 and calcium carbonate ($CaCO_3$) nanoparticles utilized charge to scavenge protons from the post-surgical TME[77]. This scavenging promotes M1-type tumour-associated macrophages owing to the increase in pH, and also releases the anti-CD47 antibody that blocks the 'don't eat me' signal put forth by tumour cells, allowing for macrophage-mediated phagocytosis and consequent propagation of an antitumour immune response.

pH-mediated cleavage of acid-sensitive bonds. In addition to charge-based interactions, materials can incorporate pH-responsive bonds such as amide, ester, imine, oxime, acetal and ketal bonds that dissociate upon exposure to acidic environments[46,47]. Polymers incorporating these bonds are relatively stable in neutral and basic conditions but are labile upon exposure to acidic conditions. The decrease in pH triggers the cleavage of pH-responsive structures in the material backbone, causing internal structural transition and degradation. This mechanism can be utilized in nanomedicines to either cause nanoparticle degradation within lysosomes or cause the release of immunotherapeutics after exposure to acidic environments. However, self-assembled nanocarriers can degrade in complex biological serum before reaching the TME[33,46,53,57]. Therefore, developing materials with acid-sensitive bonds that are not susceptible to premature cleavage is key to the clinical translation of these therapies.

Another example is the use of nanogels and microgels with an acid-cleavable backbone, which can protect immunotherapeutic drugs from enzymatic degradation and result in higher cargo stability and prolonged bioavailability compared with free drugs[53]. Squaric ester-based, pH-responsive nanogels have served as versatile immune drug nanocarriers for the safe delivery of TLR7/8-stimulating imidazoquinolines[51]. The squaric ester amides were hydrophilized, affording fully hydrophilic nanogels with good stability in human plasma and stimuli-responsive degradation upon exposure to endosomal pH conditions. The platform exhibited spatially controlled immunostimulatory activity in the spleen with a minimal systemic off-target inflammatory response[78]. Nanocarriers with pH responsiveness can also be loaded with microneedles to enhance immunostimulation[79]. Microneedles can painlessly pierce into the immune-cell-rich epidermis and deliver immunotherapeutic cargoes (such as antibodies, adjuvants or vaccines) to regional lymphatic vessels and capillaries, promoting interactions with T cells for cancer immunotherapy[80,81]. Thus, pH-responsive therapeutic systems utilize a wide range of biomaterials to improve the therapeutic effect of cancer immunotherapies.

Enzyme-induced immunotherapeutic delivery

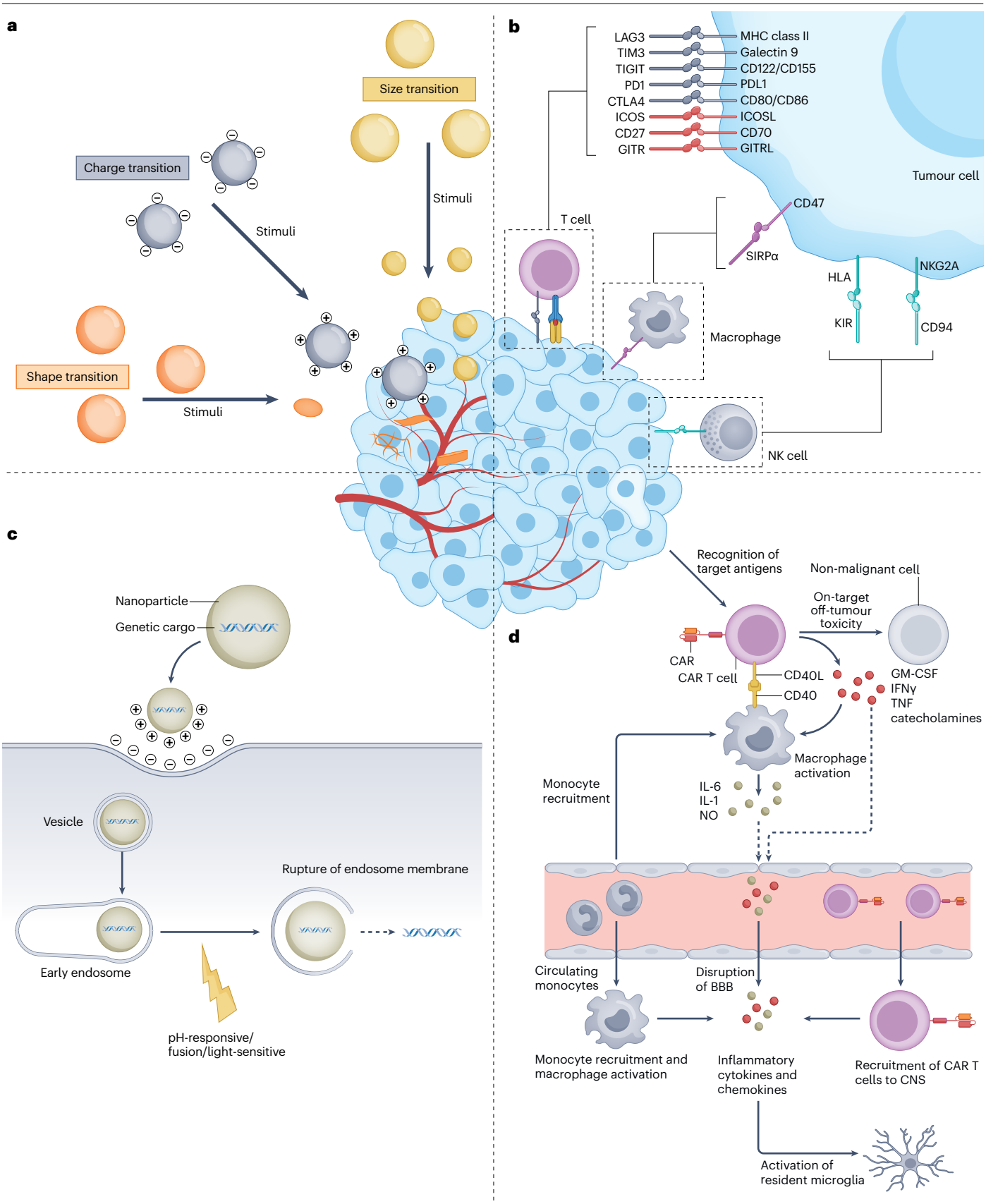
Enzymes are substantial components involved in nearly all biological processes and can serve as powerful activation stimuli for drug delivery, especially at tumour sites[82,83]. Overexpression of various enzymes, including matrix metalloproteinases (MMPs), hyaluronidase, cathepsin B, indoleamine 2,3-dioxygenase 1, esterase, carbonic anhydrases, fibroblast activation protein-α and γ-glutamyl transpeptidases, in tumours and the TME has led to the development of enzyme-responsive therapeutics[34,82,83] (Fig. 2). Leveraging the enzyme-cleavable chemical bonds of various biomaterial platforms allow for controlled release of therapeutic agents for cancer diagnosis, prognosis, evaluation and immunotherapy, and can also transform therapeutics into smaller subsidiaries to improve their penetration through the dense TME. The most common strategy used in designing enzyme-responsive biomaterial platforms is the use of peptide sequences linked to immunotherapeutic drugs; these peptides can be specifically cleaved by the desired enzyme at tumour sites, resulting in the specific release of immunotherapeutic payloads. For example, an MMP2-sensitive anti-PDL1 nanoplatform was developed to improve ICB therapy[84]. Designed particles remained stable in circulation and only released their anti-PDL1 payload once they reached tumour sites with increased MMP2 expression. This enzyme-responsive, specific delivery generated efficient $CD8^+$ T cell infiltration and induced a strong antitumour response.

Cancer-associated fibroblasts (CAFs) in the tumour stroma form a major barrier that impedes the penetration of immunotherapeutics into solid tumours and leads to low tumour immunogenicity within the TME[83,85]. Compared with healthy tissues, CAFs can selectively overexpress certain proteins such as α-smooth muscle actin and FAPα in solid tumours; thus, the development of CAF-responsive biomaterials can be a specific and efficient strategy to overcome these obstacles for improving antitumour immunity[86,87]. An amphiphilic bifunctional PD1/PDL1 peptide antagonist was linked by an FAPα-responsive peptide segment, which was further co-assembled into nanoparticles to deliver TLR7/8 agonist. Upon reaching the tumour tissue, FAPα triggered disassembly of nanoparticles to locally release the TLR7/8 agonist for eliciting antitumour immunity. Subsequently, PD1 or PDL1 peptide antagonists mediated PDL1 pathway blockade for further activation and reduced exhaustion of cytotoxic T lymphocytes (CTLs)[87].

Despite this encouraging progress, enzyme-responsive biomaterials have some inherent drawbacks[82,83]. Enzymatic engagement is present in numerous physiological processes, exhibiting heterogeneity across individuals and overlapping in healthy and pathological contexts; thus, there is a lack of specificity that is necessary for targeted cancer immunotherapy[44]. Such nonspecific enzyme activity could potentially induce off-target effects, wherein activation of biomaterials could ensue from enzymes residing within healthy tissues[83]. Additionally, the kinetics of enzymatic reactions can be complex, and achieving precise control over immunotherapeutic payload release can be challenging[82]. The next generation of enzyme-based responsive biomaterials should specifically respond to selective enzymatic processes and time subsequent therapeutic release and delivery for both efficient and safe immunotherapeutic interventions.

Redox-induced immunotherapeutic delivery

The redox environment of tumour tissues is another important physiological stimulus that has been used for cancer immunotherapy[30,31,33,88]. Tumour cells produce higher levels of ROS — as much as 100 times higher — than healthy cells through pathways involving the mitochondrial respiratory chain and nicotinamide adenine dinucleotide phosphate oxidase that are deregulated by genetic and energetic (metabolic) changes[29,30,33]. These processes have been implicated in aiding the occurrence and development of tumours; thus, ROS-responsive biomaterials for cancer immunotherapy hold great promise. ROS are typically regulated in the body via the tripeptide glutathione (GSH), which reduces excessive ROS and maintains the redox state of tissues[89]. Thus, the increased ROS levels in tumours also cause increased GSH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Early endosome
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cytokines and
chemokines
Recruitment of CAR T
cells to CNS
Activation of
resident microglia

Fig. 3 | Key biological barriers for cancer immunotherapy. a, Strategies to improve tumour penetration using nanoparticles with bioresponsive design. Under stimuli, nanoparticles can undergo size transition, charge transition and shape transition for enhanced tumour penetration. **b**, Emerging cellular targets for cancer immunotherapy. Using various cellular targets, immunotherapies can target lymphocytes associated with adaptive immunity by blocking immune-inhibitory checkpoints or agonizing immunostimulatory pathways. They can also target innate immune processes mediated by macrophages and natural killer (NK) cells. **c**, Genetic cargoes loaded in nanoparticles need to escape from endosomes into the cellular cytosol for functional delivery. Representative endosomal escape mechanisms include the proton-sponge effect for pH-responsive designs, membrane fusion for designs incorporating fusogenic materials and rupture upon light exposure for designs with photochemical responsiveness. **d**, Toxicity in cancer immunotherapy upon chimeric antigen receptor (CAR) T cell therapy. Upon target recognition, CAR T cells can activate pro-inflammatory macrophages through both cytokine-mediated and cell-mediated mechanisms, leading to pathologies such as cytokine release syndrome and neurotoxicity. CAR T cells may also recognize target antigen on healthy cells, resulting in on target off-tumour toxicity. Dashed lines denote hypothesized pathways that have not been experimentally confirmed in the context of cytokine release syndrome. BBB, blood–brain barrier; CNS, central nervous system; GITR, glucocorticoid-induced TNFR-related protein; GITRL, glucocorticoid-induced TNF-related ligand; GM-CSF, granulocyte–macrophage colony-stimulating factor; HLA, human leukocyte antigen; ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; IFNγ, interferon-γ; KIR, killer immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3; MHC, major histocompatibility complex; NO, nitric oxide; SIRPα, signal-regulatory protein-α; TIGIT, T cell immunoglobulin and ITIM domain; TIM3, T cell immunoglobulin mucin receptor 3; TNF, tumour necrosis factor.

levels, resulting in a highly reductive environment that can be leveraged for therapeutic targeting in cancer immunotherapy. As a result, redox-sensitive materials — specifically materials containing reducible bonds such as diselenide bonds (-Se–Se-)[90], disulfide bonds (-S–S-)[91], thioether bonds (-C=S-)[32], cysteine–serine–serine (CSS) bonds[92] and thioketal linkers[32] — have been explored for conjugating and delivering various immunotherapeutic payloads, including antigens[88,91], antibodies[93,94], inhibitors[95,96], agonists[97,98] and mRNA vaccines[99,100] (Fig. 2). For example, diselenide-based hollow mesoporous nanoparticles were used to deliver annexin A5 to tumour cells to generate antitumour immunity[90]. Upon exposure to the highly oxidizing TME, the diselenide bonds were reduced, cleaved and the subsequent annexin A5 that was released was able to block immunosuppressive apoptosis and bind to tumour cells to propagate secondary necrosis. Similarly, CSS bonds were used to conjugate antigen peptides and adjuvants onto the surfaces of synthetic high-density lipoprotein nanodiscs and were delivered to lymphoid organs to generate a strong antitumour response[92]. The reduction of the CSS bond in the TME enabled release of both antigen and adjuvant, enhancing antigen presentation on dendritic cells as well as producing a robust antigen-specific CTLs response that was 47-fold greater than general soluble vaccines[92]. Finally, reducible bonds have been utilized to locally deliver several immunotherapeutic agents at once to tackle tumours using a multifaceted approach. Because of its reducible disulfide bonds, an in situ forming GSH-responsive hydrogel system containing the STING agonist cyclic di-AMP complexed with nanotubes consisting of the hydrophilic iRGD peptide and the hydrophobic drug camptothecin (CPT)[101] was able to degrade in the TME and release the cyclic di-AMP. The cyclic di-AMP converted the TME from immunosuppressive to immunostimulatory, reducing tumour burden and preventing the formation of metastases. Together, these redox-sensitive approaches have demonstrated robust therapeutic efficacy and have paved the way for developing personalized cancer vaccines.

Despite their promise, current redox-responsive biomaterials lack the selectivity required for effective immunotherapeutic effect[102,103]. These biomaterials may be subjected to a spectrum of oxidative and reductive conditions existing both within healthy and pathological tissue niches[103]. This overarching feature might instigate unintended and indiscriminate release of immunotherapeutic payloads and immunomodulators[102]. Furthermore, the heterogeneity of redox environments in different individuals and disease states imparts a challenge for achieving a consistent and predictable response from redox-responsive biomaterials[88]. Thus, the development of next-generation redox-responsive biomaterials should take into consideration the similarities and differences between redox states across tumours and healthy tissues and design redox-responsive immunotherapies that are able to achieve greater specificity and sensitivity.

Exogenous stimuli to regulate cancer immunotherapy

Although endogenous physiological stimuli offer convenient strategies for cancer immunotherapy in terms of spatial control, they lack the potential for highly specific temporal control. In particular, once the therapeutic reaches the tumour cell or the TME, the endogenous stimulus will immediately result in release of the therapeutic payload. However, intervention using biomaterial-based platforms that respond to exogenous stimuli can lead to the development of spatiotemporally controlled cancer immunotherapies. These platforms can respond to various exogenous stimuli (such as light, magnetism and ultrasound) to release their therapeutic payload, providing real-time control and achieving an even greater degree of specificity[104–107] (Fig. 4).

Light-regulated immunotherapy

Light is a powerful tool for remotely triggering immunotherapeutic payload release from materials in an on/off switchable manner[105,108]. Light can be modulated using a broad range of parameters, including wavelength, intensity and beam diameter, and can be tuned according to the desired application. Furthermore, photosensitive biomaterials, including antibody–siRNA conjugates (ARCs)[109] and polyamidoamine dendrimers[110] (which respond to ultraviolet (UV) light) as well as polymeric nanoparticles[111] and upconversion nanoparticles (UCNPs)[112] (which respond to near-infrared (NIR) light) are physicochemically tunable and exhibit highly modular photosensitive chemical properties (Fig. 4a). For example, photo-responsive ARCs, in which an anti-PDL1 antibody was conjugated to a PDL1 siRNA using a photocleavable nitrobenzyl-based linker[109], were internalized by tumour cells, upon which UV light was used to cleave the ARCs and release the PDL1 siRNA. The release, in turn, led to knockdown of PDL1 and boosted immune cell activity within the tumour.

Although highly effective in cleaving photosensitive bonds, UV light has limited penetration within tissues, limiting its application in vivo[105]. By contrast, NIR light has a deeper penetration depth in tissues; therefore, several groups have turned to using UCNPs that are able to act as transducers to convert NIR light irradiation into UV or visible light[113–116]. In this way, the exogenous stimulus (NIR) can still reach deep within tissues to activate a secondary stimulus (UV or visible light),

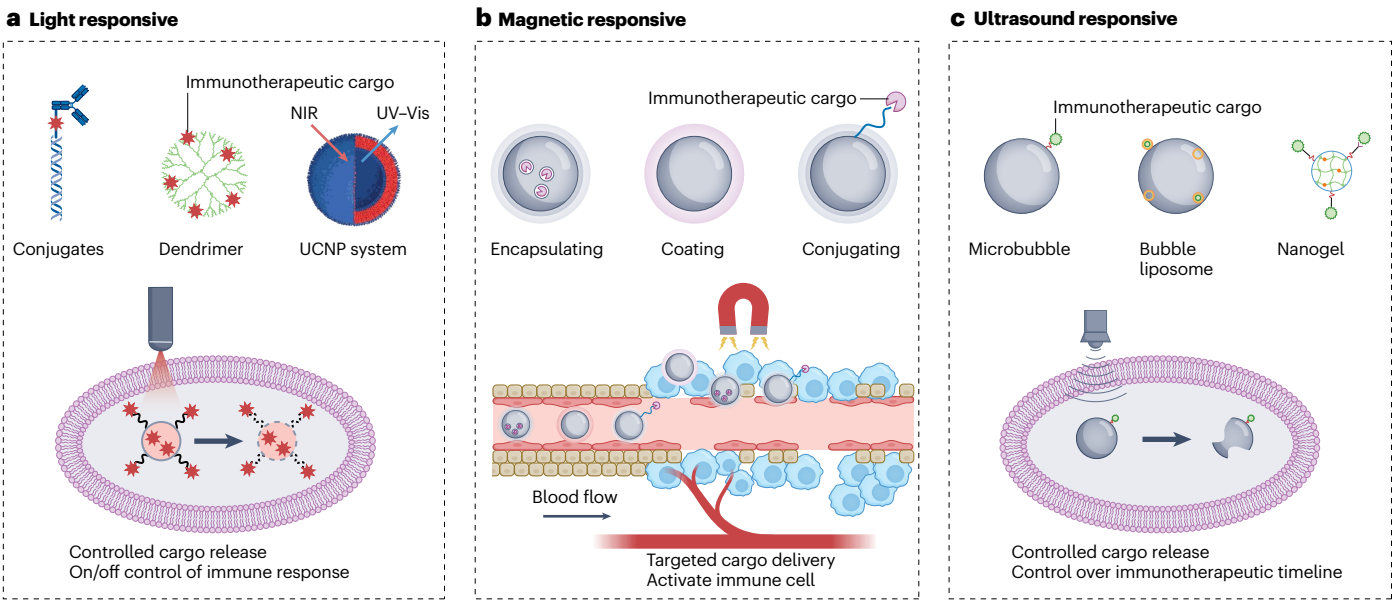


Fig. 4 | Biomaterials incorporated with exogeneous stimuli for boosting cancer immunotherapy. a, Light-responsive biomaterial system showcasing representative materials including antibody-prodrugs, dendrimers and upconversion nanoparticle (UCNP) systems. Ultraviolet (UV) light and near-infrared (NIR) light are representative light sources for triggering immunotherapeutic cargo release and controlling the following immune response. **b**, Magnetic-responsive biomaterial system in which immunotherapeutic cargo can be encapsulated, surface-coated and conjugated onto magnetic materials. Upon stimulation by a magnetic field, the responsive material can aid targeted cargo delivery to activate an immune response. **c**, Ultrasound-responsive biomaterial system displaying representative materials including microbubbles, bubble liposomes and nanogel-based systems. The ultrasonic stimulus can promote cargo release, improve intracellular delivery through disrupting cell membranes and spatially control the immunotherapy.Vis, visible.

which can act upon photocleavable moieties. To this end, an immunodevice containing UCNPs allowed for the controlled release of CpG oligonucleotides upon internalization by tumour cells and stimulation with NIR[112], avoiding extracellular activation of TLR9 and boosting the intratumoural immune response.

The drawback of light-responsive biomaterials for cancer immunotherapy lies in their limited scope of efficacy within regions of deeper tissues or locations that are less accessible to light penetration[105,117,118]. Although longer wavelengths of light such as NIR light can be used to reach deep into tissues, materials responding to these wavelengths have been relatively underexplored for cancer immunotherapy. Moreover, achieving precise spatiotemporal light activation is challenging owing to the differing physiological characteristics of tissues, which can cause varying outcomes for light-based therapies in complex biological systems[117]. Furthermore, the potential cytotoxicity of certain light-sensitive components and the necessity for specialized apparatus to deliver precise light stimuli could pose biosafety concerns and practical limitations within the clinical landscape[105]. Therefore, the design of next-generation light-regulated biomaterials should consider light penetration, spatiotemporal control and cytotoxicity of therapeutic interventions while maintaining immunotherapeutic efficacy.

Magnetically guided immunotherapy

Magnetically controlled systems have several benefits when utilized in biological systems, including biocompatibility, large field penetration depth and high specificity to magnetic stimuli compared with biological tissues[106,119]. Given these benefits, magnetic materials (including superparamagnetic nanoparticles[120], magnetite[121], iron platinum[122] and cobalt–iron[123]) have been widely explored as platforms for magnetically driven targeting, magnetically activated remote drug delivery and magnetic resonance imaging (MRI)[106,119,124]. Additionally, they hold great promise in cancer immunotherapy; they have been shown to regulate the immunological TME by producing tumour-killing hydroxyl radicals and cause tumour cell death by magnetic force, thereby releasing TAAs to induce macrophage polarization and T cell infiltration into tumours[106,119,125].

The most common magnetic-responsive materials in targeted immunotherapy delivery are superparamagnetic iron oxide nanoparticles (SPIONs) in which immunotherapeutic drugs (such as immune adjuvants, TAAs and checkpoint blocking antibodies) are encapsulated, surface-coated or conjugated[106,126,127]. These modified SPIONs can then be guided through the body using magnetic fields to accumulate within immune cells, tumours and the TME (Fig. 4b). This methodology was used to conjugate anti-PDL1 antibody as well as the T cell agonists anti-CD3 and anti-CD28 antibodies onto SPIONs and magnetically navigate them into tumours to boost T cell responses[126]. Similarly, coated SPIONs with dimercaptosuccinic acid, which allows for IFNγ to adsorb to the SPION surface, were magnetically navigated to tumours to release the cytokine and increase macrophage and T cell infiltration[127]. In addition to magnet-guided transport of immunotherapeutic drugs into tumour sites, magnetic-responsive materials can undergo structural changes to facilitate drug release by magnetic force. The majority of these systems have been applied to release chemotherapeutic drugs[106,119], and they are a promising platform for immunotherapy owing to their ability to minimize off-target effects and control the kinetics of drug release.

Although the remote activation of magnetic biomaterials is advantageous, the accurate spatial localization of magnetic fields within intricate biological systems can be difficult[106,119,128]. This in turn can cause off-target delivery or reduced therapeutic levels[128]. In addition, the need for specialized equipment to generate and sustain magnetic fields introduces potential impediments in both safety and practicality[106]. Finally, the biocompatibility of the magnetic nanoparticles or of the components used in the magnetic biomaterials could be an issue and must be thoroughly tested[119]. Therefore, next-generation magnetic-guided biomaterials should overcome these limitations to speed up their clinical translation.

Ultrasound-assisted immunotherapy

Ultrasound-guided therapy holds great promise for immunotherapeutic and diagnostic applications[107]. Ultrasound stimulation inherently disrupts tumour cells, exposing their antigens to maturing APCs and leading to subsequent adaptive immune cell infiltration. Furthermore, utilizing ultrasound as a therapeutic modality is simple, inexpensive and allows for remote spatiotemporal control of various ultrasound-responsive biomaterials such as microbubbles[129,130], bubble liposomes[131] and hydrogels[33,132] (Fig. 4c). For example, nanocomplexes consisting of APC-targeting microbubbles are able to respond to ultrasonic stimulation to release 2′3′-cyclic GMP-AMP and cationic biopolymer conjugates[133]. Specifically, after their attachment to the APC surface, the microbubbles are able to create small pores in the cell membrane upon ultrasonic stimulation, allowing for efficient cytosolic delivery of the immunotherapeutic payload and activation of downstream pro-inflammatory immune pathways. Ultrasound-guided biomaterial platforms can also be utilized for repeatedly releasing immunotherapeutic drugs at desired times to optimize cancer immunotherapy. An ultrasound-responsive self-healing hydrogel loaded with ovalbumin-based antigen and imiquimod-based adjuvant was developed in efforts to temporally control the release of a tumour nanovaccine[134]. Upon ultrasound stimulation, the hydrogel was able to transform to a sol state, allowing for burst release of the nanovaccine, and then 'self-heal' into the gel state in which it could be stimulated again to release another dose of the nanovaccine. Thus, applying ultrasound-controlled biomaterial platforms allows for precise control of the immunotherapeutic timeline as well as the location of therapeutic release.

Ultrasound-responsive biomaterials bear challenges associated with their controlled cargo deployment and potential biological effects[107,135,136]. Despite their non-invasive nature, attaining precise spatial governance over ultrasound waves within complex biological systems can pose a challenge[135]. The reliance on specialized equipment for the generation and precise focusing of ultrasound waves could engender logistical and safety concerns in clinical applications[107]. Additionally, the interplay between ultrasound-responsive biomaterials and biological tissues, particularly in terms of mechanical influences and localized thermal elevations, mandates the establishment of strict biocompatibility and safety standards[107,136]. Thus, next-generation ultrasound-responsive biomaterials necessitate the development of more advanced technical equipment and imaging technology to support their future clinical translation.

Harnessing responsive biomaterials for advanced cancer immunotherapy

Biomaterial platforms enable cancer immunotherapy that can be targeted, deliver a controlled payload and activate specific antitumour immune pathways. Together, these strategies can lead to the development of novel immunotherapies, as well as elevate existing immunotherapies and result in better patient outcomes. Here, we discuss how stimuli-responsive biomaterials can be used to promote three key approaches in cancer immunotherapy: cancer vaccines, T cell-based therapies and sustained delivery for local antitumour immunity (Fig. 5).

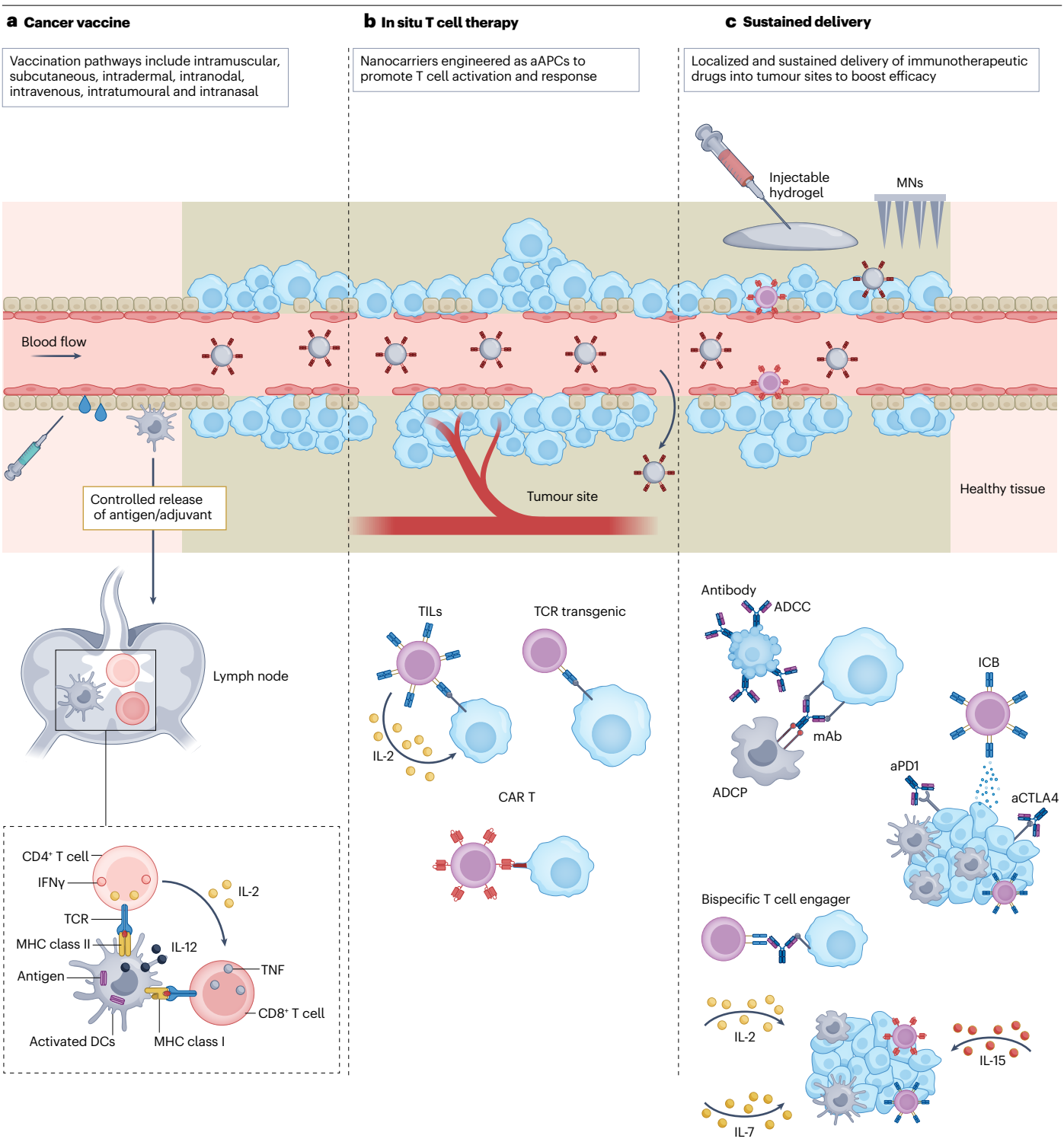
Responsive cancer vaccines

Cancer vaccines aim to overcome the 'immune tolerance' of cancer cells and elicit robust antitumour immune responses[24,137–139]. Cancer vaccines generally provoke immune activation by delivering antigens and adjuvants into lymph nodes where APCs reside (primarily dendritic cells). However, rapid elimination and complex biological barriers impede the access of free antigens and adjuvants to lymph nodes (Box 1). Responsive biomaterial-based platforms with tunable size, shape, charge and other physicochemical properties can overcome these barriers and allow for greater control over the site and kinetics of antigen release[24,34] (Fig. 5a). Responsive cancer vaccine strategies have been incorporated with pH[81,140,141], redox[88,93], ultrasound[142] and light responsiveness[143,144] to achieve controlled, on-demand antigen release.

The size of the nanomaterial has an impact on its transit; nanomaterials from 10 nm to 100 nm facilitate greater degrees of lymphoid draining while larger sizes are prone to become trapped within the interstitial matrix[52,137,145]. However, these larger nanomaterials (50–500 nm in particular) are effectively taken up by dendritic cells[146]. This transitory difference has led to the rise of size-switchable cancer vaccines, in which the responsiveness of the nanomaterial platform enables the vaccine system to increase in size within the lymphatic system. In one example, the administered cancer vaccines remained smaller in size (24.4 ± 3.1 nm) during lymph node draining and transformed into a larger size (483.0 ± 41.6 nm) upon light stimulation once arriving at the lymph nodes, assuring efficient endocytosis by the lymph node-resident dendritic cells and exhibiting sufficient in situ tumour growth restriction in a mouse melanoma model[146].

Along with antigen release, cancer vaccine approaches have also used the coadministration of adjuvants, which provide the required 'danger signals' recognized by pattern recognition receptors to stimulate APCs and boost antitumour responses[52,139]. Thus, smart materials have been designed to perform structural transformation, hydrophilicity change and charge reversal to monitor and release antigens and adjuvants with high spatiotemporal control[24,34,145]. A pH-responsive DNA-based transformable nanodevice vaccine was designed to deliver two types of molecular adjuvants and an antigen peptide to lymph nodes in mice[147]. Initially, the DNA locks were folded to protect the payload through origami and assembling. In the acidic lysosomes of APCs, however, they underwent conformational changes to mechanically release antigens and adjuvants, eliciting a ~45-fold increase of antigen-specific $CD8^+$ T cells and a ~30-fold increase in CTL response in comparison to free antigens and adjuvants, substantially inhibiting tumour growth and generating long-term T cell responses that protected the mice against tumour rechallenge.

In addition, some biomaterials inherently demonstrate adjuvant effects upon response to a controlling stimulus. Thus, various efforts have been made to construct self-adjuvanted biomaterials through rational structure and composition design, such as using hydroxyl group-dependent pathways for complement system activation[148], responsive-induced autophagy-regulation nanoactivation[149] and inflammasome activation[150,151]. Adjuvant-like poly(lactic-co-glycolic acid) (PLGA) Pickering emulsions — flexible particle-stabilized emulsion systems with the ability to increase the contact area between antigens



and APCs in response to external forces — were used to build 'elastic vaccines'[152]. When wrapped by cells, these nanoparticles deformed in response to mechanical force, enlarging the contact area between antigens and APCs and dynamically activating immune recognition to enhance the immune response. The lateral flow of antigens within this antigen-APC synapse zone then allowed multivalent binding with receptors for phagocytosis. In the lysosome, acid-mediated protonation of these PLGA nanoparticles caused charge reversal of the polymer from negative to positive, thus causing endosomal rupture and improving endosomal escape. The subsequent delivery of the antigen led to increased immune cell recruitment in situ after subcutaneous administration and promoted antigen capture and activation by APCs.

Fig. 5 | Approaches benefitting from biomaterial-based intervention to bolster cancer immunotherapy. a, Responsive cancer vaccines, in which vaccines can be administered through various vaccination pathways and can release immunotherapeutic payloads in a controlled manner. This spatial and temporal regulation can lead to controlled activation of dendritic cells (DCs) for T cell priming and activation. **b**, In situ T cell therapy, in which responsive biomaterials (in this case nanocarriers) can be engineered as artificial antigen-presenting cells (aAPCs) for T cell activation for tumour-infiltrating lymphocyte (TIL), T cell receptor (TCR) and chimeric antigen receptor (CAR) T cell therapy. **c**, Sustained delivery of immunotherapeutic drugs for local antitumour immunity, in which biomaterials can be injected into (hydrogels) or adhered to (microneedles (MNs)) the tumour site for sustained delivery of antibodies, immune checkpoint blockade (ICB) inhibitors and cytokines. Cancer vaccine and T cells can also be encapsulated in these biomaterials for sustained release and immune response activation to boost cancer immunotherapy. ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; IFNγ, interferon-γ; mAb, monoclonal antibody; MHC, major histocompatibility complex; TNF, tumour necrosis factor.

The optimized Pickering emulsions potently stimulated both humoral and cellular adaptive response, leading to increased survival of mice upon lethal challenge.

One of the hallmarks of cancer is genome instability and mutation, resulting in the generation of neoantigens with epitopes that differ from patient to patient[153,154]. Therefore, personalized cancer vaccines targeting these neoantigens have important potential advantages[26,92,138]. For example, DNA–RNA therapeutic microflowers were constructed and shrunk by positively charged PEG-grafted polypeptide (PPT-g-PEG) copolymers where the hydrophobic PPTs complexed with tumour-specific neoantigens through hydrophobic interactions, allowing for co-delivery of DNA CpG and short hairpin RNA adjuvants and antigens[155]. When the DNA–RNA microflowers were delivered to APCs, the acidic endolysosomal environment made the acid-labile PEG shed, exposing the cationic PPTs and promoting endosomal escape of encapsulated antigens and adjuvants. The resulting antigen-specific $CD8^+$ T cells further inhibited tumour metastasis in the lung and potentiated immune memory upon activation.

Furthermore, mRNA-based therapies are emerging as potent candidates for personalized cancer vaccines owing to their ability to overcome tumour heterogeneity by encoding personalized proteins and/or antigens according to the genetic expression profile of the tumour. Excitingly, a phase I study exploring a lipid-encapsulated personalized neoantigen mRNA nanovaccine (mRNA-4157, Moderna, NCT03897881; Table 1) demonstrated clinical safety, tolerability, immunogenicity and recurrence-free survival in various malignancies when dosed in combination with a checkpoint inhibitor[156].

In situ T cell-driven immunotherapy

T cells play an important role in cell-mediated immunity against tumours, and hence, have been commonly weaponized for cancer immunotherapy[4,6,7,9]. Several T cell-based therapies, including therapies incorporating tumour-infiltrating lymphocytes[157], CTLs[158], TCR-transduced T cells[159] and CAR T cells[160], are being developed and have shown great promise in clinical trials. Specifically, six CAR T cell therapies currently have FDA approval and are actively being used in the clinic today[161]. Despite their great success, T cell-driven immunotherapy faces several challenges, including inefficient expansion, fast exhaustion, target loss and inefficient trafficking to tumour sites. To address these challenges, smart biomaterials can be engineered as artificial APCs (aAPCs) to amplify T cell expansion, as immunomodulators to improve T cell-targeted delivery and as backpacks to direct adoptive T cell activation and expansion in vivo[7] (Fig. 5b).

Adoptive T cell therapies generally use dendritic cells to activate and expand T cells to therapeutically relevant numbers[157]; however, this method of activation has high patient-to-patient variability. As an alternative, aAPCs with tunable size, shape, rigidity and mobility that mimic the function of dendritic cells have been developed[162]. Nanoscale aAPCs (naAPCs) made from iron-dextran nanoparticles decorated with peptide–MHC–immunoglobulin dimers and anti-CD28 antibodies have been used to magnetically assemble T cells into large aggregates, resulting in the doubling of TCR cluster size and increased T cell expansion in vitro and after adoptive transfer in vivo[163]. The introduction of a magnetic field increased the proportion of $THY1.1^+$ T cells in the spleen, highly inhibiting tumour growth. Another study utilized size-transforming aAPCs; beginning at the nanoscale (naAPCs) (where the aAPCs possess a desirable safety profile), naAPCs transformed into microscale aAPCs (maAPCs) upon exposure to a highly oxidizing environment. The naAPCs were fabricated by assembling redox-sensitive copolymer and biotin-labelled polymers, loaded with IL-2 and decorated by peptide–MHC complexes and anti-CD28 antibodies. The free thiols on the surface of pre-activated $CD8^+$ T cells resulted in the breakage of disulfide bonds present in the naAPCs, enabling their conversion to maAPCs within the tumour tissue. This size conversion was important as maAPCs have increased surface area, enabling more efficient T cell activation and downstream tumour killing.

To circumvent the problem of ex vivo T cell activation and expansion, technologies have been developed to activate and expand T cells in vivo, specifically through the delivery of antibodies, genes, cytokines and small molecules[7,154,162]. For example, synthetic biodegradable poly(β-amino ester) polymer-based DNA nanocarriers loaded with plasmids encoding for leukaemia-targeting CAR transgenes and piggyBac transposase were developed, in which the CAR plasmid endowed T cells with CAR and the transposase enabled the programming of circulating T cells with tumour-recognizing capabilities in vivo[164]. In the acidic lysosomal environment, the controlled release of plasmids aided in potent CAR expression on T cells in vivo, demonstrating high-proportioned CAR T cell generation and vigorous proliferation in mice challenged with leukaemia. This promising nanocarrier was further used for T cell-targeted mRNA delivery, in which mRNA encoding for a rare-cleaving megaTAL nuclease efficiently knocked out selected genes in anticancer T cells, and mRNA encoding for a transcription factor of memory formation improved antitumour activities into T cells[165].

T cell backpacking with immunotherapeutic payloads is another strategy for controlled T cell activation to increase tumour specificity and antitumour efficacy[7,166]. ROS-responsive poly(ethylene glycol)-b-poly(L-lysine) nanogel backpacks loaded with anti-CD45 antibodies and human IL-15 agonist (IL-15SA) demonstrated binding potential and redirection of $CD8^+$ T cells[167]. After being infused back into a mouse tumour model, IL-15SA was slowly released to expand both endogenous T cells and transferred PMEL1 $CD8^+$ T cells in a controlled manner. The backpacked nanogel system induced a 16-fold increase in T cell number and presented improved antitumour efficacy and prolonged animal survival. Owing to this spatiotemporally controlled release of agonist to direct T cell activation, this backpacked material showed

limited systemic adverse effects, demonstrating immense progress for delivering immune agents to T cells.

Sustained delivery for local antitumour immunity

Current immunotherapies, including ICB therapies, cytokine therapies, cancer vaccines and CAR T cell therapies, substantially hinder tumour immune suppression while activating cellular immune responses to restrict tumour growth, metastasis and recurrence[3,11,13,160]. However, these therapies are largely systemic, elevating the risk of systemic toxicity and limiting them to short therapeutic cycles in the clinic. Therefore, designing a sustained therapeutic delivery platform that can enable precise administration to the tumour and/or TME, prolong the drug release rate and reduce systemic toxicity is a key goal in cancer immunotherapy[168,169] (Fig. 5c).

Implantable and injectable biomaterials with degradable bonds have opened new doors for the local delivery of immunotherapeutic agents such as antibodies, cytokines, agonists, cancer vaccines and CAR T cells[170–172]. In particular, hydrogels, microneedles and biopolymer implants can encapsulate immunotherapeutic drugs through adsorption, entrapment and chemical modification to maximize drug loading and to recruit immune cells within the targeted site[168,170,171]. Meanwhile, the ability of these biomaterials to undergo a kinetically favourable conformational change upon exposure to the TME allows for sustained release kinetics and improved therapeutic efficacy[131]. Antibody-based immunotherapy can enhance tumour killing by preventing ICB, bridging T/natural killer cells to cancer cells through bispecific antibodies, inducing antibody-dependent cell-mediated phagocytosis/cytotoxicity and targeting co-stimulatory receptors to improve immunotherapies[173–175]. These advantages have resulted in more than 20 antibody drugs for cancer therapy being approved by the FDA[176], highlighting the considerable breakthroughs and importance of immunomodulating antibodies for tumour treatments. Microneedles and hydrogels with tunable drug-loading capacity, controlled release ability and unique hierarchical structures, have been studied to deliver PD1, PDL1, CTLA4 and CD47 antibodies for immunogenic cancer cell death therapy[79,132,171]. Enzyme responsiveness can also be utilized to better tune localized and sustained immunotherapeutic strategy. For example, an MMP2-sensitive prodrug system was constructed by MMP2 substrate-linked CPT and iRGD to form nanotubes that encapsulated anti-PD1 to form a hydrogel in situ[177]. The overexpression of MMP2 in tumours accelerated the sustained release of CPT and aPD1 to create an immune-stimulating TME and induce a robust PD1 blockade immune response. The localized and sustained delivery of the immunotherapy induced systemic antitumour immunity with increased infiltration of $CD8^+$ T cells in primary and untreated distant tumours, effectively inhibiting tumour growth across the body. This technology could induce the abscopal effect (a hypothesis in the treatment of metastatic cancer, in which shrinkage of untreated tumours occurs concurrently with shrinkage of tumours within the scope of the localized treatment) to fight potential tumour metastasis in distal sites through locally altering biological mechanisms. Other responsive biomaterials, such as ROS[178], thermo-responsive[179] and bio-responsive scaffolds[180,181], have also been examined to boost the localized and sustained delivery of immunotherapeutic drugs into tumour sites.

Cytokine-based immunotherapy is effective but is limited by high dosing requirements, short in vivo half-life, low bioavailability and off-target toxicity[182,183]. To improve on these limitations, localized and sustained delivery of cytokines (such as interleukins, interferons and chemokines) can maximize the concentration at the target site while preventing their exposure in normal tissues, thereby improving therapeutic effect[168,169]. Hydrogel-based systems formed in situ can work as a depot for the sustained release of IL-2, IL-15, IFNα, IFNγ, CCL17 and CXCL10 to prolong long-term therapeutic outcome following a single dosage[132,168,184–187]. This localized and sustained cytokine release generates an immunostimulatory microenvironment for immune cell communication, residence and proliferation, effectively inhibiting tumour growth and postoperative tumour recurrence[168,169,185].

In addition to covalently bonded biomaterials, dynamically bonded biomaterials also exhibit excellent drug delivery to tumours[188,189]. These biomaterials are constructed using dynamic crosslinking that is mobile under physiological conditions and exhibits the plasticity required for the sustained release of immunotherapeutic drugs. For example, transformable hydrogel–LNP systems can store mRNA vaccines at room temperature for durable immunotherapy in vivo[188]. The injected gel-like hyaluronan underwent a state transition, triggering sustained release of ovalbumin mRNA and immune adjuvants that were taken up by dendritic cells for antigen presentation to induce antigen-specific $CD8^+$ T cells. This biomaterial prolonged the exposure time of mRNA and immune adjuvants to immune cells and efficiently inhibited tumour growth and metastasis formation. With a similar strategy, injectable polymer–nanoparticle hydrogels were utilized to encapsulate CAR T cells and stimulatory cytokines to improve treatment of solid tumours[189]. The unique architecture of this biomaterial simultaneously inhibited passive diffusion of entrapped cytokines and permitted active motility of entrapped cells to enable long-term retention, viability and activation of CAR T cells. The generation of a transient inflammatory niche following administration enabled localized and sustained delivery of CAR T cells, inducing a tumour-reactive CAR T phenotype as well as improving efficacy in treating solid tumours and metastases. A pioneering strategy known as Multifunctional Alginate Scaffold for T Cell Engineering and Release (MASTER) has been described to revolutionize in vivo CAR T cell manufacturing by condensing the process into a single day and bypassing the lengthy, costly and labour-intensive ex vivo manufacturing process[190]. The MASTER methodology entails direct loading of patient-derived T cells onto the scaffold alongside viral particles encoding the CAR and implanting the scaffold on the same day to locally generate and expand CAR T cells in vivo. The generated CAR T cells can be gradually released into the bloodstream, thereby orchestrating control over distal tumour progression[190].

Although these sustained delivery systems have made great progress for various cancer immunotherapy strategies, clinical translation remains challenging. First, several of these synthetic biomaterials are developed in a laboratory setting and are difficult to scale up in manufacturing. Second, controlling the release kinetics of these materials in a reproducible fashion is imprecise. Finally, the biological activity and stability of immunotherapeutic drugs are variable and result in complex evaluation steps for high fidelity demonstration. Keeping these factors in consideration is key in the development of future biomaterials for sustained cancer immunotherapy.

Future perspectives and outlook

ICB-based immunotherapy has been widely used in the treatment of various tumours; this strategy has low toxic side effects and can prolong patient survival because it specifically blocks immune inhibitory molecules, prevents immune escape of tumour tissues and activates the cytotoxic functions of endogenous immune cells[191,192]. However, owing to the complex mechanism of ICB action, the cross-reactivity of

signalling pathways and the metabolic effects of the immune microenvironment, the clinical response to ICB therapy is weak and differs from patient to patient[15,192,193]. Moreover, ICB therapy is expensive and inaccessible for most of the global population affected by cancer[15]. Therefore, to achieve better clinical outcomes in different cancer patients, these issues must be overcome. To boost the efficacy of endogenous adaptive immune response against tumour sites while suppressing complications or side effects, ICB should be combined with other therapeutic approaches such as cancer vaccines, cytokines and chemoradiotherapy. Responsive biomaterials can be designed to deliver these therapeutics with optimized release profiles to generate more effective cancer immunotherapies.

Constituting the second-largest number of active immunotherapy clinical trials, adoptive T cell therapies provide the opportunity to select, activate and expand highly reactive tumour-specific T cell subpopulations ex vivo and transfer them back into patients to reinvigorate antitumour immunity[7,9,194]. However, only 50% of clinical trials related to adoptive T cell therapies are devoted to solid tumour treatments owing to complex tumour heterogeneity, suboptimal intratumoural T cell seeding and the highly immunosuppressive TME. Furthermore, the safety of T cell therapy is an important issue. Fine control over T cell activity could, in theory, allow one to personalize immune cell activity on the basis of early readouts of toxicity. Thus, responsive biomaterials can be utilized to remodel the TME and induce immunogenic or inflammatory cell death to perpetuate T cell-initiated therapeutic processes.

Although responsive biomaterial-based approaches hold potential, several factors still need to be considered to optimize these approaches and bring them from bench to bedside. The first consideration arises from the wide array of physiological disruptions that accompany tumour formation. The development of tumours results in several aberrant changes in cellular organization and proliferation, signalling cascades, vascular permeability, lymphatic trafficking and genomic stability[153]. Moreover, these changes are not generalizable across all tumour types and lead to severe heterogeneity in the clinical presentation of cancer, making this a major barrier in detection, diagnosis and treatment using both traditional cancer therapies such as radiation and chemotherapy and novel biomaterial-based strategies. As a result, the design of future immunotherapies must consider each tumour and its associated TME as a unique physiological niche, perform comprehensive characterization to form a detailed understanding of the determinants of each niche and specifically tailor therapeutics to elicit antitumour immunity in the context of each niche. One methodology that could be leveraged here is single-cell RNA sequencing, which enables comprehensive profiling of the tumour and TME and can deconvolute how subtle differences in tumour biology contribute to therapeutic resistance[195]. Single-cell RNA sequencing identifies a large number of patient-specific somatic mutations in tumour cells, providing a rich source of tumour-specific and patient-specific targets that could be further developed for cancer immunotherapy. Associated with the discovery of these targets, suitable biomaterial-based tools are needed to deliver patient-specific immunotherapies, such as personalized cancer vaccines and CAR T cell therapy, to each individual tumour niche for effective treatment.

The second consideration is the effect of existing cancer treatments on responsive biomaterial-based immunotherapies. Oftentimes, patients have undergone some form of cancer treatment such as chemotherapy, radiation, surgery or immunotherapy, which could have altered their physiological states and immunity. Hence, testing new biomaterials-based therapies alongside tried and tested cancer therapies is key; for example, UCNPs encapsulating photosensitizers and adjuvants, delivered along with anti-CTLA4 antibodies, could have a synergistic effect — the photosensitizers activated by UCNPs could completely eliminate primary tumours and the CTLA4 blockade could strongly inhibit the growth of distant tumours[196]. Perhaps, a more promising alternative than CTLA4 blockade therapy could be the use of anti-PD1 blockade therapy — which has been utilized extensively in cancer immunotherapy as evidenced by the large number of ongoing clinical trials today — in combination with novel responsive biomaterials to elicit a robust antitumour response. Anti-PD1 antibodies could be incorporated into responsive biomaterials through various methods including immobilization and encapsulation for sustained delivery. Moreover, constructing anti-PD1-based bispecific antibodies or agonists could improve the antitumour immune response for future clinical investigations. As such, cell-based therapies such as CAR T cells, CAR macrophages, CAR natural killer cells and other engineered cells that have been well established in cancer immunotherapy could also be therapeutically elevated by incorporating them with biomaterials. For example, CAR T cells could be encapsulated within responsive biomaterials for localized and sustained delivery, which could potentially alleviate concerns of massive cytokine release syndrome and neurotoxicity upon bolus administration. Thus, combining existing and novel therapeutic strategies will result in the greatest degree of clinical translation and therapeutic efficacy.

Next, safety issues resulting from the use of responsive biomaterials should be considered. As non-degradable biomaterials may result in toxicity and undesirable foreign responses, smart, responsive biomaterials should ideally be designed to be biodegradable and biocompatible with low reactogenicity: examples include liposomes, LNPs, albumin nanoparticles, biodegradable polymeric nanoparticles, microparticles and microneedles. PLGA-based scaffold vaccines — now in phase I clinical trials for stage IV melanoma and licensed to Novartis for commercial use — could be used as a safe platform to treat a myriad of tumour types[197]. Additionally, naturally derived materials such as extracellular vesicles, hyaluronic acid, chitosan and collagen, which are more biocompatible than synthetic materials, could be engineered to be responsive[198–200]. To counteract the issues of toxicity, biomaterials that have appropriate clearance times could be utilized. This is to ensure that the biomaterial and immunotherapeutic payload is able to have a therapeutic effect and be cleared before toxicity arises. Therefore, the undesirable host immune response and the metabolism and systemic clearance of the employed biomaterials should be thoroughly investigated in clinical testing. Overall, considering the biological effect and rationally designing biomaterial-based platforms are crucial to improve immunotherapeutic efficacy and safety for clinical translation.

Finally, the scale-up of these materials should also be considered. Specifically, the design of responsive materials should be based on FDA-approved materials, should be easily scalable for high-throughput production and should be reproducible with low batch-to-batch variability. The necessity of this standardization was demonstrated by the FDA-approved COVID-19 mRNA vaccine, which utilized stimuli-responsive LNPs for delivering mRNA cargo. When vaccines were needed to combat the global spread of COVID-19, the production of these LNP vaccines was massively scaled up to meet the high global demand. Moreover, the scale-up retained the physicochemical properties, delivery efficacy, immunogenicity and reactogenicity of the LNPs, resulting in the quick roll-out of vaccines around the world. The clinical success of the COVID-19 vaccine has resulted in several groups exploring the use of LNPs for cancer immunotherapy, with LNPs

delivering various immunotherapeutic payloads. Although LNP gene therapeutic technology is still relatively new, its highly translational and scalable nature enables it to be thoroughly explored for a myriad of applications, including cancer immunotherapy.

In conclusion, smart biomaterials with stimuli responsiveness demonstrate great success for spatiotemporally controlling the anti-tumour immune response and boosting the efficacy of cancer immunotherapy. Endogenous stimuli such as pH, redox potential and enzymatic activity, and exogenous energetic stimuli such as light, magnetic and acoustic energy, result in a wide array of tools that can be exploited for the precise control of therapeutic delivery and action. As a result, responsive biomaterial-based platforms can be used to tackle several aspects of cancer, which will ultimately allow for enhanced cancer immunotherapy and improved patient outcomes.

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Author contributions

L.X., A.S.T. and M.J.M. conceived and outlined the general manuscript. L.X., A.S.T., D.M. and R.M.H. wrote the initial manuscript with contributions from X.H., N.G., K.W., N.C.S., C.H.J. and M.J.M. All authors edited the manuscript and figures and approved the final version for submission.

Competing interests

N.C.S. holds equity in Tmunity Therapeutics. C.H.J. has received financial support from Novartis and has patents related to CAR therapy with royalties paid from Novartis to the University of Pennsylvania. C.H.J. is a scientific adviser for Alaunos, BluesphereBio, Cabaletta, Carisma, Cartography, Cellares, Cellcarta, Celldex, Danaher, Decheng, ImmuneSensor, Poseida, Verismo, Viracta and WIRB-Copernicus group and is a co-founder and holds equity in Capstan Therapeutics and Tmunity Therapeutics. The other authors declare no competing interests.

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