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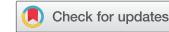


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FULL CRITICAL REVIEW



## Biomaterial-based strategies to prime dendritic cell-mediated anti-cancer immune responses

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### ABSTRACT

Cancer immunotherapy has been extremely successful in curing patients over the last decade. Immune checkpoint blockades (ICBs) that unleash the brakes in T-cells to promote cytotoxicity against cancer cells are the most successful forms of cancer immunotherapy, yet therapeutic efficacy needs to be improved as only a fraction of patients responds. Dendritic cells (DCs) are immune cells that prime immune responses by collecting information in tumour tissues, and carrying that information to T-cells, thus delivering proper information to DCs is essential. Biomaterial-based approaches can be powerful tools for this purpose, as biomaterials allow us to deliver a variety of immunotherapeutic agents at the right time and place. Herein, we review the key concepts of cancer immunotherapy; discuss the principles for designing biomaterials to deliver immunomodulatory molecules; and outline biomaterial-based strategies to prime anti-cancer immune responses. Specifically, we focus on two widely used forms of biomaterials, multifunctional nanoparticles and biocompatible scaffolds.

**Abbreviations:** Anti-PD-1: Anti-programmed death 1; APCs: Antigen-presenting cells; CAR: chimeric antigen receptor; CCL20: CC-chemokine ligand 20; CCR7: Chemokine receptor type 7; CD40L: CD40 ligand; cGAMP: Cyclic guanosine monophosphate-adenosine monophosphate; CpG ODN: CpG oligodeoxynucleotide; CRT: Calreticulin; CSF2RA: Colony-stimulating factor 2 receptor alpha subunit; DAMPs: Danger-associated molecular patterns; DAP12: DNAX activation protein 12; DCs: Dendritic cells; DOX: Doxorubicin; dsRNA: Double-stranded viral RNA; ECMs: Extracellular matrices; FLT3L: FMS-related tyrosine kinase 3 ligand; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HA: Hyaluronic acid; HA-DOX: DOX conjugated with HA via acid-degradable linkage; HDL: High-density lipoprotein; HMGB-1: High mobility group box 1; ICBs: Immune checkpoint blockades; ICD: Immunogenic cell death; IFN- $\alpha$ : Interferon- $\alpha$ ; IL-1 $\beta$ : Interleukin-1 $\beta$ ; IL-6: Interleukin-6; LNs: Lymph nodes; LPS: Bacterial lipopolysaccharide; MHC: major Histocompatibility complex; MPL: Monophosphoryl lipid A; MSRs: Mesoporous silica rods; NIR: Near-infrared; NPs: Nanoparticles; OXA: Oxaliplatin; PAMPs: Pathogen-associated molecular patterns; PCL: Polycaprolactone; PDCD1LG2: Programmed cell death 1 ligand 2; PEG: Poly(ethylene glycol); PEG-PE: PEG phosphoethanolamine; PEI: Polyethylenimine; PHIS: Poly(L-histidine); PLGA: Poly(lactic-co-glycolic acid); PMA: Poly(methacrylic acid); P-MHC: Peptides presented on MHC molecules; Poly-ICLC: Polyinosinic-polycytidyllic acid with polylysine and carboxymethylcellulose; PRRs: Pattern recognition receptors; PSA: Polyethylenimine-stearyl acid conjugate; ROSs: Reactive oxygen species; STING: Stimulator of interferon genes protein; TAAs: tumour-associated antigens; TCRs: T cell receptors; TLRs: Toll-like receptors; TME: tumour microenvironment; TNF- $\alpha$ : tumour necrosis factor- $\alpha$ ; TREM-2: Triggering receptor expressed on myeloid cells-2; TSLP: Thymic stromal lymphopoietin.

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## Introduction

Cancer is one of the major causes of death, responsible for approximately 10 million deaths each year worldwide. Cancer cells are cells that undergo uncontrolled proliferation due to genetic mutations [1].

Conventional cancer therapies have primarily been designed to directly eliminate cancer cells [2], either by targeting rapidly proliferating cells (cytotoxic therapy) or by inhibiting specific pathways driving carcinogenesis and tumour growth (targeted therapy).

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Cancer immunotherapy is conceptually different from conventional cancer therapies because it takes advantage of the ability of our immune system to recognise and kill cancer cells [3,4]. Cancer immunotherapy has been extremely successful over the last decade. In particular, immune checkpoint blockades (ICBs) that unleash the brakes on T-cells, the strongest cytotoxic cells in our immune system, have been exceedingly successful at improving the survival of patients with many different types of cancer [5,6]. Consequently, Drs James P. Allison and Tasku Honjo, two pioneers of ICBs, won the 2018 Nobel Prize in Physiology or Medicine.

While ICB-based cancer immunotherapy has been greatly successful, a number of issues remain. First, only a small fraction of cancer patients (this number depends on the cancer type, but is typically around 20%) respond to ICBs [5,6]. Second, some patients develop severe autoimmune disease as overactivated T-cells attack normal tissues/organs [7]. These issues may be addressed by biomaterial-based strategies that allow for controlled release of therapeutics to specific cells in target organs, potentially enhancing anti-cancer immunity while minimising the side effects.

In this review, we focus on biomaterial-based strategies targeting dendritic cells (DCs), which play a central role in priming anti-cancer immune responses [8,9]. T-cell-based immunotherapies, including ICBs and chimeric antigen receptor (CAR) T-cells [10], which augment T-cell functions to maximise cancer cell killing, have been successful for only a fraction of patients. Priming anti-cancer immune responses is necessary for the development of T-cell functions [11,12]. Therefore, we believe that DC-targeting immunotherapy based on biomaterials could be the next breakthrough in cancer immunotherapy.

In this review, we first briefly summarise the key concepts in cancer immunology and immunotherapy, with an emphasis on DC biology. Then, biomaterial-based strategies targeting DCs to prime anti-cancer immune responses are extensively reviewed. We focus primarily on two different types of biomaterials, multifunctional nanoparticles (NPs) and biocompatible scaffolds (Figure 1, please see appendix in the supplemental material). Multifunctional nanoparticles [13–15] can be used to deliver immune modulatory compounds to target immune cells in specific tissues/organs. Biocompatible scaffolds, which were initially developed in the context of tissue engineering and regenerative medicine [16,17], release various factors with controlled kinetics to recruit/educate immune cells and re-programme local immune microenvironments. The key physiochemical parameters of each biomaterial are described, and how these parameters can be modulated to achieve properties optimal for specific cancer immunotherapeutic settings are discussed.

## Basic concepts of cancer immunology and immunotherapy

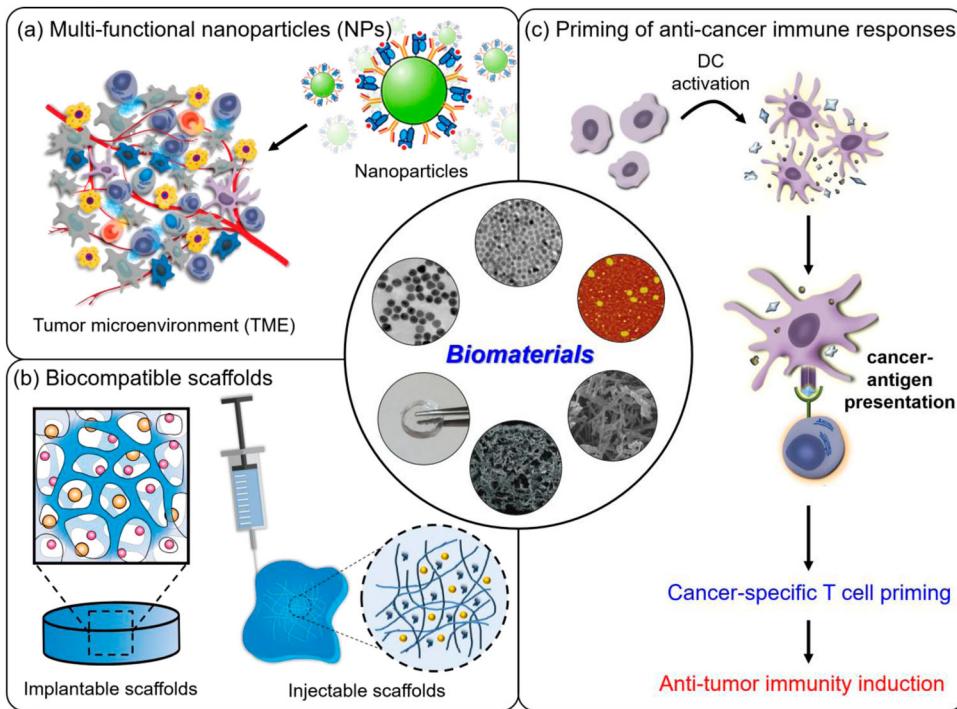
### *Cancer-immunity interactions*

Cancer-specific immune responses are mounted by dynamic interactions between T-cells and DCs migrating through the tumour and LNs, as shown schematically in Figure 2 [18]. First, DCs carrying antigens from the tumour migrate to the LNs. Then, DCs prime T-cells in the LNs. Finally, activated T-cells in the LNs migrate to the tumour to kill cancer cells. Cancer cell death can further enhance DC activation by releasing cancer antigens and danger signals. Thus, cancer-immune cell interactions form a positive feedback loop to amplify anti-cancer immune responses, in a process called the cancer-immunity cycle.

ICBs enhance T-cell activation and function either in the LNs, where T-cells are primed by DCs, or in the tumour, where T-cells kill cancer cells [6]. Anti-cancer immune responses are often compared to driving a car. In this analogy, immune checkpoint molecules are the brakes, and DC-mediated priming is the ignition that starts the car. You can accelerate a car by releasing the brakes, but only when the car is already running. Likewise, without DC activation in the tumour, there is no T-cell priming, and ICBs will not have any effect. Indeed, the major reasons for resistance to ICBs are a lack of DCs in the tumour or defects in DC activation [5,9]. Therefore, triggering robust DC activation would be a breakthrough in cancer immunotherapy that would help overcome the limitations of ICBs.

### *DCs: A key player in priming anti-cancer immunity*

DCs were first identified by Ralph Steinman, who won the 2011 Nobel Prize in Physiology or Medicine. These cells were named based on their unique morphology, with dendritic structures that they use to dynamically probe their environment [8]. DCs reside in all tissues and act as sentinel cells. They express pattern recognition receptors (PRRs), which they use to sense abnormalities in their environment. There are two types of molecular patterns recognised by PRRs expressed by DCs [19]. Pathogen-associated molecular patterns (PAMPs) are expressed by microbes such as bacteria and viruses, but not by host cells. Danger-associated molecular patterns (DAMPs), on the other hand, are biomolecules that are typically expressed within host cells but are released when cells are damaged or dying. Virus-infected cells and cancer cells release DAMPs to induce local inflammation and immune responses. Therefore, DCs sense tissue damage as well as infections in the peripheral tissues using PRRs. Signals transduced through PRRs lead to



**Figure 1.** Biomaterial-based strategies for priming anti-cancer immune responses. (a) Multi-functional nanoparticles (NPs) were developed to deliver immune modulatory signals to target immune cells residing in specific tissues and organs. (b) Biocompatible scaffolds were developed to deliver various factors with controlled release kinetics to educate immune cells and re-programme local immune environments. (c) Biomaterial-based strategies priming of anti-cancer immune responses were developed for cancer immunotherapy. The image is reproduced with permission from [54,78,90,94,127,138]. The Figure from [54] was available via the Creative Commons Attribution 4.0 International License (CCBY4.0, <https://creativecommons.org/licenses/by/4.0/>).

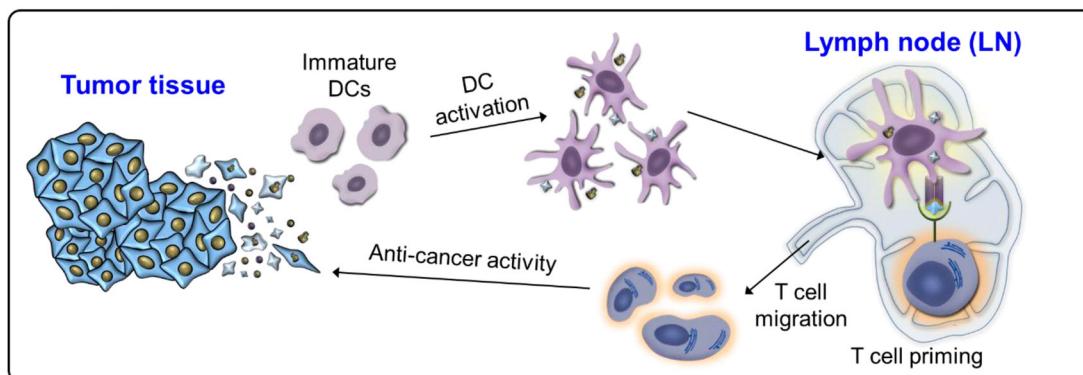
activation of the DCs. Activated DCs up-regulate C-C chemokine receptor type 7 (CCR7), which allows them to migrate to the LNs, where they can prime T-cells.

In addition to their roles as sentinel cells sensing pathogen invasion and tissue damage, DCs are antigen-presenting cells (APCs) that capture antigens in the peripheral tissue and present them to T-cells in the LNs [3]. DCs engulf microbes and cancer cells, break their proteins down into short peptide antigens, and present these antigenic peptides on their surface within major histocompatibility complex (MHC) molecules. T-cells expressing T-cell receptors (TCRs)

specific for the antigenic peptides presented by DCs become primed. These primed T-cells then undergo clonal proliferation, differentiate into effector T-cells, and migrate to infected/tumour tissues to eliminate microbes/cancer cells.

#### Key signals for DCs to prime cancer-specific T-cells

As mentioned above, DCs must receive the proper signals to prime cancer-specific T-cells. Two distinct signals, such as cancer antigens and ligands for PRRs, are



**Figure 2.** The cancer-immunity cycle mounting cancer-specific immune responses via dynamic interactions between T cells and dendritic cells (DCs) migrating across tumour tissues and lymph nodes. Activated DCs carrying tumour antigens migrate to lymph nodes and prime T cells. T cells activated by the DCs traffic to tumour tissues and eliminate cancer cells. Cancer antigens and danger signals released during the cancer cell death further enhance DC activation.

required. Indeed, cancer cells themselves contain both signals. Cancer antigens are proteins specifically expressed in cancer cells, and all cells express DAMPs. Therefore, whole cancer cells can be used to generate DCs for priming anti-cancer immune responses. A number of different methods to prepare dying/dead cancer cells or their lysates have been developed to maximise immunogenicity [20]. However, whole cancer cell-based approaches have demonstrated limited clinical efficacy, presumably due to inefficient presentation of cancer-specific antigens and DAMPs [21].

Biomaterial-based synthetic platforms presenting cancer antigens and key molecules for DC activation would allow us to optimise immunogenicity and deliver the stimulatory molecules under the proper physiological context. In this section, the key signaling molecules involved in DC activation and priming of cancer-specific immune responses are summarised. Then, in the following chapters, detailed biomaterial-based strategies for the assembly and release of these signaling molecules are reviewed.

The first signal that needs to be delivered for DCs to prime cancer-specific T-cells is the cancer antigen. There are two types of cancer antigens that can be targeted for immunotherapy [22,23]. tumour-associated antigens (TAAs) are expressed at low levels in normal cells but high levels in cancer cells. Neoantigens, on the other hand, are only expressed in cancer cells. TAAs have been major targets for cancer therapy until recently, as identification of neoantigens is technically challenging. However, advances in genome sequencing technology and deep learning-based prediction algorithms now allow neoantigens to be predicted with reasonable precision. Therefore, neoantigen-based cancer targeting would enable personalised treatment of cancers, as neoantigens are mostly patient-specific. Once cancer antigens are identified, they can be formulated into many different types of biomolecules. Cancer antigens are derived from proteins expressed by cancer cells that are presented by DCs as short peptides, typically 8–10 mers, and thus they can be delivered to DCs as proteins or short peptides. Alternatively, DNA or mRNA that encodes information about cancer antigens could be used. As proteins are expensive to synthesise, and DNA-based vaccines are inefficient, peptides and mRNAs are the two major formats being used for cancer antigen delivery [21].

The second signal required for DCs to prime anti-cancer immune responses is an activation signal, which can be provided by an adjuvant. DCs can be activated by various factors such as PAMPs derived from microorganisms, DAMPs released by dying cells, CD40 ligand (CD40L) expressed on activated T-cells, inflammatory cytokines, and other endogenous ligands (Table 1). In particular, ligands for Toll-like receptors (TLRs), a major class of PRRs for various PAMPs

**Table 1.** Key signals for DC activation

| Class                   | Ligand   | Receptor   |
|-------------------------|--|--|
| TLR agonists            | Bacterial lipopeptides   | TLR1   |
|                         | Peptidoglycans, lipoproteins, glycolipids, Hsp70                         | TLR2   |
|                         | Poly-ICLC, dsRNA   | TLR3   |
|                         | MPL, LPS, oligosaccharides of hyaluronan, HMGB1                          | TLR4   |
|                         | Flagellin  | TLR5   |
|                         | Imiquimod, R-848   | TLR7   |
|                         | R-848  | TLR8   |
|                         | CpG ODN  | TLR9   |
|                         | CD40L (CD154), agonistic antibody  | CD40   |
|                         | Agonistic antibody (sHlgM12)   | PDCD1LG2   |
| Immune cell factors     |  |  |
| Costimulatory molecules |  |  |
| DAP12-mediated pathway  | Agonistic antibody   | TREM-2   |
| Cytokines               | TNF- $\alpha$<br>IFN- $\alpha$<br>IL-1 $\beta$<br>IL-6<br>TSLP<br>GM-CSF | TNFR<br>IFNAR1<br>IL-1R<br>IL-6R<br>IL-7Ra<br>CSF2RA<br>(CD116)<br>STING |
| Endogenous ligands      | cGAMP<br>Uric acid   |  |

TLRs: Toll-like receptors; Poly-ICLC: Polyinosinic-polycytidylic acid with polylysine and carboxymethylcellulose; dsRNA: Double-stranded viral RNA; MPL: Monophosphoryl lipid A; LPS: Bacterial lipopolysaccharide; HMGB1: High mobility group box 1; CpG ODN: CpG oligodeoxynucleotide; CD40L: CD40 ligand; PDCD1LG2: Programmed cell death 1 ligand 2; DAP12: DNAX activation protein 12; TREM-2: Triggering receptor expressed on myeloid cells-2; TNF- $\alpha$ : tumour necrosis factor- $\alpha$ ; IFN- $\alpha$ : Interferon- $\alpha$ ; IL-1 $\beta$ : Interleukin-1 $\beta$ ; IL-6: Interleukin-6; TSLP: Thymic stromal lymphopoietin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; CSF2RA: Colony-stimulating factor 2 receptor alpha subunit; cGAMP: Cyclic guanosine monophosphate-adenosine monophosphate; STING: Stimulator of interferon genes protein.

and DAMPs, have been used to augment anti-cancer immune responses. For example, polyinosinic-polycytidylic acid with polylysine and carboxymethylcellulose (poly-ICLC) [24], monophosphoryl lipid A (MPL) [25], imiquimod, resiquimod (R-848) [26], and CpG oligodeoxynucleotides (CpG ODN) [26] have been used as agonists for TLR3, TLR4, TLR7, TLR7/8, and TLR9, respectively. Agonistic antibodies for CD40 can mimic CD40 ligand (CD40L) expressed on activated T-cells and activate DCs synergistically with TLR agonists [27]. Additionally, granulocyte-macrophage colony-stimulating factor (GM-CSF) [28], a critical cytokine for DC generation and activation, and agonists for stimulator of interferon genes (STING) [29], such as cyclic dinucleotide derivatives and cyclic di-guanosine monophosphate, which induce type I interferon production, are widely used adjuvants for DC activation. In the absence of activation signals, DCs induce immune tolerance rather than immune responses. Proper presentation of immune adjuvants to DCs is therefore indispensable for successful cancer immunotherapy.

### Biomaterials for priming anti-cancer immune responses in the tumour

The cancer-immunity cycle, shown in Figure 2, is initiated by cancer cell death and the subsequent

uptake of dying cancer cells by DCs. Therefore, conventional cancer therapeutics that directly kill cancer cells can be combined with cancer immunotherapy if they induce immunogenic cell death (ICD) [30]. To achieve this goal, cytotoxic therapies should be delivered first, to maximise cancer cell death and minimise normal tissue damage. Then, immune-based strategies could be used to overcome the immunosuppressive tumour microenvironment (TME) and to prime strong anti-cancer immune responses. In this section, various biomaterial-based strategies to deliver cancer therapeutics to tumour tissues to prime strong anti-cancer immune responses will be reviewed. Specifically, nanomaterials designed to induce ICD of cancer cells, and biocompatible scaffolds designed to release various therapeutics to overcome immunosuppression in TME and maximise immune priming will be described in detail.

### **Nanoparticles for inducing ICD of cancer cells**

#### **Biomaterial-based strategies to maximise ICD and minimise side effects**

To induce ICD, sufficient amounts of DAMPs need to be released by dying cancer cells to trigger local inflammation in the tumour. In addition, damage to immune cells by the therapy should be minimised. Conventional cancer therapies, such as chemotherapy and radiotherapy, have been developed mainly to maximise cancer cell killing. Because these therapies target rapidly dividing cells, which includes immune cells, conventional cancer therapies tend to weaken patients' immune systems [31,32]. Biomaterial-based strategies are ideal to address this issue by delivering cytotoxic reagents directly to cancer cells, thus minimising effects on the immune system (Figure 3(a)). NPs can be delivered directly to cancer cells by attaching binder molecules that specifically target cancer cells, such as antibodies and aptamers (Figure 3(b)) [33,34]. In addition, payloads encapsulated in NPs can be released within cancer cells using NPs that release their cargo under certain conditions, such as low pH (Figure 3(c)) [34–36].

In addition to specifically killing cancer cells, it is important to subsequently trigger strong anti-cancer immune responses. DAMPs released by dying cancer cells play an essential role in priming strong anti-cancer immune responses by recruiting DCs and activating them to efficiently present cancer antigens to T-cells. For example, adenosine triphosphate (ATP) acts as a 'find me' signal to recruit DCs to dying cancer cells [37]; calreticulin (CRT) serves as an 'eat me' signal to encourage engulfment of dying/dead cancer cells [38]; and high mobility group box 1 (HMGB-1) promotes antigen presentation by DCs [39]. Two strategies have been devised to maximise ICD. First, cancer antigens and DAMPs released by dying/dead cancer cells

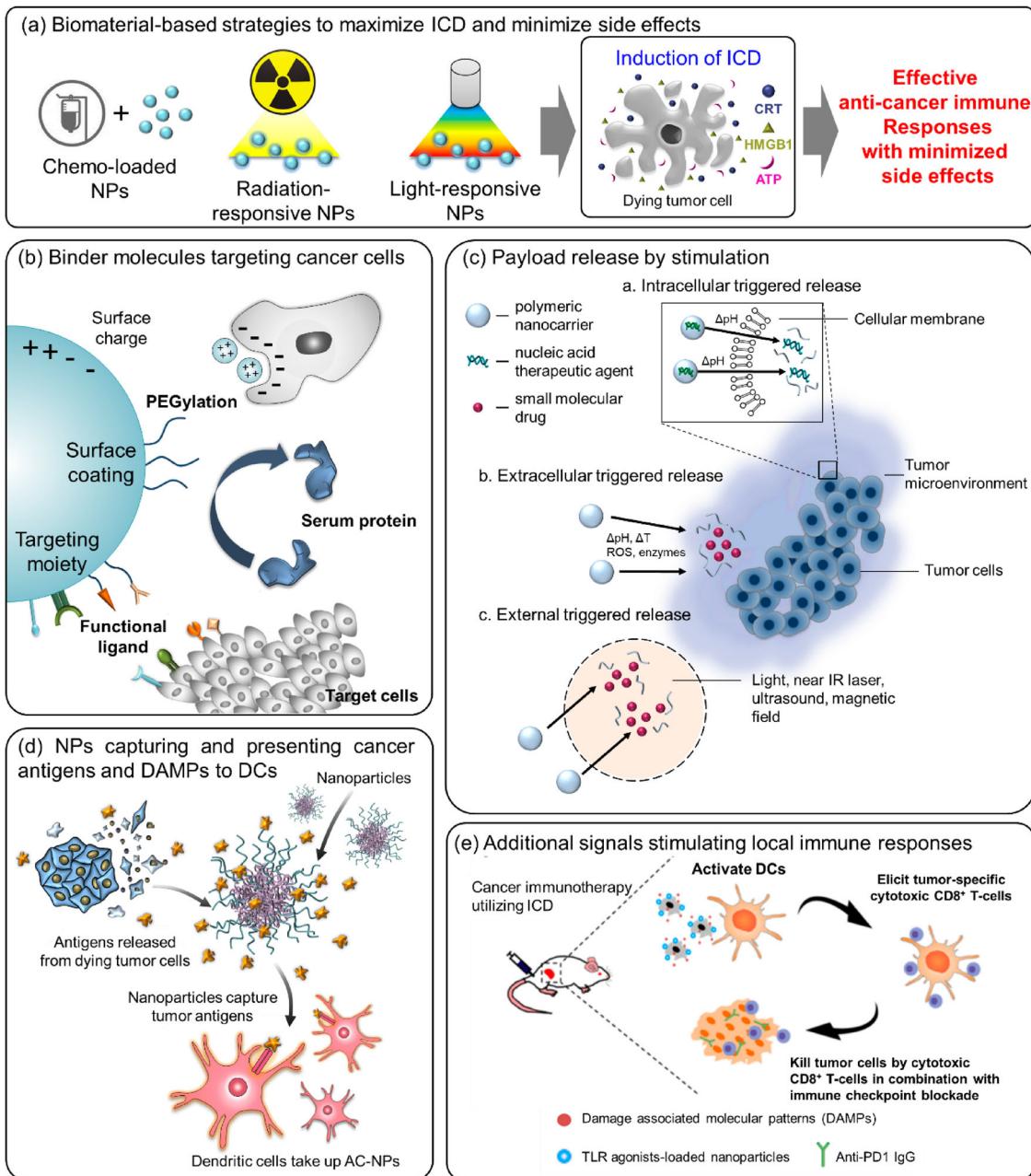
are captured by nanomaterials and presented to DCs to prevent their loss by diffusion (Figure 3(d)) [40–42]. Second, additional signals that stimulate local immune responses, such as TLR agonists, are incorporated into the nanomaterials (Figure 3(e)) [43–48].

With these principles, detailed examples of how nanomaterials are being utilised to maximise ICD mediated by conventional cancer therapies, as well as light-responsive nanomaterials that induce ICD with irradiation in light-illuminated areas, will be described in the following sections.

### **Nanoparticle-mediated delivery of chemotherapeutics**

Chemotherapeutics can either attenuate the immune system or boost anti-cancer immunity, depending on their mode of action [49]. NP-based delivery of some chemotherapeutics demonstrated effective induction of ICD, resulting in anti-cancer immunity (Figure 4(a)). Doxorubicin (DOX) is a widely used cancer therapy and has frequently been used to induce ICD in conjunction with NP-mediated delivery [50–52]. Specifically, DOX conjugated with hyaluronic acid (HA) via acid-degradable linkage (HA-DOX) was coated onto nanocores composed of the TLR7/8 agonist R848 encapsulated in poly(L-histidine) (PHIS) and was used to treat mice with 4T1 breast tumours (Figure 4(b)) [53]. The core-shell NPs were stable in the bloodstream and normal tissue, but dissociated in slightly acidic environments (pH of approximately 6.5), such as the TME, because the PHIS became ionised, resulting in the release of HA-DOX and R848. HA-DOX was preferentially taken up by breast cancer cells overexpressing CD44, a receptor for HA, and the acid-degradable linker connecting HA-DOX was degraded in endo/lysosomes (pH of approximately 5.5), resulting in DOX delivery into the breast cancer cells. In addition to inducing ICD of breast cancer cells, R848 triggered local inflammation by activating DCs expressing TLR7/8, and thus both reagents synergistically inhibited tumour growth. DOX has also been attached to synthetic high-density lipoprotein (sHDL)-mimicking nanodiscs to minimise off-target side effects and trigger ICD (Figure 4(c)) [51]. Cancer cells treated with sHDL-DOX upregulated CRT and released HMGB1 to activate local DCs and trigger cancer cell uptake. In combination with an antibody against programmed death 1 (anti-PD-1), which is an ICB, sHDL-DOX -loaded nanodiscs completely eradicated colon carcinomas from 80% of mice and prevented tumour recurrence.

Oxaliplatin (OXA) is another clinically used chemotherapeutic known to induce ICD. When magnetic nanoparticles coated with tumour-targeting and OXA-bearing polymers were used in the 4T1 breast cancer model, the particles actively accumulated at tumour sites and released ferric ions and OXA (Figure 4(d))



**Figure 3.** NP-based strategies to maximise immunogenic cell death (ICD) and minimise side effects. (a) Chemotherapeutic agent-loaded and radiation/light-responsive NPs were utilised to efficiently induce ICD with minimal side effects. (b) Surface of NPs were modified with binder molecules to specifically target cancer cells. The image is reproduced with permission from [139]. (c) Stimuli-responsive NPs were exploited to release payload within cancer cells. The image is reproduced with permission from [34]. (d) NPs were designed to capture cancer antigens and DAMPs released during ICD and deliver them to DCs. The image is reproduced with permission from [40]. (e) Additional signals stimulating local immune responses were delivered through NPs. The image is reproduced with permission from [43].

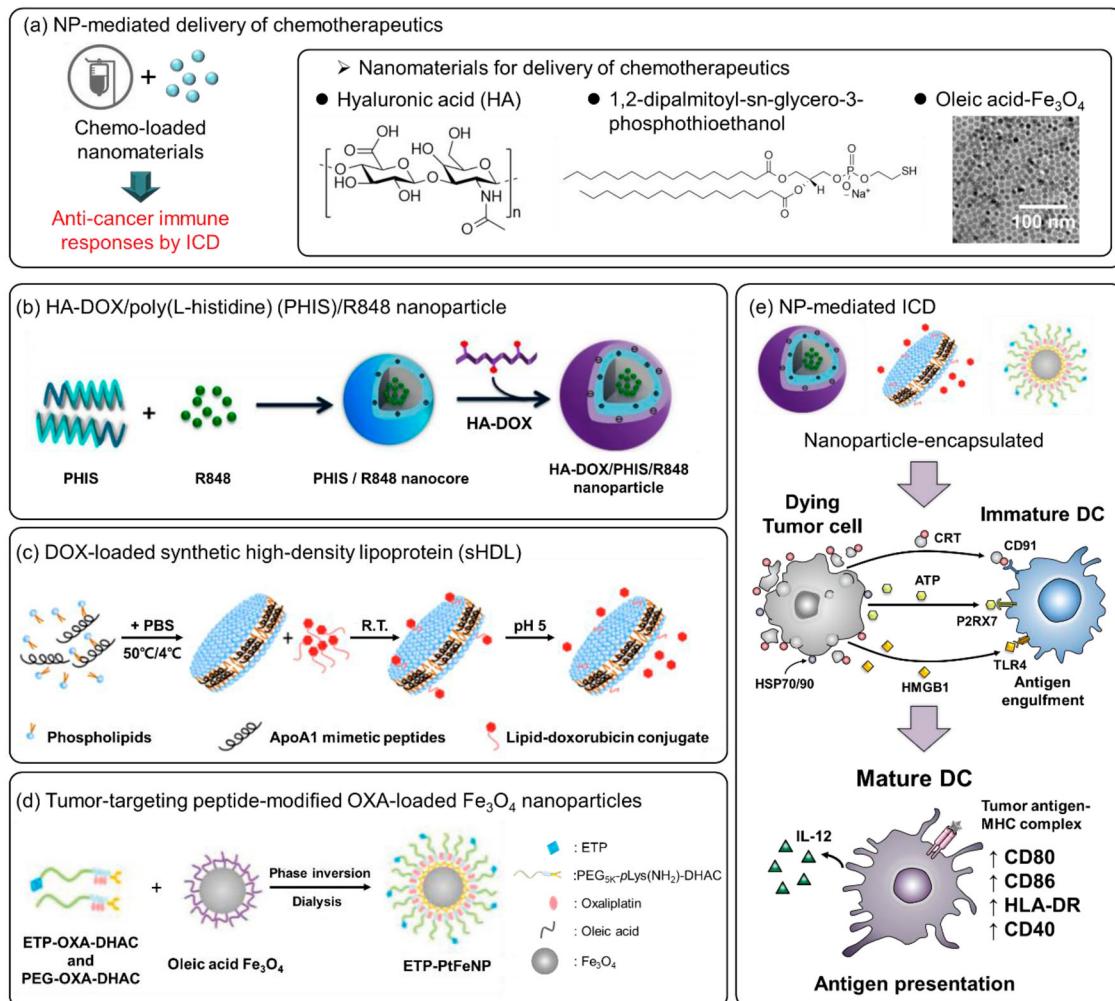
[54]. Ferric ions triggered ROS generations that synergise ICD induction by OXA, resulting in enhanced exposure of DAMPs. Additionally, the magnetic nanoparticles that accumulated at the tumour sites were used as a highly sensitive magnetic resonance imaging (MRI) contrast agent.

#### Nanomaterials enhancing ICD by radiotherapy

Radiotherapy is routinely used in cancer therapy based on high energy ionising radiation [55]. Irradiation generates free radicals that damage cellular components, including DNA, to induce cancer cell death [56].

Interestingly, radiotherapy can trigger the regression of tumours that are distant from the irradiated area. This abscopal effect is primarily due to anti-cancer immune responses caused by radiation-mediated ICD [57].

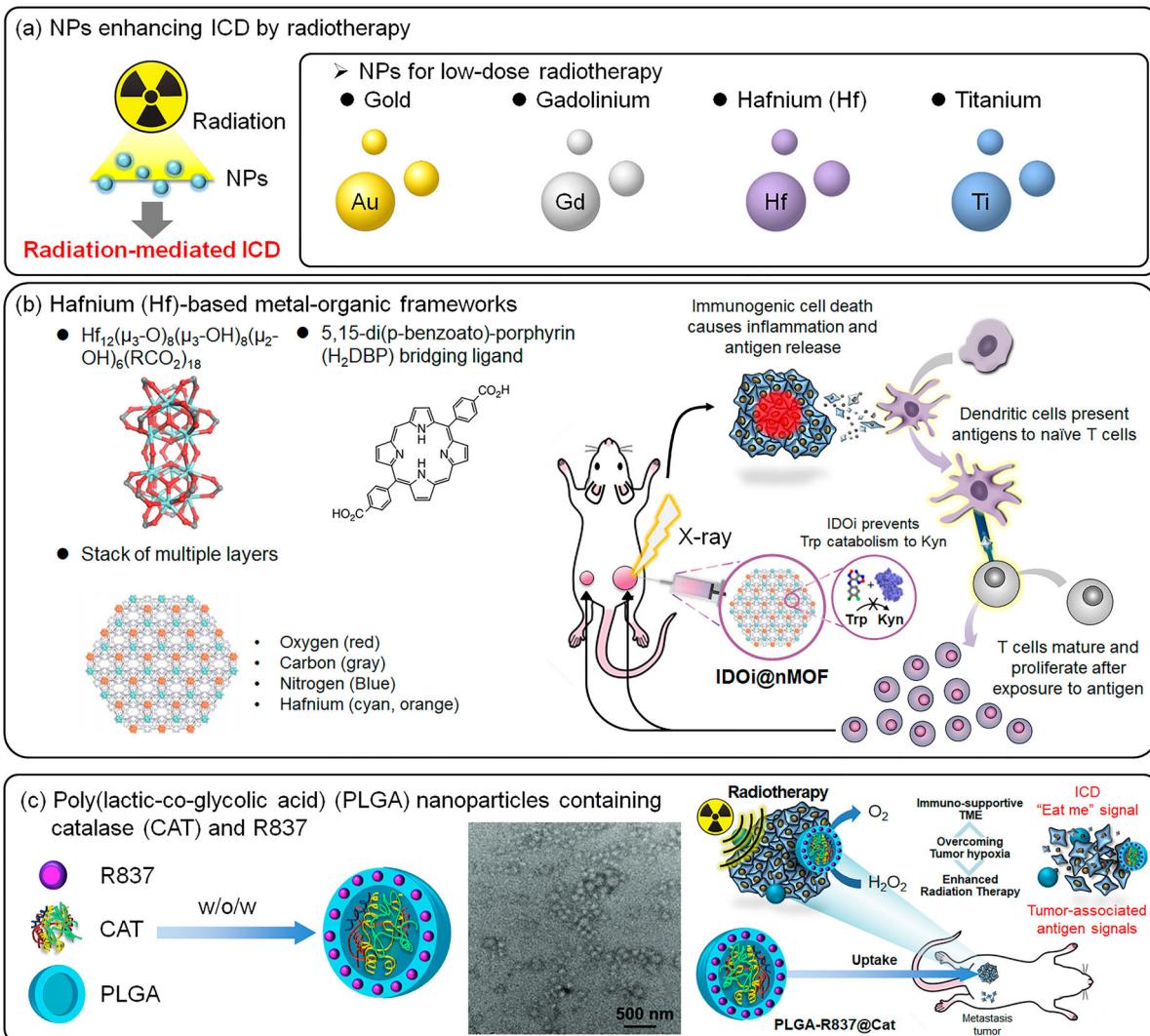
Diverse NPs have been used to enhance the therapeutic efficacy of radiotherapy and reduce side effects caused by high-dose irradiation (Figure 5(a)) [58,59]. Importantly, high-dose radiation not only ablates cancer cells but also damages normal cells, resulting in immunosuppression that potentially interferes with the abscopal effect [31,32]. To overcome this issue,



**Figure 4.** NP-based delivery of chemotherapeutics to induce ICD eliciting anti-cancer immune responses. (a) Nanomaterials were developed to deliver chemotherapeutics inducing ICD. (b) Doxorubicin (DOX) conjugated with hyaluronic acid (HA) coated on nanocores of PHIS and R848 (HA-DOX/PHIS/R848 NPs) was delivered to treat 4T1 breast cancer models. The image is reproduced with permission from [53]. (c) In combination with an immune checkpoint blockade (ICB), DOX was delivered via high-density lipoprotein (HDL) nanodiscs to eradicate colon carcinoma tumours and prohibit tumour recurrence. Reprinted/modified from [51]. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) <http://creativecommons.org/licenses/by-nc/4.0/>. (d) Magnetic NPs modified with tumour-targeting and Oxaliplatin (OXA)-bearing peptides (ETP-PtFeNPs) were delivered to treat 4T1 breast cancer models. The image is reproduced with permission from [54]. The Figure from [54] was available via the Creative Commons Attribution 4.0 International License (CCBY4.0, <https://creativecommons.org/licenses/by/4.0/>). (e) Mechanisms of ICD induced by nanoparticles in b, c, d. The images are reproduced with permission from [51,53,54]. Reprinted/modified from [51]. © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC) <http://creativecommons.org/licenses/by-nc/4.0/>. The Figure from [54] was available via the Creative Commons Attribution 4.0 International License (CCBY4.0, <https://creativecommons.org/licenses/by/4.0/>).

NPs that can sensitise cancer cells to undergo cell death under low-dose radiation, including gold- [60], gadolinium- [61], hafnium- [62,63], and titanium-based NPs [64,65], have been developed. Targeted delivery of these nanomaterials to cancer cells can increase the accumulation of radiation energy within the TME, thus allowing the use of a lower dose of radiation. Radiation can directly damage cancer cells through various biochemical pathways [66,67] and lead to the generation of ROS to eliminate radiation-resistant cancer cells [68]. A porous nanoscale metal–organic framework (nMOF) based on hafnium (Hf)/porphyrin-based photosensitiser loaded with an inhibitor for indoleamine 2,3-dioxygenase (IDOi), an

immunosuppressive enzyme, induced an abscopal effect with low-dose X-ray irradiation, leading to local and distal tumour regression in breast and colorectal cancer models (Figure 5(b)) [63]. Mechanistically, Hf clusters in nMOF promoted X-ray photons absorption to generate radicals (radiotherapy) and to excite photosensitisers (radiodynamic therapy), resulting in ICD of tumour cells with minimal X-ray dose. Release of IDOi loaded in porous nMOF further enhanced anti-cancer immune responses by inhibiting immunosuppressive enzyme IDO. PLGA core–shell NPs loaded with a catalase in core and imiquimod (R837) in the PLGA shell, a TLR7 agonist, significantly enhanced the efficacy of radiotherapy in breast and colorectal



**Figure 5.** NP-based strategies to enhance efficacy of radiotherapy and reduce high-dose irradiation-mediated side effects. (a) Nanomaterials were developed to induce ICD via low-dose radiation. (b) Hafnium (Hf)-based metal-organic frameworks were delivered to induce ICD via low-dose irradiation to synergistically treat breast and colorectal cancer models with an ICB. The images are reproduced with permission from [63]. (c) Poly(lactic-co-glycolic acid) (PLGA) NPs containing catalase (CAT) and imiquimod (R837) enhanced efficacy of radiotherapy on breast and colorectal cancer models by alleviating hypoxia and triggering anti-cancer activities. The images are reproduced with permission from [69].

cancer models (Figure 5(c)) [69]. In this case, catalase released from the core of NPs generated oxygen by decomposing  $\text{H}_2\text{O}_2$ , thus substantially alleviated hypoxia, whereas R837 loaded in the shell of NPs triggered TLR7/8 signaling to activate DCs to efficiently mount anti-cancer immune responses.

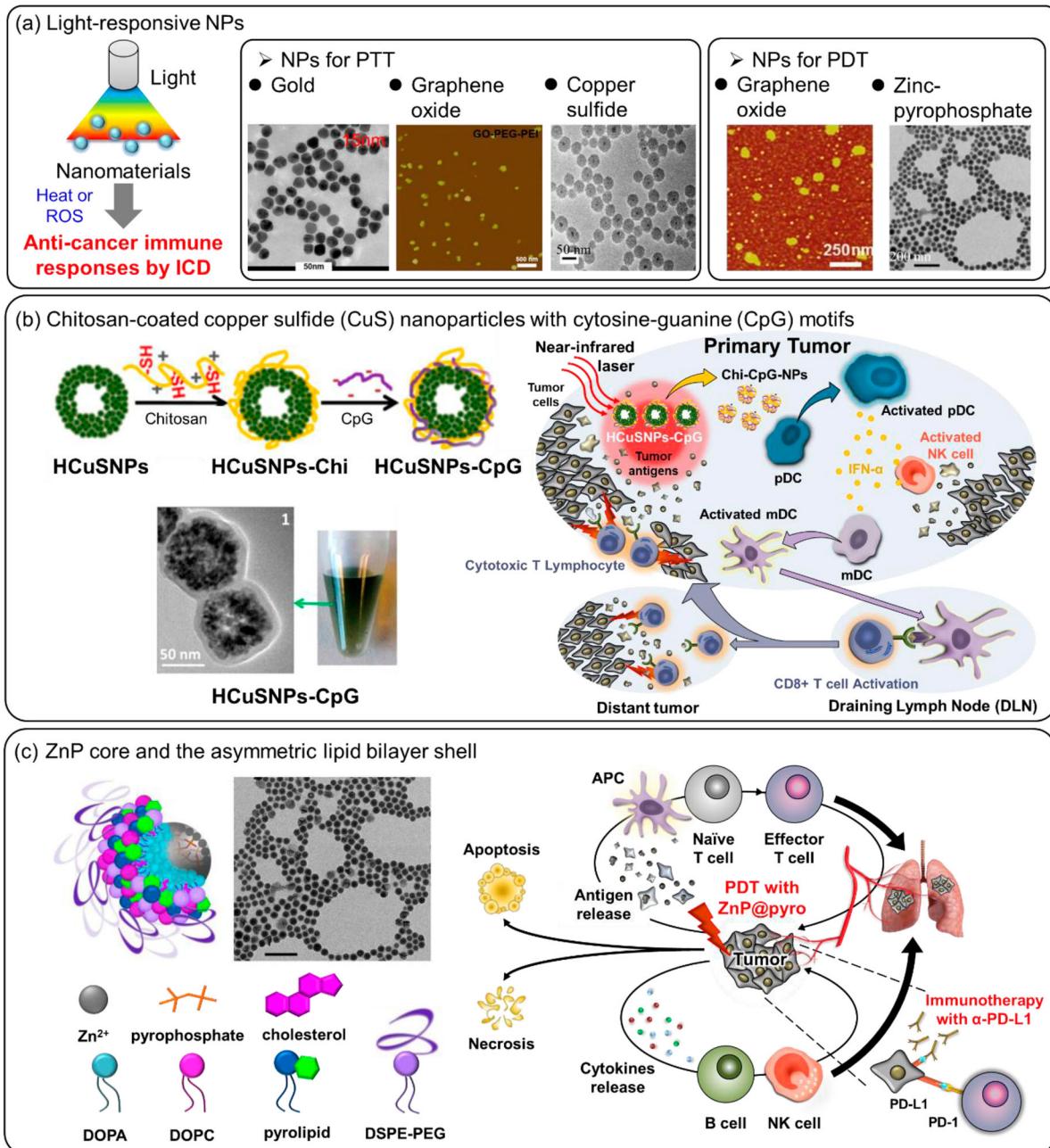
#### Light-responsive nanomaterials

Light-responsive NPs have been developed for cancer therapy, as some NPs absorb light and generate local heat or ROS, which can be used to kill cancer cells [70–72]. Cancer therapies based on light-mediated heat or ROS generation, so-called photothermal or photodynamic therapy, respectively, have recently been combined with immunotherapy, as they can also trigger anti-cancer immune responses (Figure 6(a)) [73,74].

In photothermal therapy, locally administrated light is converted to heat by light-responsive nanomaterials, leading to a local temperature increase. The typical target

temperature for photothermal therapy is 40–45°C, which is known to kill cancer cells by denaturing proteins and inducing cellular programmes for cell death [75]. In addition, hyperthermia can trigger immune responses that promote anti-cancer immunity [76]. To generate light-induced heating in the TME, inorganic NPs that absorb near-infrared (NIR) light and efficiently convert it to heat (e.g. gold [77,78], graphene oxide [79,80], and copper sulphide [81–83]) are delivered to the tumour. NIR light is preferentially used in light-responsive nanomaterials because it has optimal tissue penetration with minimal light scattering and tissue absorption [84,85]. Photothermal ablation of the tumour not only directly kills cancer cells, but also induces the release of cancer antigens and pro-inflammatory cytokines, promoting anti-cancer immune responses.

To further enhance the anti-cancer immune responses induced by photothermal therapy, immune adjuvants such as TLR agonists or ICBs are frequently



**Figure 6.** Light-responsive NP-based strategies to enhance photothermal or photodynamic therapy via generating heat or ROS, respectively. (a) Light-responsive NPs were developed to generate heat or ROS for inducing ICD via absorbing light. The images are reproduced with permission from [78,79,81,90,91]. (b) Chitosan/immune adjuvant-coated copper sulphide NPs were delivered to treat EMT6 mammary carcinoma by near-infrared (NIR) irradiation-mediated photothermal ablation and adjuvant-mediated enhancement of immune responses. The image is reproduced with permission from [86]. (c) In combination with an ICB, a photodynamic therapy using zinc-pyrophosphate (ZnP) NPs loaded with a lipid-containing photosensitiser moiety was developed to treat 4T1 breast cancer models. The images are reproduced with permission from [91].

added. For instance, hollow copper sulphide nanoparticles coated with CpG ODN have been used in the EMT6 mouse model of mammary carcinoma (Figure 6(b)) [86]. NIR irradiation initiated copper sulphide-mediated photothermal ablation, resulting in ICD of cancer cells and priming of anti-cancer immune responses, and the release of CpG ODN further enhanced local immune responses in the tumour tissue. Photothermal therapy based on single-walled carbon nanotubes (SWNTs) in combination with a cytotoxic T-lymphocyte-associated (CTLA-4) antibody effectively ablated primary tumours

and inhibited metastasis in mice inoculated with 4T1 breast cancer cells [87]. Notably, SWNT itself activated DCs to upregulate activation receptors such as CD80 and CD86, and to secret inflammatory cytokines such as TNF- $\alpha$ , IL-20, and IL-6, further enhancing ICD induced by photothermal NIR irradiation.

Photodynamic therapy utilises a photosensitiser (e.g. hydrogen peroxide, superoxide anion radicals, singlet oxygen) that generates ROS upon light illumination [88]. Nanomaterials have been employed as carriers of photosensitisers or as new types of photosensitisers

with unique optical properties [89]. Like photothermal therapy, photodynamic therapy can also trigger anti-cancer immunity by inducing ICD of cancer cells and stimulating local immune responses.

For instance, graphene oxide loaded with photoclor [2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide- $\alpha$ ], a hydrophobic photosensitiser, (GO(HPPH)) by hydrophobic and  $\pi$ - $\pi$  stacking triggered strong anti-cancer immune responses that suppressed tumour growth and lung metastasis in mice with 4T1 tumours [90]. Photodynamic therapy mediated by GO(HPPH) successfully induced DC activation in tumour draining lymph nodes, and suppressed distal tumour growth. Photodynamic therapy using Zinc-pyrophosphate NPs loaded with pyrolipid (ZnP@pyro), a lipid-containing photosensitiser, successfully treated primary and metastatic tumours, and exhibited abscopal effects to eradicate tumours at distal sites when combined with anti-PD-L1 ICB in the 4T1 breast cancer model (Figure 6(c)) [91]. Upon light irradiation, ZnP@pyro treated tumour cells expressed CRT, which enhances tumour cell uptake by DCs. When photodynamic therapy was performed for tumour-bearing mice, blood level inflammatory cytokine such as TNF- $\alpha$ , IL-6, and IFN- $\gamma$  were substantially increased, indicating ZnP@pyro-mediated photodynamic therapy induced acute inflammation *in vivo*.

### **Biocompatible scaffolds for sustained priming**

In the previous section, NPs targeting tumour tissues to prime anti-cancer immunity were reviewed. NPs can induce ICD and stimulate local immune responses, but delivering sufficient amounts of NPs to the tumour is technically challenging. Typically, less than 1% of NPs infused intravenously reach the tumour, whereas the majority of NPs either accumulate in other tissues, such as the liver and spleen, or are cleared in the kidney [92]. NPs can be directly injected into tumours, but intratumoural administration is only possible for a few cancers, such as skin cancer, where the tumour is directly accessible, and is not possible for the majority of tumours. One exception to this occurs during surgery to remove a tumour mass. Scaffolds that are implanted surgically into the tissue where the tumour was resected have been recently developed to prime local anti-cancer immune responses by the controlled release of immunotherapeutics (Figure 7(a)).

Surgery is the most frequently used treatment with the longest history in cancer therapy. Surgical resection of the tumour can enhance the efficacy of immunotherapy by eliminating the immunosuppressive microenvironment. However, tumour-reactive immune cells and tumour antigens are also removed, making it difficult to induce anti-tumour immune responses. Furthermore, upon surgery, the tissue undergoes a wound healing process, temporarily resulting in an

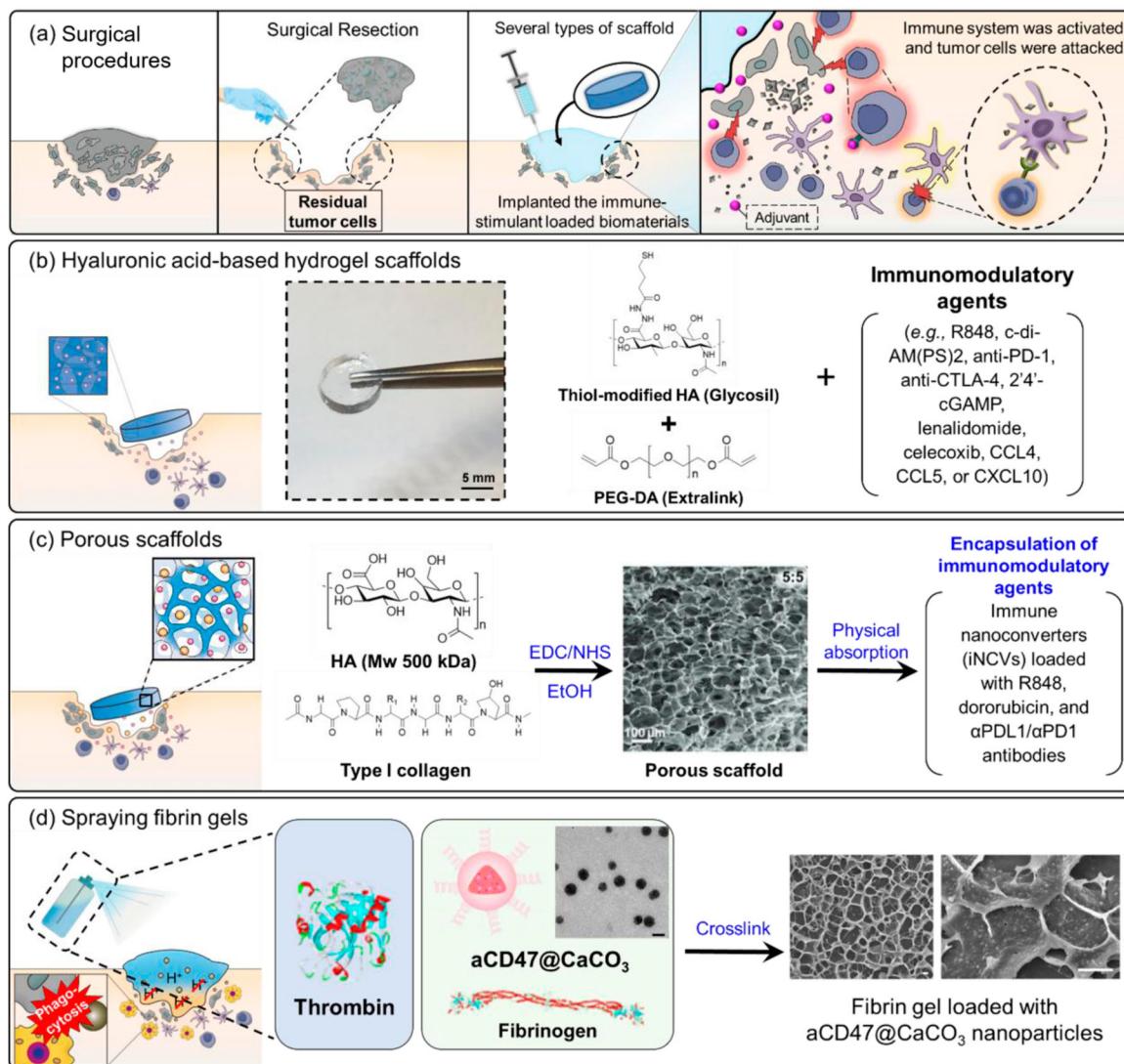
immunosuppressive local environment. Consequently, surgical removal of the tumour often causes recurrence and metastasis, which accounts for 90% of cancer deaths [93]. To address this problem, biomaterials releasing immune stimulators over a prolonged period of time are applied to the surgical site in the form of preformed scaffolds [94–96] and injectable [97,98] or sprayed [99] hydrogels.

Hyaluronic acid-based hydrogel scaffolds containing various immune stimulators were implanted into tumour-resected mouse models to identify key signals to prevent tumour recurrence and metastasis (Figure 7(b)) [94]. Implanted hydrogels that locally release agonists of TLR7/8 or STING in a sustained manner induced the best therapeutic outcomes by recruiting immune cells, including DCs and T-cells, to the surgical sites and activating them. Porous scaffolds loaded with DOX, a chemotherapeutic inducing ICD, and PLGA nanoparticles containing R848, a TLR7/8 agonist, were implanted in surgical sites and primed anti-cancer immune responses by inducing ICD, and further amplified anti-cancer immune responses by R848-mediated conversion of immunosuppressive cells to immune-stimulatory cells in the TME (Figure 7(c)) [96]. When combined with anti-PD-1 ICB, these scaffolds prevented tumour recurrence and metastasis.

Fibrin gels loaded with calcium carbonate nanoparticles containing an anti-CD47 antibody, which promotes engulfment of cancer cells by phagocytes, such as DCs and macrophages, by blocking a ‘don’t eat me’ signal [100], were formed by spraying (Figure 7(d)) [99]. Dissolution of the nanoparticles released calcium carbonate into the TME, which scavenged H<sup>+</sup> to neutralise the acidic local pH, which is immunosuppressive, and released anti-CD47 to enhance cancer cell phagocytosis and antigen presentation.

### **Biomaterials for priming anti-cancer immune responses from peripheral tissues**

The biomaterial-based strategies described in the previous chapter are mainly based on inducing ICD of cancer cells in the tumour and stimulating local immune responses. These strategies are powerful, as cancer antigens in tumours are directly used to prime immune responses, abrogating the need to identify cancer antigens. However, directly targeting the tumour is technically challenging, as tumours are mostly located in internal organs only accessible by invasive surgery, and only a fraction of NPs injected into the blood reach the tumour. In addition, priming strong immune responses in the tumour is technically challenging due to immune suppression in the TME. To overcome these limitations, strategies to prime anti-cancer immune responses in the peripheral tissues have been devised, as T-cells activated in peripheral LNs can migrate to the tumour through the bloodstream.



**Figure 7.** Postsurgical biocompatible scaffold-based strategies priming local anti-cancer immune responses. (a) HA-based/porous hydrogel scaffolds or fibrin gels were implanted or sprayed, respectively, into tumour-resected area for priming local anti-cancer immune responses. (b) HA-based hydrogel scaffolds were implanted into tumour-resected area to identify key signals inhibiting tumour recurrence and metastasis by delivering various immune stimulators. The image is reproduced with permission from [94]. (c) Porous scaffolds loaded with DOX and PLGA NPs containing R848 were implanted in postsurgical sites to prime anti-cancer immune responses by inducing ICD and R848-mediated enhancement of immune responses. The image is reproduced with permission from [96]. (d) Fibrin gels delivering calcium carbonate ( $\text{CaCO}_3$ ) NPs loaded with anti-CD47 were sprayed at tumour-resected area to trigger anti-cancer immune responses by neutralising acidic environments and enhancing cancer cell phagocytosis and antigen presentation. The images are reproduced with permission from [99].

However, these approaches, known as cancer vaccines, have shown poor therapeutic efficacy [21].

To induce ample anti-tumour immune responses, immunomodulatory compounds, including cancer antigens and adjuvants, must be effectively delivered to DCs in the peripheral tissues or draining lymphoid organs. Biomaterial-based strategies allow for controlled delivery of key signals to DCs located in either the peripheral tissue or the draining LNs, and thus can overcome the limitations of conventional cancer vaccines by maximising efficacy and minimising side effects. Similar to biomaterials targeting tumour tissues, NPs and biocompatible scaffolds that release immune modulators have been used to promote anti-cancer immune responses in the peripheral tissues.

### Nanoparticle-based cancer vaccines

DC-targeting NPs containing cancer antigens and adjuvants have been administrated in the peripheral tissues as cancer vaccines [101,102]. NPs are ideal platforms for cancer vaccines, as their physicochemical properties can be fine-tuned to optimise specific delivery to DCs, to maximise efficacy and minimise side effects (Figure 8). In addition, some NPs themselves serve as adjuvants that can further enhance anti-cancer immune responses.

NP-based cancer vaccines can either target tissue-resident DCs, which migrate to the LNs upon activation, or LN-resident DCs. NPs injected into the peripheral tissue can remain in the tissues, flow through the capillaries to enter the circulation, or drain into

the lymphatics to the reach LNs, depending on their size and surface charge [103]. Therefore, to precisely target DCs, we first need to understand the transport of NPs injected into the peripheral tissues.

NP size plays a predominant role in their transport in the peripheral tissue. NPs greater than 100 nm in size tend to become entrapped in the peripheral tissue due to their limited diffusion. Although it depends on the type of capillary and its vascular tight junction [104], NPs less than 10 nm in size are generally absorbed in the capillaries. However, NPs that are between 10 and 100 nm drain through the lymphatics because they are small enough to be transported within the interstitium but are too large to access the blood vessels [105]. Thus, NPs greater than 100 nm are typically used to target DCs in the peripheral tissues, and NPs between 10 and 100 nm in size are optimal for targeting LN-resident DCs. The surface charge of the NPs is another important factor, as the interstitium is negatively charged. Typically, positively charged NPs exhibit poorer transport through the interstitium than neutral or negatively charged NPs.

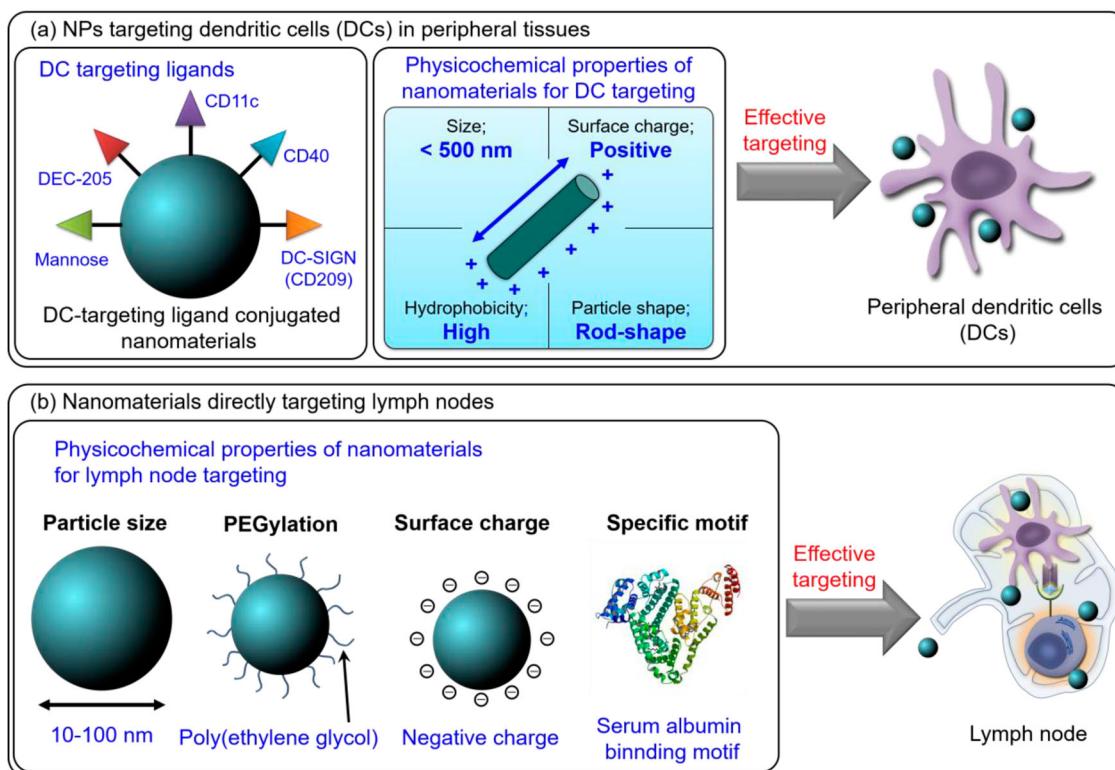
### NPs targeting the DCs in peripheral tissues

NPs that remain in the peripheral tissue can be engulfed by phagocytic cells, but only DCs can prime strong anti-cancer immune responses. The number of DCs present in the peripheral tissue is relatively low compared with other phagocytic cells, such as

macrophages, so strategies for specifically targeting DCs are important [101,106].

To deliver NPs to DCs, various receptors expressed on DCs such as mannose receptors, DEC-205, CD11c, CD40, and DC-SIGN (CD209) can be specifically targeted (Figure 8(a)) [102]. Nanomaterials have been coated with mannose or mannan to improve DC targeting [107,108]. Anti-DEC205-conjugated NPs exhibited enhanced uptake by DCs and consequently induced strong immune responses [109]. Recently, anti-DC-SIGN-conjugated porous silicon NPs were used to effectively deliver immunomodulatory agents to human DCs [110,111]. Interestingly, multiple DC-targeting ligands combined on PLGA NPs substantially enhanced immune responses by triggering activation of heterogeneous subsets of DCs [112].

In addition to attaching NPs to DC ligands, DC targeting can be enhanced by optimising the physicochemical properties of NPs, such as their size, surface properties, and shape. NPs less than 500 nm in diameter induced stronger immune response than larger NPs [113,114]. Positively charged gold NPs were engulfed by DCs more effectively than negatively charged ones [115]. Hydrophobic NPs can also trigger strong immune responses by acting as DAMPs [116,117]. Indeed, the ability of amphiphilic poly( $\gamma$ -glutamic acid)-g-L-phenylalanine nanoparticles to deliver antigen and activate DCs increased as the hydrophobicity of the side chains increased [118]. The shape of the NPs can also affect their recognition



**Figure 8.** Strategies for NP-based cancer vaccines. As cancer vaccines, NPs containing cancer antigens and adjuvants were developed to target DCs. (a) NPs were developed to target DCs in peripheral tissues by modifying DC targeting ligands or optimising physicochemical properties. (b) NPs were developed to directly target lymph nodes by optimising physicochemical properties.



and internalisation by DCs. For example, rod-shaped gold NPs displayed higher uptake by DCs than spherical NPs of the same size [119].

### **NPs directly targeting lymph nodes (LN)**

LN are the location of T-cell priming by antigens presented by DCs. DCs residing in the LN collect antigens draining through the lymphatics and present them to T-cells to prime immune responses. Therefore, LN-resident DCs are good targets for cancer immunotherapy. Generally, nanoparticles with a size of 10–100 nm and a neutral or anionic surface charge drain to the LN when they are injected into peripheral tissues (Figure 8(b)) [103]. PEGylation of nanomaterials can further enhance LN targeting by minimising nanoparticle-ECM interactions, as has been shown with poly(methacrylic acid) (PMA) NPs [120]. However, PEGylation may reduce the retention of NPs in the LN and prevent NP engulfment by DCs [121]. PEG-phosphoethanolamine (PEG-PE) and PEG-polyethylenimine-stearic acid (PSA) conjugates formed polymer hybrid micelles through hydrophobicity and electrostatic interactions, which were delivered to LN to induce strong anti-tumour responses [122]. In addition to using nanomaterials with controlled sizes and surfaces, NPs can be designed to ‘hitchhike’ with proteins in the peripheral tissue that drain to the LN, such as albumin, to target LN-resident DCs [123].

### **Biocompatible scaffolds for recruiting and educating DCs**

As mentioned in the previous section, priming strong anti-cancer immune responses by targeting DCs in the peripheral tissues is technically challenging because the number of DCs in the peripheral tissue is low compared with the number of macrophages. Therefore, macroscopic scaffolds that recruit DCs, and deliver cancer antigens and DC activation signals are an attractive strategy because the number of activated DCs can be maximised (Figure 9(a)) [124]. David Mooney pioneered this idea by adapting scaffolds developed for tissue regeneration [125,126]. Porous scaffolds implanted in peripheral tissues attracted and educated DCs to promote anti-cancer immune responses by other immune cells. Various scaffolds that release DC-attracting molecules, cancer antigens, and immune adjuvants have been developed.

### **Polymeric scaffolds**

Porous PLGA scaffolds, which are similar in shape to those used in conventional tissue engineering, have been designed to contain cancer antigens, CpG ODN, and GM-CSF (Figure 9(b)) [125]. GM-CSF released from the scaffolds induced the recruitment of DCs into the scaffolds. DCs in the scaffolds that take up cancer antigens become activated by CPG ODN and

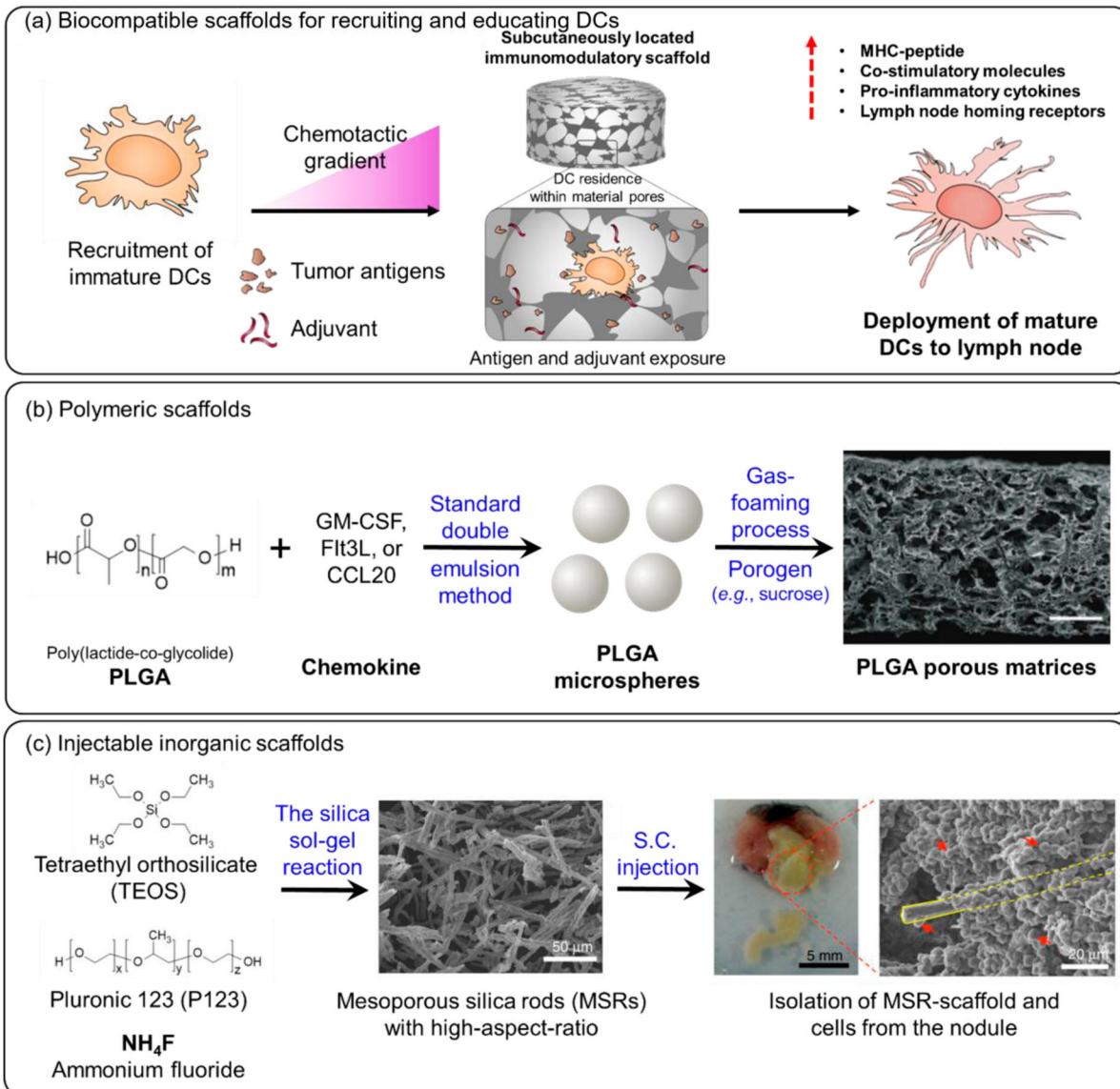
migrate to LN. A PLGA scaffold-based cancer vaccine implanted in tumour-bearing mice primed strong anti-cancer immune responses and improved the survival of the mice by 50% compared with the control groups. Polymeric scaffolds are versatile platforms that can be designed to incorporate multiple bioactive compounds and release them in a controlled manner by selecting the type and molecular weight of the polymer constituting the scaffold. They can thus be optimised for the delivery of different types of cancer antigens, DC-recruiting factors, and adjuvants. For example, DC-recruiting chemokines other than GM-CSF, such as CC-chemokine ligand 20 (CCL20) and FMS-related tyrosine kinase 3 ligand (FLT3L), have also been incorporated into this type of scaffold [126]. In addition, various types of cancer antigens, including peptide neoantigens and cancer cell lysates, can be loaded onto the scaffold to treat various types of cancer. This technology is currently being evaluated in clinical trials in the United States (NCT01753089) and has been licensed to Novartis.

### **Injectable inorganic scaffolds**

The biocompatible polymeric scaffolds described in the previous section are invasive because surgery is required for implantation. To avoid the need for surgical implantation of polymer scaffolds, injectable scaffolds have recently been developed (Figure 9(c)) [127]. MSRs with high aspect ratios are ideal for this application because cancer antigens and adjuvants can be loaded within their porous structures, and they can self-assemble into macroscopic porous scaffolds upon injection to provide space for DC entry. Indeed, mesoporous silica has been widely used for drug delivery due to its biocompatibility, high pore volume, and large surface area [128–130]. Upon injection into the peripheral tissues of tumour-bearing mice, the porous silica rods formed scaffolds releasing GM-CSF to recruit DCs, and delivered CpG ODN and cancer antigens to DCs within the scaffolds, resulting in strong anti-cancer immune responses and improved survival in a mouse model of lymphoma. The anti-cancer immune responses induced by the MSR scaffolds were further enhanced by coating the scaffolds with the cationic polymer polyethylenimine (PEI), which functions as an adjuvant to trigger pro-inflammatory cytokine secretion, resulting in the eradication of large established tumours [131]. Injectable hydrogels, such as sponge-like macroporous cryogels [132–134], are also used for peripheral vaccination.

### **Conclusions and future perspectives**

Various biomaterial-based strategies for priming anti-cancer immune responses developed over the last decade were extensively reviewed with an emphasis on the



**Figure 9.** Scaffold-based strategies recruiting and educating DCs for anti-cancer immune responses. (a) Biocompatible scaffolds were developed to recruit and educate DCs by releasing DC attracting molecules and cancer antigens/immune adjuvants, respectively. The images are reproduced with permission from [124]. (b) PLGA-based porous scaffolds that were formed by gas-foaming or porogen leaching processes were developed to recruit and activate DCs by delivering DC recruiting factors. The image is reproduced with permission from [138]. (c) Mesoporous silica rods (MSRs)-based scaffolds that were formed after injection into peripheral tissues were developed to recruit and activate DCs by delivering DC recruiting factors, cancer antigens and immune adjuvants. The images are reproduced with permission from [127].

principles underlying their design. Overall, biomaterials have been successfully used to induce anti-cancer immune responses in preclinical models, mostly in mice, by allowing controlled delivery of various immunostimulatory molecules. Translating the therapeutic strategies that have been successful in mice to human patients is currently under way. Biomaterials must be approved for use in humans by regulatory agencies such as the Federal Drug Administration (FDA); thus using biomaterials approved by FDA for other clinical applications may be a good strategy to facilitate clinical translation.

Priming anti-cancer immune responses is necessary, but not sufficient, to cure cancer, as many other steps in the cancer-immunity cycle may inhibit anti-cancer

immune responses. Therefore, combining the biomaterial-based strategies for priming immune responses with other strategies, including ICBs as described in a number of examples in this review, is likely to enhance their therapeutic efficacy. Personalised combination strategies would be desirable as each cancer patient exhibit distinct cancer-immune set point, or immunological status of anti-cancer immunity [135]. In addition, personalised cancer antigens can be used for each patient to maximise anti-cancer immune responses with the advancement of neoantigen prediction technology [136,137]. Biomaterials could play a critical role in personalised combination immunotherapy, as the location and timing of delivery are key factors for combining different types of therapeutics.



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