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Biomaterials for vaccine-based cancer immunotherapy

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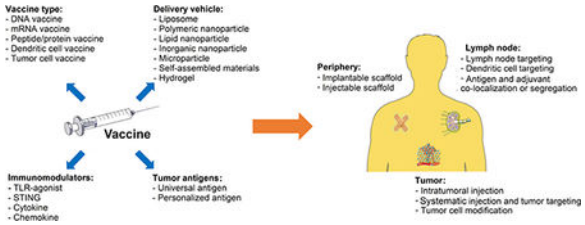
Abstract

The idea of developing therapeutic vaccines against cancer has been explored since the early discovery of tumor-specific antigens by Georg Klein in 1967. However, challenges including weak immunogenicity, systematic toxicity, and off-target effects of cancer vaccines remain as barriers to their broad clinical translation. The emerging field of biomaterials has led to advancements in many different biomedical applications, and it may also help cancer vaccines overcome the various aforementioned challenges. Here, we discuss the rational design and clinical status of several classes of cancer vaccines (*i.e.* DNA, mRNA, peptide/protein, cell-based), along with novel biomaterial-based delivery platforms that improve their safety and efficacy. Further, strategies for designing new platforms for personalized cancer vaccines are also considered.

Graphical Abstract



Keywords

Cancer vaccine; Immunotherapy; Biomaterials; Targeted delivery; Personalized therapy; Translational research

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2. Introduction

Vaccines have made a tremendous contribution 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 proven successful, most cancer vaccines have shown disappointing clinical outcomes[4]. This is likely due to a number of factors, including various biological barriers[5, 6], inherently low tumor antigen immunogenicity[7, 8], and the immunosuppressive tumor microenvironment[7, 9]. For a cancer vaccine to be effective, a number of key 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), which most notably include 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 (T_h cells) and cytotoxic T lymphocytes (CTLs) need to infiltrate the tumor site, shifting the immunosuppressive tumor microenvironment towards a pro-inflammatory environment [13, 14]. This alteration in the microenvironment aids CTLs in killing tumor cells and is accompanied by other mechanisms for tumor cell killing (e.g. natural killer cell killing, antibody-dependent cell-mediated cytotoxicity)[13, 14]. While this approach to treating a range of cancers 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]. A major reason for previous cancer vaccine failures is 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 the next generation of cancer vaccines[18].

Over the last decade, there has been exponential growth 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, cell based), 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 specific tissues with desirable drug release kinetics[40–48]. In this review article, we introduce various classes of vaccines and their clinical status (Table 1), highlight the advances made at the interface of biomaterials and cancer vaccines, summarize key design criteria for biomaterials-based delivery platforms, and provide our insights into the future directions of cancer vaccine development.

3. Different types of vaccines and their clinical status

DNA vaccines

DNA vaccines were first developed in the early 1990s[49], when researchers found that plasmid DNA can induce potent antibody responses against an encoded antigen[49–51]. The design simplicity and promising pre-clinical studies quickly sparked an interest in developing DNA vaccines for a variety of infectious diseases[52, 53]. Consequently, utilizing DNA vaccines to combat cancer has become an attractive strategy for cancer immunotherapy[54]. When DNA contains unmethylated, repeating “cytosine-guanine” regions, they cause adjuvant effects that stimulate the innate immune system[55]. As such, plasmid DNA can be designed to act as both antigen and adjuvant[56]. However, due to its low molecular weight and negatively charged backbone, naked DNA typically yields low cellular uptake, off-target effects, and systemic dissemination[57–60]. Therefore, various efforts have focused on developing methods of effectively introducing plasmid DNA into antigen presenting cells (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]. Moreover, EP has adjuvant-like properties because it induces moderate tissue injury and generates pro-inflammatory cytokines, which recruit APCs at the injection site[64]. Another promising DNA delivery strategy is gene gunning where plasmid DNA is coated with heavy metals (*e.g.* gold particles) and bombarded into APCs at the injection site, which decreased the required plasmid DNA dose by 100–1,000 fold[65, 66]. Although a variety of strategies have been developed to improve DNA vaccine delivery, these vaccines still possess low immunogenicity profiles in human trials for reasons not yet fully understood[58, 67]. As such, only few DNA vaccines have advanced beyond phase I or phase II clinical trials[68].

Despite the obstacles to their efficacy, the 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, the same success has not been found using the vaccines to target human cancers[68, 70]. Phase I and II clinical trials have been used to observe the vaccines for numerous cancer types including melanoma[71], prostate[68], lymphoma[72], and cervical[73, 74], but most cases have shown little clinical efficiency[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, it is clear that the main issue in clinical trials continues to be therapeutic efficacy rather than toxicity[68, 69]. The aforementioned methods of EP and gene gunning 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 prostate cancer and melanoma[75].

Additionally, promising pre-clinical data has led to phase I and II clinical trials for gene gunning in head and neck squamous cell carcinoma and cervical cancer[73]. Thus, the continued improvement of EP and gene gunning strategies or the investigation of alternative delivery mechanisms such as biomaterial-based vehicles[75–77] and DNA sequence optimization[75, 78] is necessary to improve vaccine immunogenicity for a broader range of cancers.

mRNA vaccines

mRNA vaccines are another promising alternative to conventional vaccine approaches. One of the first reports on mRNA cancer vaccines was from the late 1990s, shortly after the discovery of DNA cancer vaccines[79]. One major advantage of mRNA over DNA vaccines is that mRNA does not need to cross the nuclear barrier to induce protein expression[80]. Therefore, 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 including 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 and reduce immune sensing by toll-like receptors (TLRs), rig-like receptors (RIG-1), and protein kinase RNA-activated receptors (PKR)[93–96]. Other research also demonstrated that removing double-stranded RNA (dsRNA) 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 gunning approaches, a variety of biomaterial-based delivery systems such as liposomes and polymeric nanoparticles have been extensively studied, and the preclinical outcomes are quite promising[101–103].

More recently, lipid nanoparticles (LNP) have emerged as a promising delivery platform for mRNA vaccines, built off of recent success in delivering siRNAs *in vivo* and promising phase III clinical trials of siRNA-LNP patisiran by Alnylam Pharmaceuticals[104–108]. Though LNP based mRNA vaccines are in early stages of development, they have shown great promise for a range of disease including 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 cytosolic 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]. In clinical trials using naked mRNA in the absence of a delivery vehicle, such as the intranodally injected mRNA vaccine for advanced melanoma[82], repetitive injections have yielded promising results but present larger issues with convenience, cost, and off-target effects[82]. 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, though LNPs have promising preclinical data and have shown some translatability to clinical settings, additional methods for improving efficacy in human trials has been investigated[82]. One major development for mRNA vaccines has been 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 shown its ability to induce immune response and encourage longer survival time for patients[115, 116]. With multiple modification methods to improve mRNA preparation, delivery, and overall efficacy, future work must explore how these techniques can come together to fully optimize mRNA cancer vaccines.

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 usually chemically synthesized due to their short length, which is both time and cost effective[118]. In contrast, protein vaccines are often obtained by using more complex recombinant protein expression approaches[119]. The distinct advantage of both peptide and protein vaccines is their high level of safety, which has been shown in many pre-clinical 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 antigen (TAA)[121]. Because it is generally believed that multivalent antigen-specific CTL responses are necessary for cancer vaccine efficacy, a mixture of multiple antigens (peptides or proteins) is required to achieve desirable effects[121–123]. Additionally, though peptides and proteins do not have negatively charged backbones like DNA and mRNA, delivery vehicles are still necessary to improve vaccine stability and targeting and reduce off-target effects[124–127].

In clinical trials for peptide-based cancer vaccines, a number of the aforementioned limitations remain. Most clinical trials in progress rely primarily on TAA-derived short peptides, with only a 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, some early clinical trials have produced promising results. A mucin 1 TAA peptide prophylactic vaccine for colon cancer was highly immunogenic in half the trial’s 39 individuals and was able to elicit a long-term anti-tumor 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.

DC vaccines

The major target cell type for the previously described vaccines are DCs, which are essential for initiating anti-tumor immunity[132]. Thus, "vaccinating" DCs *ex vivo* is likely a more effective approach than administrating vaccines *in vivo*, where only a small portion of vaccines reach DCs. Those *ex vivo* treated DCs are called DC vaccines, and to prepare them, a patient's own DCs are isolated, co-cultured with antigens (e.g. DNA, mRNA, peptides, or proteins) and adjuvants (e.g. TLR agonists or cytokines), matured, and then loaded with TAAs[133, 134]. The treated DCs are then delivered back to the patient, where they migrate to the LN and prime naïve CD8 T cells to initiate anti-tumor immunity[134, 135]. The most distinct advantage of DC vaccines is that the DCs are treated *in vitro*, so there is less concern over off-target effects than with other vaccines that require vaccine components to be administered directly into patients[135]. However, major 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 (Sipulencel T) was approved by FDA for the treatment of metastatic prostate cancer in 2010[15], their commercialization is limited to only a few developed countries, in part due to the high cost of treatment and the strict manufacturing requirements for the 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 Sipulencel 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 pause 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 results from a clinical trial for a DC vaccine against melanoma showed that the therapy had 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, tumor lysate), or fused with live cancerous cells to generate hybrid cells, there has yet to be a unified, perfected procedure for handling them[138]. Thus, a big focus in DC vaccine development is for the optimization of *ex vivo* DC protocols[39].

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]. Instead of obtaining soluble tumor lysate antigens like 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 collected TAAs onto biomaterial delivery platforms such as nanoparticles or scaffolds for applications in cancer vaccines[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, anti-tumor immunity can be more 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 by 26 months[152]. The results have led to GVAX being investigated in a broader array of cancer types in a number of 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 a number of cancer types including ovarian, breast, colorectal, and small cell lung cancer, and it has progressed into a phase II trial for treating melanoma, ovarian cancer, and colorectal carcinoma[153]. While these vaccines tend to have varying efficacies 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 anti-tumor responses in only 11 of the 89 patients in the study[154]. However, the study was able to correlate small volume lung metastases with an increased likelihood of responding the vaccine[154]. Thus, future studies using such vaccines should focus on specific subpopulations where the vaccine will likely prove effective while potentially exploring other treatment modalities for patients outside of that subpopulation[142].

4. Bridging Biomaterials and Cancer vaccines

As discussed in the previous section, a considerable number of cancer vaccine trials have shown negative outcomes, in part due to a lack of effective delivery methods [155]. Peptide cancer vaccines provide a prime example. When unmodified and naked peptides are delivered, the overall clinical response rate 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 indicates 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, biomaterial-based delivery systems are required to help overcome the biological barriers of cancer vaccines in vivo, and enhance cancer vaccine efficacy [158]. Because of the diversity in cancer vaccine approaches, multiple classes of biomaterials are needed to overcome the varying obstacles faced by different vaccine types. Thus, biomaterials used in cancer vaccines range from the nanoscale (e.g. liposomes, polymeric nanoparticles) to larger implantable or injectable scaffolds [159, 160].

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]. Incorporating nanoparticles into a vaccine can lead to enhanced delivery to certain organs or tissues such as the lymph nodes, spleen, or solid tumors and can elevate on-target effects [18]. Liposomes are perhaps one of the first studied nanoparticles for cancer vaccines[161], with some formulations featured in ongoing clinical trials (Table 1). Because of their FDA approval, liposomes are an attractive option for fast clinical translation, and they are consistently shown to improve delivery compared to free drug[162]. However, these early generation liposomes have several disadvantages including low loading capacity, relatively low stability, and toxicity[163–165]. Another type of widely studied and FDA-approved nanoparticle-based drug carrier is PLGA nanoparticles—a type of polymeric nanoparticle—but they suffer from similar issues with low cargo encapsulation[166, 167]. However, one distinct 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]. One notable difference between liposomes and PLGA nanoparticles that affects their use as delivery platforms is the hydrophilicity and/or hydrophobicity of the therapeutic cargo[169]. Liposomes contain both a hydrophilic core and a hydrophobic bilayer that make them suitable for carrying hydrophobic and hydrophilic compounds in the same nanoparticle[169]. PLGA nanoparticles, however, have a relatively high overall hydrophilic content, which results in low encapsulation rates for hydrophobic compounds[170].

To overcome the obstacles still faced by commonly used delivery systems, significant work has been done to chemically modify liposome or PLGA formulations in order to improve stability and cargo encapsulation rates[171, 172]. From this work, rationally-designed, new classes of nanoparticles have been developed[18]. For example, self-assembled nanoparticles often have high loading capacities and have shown to successfully deliver peptide or nucleic acid-based vaccines[173–176]. Similarly, lipid nanoparticles, with their history of successful siRNA delivery, have been used extensively for mRNA vaccine delivery[82, 177]. However, both self-assembled and lipid nanoparticles are limited to specific antigen types as their nanoparticle formulations rely on the charge complexation[82, 173, 176]. Therefore, the 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 complexed and undefined antigen types (e.g. protein, tumor lysate or tumor cell)[161, 178, 179].

Biomaterial scaffold-based delivery systems

Scaffold-based cancer vaccines refer to locally delivered vaccines, such as polymeric scaffolds and hydrogel scaffolds[18]. Due to their large size, these cancer vaccines usually remain at the peripheral injection site after vaccination[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 6)[180, 181]. Commonly used cancer vaccine scaffolds include PLGA, alginate-based hydrogels, and mesoporous silica micro-rods (MSRs), all three materials are degradable and highly biocompatible[182]. PLGA is FDA approved but is not injectable and must be implanted due to its stiffness[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 result in wounds at the injection site[180]. Both PLGA and cryogel scaffolds have shown great success in encapsulating tumor cell derived antigens, but PLGA is more commonly used for encapsulating tumor lysate antigen while cryogels more commonly carry irradiated whole tumor cells[149, 181, 182]. MSRs with high aspect ratios are perhaps the most injectable form of scaffold because they assemble to form three-dimensional structures in situ after injection[181]. However, MSRs have only shown success in encapsulating 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 scaffold-based cancer vaccines need to encapsulate a significant number of molecules while allowing for immune cell infiltration, they are often designed to have porous structures[180, 181]. These pores can be adjusted to accommodate different 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 allow scaffold-based cancer vaccines to load almost all vaccine types, including nucleic acids, peptides, tumor lysates, and whole tumor cells[18, 186].

One distinct difference between nanoparticle-based and scaffold-based cancer vaccine delivery is the longevity of cancer vaccine and immune cell interaction they provide[182]. Nanoparticle-based cancer vaccines, because of their small size, can be internalized easily by APCs in the tissue or LN shortly after interstitial immunization[6]. By contrast, scaffold-based cancer vaccines, because of their large size, interact with immune cells via encapsulated therapeutic cargos that can be released over a prolonged period of time[158]. Therefore, nanoparticle-based cancer vaccines often require repeated vaccination to achieve effective anti-tumor immunity while scaffold-based cancer vaccines can achieve desirable anti-tumor responses with a single dose or few doses[123, 187]. Nevertheless, similar to other prophylactic single-dose vaccines (e.g. microparticle-based vaccines), questions may be raised against scaffold-based vaccines regarding whether encapsulated antigens or adjuvants remain stable in scaffolds after administration *in vivo* [188]. However, for antigens

that are difficult to collect or processed frequently (i.e autologous tumor cell antigens), the scaffold-based cancer vaccines may still be more desirable as their vaccination schedule generally requires less frequent dosing than nanoparticle-based cancer vaccines[123].

5. Biomaterial Vaccines for Lymph Node (LN) delivery

LN targeting

LNs and their surrounding areas contain a large, diverse population of cells 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 the magnitude of vaccine efficacy in both prophylactic and therapeutic settings[27, 191]. Although intranodal injections have shown great promise in effectively delivering vaccines to LNs[192], this technique typically requires an invasive surgical procedure[193, 194], making it less appealing. Instead, interstitial injections (*e.g.* subcutaneous, intradermal, intramuscular) are one of the most commonly utilized vaccination strategies[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. Over many years of investigation, researchers have demonstrated that physical and chemical parameters of vaccines, such as size, charge, surface properties, and material chemistry, can dramatically shift a vaccine's bio-distribution (Fig. 2).

Of these factors, the size of a vaccine and its delivery vehicle is one of the most studied characteristics[44, 201, 202]. Vaccine size is a key factor that affects biodistribution upon interstitial injection, due to the differences between the blood and lymphatic vessels that both 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 typically cross tight junctions between vascular endothelial cells and preferentially enter blood vessels[204]. Upon entering a blood vessel, the vaccine faces 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 form 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 2–200 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 to LNs and their transport via APCs within the LNs. Because of the negatively charged phospholipid bilayer structure of cell membranes, anionic vaccines create a repulsion force with cells that decreases cell-vaccine interaction. Though the surface repulsion decreases cell contact to help vaccines travel smoothly 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

before reaching LNs[16, 201, 207]. Despite their limitations, cationic vaccines 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 influence LN drainage[212]. Additionally, PEG is hydrophilic, 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 (*i.e.* DCs), further surface modifications, such as incorporation of cell penetrating peptides or DC ligand targeting sequences, are worth consideration[217, 218].

DC targeting

DCs have been extensively studied as a crucial immune cell type that can cross present antigens [219–222]. Therefore, targeting DCs is a promising strategy for priming naïve CD8 T cells and initiating anti-tumor immunity[223, 224]. However, there are several challenges in delivering vaccines to DCs. First, other phagocytic cells (*i.e.* macrophages and neutrophils) compete with DCs to phagocytose exogenous antigens, which reduces the amount of antigens taken by DCs[92, 225]. Additionally, mature DCs have reduced phagocytic properties that lower their capacity to internalize and process antigens[226]. Further, many vaccines utilize PEGylation or anionic surface to improve biodistribution to LNs[27, 212, 227], but their internalization by DCs can then be hindered due to the strong hydrophilicity difference or electrostatic repulsion between cell membranes and the PEGylated or anionic 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 CD8α+ DCs, plasmacytoid DCs, and Langherans cells, based on their different marker 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 in vaccines[230]. Among those receptors expressed on DCs, DEC-205, DC-SIGN, and CD40 have been the most successful as targeting moieties utilizing antibodies[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 extraordinarily successful for peptide-based vaccines, as a DC-targeting peptide can be tethered to the peptide epitope during the vaccine's synthesis[239, 241]. The fast and inexpensive peptide production process makes peptide-based DC targeting strategies a promising strategy for developing cancer vaccines.

Antigen and adjuvant co-localization or segregation

Recent advancements in molecular adjuvants, including TLR agonists, have accelerated the development of cancer vaccines, as traditional adjuvants (*e.g.* alum and Freund's adjuvant) fail to induce potent CTL and Th1 immune responses[26, 242–244]. One of the most important discoveries 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 many different types of 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. Though these vaccines have been successful, 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 separated 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 may still need to separate because antigens and adjuvants may function in different cell 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 to APCs. The importance of antigen and adjuvant segregation is further supported by recent work, where a vaccine with chemically-tethered antigens and adjuvants induce 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 within the same LN, the antigen and adjuvant 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 on major histocompatibility complex 1 (MHC-I)[267]. Therefore, it is important to consider the effect of cross-presentation when modifying cancerous epitopes (*e.g.* neoantigens), as potent antigen-specific CTL responses are a key factor of anti-tumor 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 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 (Figure 3B)[260, 275], so strategies such as using an extra linker between Pam_2C and the peptide epitope must be explored to prevent diminished adjuvanticity.

6. Biomaterial Scaffolds for Localized Vaccine Delivery

From physical adjuvant “scaffold” to biomaterial scaffold

Although DCs are abundant in secondary LNs, significant numbers of DCs also reside in the skin and circulate in the 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].

The strategy of recruiting DCs to peripheral tissue was early employed in the 1920s with alum adjuvant[282]. It was originally believed 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 physical adjuvants including Freund’s adjuvant, Montanide, MF59, and ASO4 have also been used in this strategy[287, 288]. However, the application of those 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 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 cancer vaccine 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 is required that enables DC infiltration[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, TLRs 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.).

Implantable scaffold

One of the first studies employing biomaterial scaffold-based vaccines was conducted in 2002, using EVA-based biomaterials[299]. In this study, macrophage inflammatory protein 3 b (MIP-3b) and TAA were entrapped in separate ethylene vinyl acetate (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, E.G7-OVA tumor, fibrosarcoma, and Lewis lung carcoma, were evaluated[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 poly(lactic-co-glycolic acid) (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 the 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-based cancer vaccine induced synergistic anti-tumor immunity by elevating CTL responses and attenuating TGF-β, IL-10, and FoxP3 regulatory T cells[149]. The scaffold has shown great efficacy in mouse xenograft model of melanoma: a single dose implantation protects over 70% of mice from melanoma cell challenging, while two doses led to complete melanoma regression in nearly 40% of the mice[149].

Injectable hydrogel scaffold

Although PLGA scaffolds have shown great promise as a cancer vaccine, one drawback of this approach is that it requires surgical implantation, the procedure is painful, and it can leave large scars on patients[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 vaccine applications[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 thaw and leave behind macropores[180, 304]. An important feature of cryogels are their shape-memory properties, which allow the gels to recover their intended configuration after a conventional 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 cancer vaccine scaffold induced a higher survival rate in mice than the previously investigated PLGA cancer vaccine scaffold, when the same immunization schedule was applied[180]. However, the first generation cryogel was not mechanically robust enough to fit in a needle smaller than 16-gauge without damaging the cryogel[184]. Therefore, 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 was injected through an 18-gauge needle without any damage to its structure[184].

Another attractive 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 an injectable scaffold as it is injectable at 4°C, but turns to gel within 5 mins 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 anti-tumor 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].

Injectable mesoporous silica micro-rod (MSR) scaffold

MSRs have recently emerged as another system for cancer vaccine scaffolds[312–314]. Mesoporous silica has been widely used in many biomaterials 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 cold PBS, but because of their high aspect ratio, they non-specifically self-assemble after injection, and generate pores that are larger than cells to allow cell infiltration[181, 312]. A single dose of MSRs loaded with TAA, GM-CSF, and CpG, induced potent anti-tumor immunity, which protected 90% mice from EG7.OVA lymphoma cell challenging[181]. Interestingly, a single dose MSR vaccine also induced durable antibody responses[181], indicating that MSRs may also be used for other types of vaccines, such as Zika, Ebola, and Plasmodium falciparum, where the circulation of high-tier antibodies are crucial for the disease prevention[318–320]. The second generation of MSR scaffold was 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, when treating more aggressive type tumors, such as B16-F10 or CT26 lung metastases, PEI-MSR scaffolds were shown to eradicate established lung metastasis when synergized with anti-CTLA4 therapy[123].

7. Biomaterials for tumor targeting and tumor modification

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, a special immunomodulator, is 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 immunomudulators do not display antigen, 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 systematic anti-tumor immunity in a vaccine-like manner[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].

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 chemo drug, had a smaller molecular weight as 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 to generate anti-tumor immunity have become a promising direction in cancer vaccine development.

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[345]. Targeting solid tumors via systemic injection requires long drug circulation times in the blood, increasing 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 drugs that are too small (less than 8 nm) are vulnerable to renal clearance while particles that are too large (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 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 exposures 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. Because different tumor types possess different vascular wall pore shapes[376], specific drug shapes may accumulate differently depending on the type of tumor[362, 378]. Overall, nanoparticles approximately 100 nm in diameter 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 (ICB), 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 helping drugs accumulate in tumor sites, further strategies—such as actively targeting cancer cells or cancer endothelium—are worth consideration to further increase the tumor targeting efficacy of vaccines[191, 380–384].

Leveraging tumor cell membranes for nanoparticle-mediated vaccine delivery

Another important strategy for utilizing tumor sites as antigen sources, as reviewed in tumor cell vaccine section, 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 biomaterial delivery platforms 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 of the 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 established colon carcinoma[252]. The 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, do currently exist and can hinder their future commercialization [126].

8. 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 subjective 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 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 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, the DNA and RNA from both normal cells and cancer cells have been extracted[7]. Subsequently, whole exosome sequencing (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 utilizing nanodiscs, a novel biomaterial

based vaccine delivery vehicle, to deliver predicted neoantigens has significant potential as a cancer therapeutic [124]. When the nanodisc vaccine is combined with checkpoint blockade therapy in murine models, it has been 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 mice study 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 novel biomaterial delivery system, may be a promising direction for personalized cancer vaccines[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 processes for personalized vaccines derived from either neoantigens or a patient's own tumor are often time consuming, costly, and complex[7, 151, 401]. Therefore, future efforts should focus on reducing production time and costs during the vaccine manufacturing process so that personalized cancer vaccines can become widely commercialized.

9. 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 into the clinic, where several challenges exist. First, the differences in immune systems between laboratory animals and humans need to be taken into consideration[386]. Although humanized mouse models are utilized to better simulate a human immune system, they are unable support the development of human innate immune cells[402]. Additionally, animal models for melanoma are mostly commonly 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 factors determined such as biomarker expression[409].

This review article has covered various aspects of biomaterial-based cancer vaccines that are capable of training immune systems to selectively attack tumor cells. Different engineering approaches, including improving lymph node delivery, enhancing immune cell recruitment, tumor targeting, and tumor cell modification, have been extensively discussed. Moreover, the identification of optimized tumor antigen sequences has been indicated as a crucial step in improving cancer vaccine efficacy. Thus, extensive collaborations between immunologists, computational scientists, and bioengineers, entrepreneurs are necessary to design safer, more effective, and more translatable next generation cancer vaccines.

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Highlights

- Cancer vaccines aim to reprogram a patient's own immune cells to target and kill cancer cells.
- Barriers to the broad clinical translation of cancer vaccines include weak immunogenicity, systemic toxicity, and off-target effects.
- Advances in biomaterial technologies can overcome the challenges faced in cancer vaccine delivery.
- Nanoparticle- and implantable scaffold-based technologies improve cancer vaccine safety and efficacy.
- Looking forward, these biomaterials-based delivery technologies can be exploited to design platforms for personalized cancer vaccines.

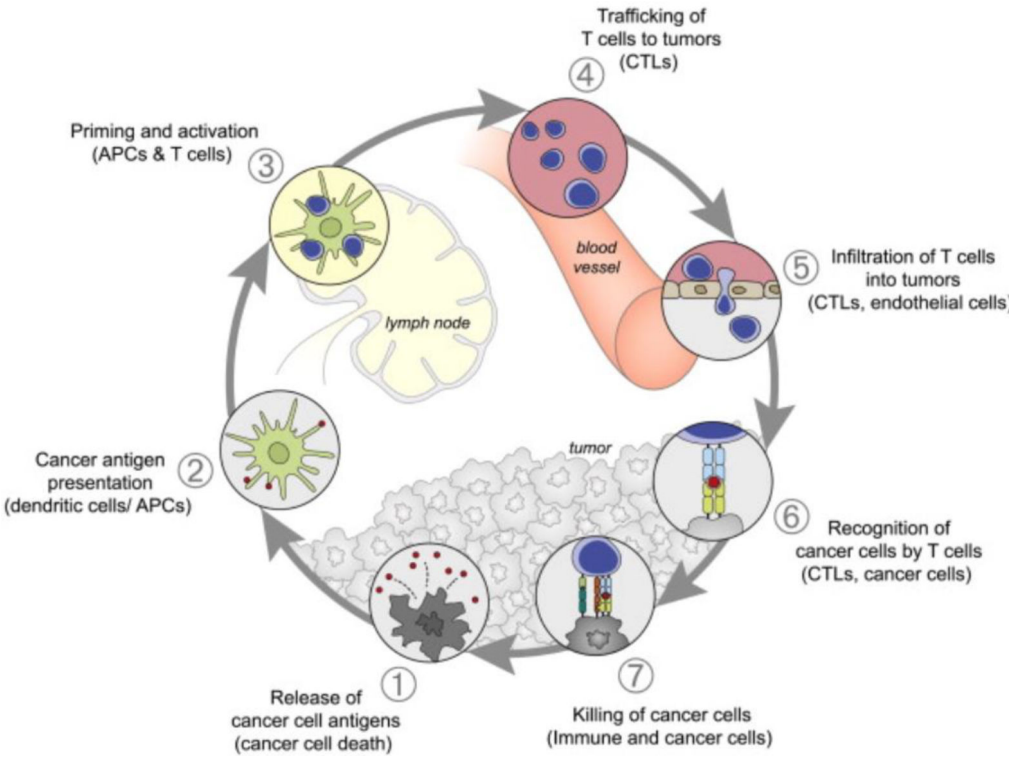

Fig. 1.

This schematic of the cancer-immunity cycle illustrates the immune response to a tumor. Ideally, successful biomaterials-based vaccine delivery technologies would enhance cancer antigen presentation. Adapted from[1]. Reprint with permission from Cell Press.

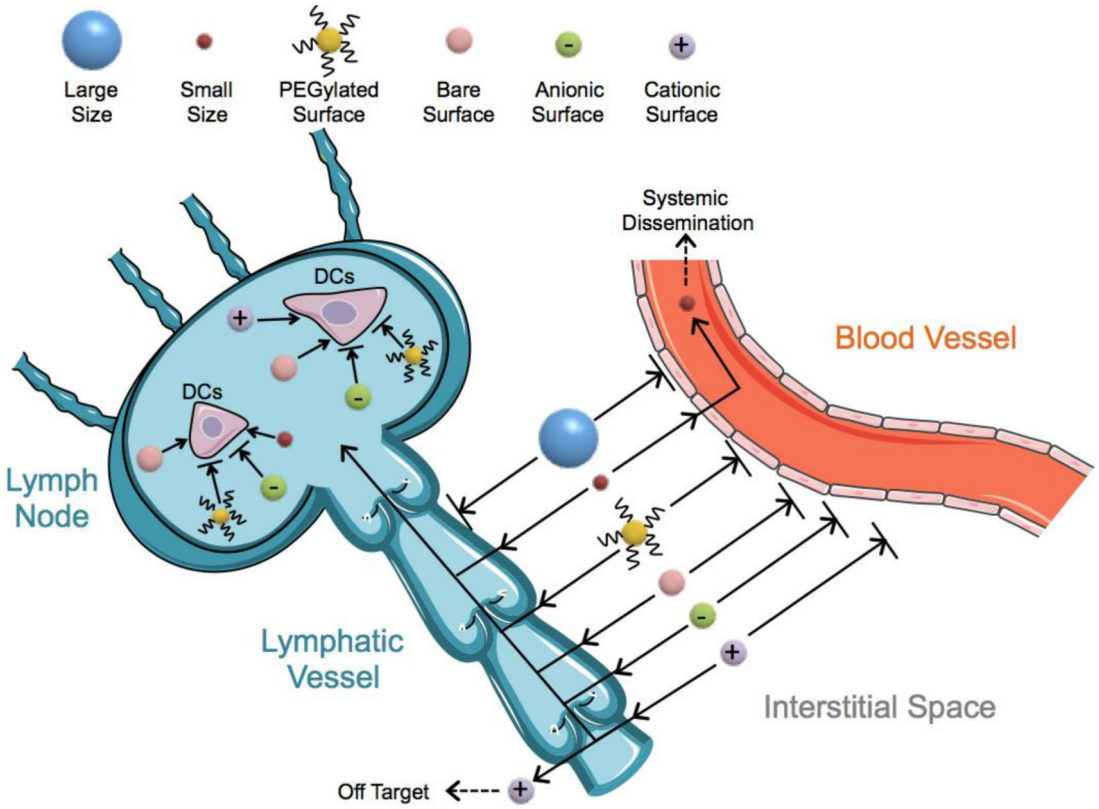

Fig. 2.

The role of biophysical properties (such as size, charge, and PEGylation) of biomaterials 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. High 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 suffer from off-target effects and toxicity.

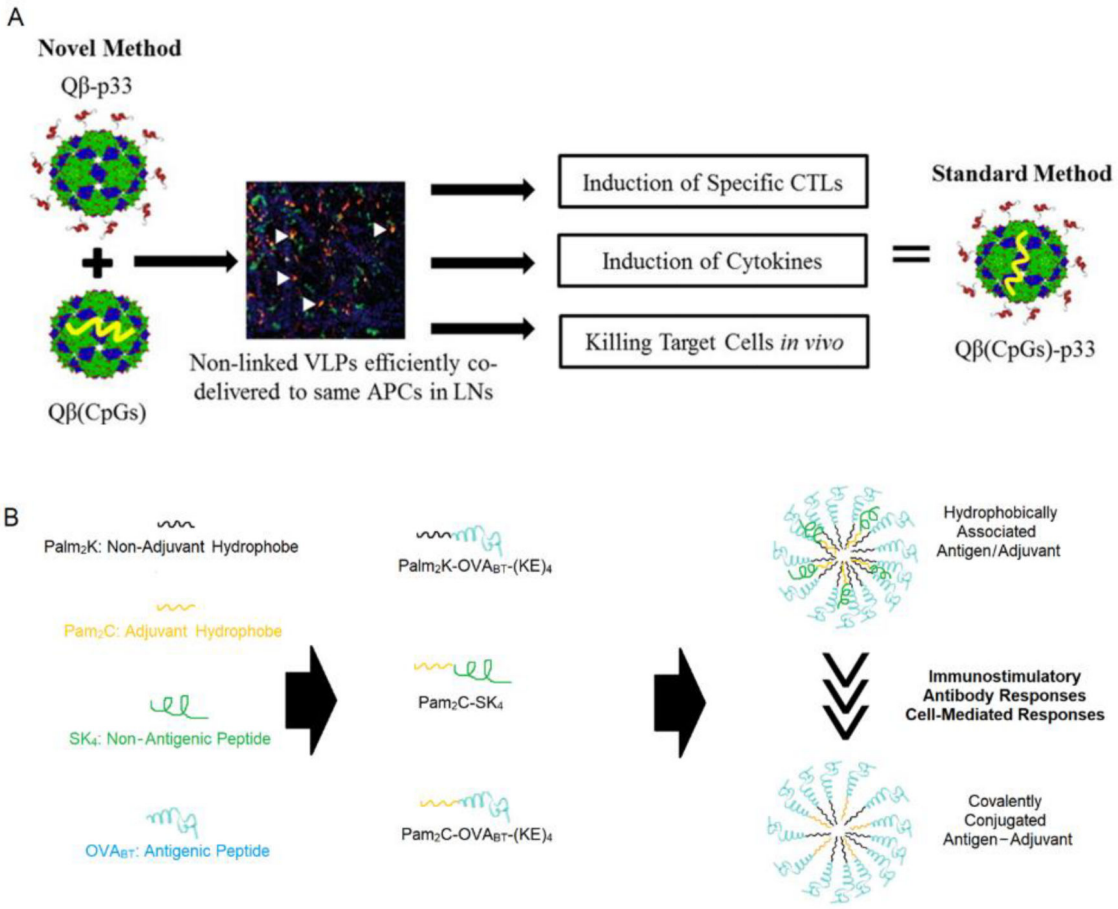

Fig. 3.

Co-localizing antigen and adjuvant to the same APCs is important and 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. (B). When antigen and adjuvant are covalently tethered, the resulting vaccine formulation induced lower immune responses than when antigens and adjuvants are hydrophobically associated.

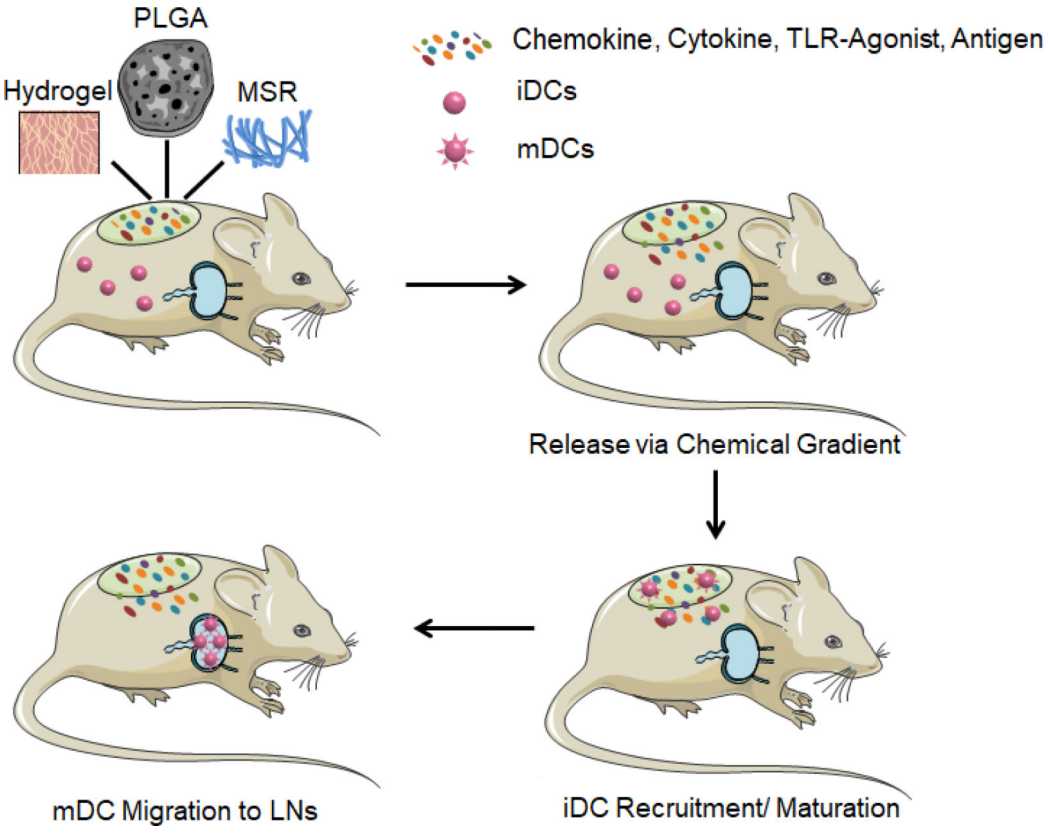

Fig. 4.

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

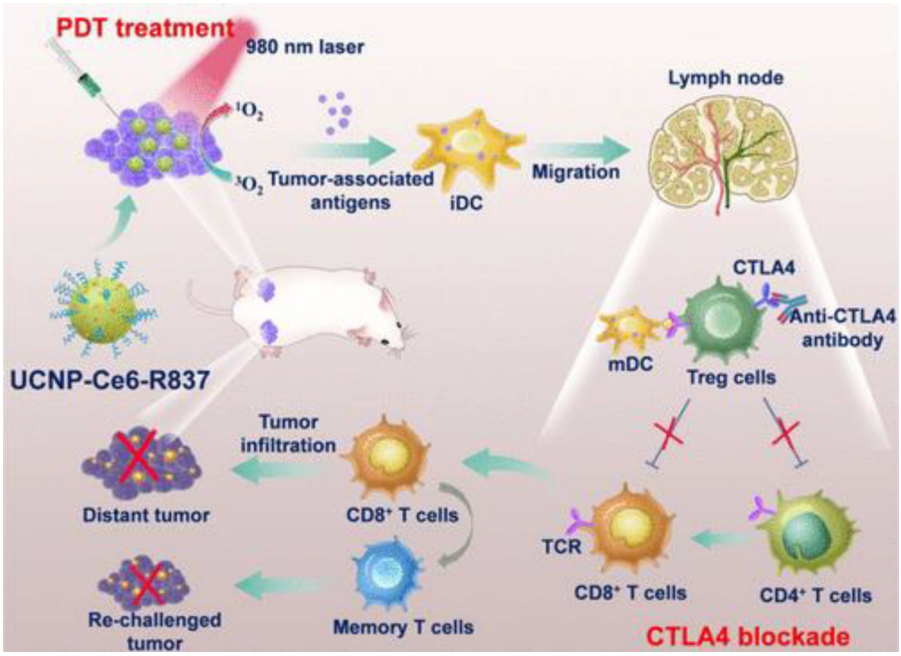

Fig. 5.

Immunomodulators turn tumor sites into antigen depots and induce anti-tumor immunity in a vaccine-like manner. Photodynamic therapy (PDT) destructs tumor cells and effectively generates TAAs. TAAs are then captured by DCs and transported to LNs, which promote strong anti-tumor immunity with the help of an anti-CTLA-4. Adapted from [335]. Reprinted with permission from ACS Publications.

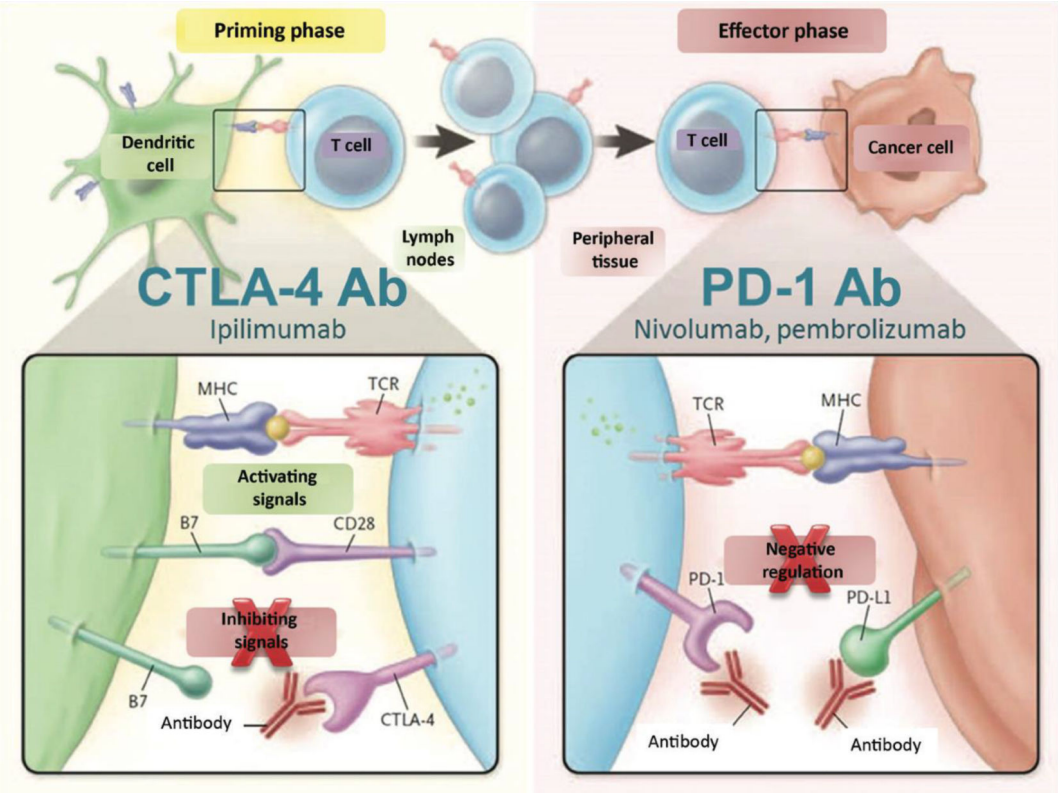

Fig. 6.

This schematic shows 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.

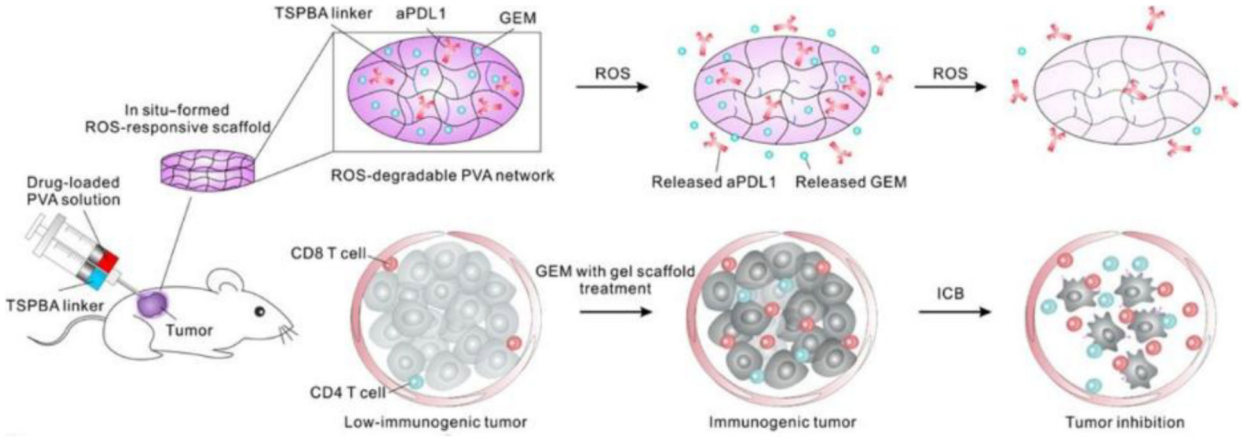

Fig. 7.

Schematic of an intratumorally injected 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 anti-tumor immunity. Adapted from [45]. Reprinted with permission from AAAS.

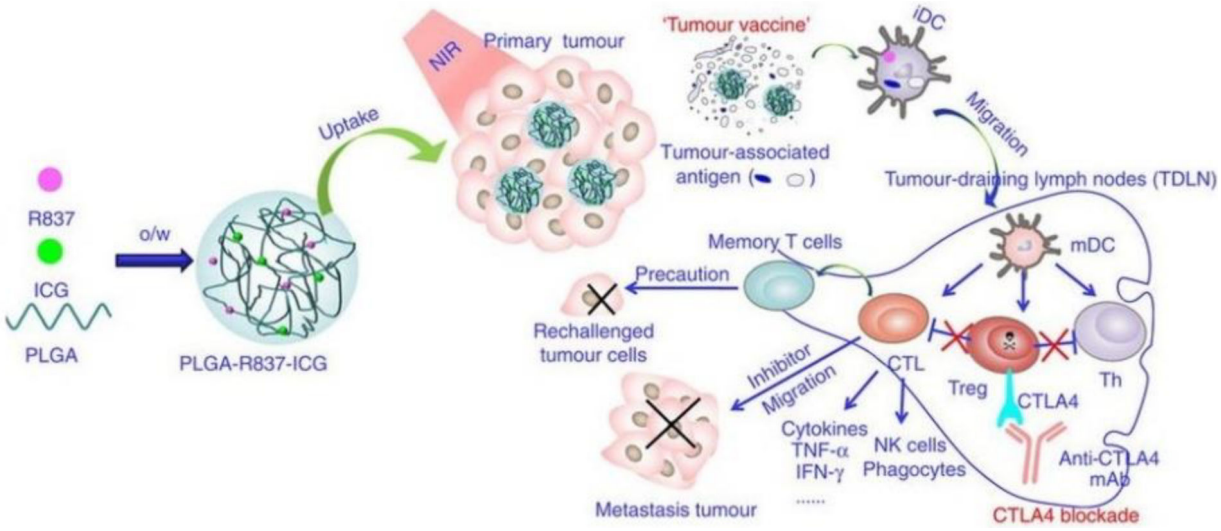

Fig. 8.

Schematic of passive tumor targeting. 100nm 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 anti-tumor immunity with the help of anti-CTLA-4. Adapted from [334]. Reprinted with permission from Nature Publishing Group.

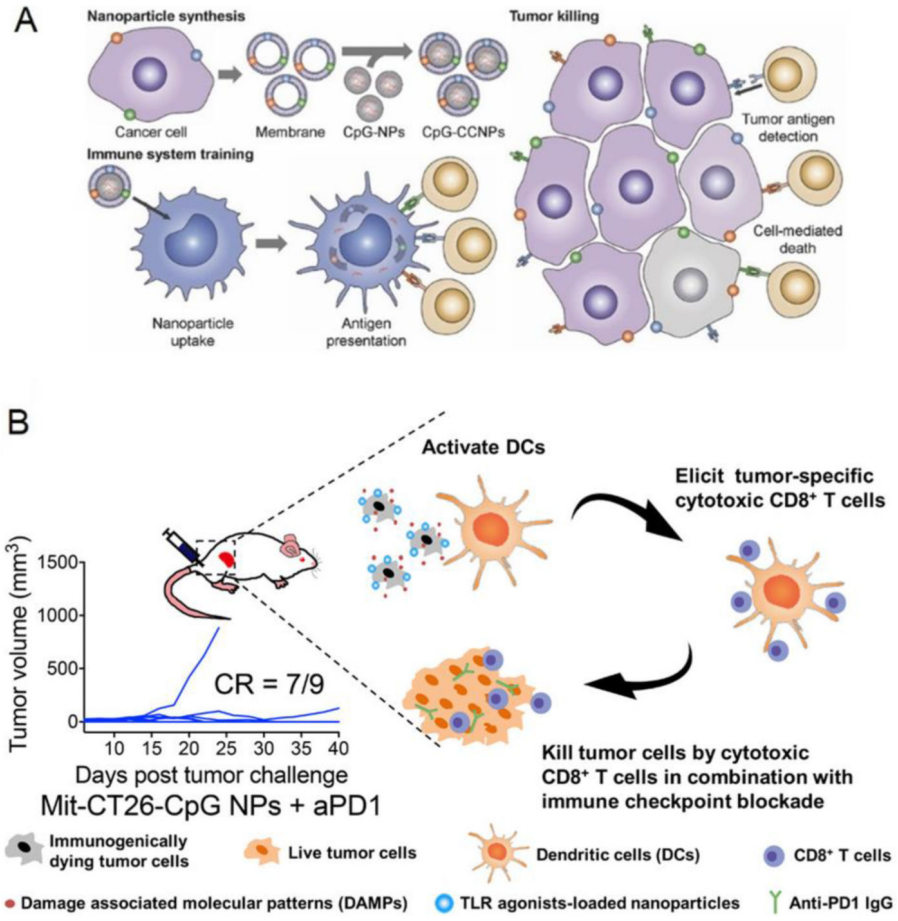

Fig. 9.

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 chemo drug, 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.

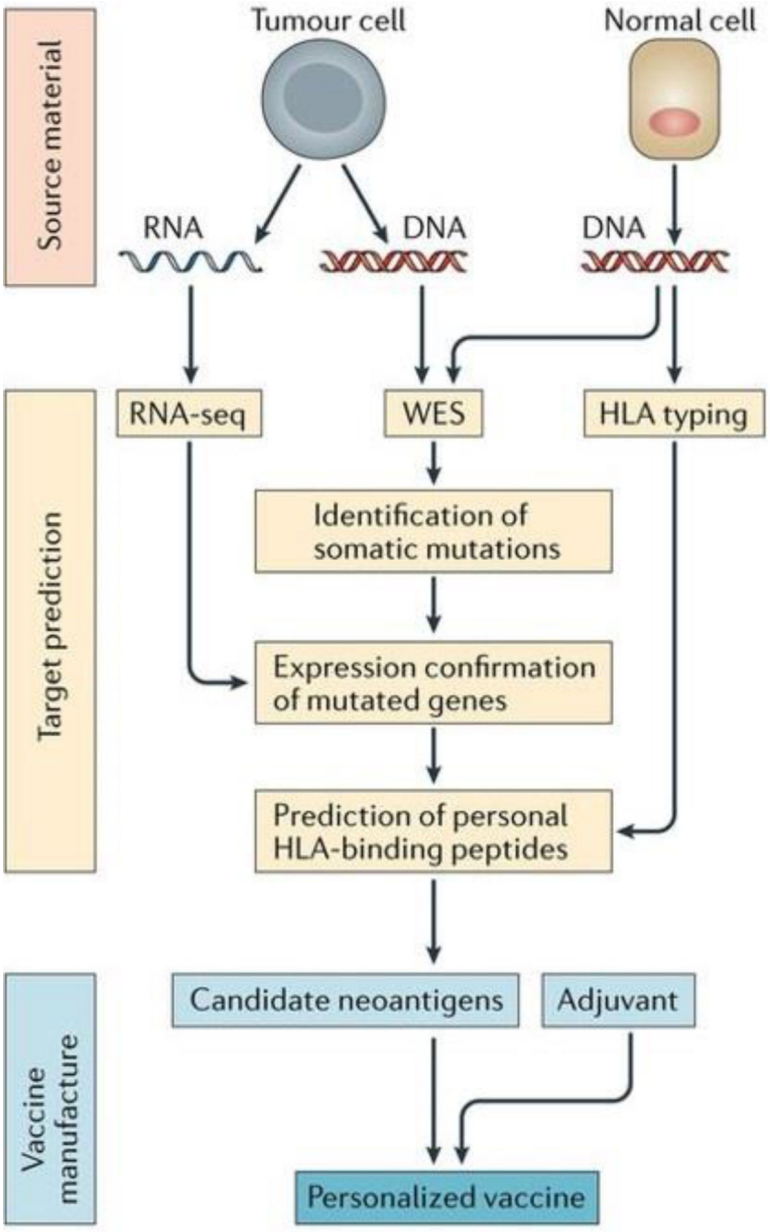

Fig. 10.

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 [124]. Reprinted with permission from Nature Publishing Group.

Table 1.

Different types of cancer vaccines in clinical development. *Denotes examples mentioned in the text

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	Nakedplasmids	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)

Type of Vaccine	Cancer	Design	Biomaterial Delivered	Delivery Strategy	Trial Number (Phase)
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)

Type of Vaccine	Cancer	Design	Biomaterial Delivered	Delivery Strategy	Trial Number (Phase)
	Colon	Radiated but live colorectal cancer cells	Modified cells	Intradermal injection	NCT02448173 (Phase 3)