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Emerging biomaterial-based strategies for personalized therapeutic in situ cancer vaccines

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Abstract

Landmark successes in oncoimmunology have led to development of therapeutics boosting the host immune system to eradicate local and distant tumors with impactful tumor reduction in a subset of patients. However, current immunotherapy modalities often demonstrate limited success when involving immunologically cold tumors and solid tumors. Here, we describe the role of various biomaterials to formulate cancer vaccines as a form of cancer immunotherapy, seeking to utilize the host immune system to activate and expand tumor-specific T cells. Biomaterial-based cancer vaccines enhance the cancer-immunity cycle by harnessing cellular recruitment and activation against tumor-specific antigens. In this review, we discuss biomaterial-based vaccine strategies to induce lymphocytic responses necessary to mediate anti-tumor immunity. We focus on strategies that selectively attract dendritic cells via immunostimulatory gradients, activate them against presented tumor-specific antigens, and induce effective cross-presentation to T cells in secondary lymphoid organs, thereby generating immunity. We posit that personalized cancer vaccines are promising targets to generate long-term systemic immunity against patient- and tumor-specific antigens to ensure long-term cancer remission.

Keywords

cancer vaccine; local controlled release; biomaterials; oncoimmunotherapy; in situ delivery

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2. Introduction

Clinical successes with oncoimmunotherapeutics have demonstrated the capability of the human immune system to eradicate cancer[1–5]. Comprehensive treatment modalities modulate host immune signaling pathways via recognition of tumor-specific components to overcome an immunosuppressive tumor microenvironment[6–11]. Immune checkpoint blockade antibodies (ICB) have revolutionized cancer treatment with remarkable tumor burden reduction in patients with hard to treat cancers [12,13]. However, ICB success is limited in solid tumors and only 13% of patients respond across cancer types[14–16]. Further, majority of responsive patients eventually experience recurrence due to immunotherapy resistance[13,16]. Consequently, there is a crucial unmet need to increase immunotherapy response rates across all cancer types. To this end, therapeutic cancer vaccines have reemerged to mobilize patient- and tumor-specific antitumor immune response[17]. By increasing immunogenicity and maintaining specificity, therapeutic cancer vaccines can evade tumor suppressive mechanisms for primary- and metastatic- tumor burden reduction[11,18,19].

Cancer vaccine development build on lessons from preventative vaccines for infectious diseases. Current Food and Drug Administration (FDA) approved prophylactic cancer vaccines with viral etiologies include HBV-associated hepatocellular carcinoma (Engerix-B, Recombivas HB, Heplisav-B) and HPV-related mucosal cancers (Gardasil, Cervarix). However, cancers with non-viral etiology are more challenging to develop. Unlike bacteria and viruses, cancerous cells resemble normal cells leading to difficulties in antigenic targeting. Therapeutic cancer vaccines, aiming to elicit in situ targeted responses, must overcome three key challenges. First, an ideal cancer vaccine must identify tumorigenic cells via conserved cell-surface markers without inducing autoimmunity. With the high diversity of tumor cell type and surface markers, there is difficulty in isolating and targeting key immunodominant antigens, potentially leading to tumor escape if unchecked. Such immunodominant antigens are still subject to central and peripheral immune tolerance. Next, to allow generalized antitumor immunity, it must surpass immune equilibrium via targeting key immune activation pathways. Lastly, care must be taken to limit systemic toxicity and off-target effects through vaccine material and design. Currently ex vivo vaccines have a high incidence of generalized constitutive symptoms (ex. fever, muscle aches, nausea, and fatigue) that remit over time[20]. Thus, improving vaccination safety is paramount for clinical translation.

Failed cancer vaccine trials can be attributed to lack of effective delivery methods[21]. For example, vaccination using unmodified peptides generated an overall response rate of 3%[22], due to difficulty in activating DCs. As such, approaches to target dendritic cells (DC) could potentially improve clinical response. Accordingly, advances in biomaterial-based delivery systems for targeted payload release could enable spatiotemporal presentation to cells and microenvironment, thus enhancing efficacy and reducing potential adverse effects. Given the diversity in vaccination approaches, different biomaterials can be used to overcome delivery challenges specific to each type of vaccine. They range from the nanoscale (e.g. liposomes, nanoparticles) to larger implantable devices or patches as well as injectable scaffolds. Further, biomaterials can be leveraged to deliver immunopharmaceutics

via different routes of administration, namely intranasal[23], oral[24], intramuscular[25,26], intravenous (NCT02410733), subcutaneous[27–30] and within or adjacent to tumor cavity[31,32].

To develop a clinically viable cancer vaccine platform, it is crucial to combine innovations in biomaterials with expanded understanding in cancer immunology (Figure 1). In this review, we will discuss emerging biomaterial-based strategies with a focus on DC-based therapeutic cancer vaccines. We will first elucidate challenges with current therapeutic cancer vaccine strategies, followed by how biomaterial-based platforms can address current obstacles. Next, we will discuss key polymeric and scaffold vaccine approaches. Lastly, we will present perspectives for biomaterial-based translational studies.

Challenges of current therapeutic vaccine strategies

Numerous therapeutic vaccine strategies and administration routes have been developed with various degrees of clinical and preclinical success (Table 1). Peptide- or protein-based vaccines have high specificity but may limit antigenic responses for widespread cancer eradication[33,34]. DNA vaccines using unmethylated, repeating cytosine-guanine (CpG) motifs have both an adjuvant and antigen effect by generating a potent and directed antibody response. However, due to their large size and negative charge, they have low cellular uptake and high off-target delivery[35,36], requiring improbably high administration doses. mRNA vaccines can encode a variety of antigens with self-adjuvanting effects and pose no infection or mutagenesis risk[37,38]. Recent success utilizing mRNA vaccines demonstrate high safety, tolerability and degree of protection against SARS-COV-2[39,40]. However, their instability and inefficient delivery, necessitating encapsulation systems linked to severe allergic reactions[41,42] may hinder these promising immunogenic effects. Additionally, their paradoxical effects on innate immunity may hinder its effect as an oncotherapeutic[43].

Cellular vaccines often target DCs, the most powerful antigen presenting cell[44], to initiate cytotoxic immunity. DC-vaccines posit a powerful regulation of key cytotoxic pathways necessary to initiate antitumor immunity[45–51]. Under investigation for numerous cancer types[52], overall clinical efficacy has yet to be achieved[52]. Further, they may induce mild to moderate toxicity[52,53]. DC-vaccines are classified by source: autologous (from patient tumors) or allogeneic (lab-generated)[54]. Autologous vaccines further divert into neoantigen vaccines, utilizing immunogenic specific antigens, or whole-cell vaccines, delivering specific and non-specific antigens. Advances in next-generation sequencing and bioinformatics have transformed our ability to identify and isolate patient-specific neoantigens over weeks to months[55–59]. While they yield favorable clinical immune responses[58,60], their complexity pose significant monetary and labor deterrents[57,58]. Conversely, whole-cell vaccines simultaneously target multiple immunodominant tumor antigens[61–64]. This expands their potential to generate favorable robust responses while limiting alloimmune reactivity[61,64–67] and tumor escape[61]. Allogeneic vaccines employ antigens identified from established cancer lines, eliminating challenging manufacturing and commercialization steps. However, lack of personalized antigens manifests poorer clinical efficacy compared to autologous counterparts[54]. Both sources necessitate numerous interventions requiring a high degree of patient adherence, often difficult to achieve[68], even with technology-based outreach efforts[69–71].

Most autologous DC-vaccines utilize ex vivo antigen-pulsed activated-DCs[53,72]. However, due to inefficient homing, less than 5% of administered DCs reach draining lymph nodes[73]. Thus, ex vivo DC-vaccines require repeated interventions on a prime-boost schedule, in potential combination with other chemotherapeutic or immunostimulatory drugs[55,73,74]. They are laboriously manufactured under strict regulation within Good Manufacturing Practices (GMP) facilities to ensure patient specificity and consistent production methods[68,72]. Batch-to-batch variability with complex GMP protocols lead to substantial monetary, time and labor cost with limited clinical benefit[52]. Therefore, although ex vivo DC-vaccines demonstrate applicability to multiple cancer subtypes, the high development cost and manufacturing challenges may impede widespread clinical use[75].

Thus far, Sipuleucel-T, an autologous ex vivo DC-based vaccine, is the only therapeutic cancer vaccine to reach the clinic. It received approval from the US Food and Drug Administration (FDA) in 2010 and European Medical Agencies in 2013 as a last-line therapeutic strategy for metastatic hormone-refractory prostate cancer[4]. With a tolerable safety profile and no demonstrated dose-limiting toxicity[76], immunization induced favorable immune responses correlating with a decline in prostate-specific antigen[76]. However, in a landmark Phase III trial, progressive disease occurred in 90% of patients[77]. Although heralded as a paradigm shift, Sipuleucel-T was plagued by notable drawbacks, leading ultimately to its termination of use. First, a single course of treatment cost USD $93,000 for a limited average survival gain of 4 months[77], limiting its translatability and use worldwide. Second, due to low manufacturing capacity, only 10% of eligible patients eligible were treated[68]. Treatment scarcity and accessibility in conjunction with reimbursement problems led to physician endorsement reluctance. Due to complex manufacturing, difficulty in administration and low sales, Dendreon filed for bankruptcy in 2014 and regulatory approval was withdrawn in Europe for commercial reasons[68].

In addition to inefficient homing, ex vivo vaccines demonstrate promising efficacy in preclinical studies but cannot be recapitulated clinically[52,78]. Reasons for clinical failure stem from variable generation, maturation and administration of DCs per dose[78]. For example, AGS-003, a combination of ex vivo DCs co-electroporated with patient's amplified tumor RNA and synthetic CD40L RNA and sunitinib, induced moderate immunological activity leading to either partial response (PR) or stable disease (SD)in 62% of patients (NCT00272649)[79]. Further, expansion of effector memory cytotoxic T-lymphocytes (CTLs) after five doses, correlated to 30 months prolonged progression free survival[79]. However, subsequent Phase II and III trials were terminated early due to lack of efficacy (NCT01582672)[79,80]. Likewise, the bioengineered GVAX and FVAX vaccines, composed of irradiated whole tumor cells genetically modified to overexpress cytokines regulating DC homeostasis (granulocyte-macrophage colony stimulating factor [GM-CSF], GVAX)[81,82] and development (fms-related tyrosine kinase 3 ligand [Flt3-L], FVAX)[83–87], have demonstrated success in Phase I and II clinical trials[83,88,89]. GVAX led to an overall increase in immunogenicity and mean survival of patients with metastatic prostate cancer, weakly correlating to dose[90]. Its success led to clinical investigations for other cancers[91] including melanoma[92], colorectal cancer[93,94], acute myeloid leukemia[95] and myelodysplastic syndromes[96,97]. Correspondingly, FVAX vaccination demonstrated a degree of cytotoxic immunity correlated with durability of clinical responses by RECIST criteria[83].

Additionally, the combination of FVAX with ICB dramatically improved tumor burden and generation of immune responses preclinically[98,99], although clinical efficacy remains to be determined.

3. Biomaterials-based cancer vaccine strategies

Need for biomaterial-based DC vaccine strategies

While most DC-vaccines demonstratively induce immunogenicity, many have failed to induce durable and meaningful therapeutic responses in clinical trials[52,100] in terms of degree of tumor burden and remission rate[101]. To address these challenges, innovations in biomaterials, biotechnology and polymer science offer alternative approaches for therapeutic cancer vaccines[102]. Harnessed since antiquity[103], biomaterials are highly versatile synthetic or natural materials used in various medical applications. In cancer, use of biomaterials have advanced drug targeting and delivery[104–107] with high clinical efficacy and improvement in patient care[108–110]. Significant advances in bioengineering and understanding of biological processes have allowed for development of macro- and micro-environments necessary for cellular manipulation[111]. To reach clinical demand, it is critical to meet four key requirements. First, platforms must be targetable for patient- and tumor-specific antigens. This ensures non-self antigen recognition, ensuring generation of cytotoxic effector T cells opposed to their regulatory counterparts. Second, strategies must be adaptable and versatile against antigenic shift from constant de novo oncogenic mutations. Third, vaccination must generate in situ immunity able to overcome the inherently immunosuppressive tumor microenvironment with efficient immune infiltration. Lastly, immune penetration into target tissue sites must self-propagate durable responses for overall survival and recurrence reduction.

Biomaterial vaccines offer numerous advantages over conventional delivery methods. Conventional systemic delivery of immune adjuvants may have off-target effects causing toxicity. Targeted co-delivery of antigens and adjuvants can limit deleterious effects. By tuning the physical properties of therapeutic cargos, targeting moieties and vehicles (ex. size, morphology, charge, physiochemistry, or porosity), biomaterial vaccines can achieve site-specific delivery with desirable release kinetics. Sustained delivery of antigens and adjuvants via a vehicle or platform could avoid repeated administrations while providing a personalized in situ vaccine platform. These vaccines can generate an immunostimulatory microenvironment to continuously recruit and activate endogenous DCs in situ without further external manipulation or modulation. In this review, we highlight key strategies ranging from the nanoscale, including nano- and microparticles[112–121], liposomes[122,123] and combinatorial approaches with current front-line therapeutics[124], to larger implantable and injectable scaffolding systems[29,30,112,125–132] (Figure 2, Table 2).

Particulate-based vaccines

Particulate-based methods have long been used to enhance therapeutic delivery to specific tissues sites without off-target or systemic adverse effects. Here, we will explore key particulate in situ cancer vaccines leveraging liposomes, nanoparticles and cell-fusion particles.

Liposomes and other lipid-based platform strategies—One of the first vaccine carrier systems, liposomes and their derivatives are a favored delivery system due to their potential for rapid clinical translation, as there is a precedent for FDA approved liposomal-based formulations[123]. Liposomes are comprised of an outer hydrophobic bilayer with an inner hydrophilic core, rendering them suitable for encapsulating both hydrophobic and hydrophilic therapeutic cargo. Due to their inherent versatility and plasticity, liposome formulations carrying adjuvants demonstrate stable formulations with long depot effect at the site of injection[123].

Often delivered via intramuscular or subcutaneous injection, liposomes can be easily modulated via addition of stability enhancers such as polyethylene glycol (PEG) and can carry a variety of cargo including novel antigenic fragments and immune adjuvants[123]. However, once released, lipid-based vaccines cannot be retrieved potentially leading to unequal and uncontrollable responses after administration. Further, significant work is required to increasing loading capacity, improving stability, and minimizing toxicity of liposome-based approaches.

When co-administered with standard-of-care chemotherapy regimens, clinical trials demonstrate favorable Phase I and Phase II results. However, these clinical trials do not lead to clinically relevant impact on overall survival or limiting disease progression[133]. For example, the BLP25 (L-BLP25; tecemotide; Stimuvax®) vaccine is a liposome-conjugated vaccine containing MUC1 peptide, a commonly overexpressed and aberrantly glycosylated membrane protein in most adenocarcinomas[20,122,124,133]. In the Phase III START trial, patients with unresectable locally-advanced non-small cell lung cancer received neoadjuvant chemoradiotherapy with BLP25[124,133]. While treatment did not manifest significant impact in overall survial with neoadjuvant therapy, a small subset of patients who received adjuvant chemotherapy experienced improved overall survival. When repurposed for therapeutic use in human epidermal growth factor receptor 2 (HER2+) breast cancer, no reduction in residual cancer burden was observed in Phase II trials[20]. An additional follow-up Phase III trial was planned to study vaccine effect patients receiving concurrent chemotherapy (START2, NCT02049151); however, negative results in other subgroups led to trial suspension[17]. Clear dose-dependent effects in similar lipid-based strategies[134] demonstrates the need for a refillable vaccine platform to confer lasting immunity without repeated administration.

While conventional liposomes have mixed clinical efficacy, novel use of lipid-based structures preclinically has led to the development of the nanodisc. Composed of cylindrical synthetic high-density lipoproteins, the nanodisc combines two Toll-like receptor (TLR) agonists, monophosphoryl lipid A (MPLA) and CpG-rich oligonucleotide (CpG-ODN) targeting TLR4 and TLR9 respectively, which can be readily combined with tumor-specific antigenic peptides and proteins[118]. Nanodisc subcutaneous vaccination demonstrated strong induction of the humoral response leading to antitumor efficacy in cervical cancer [119] and melanoma[121] murine models. It can also co-deliver chemotherapeutics, establishing broad induction of antitumor efficacy in 88% of mice immunized against colorectal carcinoma with 100% rejecting tumor rechallenge[120]. In combination with ICB, such as PD-1 and

CTLA-4, the nanodisc can further synergistically improve vaccination efficacy, eradicating 90% of colorectal carcinoma[120] and melanoma[121].

While these preclinical successes are promising, the nanodisc may pose serious limitations impeding translation. First, it requires neoantigen usage for tumor specificity. As discussed previously, while murine models have predetermined, easily identifiable highly specific and immunogenic neoantigens, finding such antigenic markers in heterogeneous human tumors is laborious. Consequently, the relative simplicity of neoantigen identification in murine models is not immediately translatable to humans and thus limits translation[68]. Additionally, it has demonstrated efficacy within a small tumor window that is not representative of clinical scenarios with large tumors at diagnosis. Thus, therapeutic efficacy may not be recapitulated in metastatic advanced tumors. Lastly, it requires multi-dose therapy to achieve therapeutic efficacy. This platform is unable to be refilled or rescaled in relation to tumor burden. Clinically, the nanodisc regimen would be no different from multi-dose single-administration of ex vivo vaccines[52,89]. As such, although the nanodisc is promising, further work is required to improved therapeutic loading with limitation to cancers with known tumor-specific antigens.

Although ICB has garnered widespread FDA approval for a variety of hard-to-treat malignancies, clinical efficacy is delayed and limited to a small subset of patients exhibiting ideal mutational load and host immune profile[135,136]. One method of improving clinical response hinges on transforming an immunologically cold tumor into a hot immune microenvironment through use of vaccines as a priming agent. Cancer vaccines co-administered with ICBs induce immune infiltration corresponding to increase in efficacy via host-directed therapy. In a Phase I study, a lipid-encapsulated personalized neoantigen mRNA nanovaccine (mRNA-4157, Moderna, NCT03739931) demonstrated high clinical safety, tolerability, immunogenicity and overall response in a variety of malignancy types[137]. Each vaccine, encoding up to 20 patient-specific neoantigens, was intramuscularly administered up to 9 times every 3 weeks. Patients with metastatic infiltrations were co-treated with pembrolizumab (Keytruda ®) a monoclonal anti-PD-1 antibody, regardless of prior non-response rate to PD-L1 inhibitor therapy. 85% and 66% of patients receiving vaccination monotherapy or combination therapy respectively displayed some effect ranging from stable disease (SD) to complete response (CR) by RECIST criteria. Of these, two patients demonstrated either CR or PR after previously failing PD-L1 inhibitor therapy[137]. Thus, mRNA-4157 exhibits potential to prime the host immune system to allow further ICB synergistic efficacy.

PLA and PLGA nanoparticles—Nanoparticles display target specificity to tissue of interest, based on size, charge, surface properties and dissemination strategy, and thus have been extensively investigated for oncotherapeutic delivery[138]. Such nanoparticles can deliver therapeutics to the targeted site with limited off-target accumulation. Poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polyethylene glycol (PEG) are the most commonly used co-polymers to synthesize nanoparticles and their slightly larger counterpart, microparticles, as biodegradable antigenic carriers. Both co-polymers are used in a number of FDA approved therapeutics[139]. These co-polymers have modifiable degradation rates, ensuring constant delivery of antigens with minimal toxicity[139,140].

Variation in coating and encapsulation compounds can help target nanoparticles to potentiate immunogenic responses. Notably, therapeutic application of PLGA nanoparticles coated with agonistic anti-CD40 encapsulating target antigens and adjuvants (NP-CD40) mediated delivery to DCs to induce antigen-specific CTL responses[141]. NP-CD40 enhanced DC maturation, CD4+ T cell proliferation and subsequently stimulated IFN-γ production in vitro leading to selective and efficient immunity in prophylactic and therapeutic challenges. Vaccination with NP-CD40 in tumor-bearing mice induced statistically smaller tumor burden leading to prolonged overall survival[141]. In addition to CD40 targeting, other immune adjuvants have been explored as immune potentiating particulate targets. For example, CpG ODN and polyriboinosinic:polyribocitidylic acid (polyI:C) have been extensively investigated as an antigen delivery system targeting DCs[142,143]. The effect of PLGA particulate systems incorporating TLR ligands on immune response has been reviewed by Silva et al[144]. Particulate targeting is critical to broadly boost immune responses against specified tumor antigens; however, they do require encapsulation of a known immunogenic antigen and were studied in early stage tumors.

To further enhance nanoparticle targeting and formulation, particulate cores with immunostimulatory agents, can be enveloped using tumor cell membranes to deliver TAAs efficiently to DCs in situ[117,145–148]. Similar to development of tumor lysates, tumor membranes are isolated via hypotonic lysing and processed via mechanical disruption[145]. With immune adjuvants, this has shown efficacy in preventing tumor growth in prophylactic[149] and therapeutic[145] murine melanoma. However, it requires frequent and repeated vaccination to protect mice from tumor growth. Additionally, in combination with ICB, long-term survival was found in half of melanoma-bearing mice[145]. These preclinical studies demonstrate that although an appropriate antitumor response is elicited, multiple doses with a complicated protocol makes it difficult to develop consistently active personalized vaccines.

Other preclinical strategies hinge on the development of microparticles for antigenic targeting. In murine models, mesoporous silicon vectors can efficiently encapsulate and co-deliver antigenic peptides and dual TLR-agonists, inducing potent antitumor immunity to prolong survival[113]. For example, calcium carbonate microparticles can encapsulate immune adjuvants and antigen with high loading capacity versus PLGA scaffolds[112]. Further, PLGA microparticles embedded with tumor lysates demonstrated 42% reduction in breast cancer induced lung via prime-boost vaccination with free TLR adjuvants[116]. These microparticles can be delivered subcutaneously[116], intravenously[113] or via oral gavage[114,115], inducing effective host immune responses.

Despite the wide variety of particle-based strategies, only ten have advanced to the clinic in both the United States and Europe[150,151]. Therapeutic efficacy is limited by delivery efficiency; only 0.7% (median) of a nanoparticle dose is delivered to the intended tumor site[138]. Therefore, nanoparticles used as cancer vaccines must overcome this fundamental delivery limitation to accelerate translation. Although PLGA nanoparticle coating allows for targeted localization of cargo[148,152], the low loading efficiency, specifically for hydrophobic compounds, necessitates large dosing to achieve therapeutic effect[139]. Due to their size, particle-based therapies are rapidly internalized by phagocytic cells and often require

repeated frequent vaccination to achieve intended immunity[138]. Notably, smaller particles induce the strongest antigen-specific T cell response[153]. Further, nanoparticles often highly rely on charge-based delivery and thus are limited to a cargo of peptides with defined sequences or naturally charged molecules such as DNA or mRNA[154].

Exosomes—Membrane-bound extracellular vesicles, including exosomes, microvesicles and apoptotic bodies, produced from the endosomal compartment of most eukaryotic cells, are used as drug delivery vehicles. Exosomes derived from DCs (Dex) display similar surface expression markers and can induce antigen-specific tumor regression in murine cancer models[155]. Dex can be engineered to express specific immunostimulatory molecules as well as incorporate TLR ligand adjuvants or mRNAs encoding neoantigens or immune signaling pathways modulators[156]. Dex is currently being investigated in clinical trials as cancer vaccines for advanced NSCLC and metastatic melanoma[156,157]. Although disease stabilization was achieved, the limited clinical efficacy emphasizes the need for enhancing Dex activity.

Tumor cell-derived apoptotic bodies engineered to deliver immunostimulatory CpG DNA represents another avenue of research[158,159]. In two Phase I studies, autologous tumor cells were harvested from patients and treated with antisense oligodeoxynuclotide against insulin-like growth factor receptor-1 (IGV-001) to induce apoptosis and release exosomes containing tumor antigens (NCT02507583, NCT01550523)[25,26]. Treated tumor cells were encased in a surgically implanted diffusion chamber in the abdomen, generating a slow-release antigen-depot to mediate the host immune system against recurrent glioblastoma and astrocytomas. While IGV-001 is generally well-tolerated, the multistep surgical timeline may contribute to adverse events. Following an invasive debulking craniotomy, loaded chambers are placed between the rectus sheath and rectus abdominis muscle on post-operative day (POD) 1 and removed either on POD 2 or 3, all performed at bedside. Additionally, due to pain and immobility, patients were subjected to long-term thrombosis prophylaxis for 3 months with repeated frequent ultrasound evaluations. Six patients suffered from adverse events including hematomas, wound complication and deep vein thrombosis[25,26]. While these adverse events were Grade 3 and less, care must be taken to ensure minimal effect on patient quality of life when designing and administering therapeutics. Additionally, protocols manufacturing and administering extracellular vesicles vary wildly leading to concerns and open questions on isolation protocols and related costs, loading techniques, establishing cGMP-grade preparation, therapeutic dosing regimen, and administration methods[160]. Detailed review of exosomes, representing an innovative strategy for cell-free therapeutic cancer vaccination, are reviewed in detail elsewhere[157,161].

In a Phase I trial for malignant astrocytomas, IGV-001 within these commercially available diffusion chambers fitted with 100nm filters resulted in observable clinical improvements in 75% of patients. Further, 37.5% of these patients manifested spontaneous regression at local and metastatic sites[25]. When applied in newly diagnosed glioblastoma followed by standard chemoradiotherapy, median progression-free survival (PFS) significantly improved by 3.3 months compared to standard of care. Furthermore, PFS was shown to be dose-dependent with an increase of 10.5 months at the highest exposure. Patients with de novo methylation of O^6-methylguanine-DNA-methyltransferase promoter (MGMT) had

maximum PFS benefit of 38.4 months[26]. This clinically meaningful improvement correlated with an increase in serum IL-17, likely due to its induction of many immune signaling molecules and cells types[26,162]. To further investigate the clinical and immunological impact of IGV-001 therapy, enrollment in a Phase II trial is currently open (NCT04485949). Overall, extracellular vesicles represent important facilitators of an antigen-specific cytotoxic response and may be effective in a combinatorial treatment regime. However, significant work is required to overcome manufacturing challenges to induce reproducible mediation of immune responses to reach their full potential.

Injectable mesoporous silica nanoparticles—The aforementioned particulate-based drug delivery systems allow for targeted drug delivery using a specific niche of drugs due to solubility, surface charge and encapsulation efficancy[163]. However, such delivery systems often demonstrate high variability in delivery efficacy dependent on cellular interactions, especially within the tumor stroma[138]. Mesoporous silica-based (MPS) approaches aim to address these challenges leveraging their well-established drug carrier properties and high versatility in conjunction with other materials[164].

Silica is a well-known biocompatible chemical catalogued as “Generally recognized as safe” by the FDA (ID Code: 14808–60-7). MPS systems are composed of nano-sized spheres or rods of silica in a predetermined non-specific geometric arrangement. This generates a large surface area for cargo loading and cellular infiltration. Addition of functional groups[165] and capping treatment[166] can further fine-tune idealized chemical and physical properties. MPS platforms can boost dissolution of poorly water soluble drugs[167], expanding the potential drug candidates that can be loaded. Prophylactically, MPS nanoparticles with CpG ODN and model antigen demonstrated enhanced DC activation and antigen presentation. It led to induction of antigen-specific cytotoxic responses with significant suppression of tumor growth with immune memory in murine melanoma[168], highlighting its feasibility and applicability.

Scaffold-based delivery systems

Scaffold-based vaccines are structures intended to initiate antitumor immunity locally at the implantation or injection site[7,169]. For in situ cancer vaccines, most deliver stimulatory adjuvants and antigens to induce in situ DC homing and subsequent antigen-specific immune activation. They often target DCs residing in the skin, subcutaneous tissue and circulating in the blood.

In addition to encountering foreign antigens, DCs require presence of a secondary ‘danger signal’ to induce protective T-cell immunity[62]. Classically, these signals emerge from tissue injury or from cytokine and chemokine secretion from immune activation[62,170]. While multiple physical adjuvants can induce reaction[171–174] and are commonly used in preventative vaccines[174,175], biomaterial research demonstrates inorganic materials and man-made technologies can also activate these required danger signals. Thus, in situ cancer vaccines utilizing scaffolds must be designed to address three key criteria. First, they should be macroporous, enabling the infiltration and dispersing of appropriate cells from peripheral tissue without inducing cellular or systemic toxicity[176]. Ideal pore size can promote cell

infiltration, adhesion and activation. However, optimal pore size must be carefully tailored to cell type to ensure homogenous spatial differentiation[177,178]. Second, bioinert scaffolds should release immune potentiating adjuvants, such as cytokines[89] and TLR-agonists[179] or their synthetic derivatives, capable of recruiting DCs. Upon antigenic presentation, either via neoantigens or tumor lysates, recruited infiltrated DCs must undergo activation steps necessary for inducing antitumor immunity[67]. Lastly, an ideal scaffold must be clinically translatable; it should address and obviate any patient adherence issues posed by current non-scaffold based strategies[58].

Dual scaffold-particulate combinatorial therapeutics—Scaffold-based strategies can also be used in combination with particulate formulations to enable geometric control of therapeutic cargo release. Spatiotemporal kinetic control is often enabled through use of hydrogel or mesoporous silica micorods (MSR) scaffolds. Such nanocarrier systems have been used in a multitude of delivery modalities[180,181] to modulate immunity. For instance, differences in charged functional groups on mesoporous silica nanoparticles (MSN) can direct distribution to certain cell types. Concurrently, 3D printed hydrogels can modulate surface chemistry to augment cellular uptake[182]. This strategy has been adapted to attune immune responses via loading immunostimulatory therapeutics within MSN. One formulation delivered ovalbumin (OVA) and CpG-ODN via MSN coupled with mesoporous silica microrods (MSR) loaded with GMCSF[183]. Once activated within the MSR macroporous scaffold, DC were able to generate antigen-specific T cells and inhibit murine melanoma burden locally[183]. Additionally, synergistic combination with four doses of intraperitoneal α-CTLA4 antibody further inhibited tumor growth. Although this suggests combinatorial vaccines efficacy, the need for repeated systemic α-CTLA4 antibody dosing may cause deleterious immunosuppressive effects. Further, the administration schedule does not address limitations to patient adherence complicating traditional DC vaccines.

Implantable PLGA scaffolds—Vaccine success hinges on the biomaterials used to initiate and sustain the required immune response. Although many scaffolding materials are available, PLGA scaffolds are a cornerstone for implantable scaffold-based vaccines owing to their use in multiple FDA approved pharmaceuticals. In one seminal preclinical study, implantable PLGA scaffolds continuously released GM-CSF and tumor-specific lysates to specifically recruit and activate DCs in situ (WDVAX)[132]. This subcutaneously implanted scaffold extended survival time in 90% of mice challenged with murine melanoma[132]. A single vaccination maintained local and systemic immunity, resulting in complete regression of primary and distant melanoma tumors in 47% of mice[131]. In intracranial glioma, WDVAX extended overall survival in 90% of rats[130,184] with a single vaccination. These successes led to an ongoing Phase I clinical trial of WDVAX for Stage IV metastatic melanoma (NCT01753089)[185] and licensing by Novartis for commercial use. One scaffold is implanted every 3–4 weeks for total of four implantations per patient. It is important to note clinically, intracranial implantation requires potentially dangerous and lengthy surgical procedures[185]. Additionally, PLGA matrices may damage or denature antigenic structure. In addition, the need of organic solvents for processing may lead to subclinical toxicity with limited preclinical detection.

Injectable hydrogel-based scaffolds—Injectable hydrogel scaffolds offer an appealing alternative to surgical implantation. Hydrogels can control the rate of adjuvant and antigen delivery while ensuring biocompatibility and biodegradability. These semisolid gels can be loaded with bioactive molecules forming an enriched microenvironment for cellular interaction[128,186]. In addition to the previously discussed PLGA, two of the most common polymer structures for cellular encapsulation are sodium alginate[187] and poloxamer 407 (pluronic F-127, PF127)[188,189]. Both are commercially available, allowing for straightforward application without the use of harsh organic solvents. Alginate is an anionic biopolymer widely used due to its biocompatibility, hydrophobicity and ease of chemical modifications[186]. Unless modified, alginate requires ionic crosslinking to undergo the sol-to-gel phase transition required for many biomedical applications[128]. Thus, vaccine strategies employing unmodified alginate require surgical implantation. Conversely, PF127 is a thermosensitive gel, undergoing gelation at physiological temperature. Thus it is an appealing hydrogel for injectable vaccine delivery[188] and sustained release depot of antigens and adjuvants[189–191].

Mooney et al. have developed a methyacrylated-alginate cryogel with shape-memory properties for easy injection[192]. This pre-formed cryogel is loaded with immune adjuvants and tumor lysates similar to WDVAX[132]. Cryogels generated in situ immune cell recruitment and trafficking and conferred long-lasting prophylactic immunity in 80% of melanoma mice[29]. However, it has a limited encapsulation efficacy and released 80% of its contents within the first week[29]. Intended to be degradable, the cryogel scaffold cannot be refilled with additional adjuvants. Thus, multiple vaccinations may be required to release sufficient immune adjuvants and tumor antigens to maintain immunity. This approach is limited to previously identified highly antigenic tumor models and does not extend to different cancer subtypes with both identified and unidentified antigens.

Chemical modification of PLGA can confer thermosensitive properties for in situ gelation. Mice immunized with PLGA hydrogels demonstrate successful DC recruitment and maturation, extending overall median survival time with reduced tumor burden. However, as with other immunization schemes, repeated systemic administrations of tumor antigens and replication-defective transduced DCs were required[127]. Addressing these limitations, another study immunized mice using PEG-PLGA hydrogel co-encapsulating GM-CSF and ovalbumin nanoparticles. This vaccination strategy released adjuvant and nanoparticles for 13 days, generating cytotoxic immunity prophylactically[129]. While promising, use of both scaffold- and nanoparticle-based delivery systems increases the drawbacks of associated with both methods.

In parallel, Li et al. have developed an injectable self-assembling hydrogel by chemically modifying key tumor peptides co-loaded with immune modulators[31]. Preclinically, these hydrogels are co-loaded with thienotriazolodiazepine (JQ1, abromodomain-containing protein 4 inhibitor) and indocyanine green (ICG, photothermal dye capable of excitation in situ by NIR irradiation) along with autologous fixed tumor cells. Use of JQ1 activates DC-mediated antigen uptake and consequent expansion of CD8+T-cell antitumor clones[193]. Additionally, they promote an activated immune microenvironment by reducing expansion of myeloid-derived suppressive cells[193]. Light-triggered release of cargo penetrated tissue

in the murine 4T1 triple negative breast cancer model. Additionally, it accelerated DC maturation in vivo corresponding to an increase in CD8+T-cell frequency and cytokine release by 2.7-fold[31]. Vaccination post surgical resection further induced a systemic immune response by blocking recurrence and distant metastasis for up to 30 days. However, this strategy is limited by complex manufacturing and repeated doses with in the surgical bed to ensure immune modulation. Further, efficacy hinges on adequate light penetration into tumor tissues. Tumors seeded deep into the body (ex. colorectal tumors, pancreatic tumors) or in an inaccessible location (ex. lung nodule, prostate tumors) will likely exhibit lower clinical success. Thus, while this strategy is a promising direction, these limitations must be addressed for widespread benefit.

Injectable mesoporous silica-based scaffolds—Previously discussed MPS can be utilized as an implantable 3D scaffold for in situ sustained cytokine release and cellular infiltration[27,28,113]. Injectable MPS scaffolds utilize high aspect ratio particles for higher cellular uptake compared to spherical particles[194,195]. Preclinically, mice were injected with spontaneously assembling loaded MPS rods form a macroporous 3D environment prime for cellular trafficking[28]. Mice prophylactically immunized exhibited significantly delayed lymphoma growth compared to bolus adjuvant delivery[28]. Although enhanced systemic serum antibody levels was observed, sustained release of immunotherapeutics was not achieved. Burst release of 80% and 60% of CpG and antigen peptide, respectively, occurred within the first day[28], resulting in the plateau in DCs recruitment by day 3. Further testing therapeutically with sustained release of adjuvants is warranted.

MPS scaffolds can be combined with polyethyeneime (PEI) to increase vaccine efficacy via stimulation of Damage-Associated Molecular Patterns (DAMP) receptors for DC signaling[27,125,166]. PEI is a potent mucosal adjuvant that forms nanoscale complexes with antigens, inducting DC homing to lymph nodes and cytokine response[125]. Immune modulation eradicated established lung carcinoma in 80% of mice and generated sustained immune memory[27]. With ICB, PEI-enhanced scaffold induced a T-cell response with enriched in situ cytokine release correlating to lung metastasis erradication[27]. PEI greatly enhances this scaffold’s therapeutic value, enabling robust vaccination. Further, it can be loaded with multiple neoantigens simultaneously, inducing immune-mediated responses in synergy with other immunotherapies.

Implantable non-degradable DC homing devices—Our lab has significant expertise in designing implantable medical devices for sustained and constant release of therapeutic cargo for different medical applications[106,107,196–200]. We have developed an immunostimulatory niche capable of maintaining allogeneic cell encapsulation and transplantation. This 3D-printed device allows for sustained local release of immunosuppressive drugs to ensure local allogeneic graft survival within our scaffold[198,199,201]. Building on this device for cell transplantation, we developed the NanoLymph, a biomaterial-based cancer vaccine platform capable of generating an immunostimulatory niche to recruit, activate and potentiate DCs in situ[202]. The NanoLymph is a subcutaneously implantable device with dual reservoir platform for immune adjuvants and hydrogel-encapsulated antigens (Figure 3). Through the sustained and constant elution

of immune adjuvants such as GM-CSF and TLR agonists via nanoporous membranes, the NanoLymph generates a cytokine gradient extending into the local tissue. This gradient recruits DCs, allowing them to interface directly with autologous tumor antigens within the cell reservoir. Activated DCs then mobilize to secondary lymphoid organs to trigger antitumor immunity. By providing constant elution of immune adjuvants, continuously recruiting DCs locally, the NanoLymph is designed to address and improve upon previous biomaterial-based vaccine platforms. The ability to be drug-agonistic, personalizable in terms of autologous antigen loading and refillable, offers design features that address unmet needs in implantable platform technologies.

4. Considerations for efficient vaccine development and future outlook

Over the past decades, improvements in material science, bioengineering, and cancer immunotherapy have ushered in a new era for cancer vaccines as a promising therapeutic modality. These vaccines can modulate key steps in the cancer immunogenic cycle in two ways. First, vaccine platforms can provide an *in situ* antigen depot for immunogenic personalized tumor antigens. Second, such engineered strategies aim to provide costimulatory activation to DC cells, potentiating effector cytotoxic T-cell mediated immunity and dampening suppressive regulatory T cell responses[203,204]. Thus, cancer vaccines aim to induce effector T-cell infiltration and homing to tumors, combating the inherently immunosuppressive tumor microenvironment. Inadequate therapies may target one step of this cycle but fail to spur impactful effects due to failure of other components. Therefore, an optimal immunotherapeutic must be targeted and adapted to immunogenic antigens of any subtype, induce a self-propagated systemic response, penetrate target tissues and establish immune memory to prevent remission and ensure long-term disease-free status. In this review, we discuss how biomaterials can be applied to vaccine strategies to devise clinically-relevant vaccine platforms. We believe that this combination can amplify and enhance clinical response rates of vaccination treatments.

Effective personalized cancer vaccines may serve dual benefit by inducement of the abscopal effect. This elusive effect, traditionally defined through use of radiotherapy, is the regression of a non-treated distant tumor following local treatment[205]. Often demonstrated in conjunction with radio-immunotherapy, this phenomena supports evidence for local immunogenic cell death (ICD) to catalyze downstream cellular responses mimicking a viral infection[206]. By generating ICD, targeted local cancer vaccination can induce tumor-specific CTL responses capable of attacking both local and distant tumor sites. Utilization of biomaterials for vaccine formulation ensure constant and effective delivery of antigens to resident APCs, yielding a systemic CTL response similar to the abscopal effect derived from radiotherapy.

Additionally, cancer vaccines used in combination with other oncoimmunotherapies can further potentiate antitumor immune responses. We have already discussed the successes of a nanoparticle formulation utilizing CD40 to target antigenic delivery to DCs[141]. Use of ICBs, including anti-CTLA-4 or anti PD-1 antibodies, can augment and amplify T cell immunity to generate tumor shrinkage. Preclinically, a PLGA scaffold vaccine co-delivering autologous tumor lysates, polythylenimine (PEI) CpG-ODN in combination with ICB

generated a higher infiltration of active cytotoxic T cells and Treg regression consistent with tumor shrinkage in a B16 murine melanoma model[207]. Moreover, augmentation with CTLA-4 enriched local cytotoxic T cell population by 5- to 10-fold over PD-1 and vaccine alone respectively[207]. Ongoing clinical trials are characterizing clinical benefit of combinatorial vaccination with ICB modulation. A p53-modified adenovirus-transduced in situ cancer vaccine (INGN-225)[208], in combination with nivolumab and ipilimumab, is currently recruiting for small cell lung cancer (NCT03406715). Thus, supplementation of other oncoimmunotherapies may support cancer vaccines in modulating and augmenting tumor-specific immunity.

Clinical translatability of biomaterial vaccine platforms hinge on harnessing an appropriate platform, cancer subtype and animal model for testing. Preclinical experiments often are performed in murine models using the prototypic B16 melanoma or renal carcinoma due to ease of tumor and antigen manipulation. Both are classified as an immunologically “hot” tumors and are highly associated with improved response to immunotherapy via immune blockade[209–211]. Their high immunogenicity and frequency of mutations lends itself well to generating large amount of neoantigenic peptides available for vaccine targeting[212] along with synergistic immunotherapy and vaccine platform designs. While these preclinical studies are critical for vaccine design, focus on non-representative models has led to generation of ineffective vaccines that fail to induce meaningful clinical responses[213], especially in other malignancies[87]. Further, differences between mice and man[214] may pose challenges in bringing vaccine to clinical trial. For realistic efficacy assessments, clinically relevant antigens and orthotropic, transgenic patient-derived xenograft models are needed, as well as the use of humanized mice that can more closely recapitulate human immune response. Thus, when designing an appropriate biomaterial-based vaccine platform, suitable testing models must be considered during early phases of research to ensure potential for clinical utility.

Additionally, it is critical to note that a majority of the reviewed vaccination trials were performed in patients from Caucasian backgrounds. Studies that rely on samples drawn entirely from Western, Educated, Industrialized, Rich and Democratic (WEIRD) societies often are the least representative populations for evaluating response to therapy[215]. WEIRD societies have little demographic variation and often fail to be generalizable across human responses. This risk of selection bias in clinical trials is not limited to the study of cancer vaccines[216,217]. In order to exclude human variation as an important confounding variable, it is crucial to be inclusive in trial design. These considerations have led to parallel trials for neoadjuvant chemoradiotherapy with tecemotide treatment in East Asian and Japanese patients, to exclude ethnicity as a factor that influences vaccination efficacy[122].

While many clinically-viable biomaterial strategies exist, care must be taken to ensure clinical translatability and feasibility when designing preclinical and clinical studies. Clinically-translatable platforms modulate engineered physical properties to target key underlying immunity mechanisms necessary for cancer eradication. Manufacturing and scaling limit a majority of the aforementioned biomaterial vaccine platforms. Unlike vaccines for infectious diseases, cancer vaccines must be tailored for each patient due to high individual heterogeneity in tumor mutation burden. However, platforms utilizing

neoantigens require use of complicated next-generation sequencing technologies for adept identification of highly immunogenic personalized neoantigens. Subsequently, this may lead to high batch-to-batch variability in neoantigen generation and loading. Use of tumor lysates provide a pool of tumor-associated antigens to activate a broad spectrum of polyclonal antitumor immune responses. Furthermore, complicated treatment regimens necessitate use of GMP grade materials, further limiting care to tertiary hospital centers. Thus, a collaboration between industry, bioengineers, immunologists and clinicians will further accelerate the generation of an engineered therapeutic cancer vaccine for clinical development and translation.

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Data Availability

As this is a review paper, we did not generate any raw or processed data in preparation of this manuscript.

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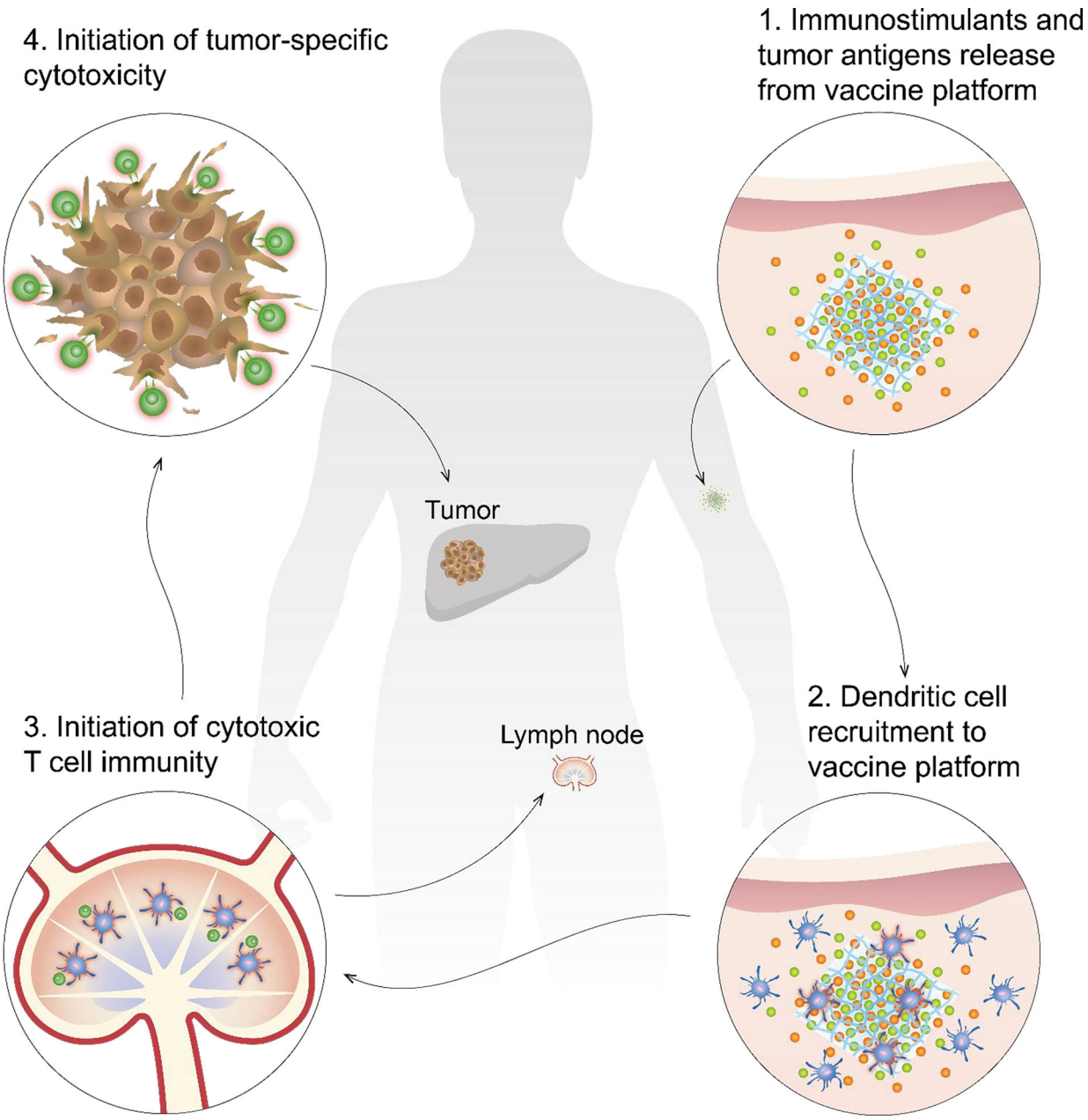

Figure 1: Targeting DC mediated cellular immunity utilizing biomaterial-based vaccine strategies.

Initiation of cellular immunity via therapeutic cancer vaccines is dependent on a four-step process. 1) Implantation of biomaterial in intended site releases encapsulated immunostimulants (green) and tumor antigens (orange) according to material-specific manner. 2) Immunostimulant release generates a local concentration gradient necessary to recruit dendritic cells (DC, blue) to vaccine platform where they are presented dominant tumor antigens and become activated (red glow). 3) Activated DC (red glow) will traffic to local draining lymph nodes for antigen presentation to CD8+ T cell (green) to initiate cytotoxic immunity. 4) Cytotoxic T cells travel systemically to target cells with featured antigenic target, reducing primary and metastatic burden systemically.

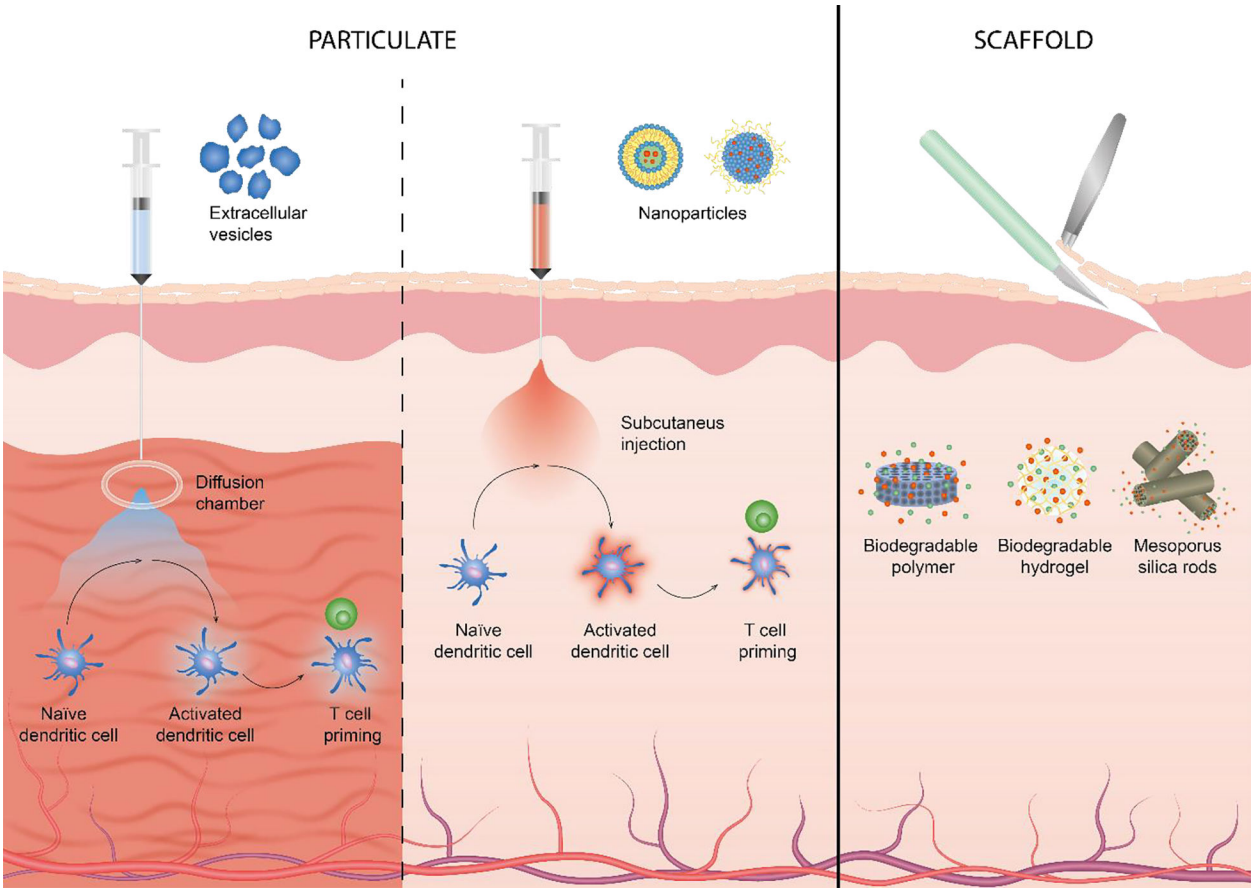

Figure 2: Biomaterial-based vaccine strategies.

Therapeutic vaccine modalities can be divided into two main categories dependent on primary material modality. Particulate-based vaccines (left) include nanoparticle, including liposomes, and extracellular vesicles such as exosomes. Polymer-based vaccines (right) can either be biodegradable or non-degradable and can be composed of polymers, hydrogels or silica rods.

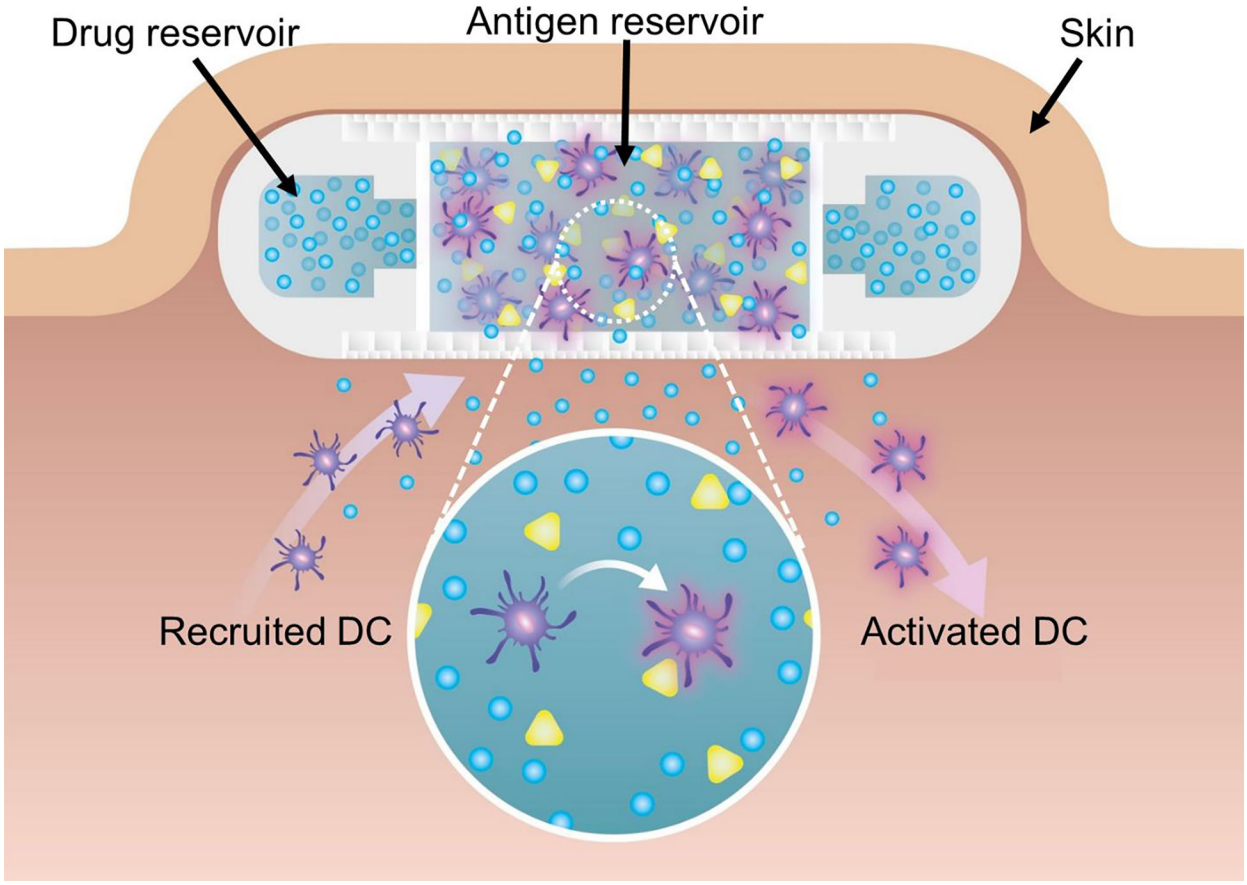

Figure 3: Immune cell recruitment and activation via NanoLymph.

Schematic representation of NanoLymph's recruitment of DCs through constant and sustained immunostimulant elution into subcutaneous space. Cross-section of NanoLymph demonstrates DCs (purple) are recruited through local release of immune adjuvants (blue) and can interface directly with the implanted NanoLymph. Upon infiltration, DCs encounter presented tumor antigen (green) and subsequently become activated (red glow). These activated DCs are able to exfiltrate the NanoLymph and home to draining lymph nodes to interact with lymphocytes.

Table 1:

Description of various vaccine strategies currently utilized in preclinical studies and clinical trials.

Vaccine Strategy	Mechanism of Action	Benefit	Limitation
DNA[35,36,218,219]	Transfection of plasmids containing immunogenic genes to induce DC antigen uptake stimulating CTL response	• Scalable • High specificity • Long half-life • Immunize against multiple antigens in single plasmid	• Low efficiency and cellular uptake with high off target delivery • Poor immunogenicity requires high administration doses • Very large size and negative charge • Mutagenesis, autoimmunity and toxicity risk • Difficult to monitor response • Requires high cell manipulation for immunogenicity
mRNA[38,43]	Delivery of synthetic mRNA that generates specific immunogenic antigen via a carrier molecule	• Scalable • Non-infectious • Non-integrating • Naturally degrading • Stimulate adaptive and innate responses	• Unstable formulation and inefficient delivery • Requires encapsulation or nanocarrier systems • Delivery systems linked to rare but severe allergic events • Paradoxical suppressive innate immunity
Peptide[220,221]	Use short antigenic peptide fragments to induce targeted response. Often delivered via liposomal formulations	• Easily produced and delivered • Low toxicity • Easy to monitor immune response • Reduced risk of allergenic or reactogenic responses • Induce immunity against multiple strains by utilization of conserved peptide	• Require use of carrier molecules for chemical stability • Elicit mainly one type of immune response (either cytotoxic or humoral) • May require booster shots • HLA-restricted • Restricted to certain epitopes • Multivalent formulations are challenging • Require new production and stability assays/protocols for each new antigen
DC[36,55,58–60,75,222]	Rely on cellular uptake of antigen either via reintroduced ex vivo pulsing or in situ phagocytosis to initiate downstream activation of adaptive immunity Currently most strategies focus on ex vivo activation and re-administration.	• Scalable • Elicit both humoral and cytotoxic response • Capable of generating memory responses • Not HLA restricted • Variation in antigen type (allogeneic vs autologous, whole-cell vs neoantigen)	• Ex vivo strategies require expansion, maturation and activation of DCs, necessitating GMP level facilities • Technically challenging • Regulatory challenges due to variability in antigen selection and conferred activity

Table 2:

Brief descriptions of discussed biomaterial-based vaccine scaffold platforms.

	Name	Mechanism of Action	Benefits	Limitations
Nanoparticle	BLP25 (L-BLP25; tecemotide; Stimuvax®)[17,20,122,124,133,134,137] NCT02049151	• DCs uptake the MUC1 peptide for specificity • Can also be optimized for other highly mutated antigens (ex. HER2Neu)	• Phase III (NSCLC) with neoadjuvant CR + BLP25 had no impact on OS • Adjuvant CR improved OS • Phase III (Her2+ BC) No impact on OS	• While promising preclinically, no effect on OS or tumor burden in several Phase III studies led to study cancellation • Most studies done in WEIRD populations
	Nanodisc[118–121]	• Synthetic HDL containing TLR agonists (MPLA, CpG-ODN) with TAAs. • Can also co-deliver chemotherapeutics and ICB	• When co-delivered with doxorubicin, 88% mice immunized against colorectal carcinoma with 100% rejecting tumor rechallenge. • When co-delivered with ICB, 90% mice eradicated established colorectal carcinoma and melanoma. • Strong humoral response in murine cervical cancer and melanoma model	• Required neoantigen identification, limiting use due to labor, cost and manufacturing capacity • Small tumor burden studied not representative of clinical burden • Requires multidose therapy with inability to be refilled or rescaled
	Lipid-encapsulated mRNA nanovaccine[137]	• Multi-dose every 3 weeks IM injections encoding up to 20 patient-specific neoantigens • Can be co-treated with pembrolizumab	• Phase I: 85% monotherapy had SD to CR, 66% combination • 2 patients demonstrated CR or PR after previously failing PD-L1 therapy • CTL responses post vaccination against immunized neoantigens with high predicted binding affinity	• Multidose therapy poses patient adherence problems • Neoantigen identification may be laborious and costly
	NP-CD40[141–143]	• PLGA nanoparticles coated with agonistic anti-CD40 with TAAs and adjuvants encapsulated • Tested CpG and polyI:C	• Murine model reduced tumor burden and prolonged OS • Enhanced DC maturation, CD4+ T proliferation and stimulated IFN-γ production in vitro • Selective and efficient immunity in prophylactic and therapeutic challenges	• Studied tumors were incipient and thus did not recapitulate clinical burden
	Tumor cell membrane with particulate core[117,145,148]	• Tumor membranes used to coat nanoparticles with immunostimulatory agents • Deliver TAAs in situ • Can be used with ICB	• 50% melanoma bearing mice had long term survival with ICB combo • Stimulation induced release of IFN-γ, IL-10, IL-12 and IL-4 in human breast cancer patients	• Required repeated doses • Tumor cell membrane only allows for targeting but can still evade TIME
Microparticle	Mesoporous silicone vectors[12,168]	• Utilizing mesoporous silicone to co-deliver antigenic peptides and dual TLR-agonists	• In prophylactic murine melanoma, suppressed tumor growth with repeated vaccination • Induced antigen-specific T cell expansion and reactivity	• Required 2 repeated doses • Only tested prophylactically.
	Calcium carbonate[112]	• Encapsulating TLR adjuvants and tumor lysates within calcium carbonate particles	• High loading capacity vs PLGA counterparts • Co-delivery with TLR agonists	• Only tested in vitro and in silico, limited preclinical data
	PLGA[113–116]	• Encapsulating autologous tumor lysates with TLR agonists (poly(I:C), MALP-2, CpG motifs))	• Reduced lung metastasis in 42% mice in 4T1 murine TNBC model	• Repeated doses required

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Extracellular Vesicles	Dex[156,157]	• Derived from DCs to express co-stimulatory surface markers with TLR adjuvants or mRNA for neoantigens	• Phase 1: safe and well tolerated in advanced NSCLC, melanoma and colorectal cancer. One patient had grade-3 hepatotoxicity • Mixed clinical responses with majority of patients presenting with SD	• Limited to no antigen-specific T cell reactivity. • Limited evidence of NK cell lytic function weakly correlating with longer PFS
	Tumor cell derived exosomes (IGV-001)[25,26] NCT02507583, NCT01550523 NCT04485949	• Express CpG DNA • Autologous tumor cells treated with antisense ODN against IGF-1	• Dual surgeries led to increased pain and immobility leading to need for long term enoxaparin for DVT prophylaxis for 3 months with repeated ultrasound evaluations • 6 patients had hematomas, wound complications and DVT • Phase 1 (malignant astrocytomas): 75% had clinical improvement. 37.5% had spontaneous regression at local/metastasis sites • Phase 1 (newly diagnosed glioblastoma with CR): PFS improved by 3.3 months. Improved PFS if de novo mutations in DNA evident in patient	• Surgically implanted diffusion chambers required multiple surgical events and complicated treatment timeline
Non-hydrogel scaffold	WDVAX[131,132] NCT01753089	• Encapsulation of tumor lysates, GMCSF and CpG-ODN in PLGA	• Single dose SQ extended survival by 90%. CR of primary and metastatic melanoma in 47% of mice. • Maintained local and systemic T cell population. • Intracranial implantation extended OS in 90% rats with glioma •	• Four SQ implantations monthly required repeated visits with DVT prophylaxis for pain and immobility. • Complex intracranial implantation PLGA matrix can potentially damage or denature antigen structure • Use of organic solvents may lead to subclinical toxicity •
Hydrogel scaffold	Methylacrylated-alginate cryogel[29,30,132,192]	• Loaded with tumor lysates, GMCSF and CpG ODN. • Has shape memory properties for needle extrusion in SQ injection • Degradable •	• Long lasting prophylactic immunity in 80% murine melanoma • In situ immune cell recruitment and trafficking	• Cannot be refilled necessitating multiple vaccinations • Limited to identified immunogenic tumor models • Rapid burst release of all components within first week
	Thermosensitive PLGA[127,129]	• Chemically modified PLGA with GMCSF and neoantigens	• Longer median survival • Reduction in tumor burden	• Repeated dosing required
	Self-assembling tumor peptides[31,193]	• Hydrogel with JQ1, ICG and autologous fixed tumor cells to excite and stimulate JQ1 release in situ by NIR irradiation	• Limited tumor recurrence and distant metastasis for 30 days post vaccination • Reduced MDSC population Accelerated DC maturation with increase in CD8T frequency and cytokine release 2.7×	• Repeated dosing required • Reformulation of tumor cells • Requires NIR irradiation tissue penetration which may be difficult for deep seeded tumors
Scaffold-particulate	Hydrogel-embedded MSN[182]	• Change functional group charge to modulate cell uptake	• Negatively charged MSN have higher cellular uptake	• Lacking in vivo efficacy
	MSR-embedded MSN[183]	• MSR with OVA and CpG-ODN embedded with MSN containing GMCSF	• Dual scaffold generated antigen-presenting DC eliciting potent CD8T response • Synergized with α-CTLA4 antibody further inhibited tumor growth	• Very high dose of systemic α-CTLA4 antibody required, may lead to toxicity • Regime doesn't address limitations in adherence
Mesoporous silica scaffold	High-aspect-ratio MPS scaffolds[28]	• 3D microenvironment releasing GMCSF, CpG and antigen fragments	• In prophylactic murine lymphoma model had delayed lymphoma growth compared to bolus vaccine delivery	• Rapid burst release of immunostimulants and antigen peptides within 1st day • Resulted in plateau of DC recruitment by

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			• Enhances systemic serum antibody levels with correlated CD8+T-cell response	day 3 Tested in lymphoma model but vaccines require immunocompetent host to modulate response
	PEI enhanced MPS	• Tested with GM-CSF, CpG-ODN and antigen • Can be delivered in combination with ICB	• Eradicated established lung carcinoma in 80% mice • Generated sustained immune memory • With ICB, induced enriched CD8+ T-cell response with enriched in situ cytokine release correlating to degree of lung metastasis eradication	• Tested on early tumors (5 days growth prior to vaccination) does not resemble clinical tumor burden

Abbreviations: non-small cell lung carcinoma (NSCLC); receptor tyrosine-protein kinase erbB-2 (Her2Neu); breast cancer (BC); triple negative breast cancer (TNBC); deep vein thrombosis (DVT); overall survival (OS); stable disease (SD); progression free survival (PFS); complete response (CR); near complete response (nCR); western, educated, industrialized, rich and democratic (WEIRD); subcutaneous (SQ); intramuscular (IM); granulocyte macrophage colony stimulating factor (GMCSF); toll-like receptor (TLR); poly(lactic-co-glycolic acid) (PLGA); monophosphoryl lipid A (MPLA); CpG-rich oligonucleotide (CpG-ODN); cytotoxic T-lymphocyte associated protein 4 (CTLA-4); high density lipoproteins (HDL); tumor associated antigens (TAA); immune checkpoint blockade (ICB); chemoradiotherapy (CR); thienotriazolodiazepine (JQ1); near-infrared spectroscopy (NIR); Dendritic cells (DC); myeloid-derived suppressor cell (MDSC); cytotoxic T lymphocyte (CTL); CD8+ T cell (CD8T); mesoporous silica-approaches (MPS); mesoporous silica nanoparticles (MSN); mesoporous silica microrods (MSR)