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Review article

Biomaterials for vaccine-based cancer immunotherapy

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ABSTRACT

The development of therapeutic cancer vaccines as a means to generate immune reactivity against tumors has been explored since the early discovery of tumor-specific antigens by Georg Klein in the 1960s. However, challenges including weak immunogenicity, systemic toxicity, and off-target effects of cancer vaccines remain as barriers to their broad clinical translation. Advances in the design and implementation of biomaterials are now enabling enhanced efficacy and reduced toxicity of cancer vaccines by controlling the presentation and release of vaccine components to immune cells and their microenvironment. Here, we discuss the rational design and clinical status of several classes of cancer vaccines (including DNA, mRNA, peptide/protein, and cell-based vaccines) along with novel biomaterial-based delivery technologies that improve their safety and efficacy. Further, strategies for designing new platforms for personalized cancer vaccines are also considered.

1. Introduction

Vaccines have made tremendous contributions to global health, having led to the elimination of small pox and near eradication of polio and diphtheria [2,3]. While these traditional, whole-pathogen based vaccines against infectious diseases have mostly proven successful, therapeutic cancer vaccines have achieved mixed clinical outcomes [4]. This is likely due to a number of factors, including biological barriers to vaccine delivery [5,6], inherently low tumor antigen immunogenicity [7,8], and the immunosuppressive tumor microenvironment [7,9]. For a cancer vaccine to be effective, numerous requirements must be satisfied in order to induce the desired immune response illustrated in Fig. 1. First, antigens need to be delivered to antigen presenting cells (APCs), including dendritic cells (DCs) but also macrophages, neutrophils, and lymphatic endothelial cells to a lesser extent [10,11]. Subsequently, APCs must process and cross-present tumor antigens to become mature and activate T cells (naïve $CD4^+$ T cells and $CD8^+$ T cells) that reside in lymph nodes (LNs) [12]. Lastly, activated T helper cells (Th cells) and cytotoxic T lymphocytes (CTLs) need to infiltrate the tumor site to shift the immunosuppressive tumor microenvironment towards a pro-inflammatory environment [13,14]. This altered microenvironment aids CTLs in killing tumor cells and is accompanied by other mechanisms for tumor cell killing (e.g. natural killer cell-mediated killing and antibody-dependent cell-mediated cytotoxicity) [13,14]. While this approach to treating tumors holds considerable promise, only one cancer vaccine formulation to date has been approved by the US Food and Drug Administration (FDA) over several decades of investigation [15]. This is due, in part, to inefficient delivery *in vivo* where administered vaccines cannot successfully reach their desired targets [16–19]. Therefore, immunologists, engineers, and clinicians, in recent years, have focused significant efforts towards developing new delivery materials for therapeutic cancer vaccines [18].

Recently, there has been exponential growth in research at the interface of biomaterial science, drug delivery, and cancer vaccines [20–34]. Various delivery approaches, such as nanoparticles [35], microparticles [36], self-assembled materials [37,38], and biomaterial scaffolds [39] have been widely utilized in combination with various forms of cancer vaccines (*e.g.* DNA, mRNA, peptide/protein, and cell-based vaccines), and their preclinical outcomes are promising. Researchers have demonstrated that biomaterial-based cancer vaccines have many key advantages over conventional vaccines [21,39]. Most notably, biomaterial-based cancer vaccines can be delivered to the body in a controlled manner, where finely tuning vaccine physical properties (*e.g.* size, shape, charge, or porosity) and targeting moieties can achieve selective delivery to target cells and tissues with desirable drug release kinetics [40–48]. In this review article, we introduce classes of vaccines and their clinical status (Table 1), highlight the advances made at the interface of biomaterials science and cancer vaccination, summarize key biomaterials design criteria to effectively present and deliver cancer vaccines, and provide our insights into the future directions of cancer vaccine development.

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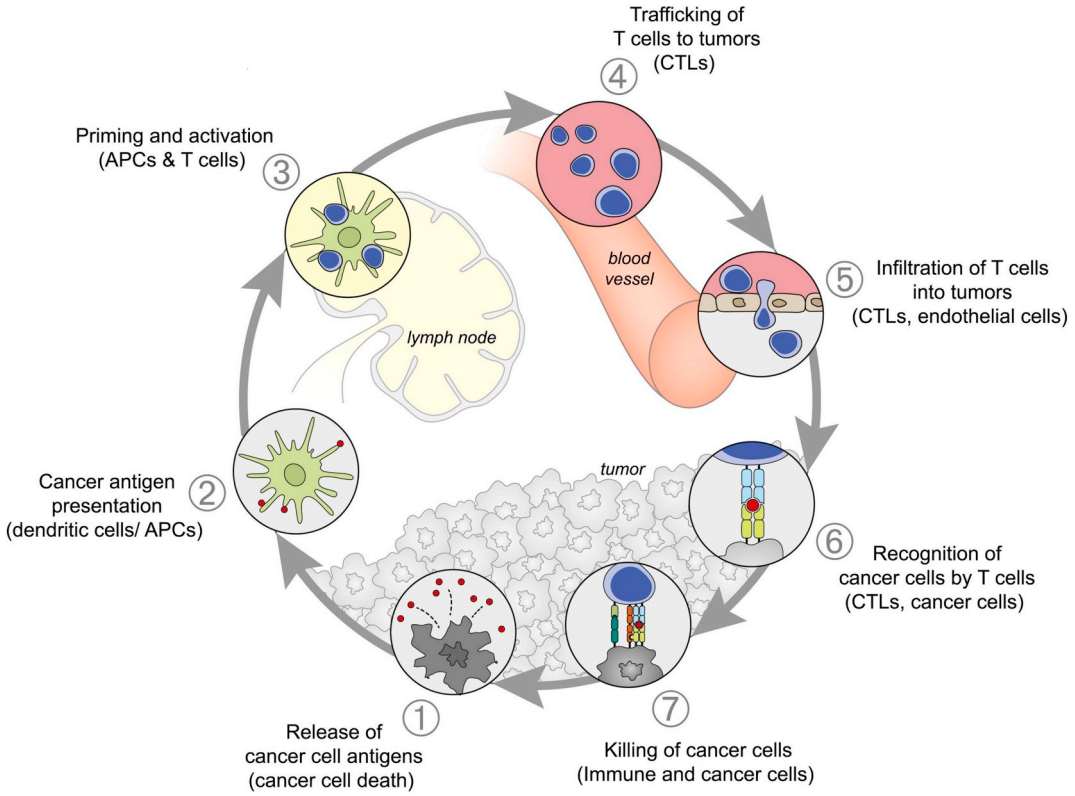

Fig. 1. Schematic of the cancer-immunity cycle, illustrating the immune response to a tumor. Successful biomaterials-based vaccine delivery technologies could enhance tumor antigen presentation and immune reactivity against tumors. Adapted from [1]. Reprint with permission from Cell Press.

2. Classes of cancer vaccines and their clinical status

2.1. DNA vaccines

Early DNA vaccines were developed in the 1990s [49], when researchers found that plasmid DNA can induce potent antibody responses against an encoded antigen [49–51]. The design simplicity and promising preclinical studies quickly sparked an interest in developing DNA vaccines for a variety of infectious diseases [52,53]. Consequently, utilizing DNA vaccines to treat cancer has become an attractive strategy in cancer immunotherapy [54]. When DNA contains unmethylated, repeating cytosine-guanine (CpG) motifs, they cause adjuvant effects that stimulate the innate immune system [55]. Thus, plasmid DNA can be designed to act as both antigen and adjuvant [56]. However, the large size and negatively charged backbone of naked DNA typically results in low cellular uptake and transfection in target cells, as well as off-target delivery [57–60]. Therefore, significant efforts have focused on developing methods to effectively deliver plasmid DNA into APCs. One commonly used strategy to enhance DNA uptake is electroporation (EP), which temporarily permeabilizes cell membranes with an electric pulse [61,62]. EP has been shown to increase antigen delivery by 100-1,000 fold compared to naked DNA vaccines alone [63]. EP also has adjuvant-like properties, as it can induce moderate tissue injury and generate pro-inflammatory cytokines, which can recruit APCs to the injection site [64]. Another delivery strategy is gene gun-mediated vaccination, where APCs are bombarded with plasmid DNA coated with heavy metals (*e.g.* gold particles) at the injection site, which decreases the required plasmid DNA dose by 100-1,000 fold [65,66]. Although several strategies have been explored to improve the delivery of DNA vaccines, most still possess low immunogenicity profiles in human trials for reasons not yet fully understood [58,67]. As such, few DNA vaccines have advanced beyond phase I or phase II clinical trials [68].

While low efficacy remains a significant challenge, benefits including the versatility, stability, scalability, and inexpensive manufacturing of DNA vaccines have led to their further development and investigation [68]. Because DNA vaccines have been extensively explored, their safety is largely accepted, which has allowed a number of clinical trials to combine phase I and phase II stages to focus on evaluating efficacy over toxicity [69]. Though the first DNA vaccine for cancer (ONCEPT®) was approved in 2010 by the United States Department of Agriculture for canine melanoma based off of data from nonrandomized clinical trials, similar success has not been found when targeting human cancers [68,70]. DNA vaccine phase I and II clinical trials have been conducted for numerous cancers including melanoma [71], prostate [68], lymphoma [72], and cervical [73,74], but most cases have shown little clinical efficacy [39,69,74]. Given that the most common side effects of the vaccines include fever, pain, and redness or swelling of the injection sites rather than more severe consequences like systemic toxicity, a major hurdle in clinical trials is therapeutic efficacy rather than toxicity [68,69]. The aforementioned methods of EP and gene gun-mediated vaccination have been implemented in clinical trials in an attempt to increase therapeutic effects, and both have shown promise. EP has been used in nearly half of the current DNA vaccine clinical trials, and has shown an ability to increase the immunological response induced by DNA vaccines for treating prostate cancer and melanoma [75]. Additionally, promising preclinical data has led to phase I and II clinical trials for gene gun-mediated vaccination in head and neck squamous cell carcinoma and cervical cancer [73]. Thus, continued improvement of EP and gene gun-mediated vaccination strategies, or the investigation of biomaterial-based delivery systems [75–77] and DNA sequence optimization [75,78], is necessary to enhance the efficacy of DNA vaccination.

2.2. mRNA vaccines

mRNA vaccines are another promising alternative to conventional vaccine approaches, as they are a non-infectious, non-integrating platform with high potency and the potential for low-cost, rapid

Table 1
Different types of cancer vaccines in clinical development.

Type of vaccine	Cancer	Design	Biomaterial delivered	Delivery strategy	Trial number (phase)
DNA vaccine	Melanoma	Plasmid DNA encoding gp100	Naked plasmids or gold particles	Intramuscular injection or epidermal application of powder (with device)	NCT00398073 (Phase 1)
		*Plasmid encoding tyrosinase 207-216, 1-17	Naked plasmids	Intranodal by pump at varying concentrations	NCT00023647 (Phase 1)
	Metastatic breast	Plasmid DNA encoding mammaglobin-A	Naked plasmids	Intramuscular injection with jet delivery device	NCT00807781 (Phase 1)
	Breast/ovarian	Plasmid-based DNA encoding HER-2/neu protein + GM-CSF	Naked DNA	Not specified	NCT00436254 (Phase 1)
	Ovarian	DNA encoding HPV E7 antigen	Naked DNA	Intradermal gene gun, intramuscular, intralesional injection	NCT00988559 (Phase 1)
	Prostate	*DNA encoding PAP + GM-CSF	Naked DNA	Intradermal injection	NCT00849121 (Phase 2)
	Merkel cell	Plasmid DNA encoding intratumoral IL-2 gene	Naked plasmid	Intratumoral injection with electroporation	NCT01440816 (Phase 2)
	Cervical	*Plasmid DNA encoding Sig and HSP70	Naked plasmid	Intramuscular injection	NCT00121173 (Phase 1/2)
	Lympohoma- B-cell	*Plasmid DNA encoding CD20	Naked plasmid	Intramuscular injection	NCT00561756 (Phase 1)
mRNA vaccine	Melanoma	*Melanoma associated antigen mRNA	Naked mRNA	Intranodal injection	NCT01684241 (Phase 1)
		4 different mRNA drugs to induce T cell response	mRNA in liposomes (Lipo-MERIT)	Intraveneous injection	NCT02410733 (Phase 1)
		mRNA for melanoma associated tumor antigen + GM-CSF	naked mRNA	Subcutaneous injection	NCT00204516 (Phase 1/2)
		Melanoma associated tumor antigen mRNA + GM-CSF	Protamine-stabilized mRNA	Intradermal injection	NCT00204607 (Phase 1/2)
	Breast	*Breast cancer associated tumor antigen mRNA	mRNA in liposomes	Not specified	NCT02316457 (Phase 1)
	Prostate	*RNActive (self-adjuvanting mRNA)	Naked and protamine-stabilized mRNA	Intradermal injection	NCT00831467 (Phase 1/2)
	Non-small cell lung	*6 RNAactive (self-adjuvanting mRNA) components	Naked mRNA complex	Intradermal injection and radiation	NCT01915524 (Phase 1)
Peptide/protein vaccine	Ovarian/tubal/peritoneal	*12 different tumor-rejection peptides known to be presented on ovarian cells	Naked peptide	Intradermal/subcutaneous injection	NCT00437502 (Phase 1)
	Any malignant tumor	NY-ESO-1 protein + CpG + montanide	Naked protein	Intradermal injection	NCT00299728 (Phase 1)
	Esophageal, stomach, breast, etc	CHP-HER2/ CHP-NY-ESO-1 protein + adjuvant OK-432	Naked proteins	Subcutaneous injection	NCT00291473 (Phase 1)
	Multiple myeloma	MAGE-A3/NY-ESO-1 peptide	Naked peptides	Subcutaneous injection	NCT00090493 (Phase 2/3)
	Melanoma	Melanoma associated tumor antigen peptide + GM-CSF	Naked peptides	Subcutaneous injection	NCT01989572 (Phase 3)
		gp100 Peptide + anti-CTLA4	Naked peptides	Intradermal injection intravenous infusion	NCT00094653 (Phase 3)
		*6 Melanoma "helper" peptides + GM-CSF	Naked peptides	Not specified	NCT00089219 (Phase 1/2)
	Colon adenoma	*MUC1 TAA peptide + adjuvant Poly ICLC	Naked peptide	Subcutaneous injection	NCT00773097 (Phase 2)
Dendritic cell vaccine	Multiple myeloma	Plasmacytoma cells and DCs from patient injected with GM-CSF	Mixed cells	Intradermal injection	NCT00459069 (Phase 1)
	Metastatic breast	Tumor blood vessel antigen pulsed DCs injected after chemotherapy	Modified cells	Intravenous infusion	NCT02479230 (Phase 1)
	Prostate	DCs pulsed with tumor lysates expressing cancer/testis antigen	Modified cells	Not specified	NCT01883518 (Phase 1/2)
	Renal cell	*DCs electroporated with RNA	Modified cells	Intradermal injection	NCT01582672 (Phase 3)
	Lung	DCs pulsed with lung cancer cells	Modified cells	Intradermal injection	NCT00103116 (Phase 2)
	Lymphoma	DCs pulsed with lymphoma cell lysate + IL-2	Modified cells	Not specified	NCT00006434 (Phase 3)
Tumor cell vaccine	Pulmonary metastases of melanoma	*Hapten dinitrofluorobenzene modified cancer cells	DNP-modified cells	Intradermal injection	NCT00298298 (Phase 1/2)
	Ovarian	*Ovarian tumor cells modified with bi-shRNA	Modified cells	Intradermal injection	NCT01867086 (Phase 2)
	Kidney	B7-1 gene-modified cancer cells + IL-2	Modified cells	Subcutaneous injection	NCT00031564 (Phase 2)
	Melanoma	Iradiated melonama cells + Bacillus Calmette Guérin + GM-CSF + IFN-a2b	Modified and dead cells	Subcutaneous injection	NCT01729663 (Phase 2/3)
		Genetically modified melonoma cells expressing HLA A2/4-1BB ligand	Modified cells	Not specified	NCT01861938 (Phase 2/3)
	Colon	Radiated but live colorectal cancer cells	Modified cells	Intradermal injection	NCT02448173 (Phase 3)

* Denotes examples mentioned in the text.

manufacturing. Early work on mRNA cancer vaccines was reported in the 1990s, shortly after the discovery of DNA cancer vaccines [79]. A major advantage of mRNA over DNA vaccines is that mRNA does not need to cross the nuclear barrier to induce protein expression [80]. By not needing to cross this additional biological barrier, mRNA can be transfected more efficiently than plasmid DNA, especially for slowly dividing cells [81]. Currently, two types of mRNA are commonly utilized in vaccines: non-replicating and self-amplifying [82]. While self-amplifying mRNA is commonly used in prophylactic vaccines for infectious diseases [83–87], most mRNA cancer vaccines use non-replicating mRNA [88–92]. One of the most explored topics in non-replicating mRNA vaccines is sequence modification, as the innate immune system can sense unmodified mRNA and induce a robust type 1 interferon response, which reduces mRNA transfection efficacy [89]. Thus, several modifications—such as using 5' caps, optimized 5' and 3' untranslated regions (UTRs), poly(A) tail additions, and the incorporation of pseudouridine sequences—have been utilized to increase mRNA stability. These modifications can also reduce immune sensing by toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and protein kinase RNA-activated receptors (PKR)[93–96]. Additional studies also demonstrated that removing double-stranded RNA (dsRNA) contaminants from mRNA vaccines is essential for improving their therapeutic effect, as dsRNA is a potent pathogen-associated molecular pattern that significantly suppresses mRNA translation [89,97–99]. While immune sensing is detrimental to mRNA transfection, it also provides a danger signal to the host which plays an important role in improving vaccine efficacy [100]. Therefore, an important step in the development of mRNA vaccines is finding the appropriate level of immune sensing that will maximize its danger signaling while minimizing its impact on mRNA transfection [82]. Another critical step in the improvement of mRNA vaccines is addressing delivery challenges similar to those faced with DNA vaccines. Beyond conventional EP and gene gun-mediated vaccination approaches, a variety of biomaterial-based delivery systems such as liposomes and polymeric nanoparticles have been extensively studied, and the preclinical outcomes are promising [101–103].

More recently, lipid nanoparticles (LNPs) have emerged as a promising delivery platform for mRNA vaccines, built off of recent success in delivering siRNAs *in vivo* and the recent FDA approval of the siRNA LNP Onpattro (patisiran) by Alnylam Pharmaceuticals [104–108]. Though LNP-based mRNA vaccines are in early stages of development, they have shown great promise for treating multiple types of cancer [80,90,92,109], as well as Zika, Ebola, and influenza [110–113]. The success of LNP delivery platforms in cancer vaccines, such as those for breast cancer [82], is likely due to their ability to increase mRNA cargo retention time *in vivo* [109] and enhance mRNA intracellular delivery [114]. Drawbacks to LNPs include their accumulation in off-target organs such as the liver, and some instances of allergic reactions in human patients [82,109]. As with DNA, mRNA vaccine efficacy is highly variable between animal models and human clinical trials, as the method of mRNA uptake into the cytoplasm depends heavily on cell type [82]. Thus, while LNPs have achieved promising preclinical results and have demonstrated some translatability into clinical settings, approaches to improve efficacy in human trials are being investigated [82]. One major development is RNActive (first developed by CureVac)—a self-adjuvanted mRNA vaccine that includes both free mRNA and mRNA strands complexed with cationic protamine [115,116]. In phase I trials for stage IV non-small cell lung cancer and phase I/II trials for prostate cancer, RNActive has elicited favorable immune responses and extended patient survival [115,116]. With multiple modification methods to improve mRNA preparation, delivery, and overall efficacy, future work must explore how these techniques can be combined to enhance mRNA cancer vaccination.

2.3. Peptide and protein vaccines

Peptide- and protein-based cancer vaccines employ either fragments of proteins or whole proteins that are specifically expressed on tumor cells as antigen sources [117]. Peptide vaccines are typically chemically synthesized due to their short length, which is both time- and cost-effective [118]. In contrast, protein vaccines are typically obtained through more complex recombinant protein expression approaches [119]. An advantage of both peptide and protein vaccines is their high level of safety, which has been shown in many preclinical and clinical studies [118–120]. However, one major drawback of peptide and protein vaccines is that they usually only target one or few epitopes of tumor-associated antigens (TAA)[121]. Because it is generally believed that multivalent antigen-specific CTL responses are necessary for cancer vaccination, a mixture of multiple antigens (peptides or proteins) is required to achieve desirable effects [121–123]. Additionally, while peptides and proteins are structurally different than DNA and mRNA, delivery vehicles are still necessary to enhance vaccine stability and targeting and reduce off-target effects [124–127].

In clinical trials, a number of the aforementioned limitations for peptide-based vaccines remain. Most clinical trials in progress rely on TAA-derived short peptides, with few investigating liposome-based delivery or longer peptide formulations [128]. Many of these vaccines fail when they reach phase III trials due to a lack of optimization of peptide formulation, vaccination schedule, peptide combination, or adjuvant selection [39]. However, early clinical trials have produced promising results. A vaccine based on the TAA mucin MUC1 for treating colon cancer was highly immunogenic in half the trial's 39 individuals and was able to elicit a long-term antitumor memory, which is important for cancer prevention [129]. Similarly, two phase I/II trials illustrated that administering peptide vaccines for melanoma and ovarian cancer—which used a combination of 6 and 12 peptides, respectively—led to an increase in overall patient survival [130,131]. Though these promising early-stage results encourage the further investigation of peptide vaccines, most of the vaccines that induce an immune response do not provide enough of a clinical benefit to be used alone [128]. Thus, further optimization of vaccines – along with the development of combination therapies – is needed.

2.4. Dendritic Cell (DC) vaccines

The major target cell type for the previously described vaccines are DCs, which are essential for initiating antitumor immunity [132]. Thus, engineering DCs *ex vivo* could be more effective than administrating vaccines *in vivo*, where only a small portion of vaccines reach DCs. DC vaccines, consisting of *ex vivo* engineered DCs, are prepared by isolating DCs from patient blood, treating them with adjuvants (e.g. TLR agonists or cytokines) to trigger DC maturation, and loading them with TAAs [133,134]. DCs are then injected back to the patient, where they migrate to the LN and prime naïve $CD8^+$ T cells to initiate antitumor immunity [134,135]. A major advantage of DC vaccines is that the DCs are treated *ex vivo*, so there is less concern over off-target effects compared to other approaches that require vaccine components to be administered directly into patients [135]. However, challenges of DC vaccine development include the complexity and substantial cost of cell biomanufacturing processes and the batch-to-batch variability between vaccines for individual patients [136]. Although the first DC-based cancer vaccine, Sipuleucel-T (Provenge), was approved by the FDA for the treatment of prostate cancer in 2010 [15], their commercialization is limited to few countries in part due to the high cost of treatment and the strict manufacturing requirements for vaccine production facilities [137].

Because DC vaccine production methods and the resulting composition vary greatly, it is difficult to compare clinical trials or generalize their outcomes. While success has been found with Sipuleucel-T and promising preliminary data emerges from phase I/II clinical trials [138], there have been a number of notable failures. Argos Therapeutics has had to halt their phase III clinical trial of a DC vaccine for renal cell carcinoma in response to the poor interim evaluation of the patients, which conflicts with promising results from earlier trials [139]. Similarly, phase III clinical trial results for a DC vaccine against

melanoma showed no significant impact on patient survival or markers of recovery [138,140]. The failures of these studies however, could be due to the complex process of obtaining, maturing, and treating DCs. Because DCs can be loaded with antigens (*e.g.* DNA, mRNA, peptide, protein, and tumor lysate), or fused with live cancerous cells to generate hybrid cells, there has yet to be a unified, perfected procedure for handling these cells [138]. Thus, a major focus in DC vaccine development is the optimization of *ex vivo* DC protocols [39].

2.5. Tumor cell vaccines

Another approach for designing cancer vaccines is utilizing TAAs from isolated tumor cells that have been either resected from patients (autologous tumor cells) or lab-grown (allogeneic tumor cells) as antigen sources [141–143]. Because live tumor cells can produce immune-suppressive cytokines and potentially form new tumors in the body, they must be inactivated before vaccination [144]. The freeze-thaw method is one of the most commonly used strategies for killing tumor cells and obtaining TAAs [142]. The repeated freezing and thawing of tumor cells induces necrotic cell death and releases cellular compartments that contain TAAs [142,145,146]. Tumor cell debris and TAAs are then separated by centrifugation, and TAAs are collected from the supernatant [147–149]. Another commonly used method to trigger tumor cell death is irradiation, which induces apoptosis [142]. Unlike obtaining soluble tumor lysate antigens using the freeze-thaw method, irradiation is milder and allows for whole tumor cells to be obtained [142]. Both methods are commonly used to obtain TAAs, and many strategies have streamlined the loading of TAAs into biomaterial delivery platforms such as nanoparticles or scaffolds [147–149]. One major advantage of utilizing tumor cells as antigen sources is that, since there is an array of mutated tumor antigens presented on tumor cells, they can generate synergistic immune responses against multiple tumor antigens, reducing the risk of tumor escape [144]. Additionally, if the tumor cells are autologous, antitumor immunity can potentially be individualized, which is considered more immunogenic than using universal tumor antigens [150]. Despite these advantages, drawbacks to using tumor cells also exist. For autologous tumor cells, similar to DC vaccines, the commercialization process can be challenging due to the high cost and strict requirements of production [150]. By contrast, allogeneic tumor cell vaccines—though they can be produced at a lower cost and faster pace [150]—may not contain patient-specific antigens, making them less effective [143,151].

As with DC vaccines, tumor cell vaccines vary widely in preparation and *ex vivo* treatment, making clinical trials very challenging to directly compare or generalize [126]. However, highly individualized vaccines have had a number of notable successes [7]. The GVAX vaccine—an allogeneic prostate tumor cell line that has been modified to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF)—has had successful phase I and II trials that were able to increase the mean survival of patients with prostate cancer [152]. The results have led to GVAX being investigated for a range of cancer types in phase I clinical trials [142]. Similarly, the FANG vaccine—a whole tumor cell vaccine with plasmid DNA as well as RNA incorporated into it—showed promising phase I results when used to treat ovarian, breast, colorectal, and small cell lung cancer and has progressed into a phase II trial for treating melanoma, ovarian cancer, and colorectal carcinoma [153]. While these vaccines tend to have varying efficacy based on individual patients and cancer types, they may also provide insight into future optimization [142]. For example, a phase II clinical trial on the regression of pulmonary metastases in patients with melanoma reported antitumor responses in only 11 of the 83 evaluable patients [154]. However, the study was able to correlate small volume lung metastases with an increased likelihood of responding the vaccine [154].

3. Bridging biomaterials and cancer vaccines

As discussed in the previous section, a considerable number of cancer vaccine trials have resulted in mixed outcomes, in part due to a lack of effective delivery methods [155]. Peptide cancer vaccines provide a prime example, as the overall clinical response rate of patients vaccinated with unmodified and naked peptides is roughly 3%[156]. However, if a patient's DCs are isolated, treated with peptides *ex vivo*, and infused back into the patient, an improved clinical response rate is observed [157]. This difference in patient response suggests that naked peptides have difficulty reaching DCs *in vivo*, which may be one reason for their low efficacy in the absence of a DC delivery platform [157]. Therefore, biomaterials are needed to help overcome the biological barriers to vaccine delivery *in vivo* [158]. Because of the diversity in cancer vaccination approaches, multiple classes of biomaterials are needed to overcome the various obstacles to delivery. Thus, biomaterials used in cancer vaccines range from the nanoscale (e.g. liposomal and polymeric nanoparticles) to larger implantable or injectable synthetic scaffolds [159,160].

3.1. Nanoparticle-based delivery systems

Nanoparticle-based cancer vaccines refer to a range of delivery systems—including liposomes, polymeric nanoparticles, self-assembled nanoparticles, and lipid nanoparticles [18]. Using nanoparticles as carriers for vaccine can enhance delivery to certain organs or tissues such as the lymph nodes, spleen, or solid tumors [18]. Liposomes are one of the first studied nanoparticles for cancer vaccination [161], with some formulations featured in ongoing clinical trials (Table 1). Liposomes are an attractive option for rapid clinical translation, as multiple formulations are FDA-approved and can enhance delivery compared to free drug administration [162]. However- depending on the formulation and the delivery cargo – early generation liposomes can have disadvantages including low loading capacity and toxicity [163–165]. Another type of widely studied and FDA-approved nanoparticle-based drug carrier are polymeric poly(lactic-co-glycolic) acid (PLGA) nanoparticles [166,167]. An advantage of using PLGA nanoparticles is that they can be accurately and consistently generated using well-established protocols that create a wide range of particle sizes [168]. However, a disadvantage of PLGA nanoparticles is their low therapeutic cargo encapsulation rates [166,167]. One notable difference between liposomes and PLGA nanoparticles that affects their use as delivery systems is the characteristics of the therapeutic cargo they encapsulate [169]. Liposomes contain both a hydrophilic core and a hydrophobic bilayer that make them suitable for carrying hydrophobic and hydrophilic compounds [169]. PLGA nanoparticles have been used to encapsulate a range of therapeutic cargo at varying rates and are particularly well suited for the encapsulation and delivery of lipophilic cargo compared to liposomes [410–412].

To overcome the obstacles faced by these delivery systems, significant efforts have focused on chemically modifying liposomal or PLGA nanoparticle formulations in order to improve stability and cargo encapsulation rates [171,172]. From this work, rationally-designed classes of nanoparticles have been developed [18]. For example, self-assembled nanoparticles often have high loading capacities and have shown to successfully deliver peptides or nucleic acid-based vaccines [173–176]. LNPs, with their history of efficacious siRNA delivery, have been used extensively for mRNA vaccine delivery [82,177]. However, both self-assembled nanoparticles and LNPs are limited to specific antigen types, as their nanoparticle formulations largely rely on charge-based complexation [82,173,176]. Therefore, self-assembled nanoparticles may be more suitable for antigens with easily modified sequences (e.g. peptide) or defined charges (e.g. DNA or mRNA), while liposomes or polymeric particles may be more suitable for other antigen types (e.g. protein, tumor lysate or tumor cell)[161,178,179].

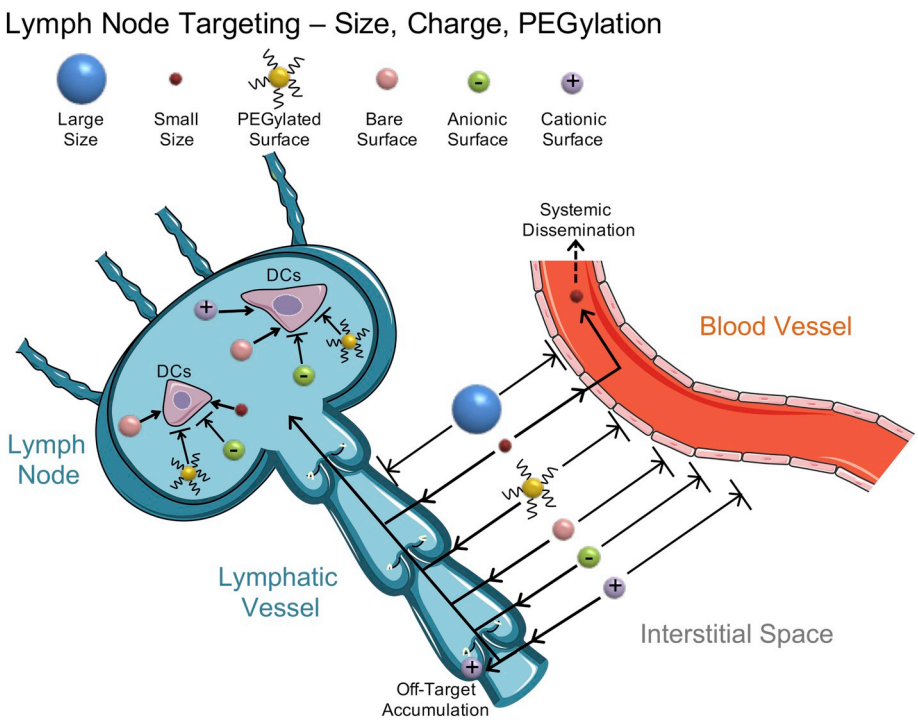

Fig. 2. The role of biomaterial biophysical properties (such as size, charge, and PEGylation) on the fate of interstitially administrated vaccines targeting LNs. Large vaccines (over 200 nm) exhibit reduced uptake in the lymphatic vessels. However, small vaccines (less than 2 nm) can easily enter blood vessels and result in systemic dissemination. Materials with high surface density PEGylation or anionic surfaces can enhance vaccine accumulation in LNs, but can also hinder their uptake by DCs. Cationic vaccines can exhibit stronger uptake by DCs, but can suffer from inefficient delivery to LNs.

3.2. Biomaterial scaffold-based delivery systems

Scaffold-based cancer vaccines refer to polymeric- and hydrogel-based scaffolds that are implanted or injected locally, to recruit and reprogram immune cells to elicit an antitumor response [18]. Due to their large size, these scaffolds are meant to remain at the implantation or injection site [18]. The scaffolds often encapsulate a variety of molecules, such as antigens and immunomodulators, that can efficiently program the peripheral tissue and facilitate immune cell infiltration (the vaccine mechanisms are more extensively discussed in Section 5) [180,181]. Commonly used scaffolds for vaccination include PLGA, alginate-based hydrogels, and mesoporous silica micro-rods (MSRs), as all three materials are degradable and highly biocompatible [182]. PLGA is FDA approved but is not injectable in scaffold form and must be implanted [149]. Alginate-based hydrogels can be processed under cryogenic conditions to form cryogels, which have strong shape-memory properties that allow them to be injected instead of implanted into patients [182]. However, cryogels require large gauge needles that can result in tissue damage at the injection site [180]. Both PLGA and cryogel scaffolds have shown great success in encapsulating tumor cell derived antigens. PLGA is more commonly used for encapsulating tumor lysate antigen, while cryogels are used to encapsulate and deliver irradiated whole tumor cells [149,181,182]. Scaffolds consisting of MSRs with high aspect ratios are perhaps the easiest to inject, as they assemble to form three-dimensional structures *in situ* after injection [181]. However, MSRs have been used to encapsulate relatively small cargo (e.g. nucleic acids, peptides, or proteins), so they may not be suitable for encapsulating whole tumor cells as antigen sources [183]. Because the scaffolds need to encapsulate, present, and release cargo while allowing for immune cell infiltration, they are often designed to have porous structures [180,181]. These pores can be adjusted to accommodate different sizes and types of cargo. For example, cryogels with larger pores are well-suited for antigens of a larger size such as whole tumor cells – as they allow for immune cell infiltration while still efficiently encapsulating large cargo [184,185]. Additionally, chemical modifications to scaffolds can enable loading and immobilization of almost all vaccine types, including nucleic acids, peptides, tumor lysates, and whole tumor cells [18,186].

Two major differences between nanoparticle- and scaffold-base cancer vaccines are the time duration that the cancer vaccine resides in a given tissue and the type of immune cell interactions they enable [182]. Nanoparticle, because of their small size, can be internalized easily by APCs in tissues or LNs shortly after interstitial immunization [6]. Scaffolds, due to their large size, interact with immune cells via encapsulated therapeutic cargo that can be released over a prolonged period of time [158]. Therefore nanoparticles often require repeated vaccination to achieve effective antitumor immunity, while scaffolds can achieve desirable antitumor responses with single or few doses [123,187]. Nevertheless, similar to other prophylactic single-dose vaccines (e.g. microparticle-based vaccines), challenges with scaffold-based vaccines could include whether encapsulated antigens or adjuvants remain stable within scaffolds after administration *in vivo* [188]. However, for antigens that are difficult to collect or processed frequently (i.e autologous tumor cell antigens), scaffolds may be more desirable, as their vaccination schedule generally requires less frequent dosing than nanoparticle-based vaccination [123].

4. Biomaterial vaccines for lymph node (LN) delivery

4.1. LN targeting

LNs and their surrounding microenvironment contain a large, diverse population of cell types (*e.g.* APCs, T cells, and lymphatic endothelial cells) that orchestrate immune responses [189,190]. Therefore, targeting LNs is a promising strategy for controlling vaccine efficacy in both prophylactic and therapeutic settings [27,191]. While intranodal injections have shown great promise in delivering vaccines to LNs [192], this technique typically requires an invasive surgical procedure [193,194]. Instead, interstitial injections (*e.g.* subcutaneous, intradermal, and intramuscular) are a more accessible route of administration and are commonly utilized for vaccination [195–197]. Though successful in preventing some diseases (*e.g.* hepatitis B, smallpox, and measles-mumps-rubella [198–200]), their broader applications have been severely limited due to pre-existing biological barriers that prevent interstitially administered vaccines from reaching LNs. In recent years, researchers have demonstrated that the physical

and chemical parameters of vaccines, such as size, charge, surface properties, and material chemistry, can dramatically alter vaccine biodistribution (Fig. 2).

Of these factors, the size of a vaccine and its delivery system are among the most studied characteristics [44,201,202]. Vaccine size is a key factor that affects biodistribution upon interstitial injection, due to the differences between blood and lymphatic vessels that reside in the interstitial space [203]. While vascular endothelial cells form tight junctions (less than 10 nm in size) around blood capillaries, lymphatic endothelial cells form discontinuous junctions (hundreds of nanometers in size) surrounding the lymphatic capillaries [16]. Additionally, blood flow rates through vascular capillaries are 100-500 times greater than lymphatic capillaries [16]. As a result, when a vaccine is less than 2 nm in size, it can cross tight junctions between vascular endothelial cells and preferentially enter blood vessels [204]. Upon entering a blood vessel, vaccines encounter many obstacles to delivery, including serum-induced instability and the mononuclear phagocyte system that rapidly clears vaccines [205]. In contrast, vaccines over 200 nm in size are excluded from directly entering lymphatic vessels via passive diffusion [206] and must rely on tissue-resident APCs for transport to LNs. Therefore, the ideal vaccine size ranges from 2 to 200 nm, which reduces blood vessel entry and systemic dissemination while enabling entry into lymphatic vessels.

In addition to size, charge is an important factor that affects vaccine trafficking and transport via APCs within LNs. Because of the negatively charged phospholipid bilayer structure of cell membranes, anionic vaccines create a repulsive force with cells that dampens cell-vaccine interactions. While surface repulsion decreases cell contact to aid vaccines transport within the lymphatic vessel [201,207], it also inhibits uptake by APCs after they reach LNs. In contrast, cationic vaccines exhibit stronger cell-vaccine interactions, but may become trapped within the interstitium or lymphatic endothelium and ultimately not reach LNs [16,201,207]. Despite their limitations, cationic nanoparticles for vaccine delivery are heavily investigated and have shown promising experimental results [208–211]. Dampening of surface charge via incorporation of polyethylene glycol (PEG) in vaccine formulations also impacts cell-vaccine interactions, which ultimately influences LN drainage [212]. PEG is also hydrophilic, and therefore PEGylated vaccines have decreased interactions with hydrophobic cell membranes [213,214] and excel at accumulating in LNs [215,216]. To increase vaccine uptake in cells of interest (*e.g.* DCs), further surface modifications, such as incorporation of cell-penetrating peptides or DC ligand targeting sequences, are worth consideration [217,218].

4.2. DC targeting

Targeting DCs *in vivo* is a promising strategy for priming naïve $CD8^+$ T cells and initiating antitumor immunity [223,224]. However, there are several challenges in delivering vaccines to DCs. First, other phagocytic cells (*e.g.* macrophages and neutrophils) compete with DCs to uptake exogenous antigens, which reduces antigen uptake by DCs [92,225]. Mature DCs also have reduced endocytic rates, which lowers their capacity to internalize and process antigens [226]. Further, many vaccines utilize PEGylated or anionic surface coatings to improve biodistribution to LNs [27,212,227], but their internalization by DCs can then be limited by steric hindrance or electrostatic repulsion between cell membranes and the PEGylated or anionic surface of the vaccine (Fig. 2) [201,228]. Therefore, once vaccines reach the LNs, additional strategies are required to enhance uptake into DCs residing in LNs. DCs can be classified into several subtypes, such as $CD8\alpha^+$ DCs, plasmacytoid DCs, and Langherans cells, based on their varying biomarker expression (e.g. CD11c, MHC-I, MHC-II, DEC-205, DC-SIGN, and CD40, comprehensively reviewed in [229]). Thus, actively targeting specific DC ligands has become an attractive approach to reduce off-target effects [230]. Among those receptors expressed on DCs, DEC-205, DC-SIGN, and CD40 have been the most successful as targeting moieties [231–234]. Antibody-functionalized vaccines allow for not only improved targeting specificity, but also the capacity to enhance antigen cross-presentation [218,235,236]. Though promising, antibody production can be time- and cost-intensive [237]. Therefore, recent work has focused on utilizing short peptide fragments, such as the WH peptide [238] and NW peptide [239], to target DC surface receptors and improve vaccine efficacy [240]. This strategy has been very successful for peptide-based vaccines, as a DC-targeting peptide can be tethered to the peptide epitope during vaccine synthesis [239,241].

4.3. Antigen and adjuvant co-localization or segregation

Advancements in the development of molecular adjuvants such as TLR agonists, have accelerated the development of cancer vaccines, as traditional adjuvants (*e.g.* alum and Freund's adjuvant) typically fail to induce potent CTL and Th1 immune responses [26,242–244]. An important discovery from the last decade is that the co-delivery of antigen and molecular adjuvants encapsulated within a biomaterial carrier tends to induce stronger immune responses than the delivery of soluble antigens and adjuvants in the absence of a carrier [245]. This concept prompted the development of various biomaterial-based vaccines, including polymeric nanoparticles [246–248], inorganic nanoparticles [176,208,249], and biomimetic nanoparticles [250–253], where antigens and adjuvants are encapsulated within a single nanoparticle platform. Additionally, recent results demonstrated that encapsulating antigens and adjuvants in separate particles induced similar or even stronger immune responses than platforms containing both antigen and adjuvant within a single nanoparticle platform [254–256] (Fig. 3A).

In the above mentioned studies, it is important to note that co-encapsulation of antigens and adjuvants into the same nanoparticles or separation into different nanoparticles does not impact the biodistribution of the cargo [254]. Both delivery strategies include nanoparticles that can be trafficked to LNs and subsequently taken up by APCs in a similar manner [254]. However, once the antigen and adjuvant reach to the same APCs, they could still need to separate as antigens and adjuvants may function in different cellular compartments [257–262]. Therefore, segregating antigens and adjuvants into separate nanoparticles allows them to be easily divided and transported to the desirable cell compartments after they both reach APCs. The importance of antigen and adjuvant segregation is further supported by recent work, where a vaccine with chemically-tethered antigens and adjuvants induced weaker immune responses than the vaccine with hydrophobically associated antigens and adjuvants [260] (Fig. 3B). Hence, while antigens and adjuvants need to be taken up by the same APC in LNs, they may not necessarily have to be encapsulated in the same particle or chemically linked together to be effective.

Chemical modifications of antigens and adjuvants are frequently utilized to induce their co-localization [208,263–266]. However, several factors need to be taken into consideration when modifying antigens and adjuvants for cancer vaccines. For instance, peptide terminus modification can affect the capacity of peptides to be cross-presented via the major histocompatibility complex I (MHC-I)[267]. Therefore, it is important to consider the effect of cross-presentation when modifying cancer epitopes (*e.g.* neoantigens), as potent antigen-specific CTL responses are a key factor for antitumor immunity. Additionally, terminus modification methods for adjuvants can greatly affect their activity—as shown by CpG, a TLR-9 agonist. As one of the most commonly used adjuvants for cancer vaccine development, it has been modified using various strategies, and experimental results demonstrated that the 5' end of CpG is critically important for interacting with its receptor, TLR-9[268]. Thus, modifications on the 3' end of CpG maintain its bioactivity, while 5' modifications diminish adjuvanticity [268–271] with limited exceptions [225,272]. Another commonly utilized adjuvant, Pam_2C, a TLR-2 agonist, has also demonstrated changes in bioactivity resulting from chemical modifications. The structure of Pam_2C includes a –COOH group that makes it easy to conjugate with peptides, but the

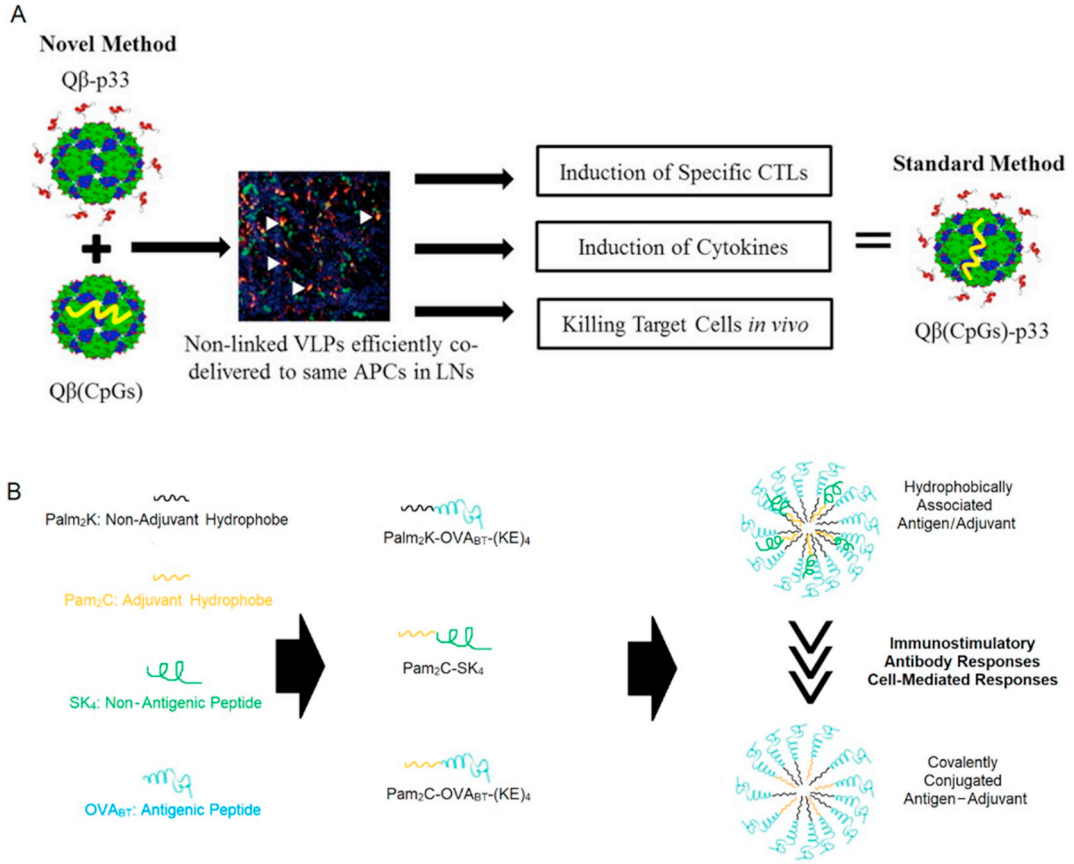

Fig. 3. Co-localizing antigen and adjuvant to the same APCs can be achieved without the need for physical (A) or chemical linkage (B). (A). Antigen and adjuvant are delivered separately by different nanoparticles but are still co-localized within the same APCs in LNs, thereby inducing similar immune responses as when antigens and adjuvants are engineered into the same nanoparticle. Adapted from [254]. (B). When antigen and adjuvant are covalently tethered, the resulting vaccine formulation induced lower immune responses than when antigens and adjuvants are hydrophobically associated. Adapted from [260].

adjacent amino acid residues appear to play an important role in modulating Pam_2C adjuvanticity [273–276]. Therefore, directly conjugating antigens to Pam_2C can decrease Pam_2C adjuvanticity (Fig. 3B) [260,275], and strategies such as using an extra linker between Pam_2C and the peptide epitope must be explored to prevent diminished adjuvanticity.

5. Biomaterial scaffolds for localized vaccine delivery

5.1. From physical adjuvant "scaffolds" to biomaterial scaffolds

Although DCs are abundant in secondary LNs, significant numbers of DCs also reside in the skin and circulate in blood [277,278]. While these DCs are accessible targets for therapeutic delivery, it remains challenging to selectively deliver antigens while avoiding off-target cells and tissues. To overcome this, delivery technologies that recruit DCs to specific peripheral tissue can concentrate these cells at a given site to deliver antigen cargo while avoiding systemic toxicity [279,280]. Subsequently, these DCs can be activated *in situ* with additional reagents and then migrate to LNs to initiate immune responses [281].

Early examples of recruiting DCs to peripheral tissue were employed in the 1920s with alum adjuvant [282]. It was originally thought that alum would function as a depot that sustainably releases antigen to LNs [283]. However, recent research has found that alum acts like a "scaffold", as it stimulates chemokine and cytokine induction at the injection site, which subsequently recruits and activates DCs *in situ* [284–286]. Other types of adjuvants including Freund's adjuvant, Montanide, MF59, and ASO4 have also been used in this strategy [287,288]. However, the application of these physical adjuvants in cancer vaccines is quite limited because they typically initiate strong Th2 but weak Th1 and CTL responses [289]. Nevertheless, potent Th1 and CTL responses are essential for cancer vaccines because Th1 cells produce large amounts of pro-inflammatory cytokines (most notably IFN-γ) that alter the immune-suppressive microenvironment, while CTLs are responsible for the direct killing of tumor cells [290–293]. Therefore, new vaccine scaffolds capable of triggering potent Th1 and CTL responses are an emerging need in cancer vaccine development [294,295]. The design of these scaffolds must address several engineering criteria: first, the scaffold should contain chemical signals, such as cytokines or chemokines, that enable DC recruitment [296]. Additionally, a 3D macroporous structure that enables DC infiltration is required [297]. After infiltration, DCs need to be able to uptake antigen within the scaffold and undergo maturation. Therefore, TAAs are incorporated within the scaffold and function as antigen sources [180,181]. Additionally, TLR agonists are usually included to help induce potent Th1 and CTL responses [123,298]. Collectively, the design requirements for this ideal system are too complex to be addressed by traditional physical adjuvants. As an alternative approach, biomaterials have recently been used to develop cancer vaccine scaffolds to address these needs, and their design is being continuously improved to enhance vaccine delivery (Fig. 4).

5.2. Implantable scaffold

Early studies employing biomaterial scaffold-based vaccines were conducted in 2002, using ethyl vinyl acetate (EVA)-based biomaterials [299]. In this study, macrophage inflammatory protein 3b (MIP-3b) and

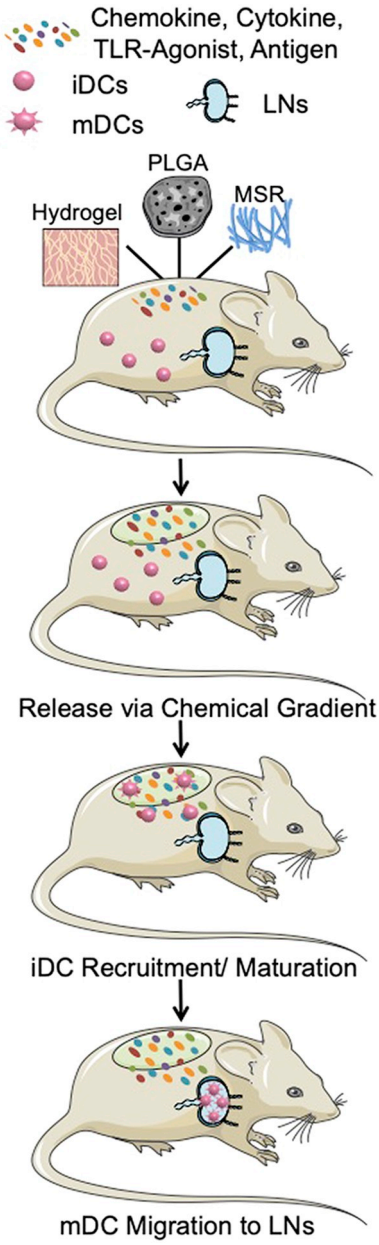

Fig. 4. Schematic of biomaterial-based scaffold vaccines. Various classes of biomaterial scaffolds, such as hydrogels, poly(lactic-co-glycolic acid) (PLGA), and mesoporous silica micro-rods (MSR), encapsulating antigens and immunomodulators (*e.g.* chemokines, cytokines, and TLR-agonists) can be implanted or injected to peripheral tissue for vaccination. Immature DCs (iDCs) are then recruited to the scaffold, become mature DCs (mDCs), and migrate to lymph nodes (LNs) to initiate antitumor immunity.

TAA were entrapped in separate EVA tubes and co-implanted subcutaneously in mice [299]. MIP-3b was used to recruit Langerhans cells (LCs) that subsequently load TAA *in situ* [299]. Three different tumor models, including E.G7-OVA, fibrosarcoma, and Lewis lung carcoma, were evaluated using this scaffold [299]. Mice that received multiple doses of EVA vaccine showed significantly inhibited tumor growth in both prophylactic and therapeutic settings [299]. The success of this proof-of-concept study encouraged researchers to develop other rationally designed cancer vaccine scaffolds, which led to the utilization of PLGA—an FDA-approved, biodegradable polymer [167]. In this model, PLGA scaffolds were formed using a gas-foaming process [300], where GM-CSF, TLR agonists (CpG or poly(I:C)), and tumor lysate antigen were incorporated into the structure [149,301,302]. GM-CSF was released from the PLGA scaffold over a 30-day period, which created a cytokine gradient to recruit DCs [149]. The recruited DCs then encountered TAA and danger signals, matured, and subsequently migrated to LNs [18,294]. This PLGA scaffold induced synergistic antitumor immunity by elevating CTL responses and attenuating TGF-β, IL-10, and FoxP3 regulatory T cells [149]. The scaffold has demonstrated great efficacy in a mouse xenograft model of melanoma, as a single dose implantation protected up to 90% of mice from melanoma cell challenging, while two doses led to complete melanoma regression in 47% of the mice [149].

5.3. Injectable hydrogel scaffold

Although PLGA scaffolds have shown great promise, one drawback of this approach is that it requires surgical implantation [303]. Therefore, recent studies have focused on developing injectable cancer vaccine scaffolds [180,181,298]. Cryogels are one of the first injectable scaffolds developed for cancer vaccination [180,304]. To form cryogels, methacrylated-alginate is first polymerized at -20 °C, allowing ice crystals to form within the cryogel structure [180,304]. Subsequently, the cryogels are exposed to room temperature, allowing ice crystals to thaw and leave behind macropores [180,304]. An important feature of cryogels is their shape-memory properties, which allows them to recover their intended configuration after a 16-gauge needle injection [304,305]. To test their bioactivity as a cancer vaccine, cryogels were loaded with GM-CSF, CpG, and irradiated tumor cells, then injected subcutaneously in a mouse model of melanoma. Results indicated that the cryogel induced a higher survival rate in mice than the previously investigated PLGA scaffolds, when the same immunization schedule was applied [180]. This cryogel required a more invasive 16-gauge needle, which created large wounds at the injection sites [184]. To improve injectability, a second generation cryogel was developed by incorporating additional ionic crosslinks to improve its elasticity, and it was injected through an 18-gauge needle without any damage to its structure [184].

Another strategy for designing injectable cancer vaccine scaffolds is inspired by stimuli-responsive hydrogels, which have been widely used in biomedical research [306–309]. One thermo-responsive polymer, monomethoxypoly (ethylene glycol) – co–poly(lactic-co-glycolic acid) copolymer (mPEG-PLGA), has shown great promise as it is injectable at 4 °C, but turns into a gel within 5 min at body temperature [298,310]. When the scaffold is loaded with GM-CSF, it is released over a 15 day period and recruits DCs to the scaffold site [298]. Interestingly, the most potent antitumor immunity was generated when a lentivirus-encoding antigen and adjuvant (CpG or MPLA) were administered 7 days post-injection of a hydrogel loaded with GM-CSF, which extended survival in a mouse model of melanoma [298]. This indicates that there may be a time period between DC recruitment signaling and DC activation signaling from the scaffold that can affect therapeutic efficacy. More recently, researchers demonstrated that these hydrogels can be used to encapsulate nanoparticles loaded with antigen, in addition to soluble antigen [311]. This dual delivery system enhanced antigen uptake by recruited DCs and induced potent CTL responses, indicating that it is a platform worth further investigation for vaccine delivery [311].

5.4. Injectable mesoporous silica micro-rod (MSR) scaffold

MSRs have recently emerged as another system for cancer vaccination [312–314]. Mesoporous silica has been used in many biomedical applications because of its high biocompatibility [315–317]. For cancer vaccine scaffolds, hexagonal MSRs with certain aspect ratios (88 μm × 4.5 μm) were synthesized. MSRs are injectable after reconstitution in PBS, but, because of their high aspect ratio, they non-specifically self-assemble after injection and generate pores that are large enough to enable cell infiltration [181,312]. A single dose of MSRs loaded with TAA, GM-CSF, and CpG induced potent antitumor immunity, which protected 90% of mice from EG7.OVA lymphoma cell challenging

[181]. Interestingly, a single dose of MSR vaccine also induced durable antibody responses [181]. This indicates that MSRs may also be used for other types of vaccines, such as Zika, Ebola, and Plasmodium falciparum, where the circulation of high-titer antibodies are crucial for disease prevention [318–320]. A second generation of MSR scaffolds were further modified by mixing polyethylenimine (PEI) and MSR to form PEI-MSR scaffolds [123]. PEI-MSR scaffolds alone have been shown to stimulate multiple damage-associated molecular pattern (DAMP) receptors and exert potent adjuvanticity, which assists in DC activation and cross-presentation [123,321,322]. When loaded with GM-CSF, CpG, and TAAs, a single dose vaccination of PEI-MSR scaffolds eradicated established, large TC-1 tumors in 80% of mice [123]. Moreover, PEI-MSR scaffolds were shown to eradicate established lung metastases when combined with an anti-CTLA4 therapy [123].

6. Biomaterials for tumor targeting and tumor modification

6.1. Immunomodulators turning tumor site into antigen depot

In the 19th century, a surgeon named William Coley discovered that repeated intratumoral injections of bacterial lysate reduced the progression of carcinomas [323]. However, it was not until almost a century later that researchers identified CpG, an immunomodulator, as the key component of the lysate that induced tumor regression [324,325]. Since this discovery, delivering immunomodulators directly to tumors has become an attractive strategy for cancer immunotherapy [326–331]. Although immunomodulators do not display antigens, they can turn tumor sites into antigen depots by inducing tumor cell death and releasing tumor antigens *in situ* [332–335]. Subsequently, tumor antigens are taken up by DCs that either reside in the tumor stromal area or are recruited to this area. After DCs mature, they migrate to LNs and generate systemic antitumor immunity [332,335] (Fig. 5).

In many studies, checkpoint blockade therapies are combined in order to improve the therapeutic outcomes of cancer vaccines by reducing the immunosuppressive tumor microenvironment [336]. For instance, CTLA-4 antibodies are used to block CTLA-4 receptors (highly expressed on exhausted T cells) that reside in tumors, which strengthens the co-stimulatory signals (CD28 and B7 engagement) for T cell activation and subsequent enhancement of T cell effector function [336]. In addition, blocking PD-1 (highly expressed on exhausted T cells) and its ligand PD-L1 (highly expressed on cancer cells) serves the same purpose—to improve T cell activation (Fig 6) [337].

6.2. Intratumoral injection

Intratumoral injection is one of the earliest and most direct methods for delivering immunomodulators to tumor sites [339]. Many types of immunomodulators, such as TLR agonists, stimulator of interferon gene (STING), chemotherapeutics, cytokines, and antibodies have been used in intratumoral injections [326,340,341]. However, because of their small size, these therapeutics can rapidly leak out of the tumor and enter the circulatory system within minutes, causing systemic toxicity [342–344]. Thus, various types of biomaterials have been developed to increase the retention time of immunomodulators at tumor sites [345]. Several particle-based delivery systems, such as liposomes [346,347], polymeric nanoparticles [348–350], and inorganic nanoparticles [351,352] have been shown to enhance retention of immunomodulators in the tumor microenvironment and reduce systemic toxicity. Hydrogel-based delivery systems are also an attractive platform to increase drug retention at tumor sites [45,353,354], and their distinct degradation profiles allow for therapeutics to be slowly released with finely tuned kinetics [158,355–357]. As prior reports have shown that chemotherapy enhances immunotherapy efficacy [358–360], a recent study designed a hydrogel system to release chemotherapeutics faster than immunomodulators [45]. In the design, gemcitabine (GEM), a chemotherapeutic, had a smaller molecular weight than the checkpoint blockade (anti-PD-L1), allowing it to release faster from the hydrogel [45] (Fig. 7). The results indicated that a single dose injection significantly prolonged survival in mouse xenograft models of melanoma and breast cancer [45]. Therefore, intratumorally-injected hydrogels formulated to release immunomodulators in a controlled manner have become a promising direction in cancer vaccine development.

6.3. Systemic injection and tumor targeting

Though intratumoral injections show promising efficacy, one challenge to their broad implementation is that they are not a viable option for less accessible and disseminated metastatic cancers [345]. To overcome this obstacle, new strategies have been developed that utilize systemically administered vaccines that are able to reach the tumor site

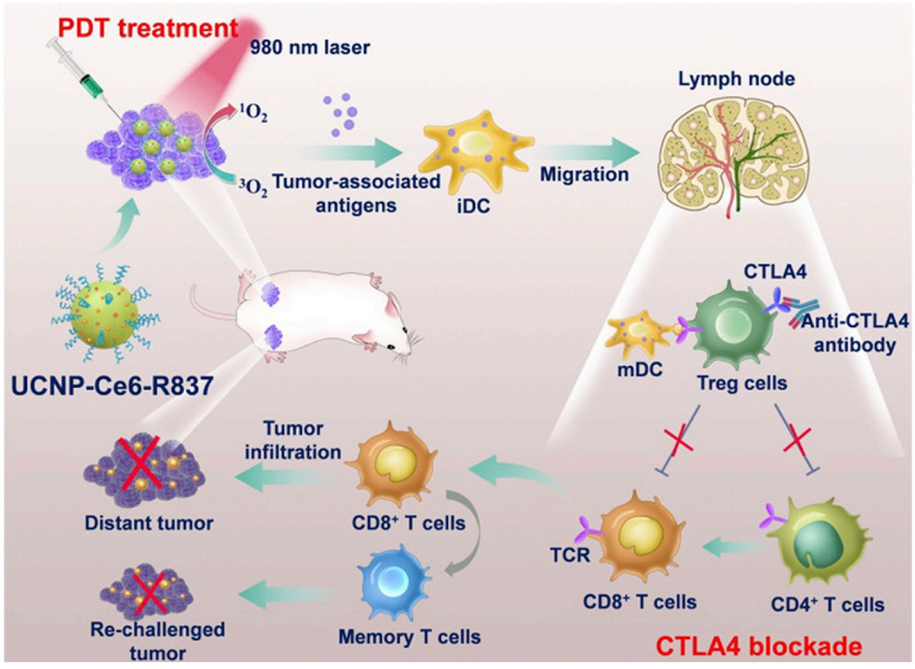

Fig. 5. Immunomodulators turn tumor sites into antigen depots and induce antitumor immunity. Photodynamic therapy (PDT) destructs tumor cells and effectively generates TAAs. TAAs are then captured by DCs and transported to LNs, which promote strong antitumor immunity when combined with anti-CTLA-4. Adapted from [335]. Reprinted with permission from ACS Publications.

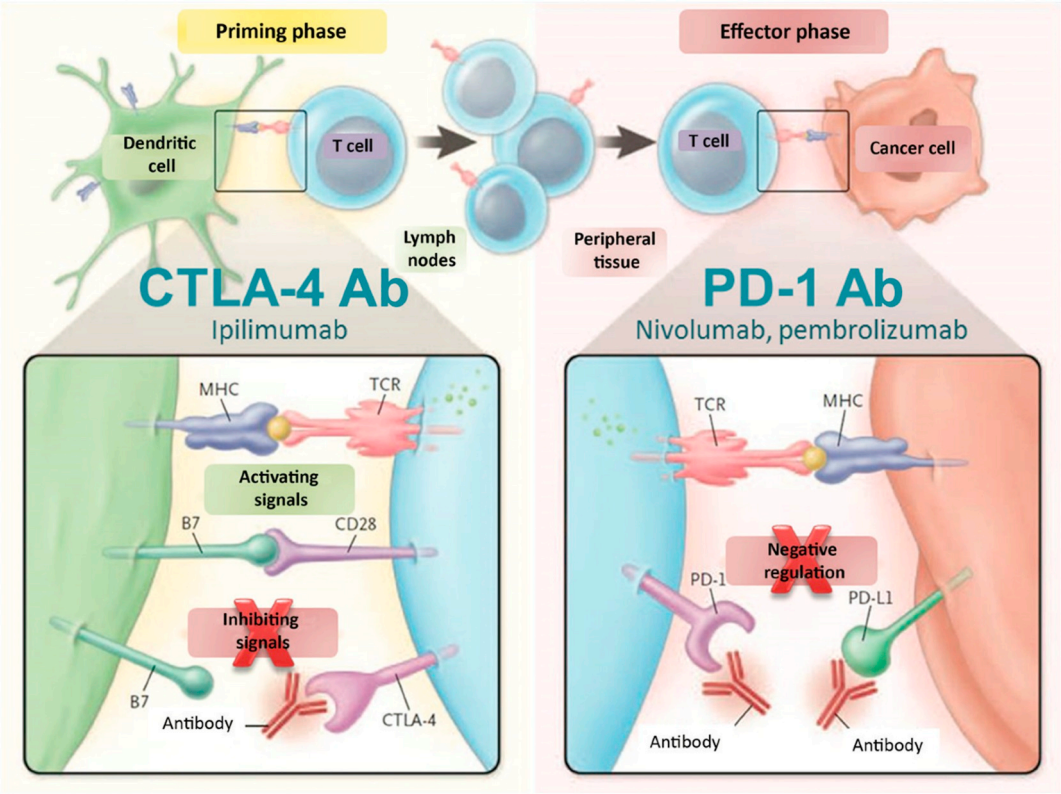

Fig. 6. Schematic showing the use of CTLA-4 and PD-1 antibodies to improve signaling in both the priming and effector phase of the immune response. Adapted from [338], Reprinted with permission from Wiley Online Library.

[345]. Targeting solid tumors via systemic injection requires long drug circulation times in the blood to increase the chances that the drug will reach the tumor [361].

Several factors affect the circulation time of drugs in the blood. Size is one of the most frequently studied topics, as smaller drugs (less than 8 nm) are vulnerable to renal clearance while larger particles (over 200 nm) tend to accumulate in the spleen and liver where they are processed by MPS cells [362,363]. PEGylation is another important parameter in increasing circulation time, as PEGylated particle surfaces help decrease non-specific interactions with the large population of phagocytic cells in the blood that work to opsonize foreign substances [364–367]. However, highly PEGylated nanoparticles may cause an accelerated blood clearance (ABC) phenomenon in later dosing [368]. The ABC phenomenon occurs when repeated exposure to PEG (on particles or in therapeutic modifications) leads to the increased production of anti-PEG antibodies, which mark PEGylated substances for endocytosis or phagocytosis [368]. PEGylated nanoparticles are then cleared to the liver more rapidly, and the decreased blood circulation time limits vaccine efficacy [369,370]. Therefore, newly developed non-fouling materials, such as zwitterionic peptides or polymers, are worth consideration for incorporation in future nanoparticle platforms to reduce the effects of the ABC phenomenon [369,371–373]. Although drug shape also plays an important role in drug circulation time [374–377], its effect in tumor accumulation is still under investigation.

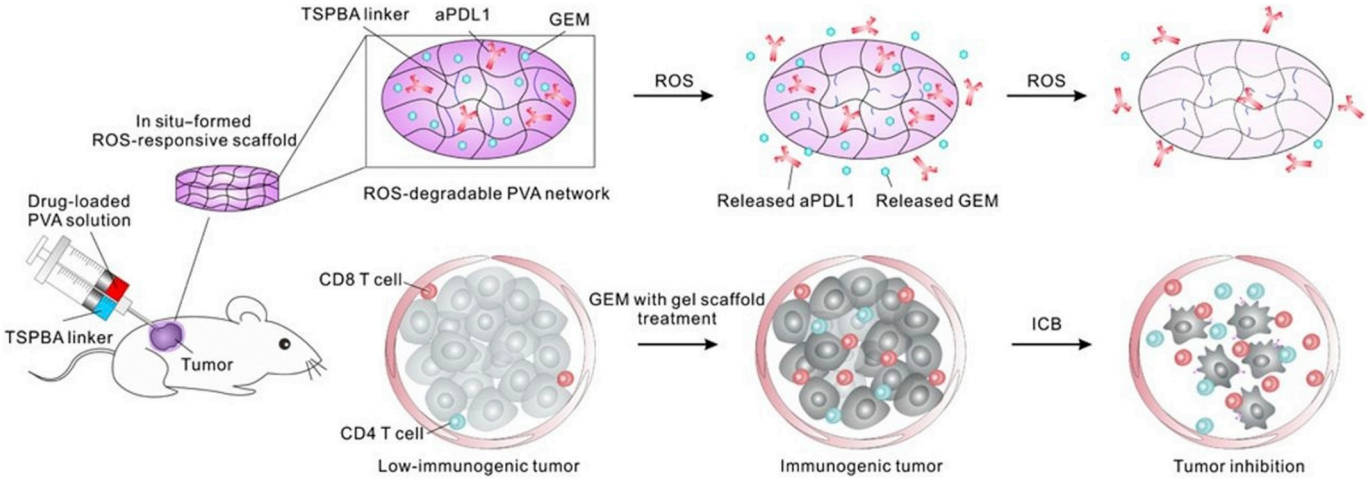

Fig. 7. Schematic of an intratumoral injection of a hydrogel vaccine. GEM and anti-PD-L1 are encapsulated within reactive oxygen species-responsive hydrogel that degrades post-injection. The smaller molecular weight GEM is released faster than larger molecular weight anti-PD-L1, which is a desirable kinetic difference to ultimately induce potent antitumor immunity. Adapted from [45]. Reprinted with permission from AAAS.

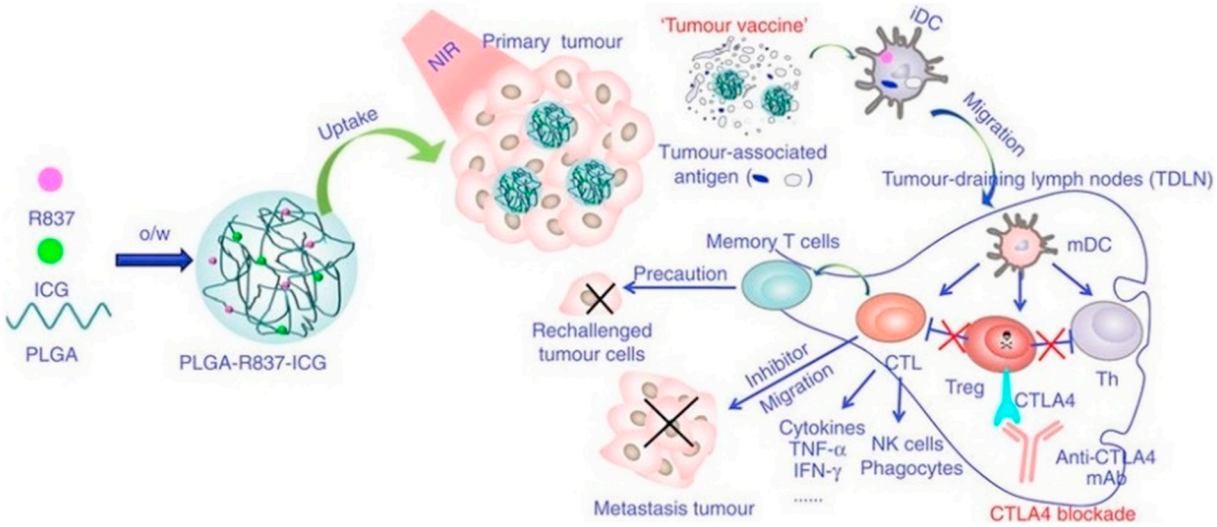

Fig. 8. Schematic of passive tumor targeting. 100 nm PLGA nanoparticles with a densely PEGylated surface were injected intravenously and passively accumulated in tumors. When combined with PDT therapy, tumor cells were disrupted and released TAAs. The TAAs were subsequently captured by DCs and transported to LNs, which promoted strong antitumor immunity with the help of anti-CTLA-4. Adapted from [334]. Reprinted with permission from Nature Publishing Group.

Because different tumor types possess different vascular wall pore sizes [376], specific drug shapes may accumulate differently depending on the type of tumor [362,378]. Overall, nanoparticles with a densely PEGylated surface tend to accumulate more at tumor sites, in a process known as passive targeting [362,379]. One recent example was a study using a highly PEGylated, 100 nm PLGA particle carrying TLR-7 agonist, which accumulated in the tumor following systemic injection [334]. When combined with photodynamic therapy (PDT) with indocyanine green (ICG), it inhibited tumor growth and induced immunological memory in mouse models of breast and colorectal cancer [334] (Fig. 8). Although passive targeting has shown great promise in aiding drugs accumulation at tumor sites, further strategies—such as actively targeting cancer cells or tumor endothelium—are worth consideration to further increase the efficacy of vaccines [191,380–384].

6.4. *Leveraging tumor cell membranes for nanoparticle-mediated vaccine delivery*

Another important strategy for utilizing tumor sites as antigen sources, as reviewed in Section 2.5, is processing resected tumor cells. Common methods for obtaining TAAs from tumor cells include freeze-thawing and irradiation [142,145,146]. Many strategies have streamlined the subsequent step of loading the collected TAAs onto delivery systems such as nanoparticles or scaffolds for applications in cancer vaccines [147–149]. In a manner similar to obtaining TAAs from tumor cells, tumor cell membranes have recently been isolated through hypotonic lysing and mechanical disruption for coating drug-loaded nanoparticles for *in vivo* delivery [385]. In one example, TAA-abundant tumor cell membranes were coated onto the surface of adjuvant-loaded nanoparticles to create a tumor membrane-coated nanoparticle vaccine [253,385] (Fig. 9A). When utilized in a prophylactic setting, three doses of the vaccine protected 80% of mice from a melanoma cell challenge [253]. When used in a therapeutic setting, four doses of the vaccine combined with checkpoint blockades induced long-term survival in 50% of melanoma tumor-bearing mice [253].

In addition to coating nanoparticle surfaces with tumor cell membranes, another recent study investigated the reverse strategy, where tumor cell surfaces were coated with nanoparticles [252]. In this study, isolated tumor cells were first treated with the chemotherapeutic mitoxantrone to trigger immunogenic cell death [252]. Subsequently, the dying tumor cells were purified and decorated with adjuvant-loaded nanoparticles to form a nanoparticle-coated tumor cell vaccine [252] (Fig. 9B). In this study, a single dose of the vaccine protected all mice from melanoma cell challenging [252]. Additionally, a single dose of the vaccine combined with multiple doses of a checkpoint blockade induced complete tumor regression in almost 80% of mice with colon carcinoma [252]. A major advantage of the tumor membrane-coated nanoparticle vaccine and the nanoparticle-coated tumor cell vaccine is that they closely mimic many natural properties of cancer cells [251,385]. However, several challenges, such as large scale production and batch-to-batch variability, currently exist and can hinder their future commercialization [126].

7. Outlook – towards personalized cancer vaccines

Identification of TAAs has long been a central driving force behind the development of tumor-specific cancer vaccines [7,386,387]. Most TAAs currently in clinical use are self-tumor antigens, as they are derived from healthy cells with a normally expressed protein that is overexpressed on cancer cells [7]. This strategy has led to the successful discovery of many TAAs, such as MAGE1 (a melanoma associated antigen), NY-ESO-1 (a cancer-testis antigen), and HER-2 (a breast cancer associated antigen)[388–390]. Though the identification process has proven promising, early clinical investigations have had limited success, likely due to several important factors [7,8]. First, every tumor has a unique pattern of somatic mutation that generates many different copies of TAAs, but identified self-tumor antigens are usually only a small fraction of the TAAs that share common features between individual patients [8,391,392]. Therefore, administration of only self-tumor antigens can result in tumor escape [393]. Second, as the self-tumor antigens are also expressed in healthy tissue, they are subjected to a certain degree of central tolerance and are often recognized by T cells with low affinity, resulting in low immunogenicity [7]. Moreover, the antitumor immunity developed against those self-tumor antigens can also attack these antigens expressed on normal cells, which may cause off-target autoimmune effects [8]. Collectively, new strategies are needed to discover patient-specific TAAs that are expressed exclusively on cancer cells.

Next generation sequencing has revolutionized our understanding of cancer mutations [394,395]. More importantly, recent advancements allowing for a reduction in the time and cost of sequencing provide unique opportunities for researchers to identify tumor antigens on an individual patient basis [7,8,396–398]. Thus, experimental and computational pipelines have been generated to identify personalized tumor antigens in real-time (Fig. 10) [7]. In one approach to formulate personalized cancer vaccines, DNA and RNA from both normal cells and cancer cells are extracted [7]. Subsequently, whole exosome sequencing

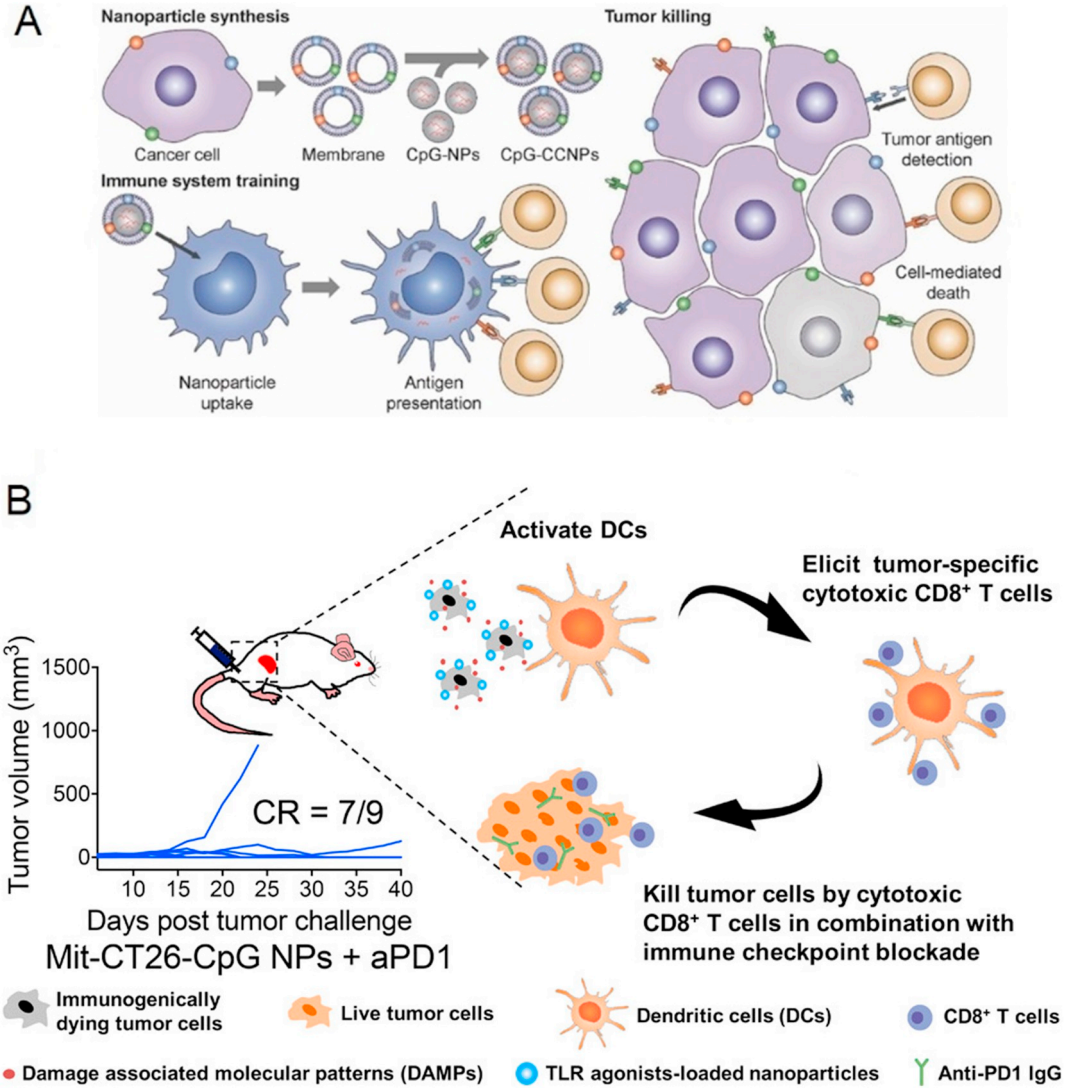

Fig. 9. Schematic of modifying tumor cells to formulate cancer vaccines. (A) Cancer membranes were isolated and coated onto the surface of CpG-loaded nanoparticles. (B). Mitoxantrone, a chemotherapeutic, was used to induce immunogenic cell death. The surfaces of dead tumor cells were coated with CpG-loaded nanoparticles. Part A is adapted from [187], part B is adapted from [252]. Reprinted with permission from Wiley Online Library and ACS Publications.

(WES) and RNA sequencing (RNA-seq) are conducted to identify mutated genes and their corresponding mutated antigens [388]. Thereafter, human leukocyte antigen (HLA) typing is carried out to determine which mutated genes have a strong binding affinity for the individual patient to then predict and personalize the cancer vaccine epitope, known as neoantigens [7,399]. Lastly, those selected neoantigens are synthesized and combined with other immunomodulators (*e.g.* adjuvants) and delivery vehicles to create the final vaccine formulation [388]. A recent study demonstrated that using nanodiscs, a novel biomaterial for vaccine delivery, to deliver predicted neoantigens has significant potential as a cancer therapeutic [124]. When the nanodisc vaccine was combined with checkpoint blockade therapy in murine models, it was shown to eradicate established colon carcinoma or melanoma in 90% of mice [124].

Another strategy for developing personalized cancer vaccines is utilizing patient-derived tumors [117]. Compared with the previously described neoantigen vaccine, utilizing a patient's own tumor cells eliminates the need for tumor antigen selection and synthesis, thus reducing vaccine production time [151]. A recent study in mice embedded autologous dead breast cancer cells, thienotriazolodiazepine (a bromodomain-containing protein 4 inhibitor), and ICG (a photothermal therapy agent) in hydrogels as a personalized cancer vaccine [151]. The vaccine induced complete remission in all mice with breast tumors, indicating that personalized vaccines developed from a patient's own tumor, coupled with a biomaterial delivery system, may be a promising therapeutic direction [151]. This strategy is especially applicable for patients with solid tumors that require surgical resection, as the excised tumors can be modified and used in biomaterial-based vaccines that are capable of preventing tumor recurrence and metastasis post-surgery [151]. This new approach may be an attractive alternative to traditional chemotherapy and radiotherapy—the current standard-of-care therapy post-surgery—as both traditional methods dramatically decrease a patient's quality of life [400]. Though promising, the production process for developing personalized vaccines derived from either neoantigens or a patient's own tumor are often time consuming, costly, and complex [7,151,401]. Future efforts should focus on reducing production time and costs during the manufacturing process, so that personalized cancer vaccines can become widely commercialized.

8. Conclusion

Though many advances have been made at the interface of cancer vaccines, biomaterials, and bioinformatics, the final key step is to effectively translate these novel techniques from academic laboratories

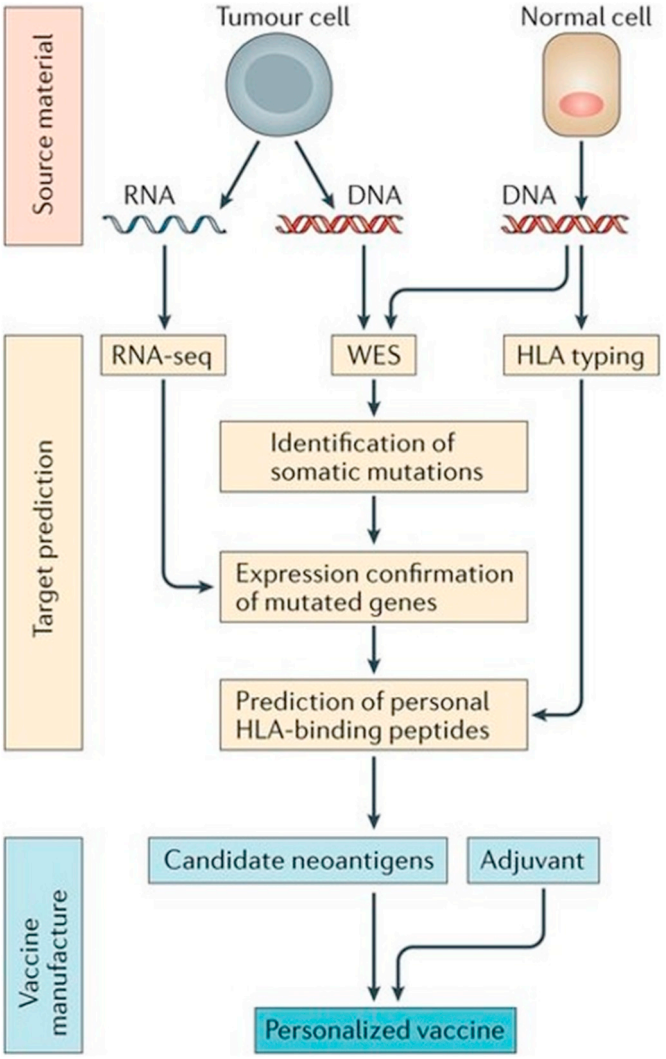

Fig. 10. Schematic of neoantigen selection and personalized cancer vaccine formulation. The mutated antigens are selected by whole-exome sequencing, RNA sequencing, and HLA typing. The selected epitopes are synthesized and formulated with other immunomodulators, yielding personalized cancer vaccines. Adapted from [7]. Reprinted with permission from Nature Publishing Group.

into the clinic, where several challenges exist. First, the differences in immune systems between small animals, larger animals, and humans need to be taken into consideration [386]. Additionally, animal models for melanoma are widely used due to their ease of tumor manipulation and assessment [402]. However, melanoma may differ significantly from other types of solid tumor or hematological cancers, which may impact the translatability of the model to other types of cancer in the clinic [403]. Lastly, the capacity of large scale production and batch-to-batch quality control are also important factors that need to be addressed before biomaterial-based vaccines can be widely commercialized [404]. One strategy to improve the potential for clinical translation is to develop delivery technologies comprised of FDA-approved materials, as a means to reduce the length of the approval process [405–407]. A prime example is the PLGA-based scaffold vaccine (WDVAX), developed by Mooney and colleagues, which has recently been licensed by Novartis for commercial use [408]. Additionally, using existing and future clinical trial data to compare vaccine efficacy across patient subpopulations may allow for vaccines to be optimized more quickly for specific groups of patients, based on determined factors such as biomarker expression [409].

Overall, various aspects of biomaterial-based cancer vaccines can be leveraged to train the immune system to selectively attack tumor cells, while possibly avoiding the off-target effects and potential toxicity of traditional vaccines. Different engineering approaches, including enhancing lymph node delivery, immune cell recruitment, tumor targeting, and tumor cell modification can be exploited using scaffold and nanoparticle-based delivery systems. Moreover, the identification of optimized tumor antigen sequences has been indicated as a crucial step in improving cancer vaccine efficacy. Thus, continuing collaborations between immunologists, computational scientists, and bioengineers, entrepreneurs are necessary to design safer, more effective, and translatable cancer vaccines for patients.

Contributions

R.Z., M.M.B. and M.J.M. conceived the ideas, researched the data for the manuscript, designed the display items, discussed the manuscript content, and wrote the manuscript. All authors reviewed and edited the article before submission.

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