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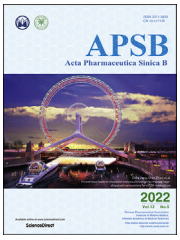

REVIEW

Emerging vaccine nanotechnology: From defense against infection to sniping cancer

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Abstract Looking retrospectively at the development of humanity, vaccination is an unprecedented medical landmark that saves lives by harnessing the human immune system. During the ongoing coronavirus disease 2019 (COVID-19) pandemic, vaccination is still the most effective defense modality. The successful clinical application of the lipid nanoparticle-based Pfizer/BioNTech and Moderna mRNA COVID-19 vaccines highlights promising future of nanotechnology in vaccine development. Compared with conventional vaccines, nanovaccines are supposed to have advantages in lymph node accumulation, antigen assembly, and antigen presentation; they also have, unique pathogen biomimicry properties because of well-organized combination of multiple immune factors. Beyond infectious diseases, vaccine nanotechnology also exhibits considerable potential for cancer treatment. The ultimate goal of cancer vaccines is to fully mobilize the potency of the immune system as a living therapeutic to recognize tumor antigens and eliminate tumor cells, and nanotechnologies have the requisite properties to realize this goal. In this review, we summarize the recent advances in vaccine nanotechnology from infectious disease prevention to cancer immunotherapy and highlight the different types of materials, mechanisms, administration methods, as well as future perspectives.

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1. Introduction

Without vaccines, infectious diseases cause several disasters for human beings. Vaccines represent an unprecedented milestone in medical history because they successfully harness the human immune system to combat pathogens. Vaccines trace back to "variolation" in the 10th century AD. In 1798, "the father of vaccines," Dr. Edward Jenner, tested his hypothesis that subjects inoculated with substances from cowpox lesions could receive immunity from smallpox, laying the foundation for modern vaccine's development. Modern vaccines predominately function by two core mechanisms that stimulate active immunity against pathogens and confer passive immunity with pre-existing antibodies or lymphocytes. Throughout human history, vaccination has saved more lives than any other forms of medical intervention, and has played an indispensable role in public health and safety. Vaccination is the most effective and efficient medical modality for combating the coronavirus disease 2019 (COVID-19) pandemic which had a negative impact on the global society and economy.

However, the development of protective vaccines against numerous lethal pathogens lacking effective protective vaccines, such as human immunodeficiency virus (HIV), tuberculosis (TB), and malaria, has proven difficult, contributing to high disease mortality rates in communities with limited resources. The difficulties associated with novel vaccine design are the products of the co-evolutionary history of the pathogen and humans (*e.g.*, virus variability). Moreover, other types of diseases, particularly cancer, benefit from the mobilization of autoimmunity. Therefore, the new era of vaccine development must overcome more challenges, such as the precise combination of humoral and cellular immunity, the ordered activation of immune components, and immune tolerance or low reactivity. The emerging concentrations of material and biomedical science may provide novel technologies for tailorable vaccine design. As one of the most promising and attractive candidates, nanotechnology approaches have a unique position to address the challenges of vaccination and mine more application potentials in cancer treatment. In accordance to their tailored structures, modular compositions, and controlled length scales, vaccine nanotechnologies possess versatile properties, including multivalent target delivery to lymphoid tissues and specific immune cells, multistage stimulating control release of immune components, key immune pathway engagement, and perfect iterative design systems[1−3]. It is worth mentioning that the successful application of the Pfizer/BioNTech and Moderna mRNA COVID-19 vaccines have drawn attention to nanotechnology and highlighted its vital role in emerging vaccination development[4,5]. As an indispensable component of the mRNA vaccine, lipid nanoparticles are vital for protecting mRNA COVID-19 vaccines from nucleases and effectively delivering these vaccines to the right place[6].

Cancer immunotherapy, particularly immune checkpoint blockade (ICB) and chimeric antigen receptor T-cell (CAR-T) immunotherapy, has already been validated successfully in the clinic. However, the low patient response rates and off-target adverse events associated with nanotechnologies indicate that there remain many challenges for the successful application of these technologies[7,8]. During an antitumor immune response, a chain of stepwise events must switch on and expand iteratively, including cancer-associated antigen release, antigen presentation, immune cells activation, T cells infiltration into tumor microenvironment, specific recognition of tumor cells, and the elimination of cancer cells[9]. Considering the feature of above mentioned antitumor-immunity process, in theory, the absence of any step would result in the final failure of the effective anti-tumor immune response. Therefore, cancer immunotherapy has shifted from focusing on one step to focusing on entire process of the cancer-immunity cycle: the combination of different immune agents that function by different mechanisms, for example, has been promising[9]. As one of the hopeful cancer immunotherapy candidates with tailorable components and ordered integration, vaccine nanotechnology may support strategies and platforms that realize more effective activation of antitumor immunity.

This review predominately focuses on the nanomaterial vaccines and provides up-to-date progress from infectious diseases prophylaxis to cancer immunotherapy. The rational structural designs of various types of nanovaccines are highlighted, ranging from polymeric nanoparticles, nanogels, inorganic materials, and membrane-coated mimic structures (Fig. 1). Moreover, we investigate the critical roles of immunity activation mechanisms, immune component combination strategies, and different administration strategies in vaccination. Finally, we discuss the perspectives and challenges of vaccine nanotechnology development, especially in clinical translation. The aim of this mini-review, therefore, is to not only summarize the recent advances but also focus on the future application of next-generation vaccine nanotechnology.

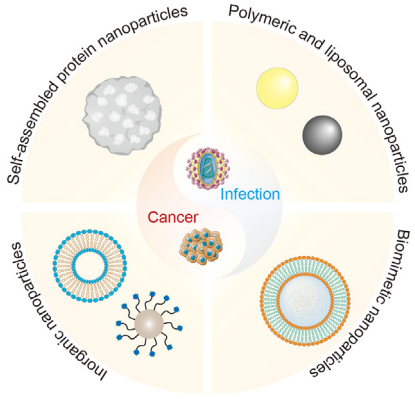

Figure 1 Schematic illustration of emerging vaccine nanotechnology for infectious diseases prevention and cancer immunotherapy. Main types of nanovaccines include self-assembled protein nanoparticles, inorganic nanoparticles, polymeric and liposomal nanoparticles and biomimetic nanoparticles.

2. Representative promising strategies to improve the immune response of nanovaccines

The key principle of vaccination is how to trigger the proper immune response to target antigens. Underlying this process is a complicated network responding to exogenous and endogenous danger stimuli, which are involved in various immune cell types and concerted by innate and adaptive immune responses. The flexible design of nanomaterials endows nanovaccines with improved specific immune responses. The vaccines mainly benefit from the unique drug/antigen delivery properties and nano-enabled immunomodulation of nanomedicine. In this section, we focus on these strategies for evoking the immune response.

2.1. Delivering antigens to key cells and tissues of the immune system

One of the most promising areas in which nanotechnology is applied is drug delivery. As for vaccination, delivering an antigen to the right place in the immune system is also of great importance. Unlike other types of drug delivery to precise cell types, the antigen vaccine delivery process involves spatiotemporal interactions of several cell types, including antigen-presenting cells (APCs), B cells, various T cells, macrophages, and neutrophils. In addition, the above interactions tend to occur in a specific tissue or location, further complicating antigen delivery. Therefore, several promising strategies have been employed to design nanovaccines, such as crossing the biological barrier, lymph node (LN) trafficking, the controlled release of antigen, APCs targeting, cross-presentation, among others[10,11].

Researchers widely hypothesized that prolonged persistence of antigen or minimized unnecessary degradation of antigen would enhance immune response. Therefore, nanomedicine researchers were devoted to increasing the persistence of antigens at the injection sites, in lymphoid tissues, and even in APCs by conjugating or encapsulating antigens in nanomaterials[12,13]. Beyond the precondition of antigen persistence in the internal environment, LN delivery is highly sought after for its design because of the large population of immune cells residing in LNs. Currently, only a small amount of the antigen at the injection site can be delivered to the LNs by APCs; to enhance LN delivery methods, researchers need to further adjust multiple physical properties of nanoparticles, such as their charge, shape, size, and flexibility[14−17]. Researchers demonstrated that nanoparticles smaller than 100 nm tend to drain to the LNs and that different nanomaterials may have different optimal sizes for LN delivery[18,19]. Given the increasing interest in the mucosal immune response, delivery methods that effectively cross the mucosal barrier are also considered highly in vaccine design. Owing to the negatively charged porous mucin glycopolymer structure, mucosal delivery efficacy depends largely on the size and surface charge of nanoparticles[20,21]. Thus, nanoparticles smaller than the cut-offs of mucosal and cationic nanoparticles (below about 200 nm) can achieve promising mucosal delivery[22]. Following the delivery of antigens in the appropriate tissues and locations, the internalization, processing, and presentation of antigens by APCs is critical to evoke a strong immune response. Hence, researchers manipulate the physical characteristics of nanoparticles (*e.g.*, their charge, shape, and size) to promote APC uptake of antigens and a consequent strong immune response[23,24]. For example, 20−200 nm nanoparticles are more easily internalized by a common type of APC, dendritic cells (DCs)[25]. Targeted nanoparticle delivery to DCs can be achieved by modifying specific ligands for affinity-based targeting DC subsets, such as C-type lectin receptors[26]. Moreover, it was revealed that multivalent antigen structures can enhance antigen recognition and activation of B cells—another type of APCs[27].

2.2. The application of multivalency effect in nanovaccine

Most viruses and bacteria have unique repetitive structures that the immune system can detect. It is revolutionary to consider this repetitive antigen structure in vaccine design. There is evidence to suggest that the multivalency effect elicits a stronger humoral and cellular immune response in self-assembled polypeptide nanoparticles[28], multiple antigen conjugated nanoparticles[29], and other multivalent assemblies[30,31]. And most encouragingly, nanotechnology has an absolute advantage in manipulating antigen density and orientation, providing great platforms for investigating the underlying mechanisms of multivalency effect and its optimizing strategies. Puffer and colleagues[32] found that the multivalency of hapten induced higher levels of antibodies, correlated with increased Ca^{2+} signaling in B cells. Moreover, multivalent hapten even confers immunogenicity to low-affinity epitopes[33]. With more in-depth research, the multivalency of antigens can be programmed to activate immune cells by several pathways, such as complement activation[34], during which B cell receptors crosslink through tyrosine-based activation motifs (ITAMs)[29]. Although the mechanism behind this phenomenon is elusive, virus-like particles (VLPs) with the multivalency effect can enhance B cell activation and downstream immune responses. The studies of nanomaterial-multivalent antigens for combating infectious diseases have exhibited great promise. For example, liposomes with multivalent HIV trimers have been found to increase antibody response breadths against target antigen protein regions, suggesting that multivalency can influence the antibody reservoir[35]. Further studies suggest that antibody responses can be shaped by programming specific epitopes; the specificity of the vaccine can be improved by burying undesirable epitopes and exposing desirable epitopes, which reduces responses to the immunodominant, non-neutralizing regions of HIV trimers[36]. Protein-based nanomaterials display alteration was also applied in screening neutralizing region for binding neutralizing antibodies[37]. Although questions about how antigen orientation influences immune responses remain, nanomaterial platforms are advantageous experimental tools for deeper investigation.

2.3. Delivering nucleic acid for antigen expression in vivo

The successful application of mRNA vaccines to combat the COVID-19 pandemic has demonstrated the limitless potential of nucleic acid-based vaccines. The efficacy of nucleic acid-based vaccines depends predominately on the delivery of DNA or RNA molecules, which upregulate the expression of target encoding antigens and evoke a specific, strong immune response in target immune cells. DNA vaccines were supposed to have great promise in infectious diseases prophylaxis and treatment because they are simple, stable, and inexpensive to mass produce[38,39]. However, inefficient plasmid DNA (pDNA) delivery *in vivo* impaired the effectiveness and limited the further preclinical application. For example, traditional DNA vaccines tend to spread rapidly after injection, resulting in a diminished probability of pDNA interacting with APCs. In addition, the inherent risk of traditional viral delivery pushed nonviral vectors, which are relatively safe, into focus. Among the promising nonviral vectors are nanomaterials,

which stand out due to their specific delivery advantages; the need to efficiently deliver novel mRNA-based vaccines further advanced the development of nanomedicine in vaccine design. As previously mentioned, nanoparticles can be programmed with specific LN and APC targeting abilities, which may apply to nucleic acid-based vaccines too[40,41]. Unlike protein/peptide antigen, nucleic acids are more susceptible to degradation by endonucleases. Additionally, the nonspecific immune response to foreign nucleic acids is a nonnegligible hindrance for clinical translation[42]. Therefore, when designing nucleic acid nano delivery systems, researchers must consider an encapsulating element to protect the nucleic acids from endonuclease enzymes[43–45].

In addition to the double-stranded DNA located in the nucleus, there is single-stranded mRNA, which the ribosomes translate codon-by-codon for protein production in the cytoplasm. Thus, mRNA vaccines can upregulate the expression of antigens in the cytoplasm directly without having to cross the nuclear envelope[42,46]. Moreover, the undesirable immune response to foreign mRNA can be assuaged by incorporating modified nucleosides, such as pseudouridine and 5-methylcytidine, into the mRNA transcript[47,48]. Considering these advantages, the mRNA vaccine was supposed to exhibit better antigen expression efficiency and faster clearance, which are conducive to clinical translation. And most encouragingly, this hypothesis was largely confirmed by the approval of the Pfizer/BioNTech and Moderna mRNA COVID-19 vaccines. It is worth mentioning that nanotechnology plays an important role in mRNA COVID-19 vaccines[4–6]. The two vaccines are cationic lipid nanoparticles, consisting of a cholesterol, an ionizable cationic lipid, a PEGylated lipid, and a phospholipid distearoylphosphatidylcholine (DSPC) helper lipid[6]. Cationic lipids, the most commonly employed nanomaterials, are often prepared by prepared by complexing cationic polymers/lipids with negatively charged nucleic acids; this structure, helps protect mRNA from degradation and immunorecognition.

Beyond treating infectious diseases, nucleic acid-based vaccines have long been promising candidates for cancer treatment. However, due to immunosuppression in the tumor microenvironment, vaccine design should involve numerous pathways to activate a sufficient antitumor immune response. It was revealed that nucleic acid molecules also participate in tumor immunomodulation[49,50]. For example, some nucleic acids can function as immune adjuvants[51], and small interfering RNA (siRNA) can inhibit PD-L1 expression for tumor suppression[52]. Besides, nucleic acids can also be used as vaccine vectors. Liu and co-workers[53] developed a DNA nanodevice with a tubular structure that loads molecular adjuvants and antigen peptides, inducing a strong antitumor immune response.

2.4. *Trigger tumor antigen release in situ*

The existence of tumor heterogeneity and immunosuppression in the tumor microenvironment complicates cancer vaccine design. Among the most difficult challenges is obtaining tumor antigens. Although there are countless types of tumor antigens employed for developing cancer vaccine, such as antigen coding mRNA, model antigens, and neoantigens, it is too difficult to obtain broad-spectrum tumor antigens for clinical vaccination because of tumor heterogeneity. For example, some nanomaterial-based cancer vaccines comprising ovalbumin (OVA) as a model tumor antigen exhibited remarkable antitumor efficacy in OVA-transfected tumor-bearing animal models, but they still stay on theoretical model and would be hard to directly achieve clinical transformation. To escape the cognitive inertia of adopting a single antigen in tumor vaccine design, researchers have studied tumor cell lysate and biomimetic cell membrane-based vaccines[54]. These strategies are limited by low immunogenicity, and thus, immune adjuvants and other evoking immunity strategies, which are reported below, are indispensable[54].

Instead of introducing an antigen *via* vaccination, it is possible to trigger the release of tumor antigens *in vivo*. One such mechanism is to trigger immunogenic cell death (ICD), which results in the release of tumor-associated antigens (TAAs), the danger-associated molecular patterns (DAMPs), and proinflammatory factors to evoke adaptive antitumor immunity[55]. The ICD process can be triggered by a series of antitumor therapies, including certain chemotherapies, phototherapies, radiotherapies, sonodynamic therapies, and local hyperthermia treatments[55–58]. The aforementioned therapies are also supposed to reverse “cold tumors” to “hot tumors” behind which the mechanisms could involve ICD induction, promoting immune cells infiltration and macrophage phenotype transition from M2 to M1. Moreover, by harnessing the superior delivery capabilities of nanomedicines, the effect of ICD inducers can be amplified synergistically with other immunotherapeutic agents, such as immune checkpoint inhibitors, indoleamine 2,3-dioxygenase 1 (IDO-1) inhibitors, and stimulator of interferon genes (STING), for combating immunosuppression[56]. Therefore, besides the classical co-delivery of antigens and immune adjuvants, the co-delivery of ICD inducers and immunotherapeutic agents is a promising design strategy for nanovaccines in solid tumor treatment.

2.5. *Immune adjuvants and other immune evoking strategies*

Immune adjuvants are an indispensable component of the vaccine and play an auxiliary role in enhancing the immune system’s response to the presence of antigens. Recently, immune adjuvant researchers have shifted their attention to natural ligands or synthetic agonist-based adjuvants for targeting pattern recognition receptors (PRRs)[51]. Although almost all of those adjuvants participate in the activation of APCs, the sciences underlying these mechanisms are diverse. Among those types of adjuvant, toll-like receptor (TLR) agonists have been studied extensively for their application to vaccination[51]. Bacterial lipopolysaccharides (LPS), for example, are TLR 4 ligands, whose detoxified derivative monophosphoryl lipid A (MPL) serves as a component of the licensed vaccines for HBV and papilloma[59]. Moreover, synthetic oligodeoxynucleotides (ODN) with optimized CpG motifs (CpG-ODN) are widely used as TLR 9 ligands in nanomaterial-based vaccines, such as antigen-adjuvants vaccines and ICD inducer-adjuvant co-delivery systems[51,60]. With the help of nanomedicine platforms, researchers can deliver adjuvants more precisely and with improved stability. It is worth mentioning that some nanomaterials exhibit the inherent adjuvant properties of promoting cytokines secretion and activating immune signal pathways[61,62]. Moreover, nanomaterials possess the properties of phototherapy or ROS generation[63–70], which can also induce ICD effect in cancer immunotherapy[63]. These self-adjuvant nanomaterials provide more possibilities and potential for the application of nanomedicine in vaccines.

As immunology develops, more immune sensing pathways and immune promoting strategies have been presented. Especially in antitumor immunotherapy, activating CTL functions and

combating immunosuppression have received increasing attention. As part of the revolution of tumor immunotherapy, several immune checkpoint inhibitors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death protein 1 ligand (PD-L1) blocking antibodies, were approved by the US Food and Drug Administration (FDA). Furthermore, vaccines combining multiple immunotherapeutic agents or immune adjuvants have successfully evoked immune response cascades[56]. Recently, some interesting results involving the enhancement of antitumor immunity have attracted attention, such as intestinal microbiota modulation[71]. The emerging strategies will yield more novel ideas and practices in combination tumor vaccine design.

3. Administration strategies

Currently, most vaccines employed the parenteral route, which is invasive and has limited compliance, for delivery. The development of nanomedicine provided various options for vaccine routes including postoperative, intradermal/subcutaneous, intranasal, inhalation, and oral administration for both cancer therapy and infectious diseases.

3.1. *Postoperative administration*

Currently, surgery remains the primary option for solid tumor treatment. However, tumor recurrence remains a challenge as residual tumor cells can be a risk that leads to fast relapse and metastasis. Strategies of nanomedicine are emerging for postoperative tumor drug delivery and immunotherapy[72].

To increase the efficiency of postoperative T-cell immunity, a thermo-responsive, curcumin-loaded polymer nanoparticles-assembled hydrogel with antigenic peptide and CpG-ODN was developed. This strategy can induce ICD and consequently enhanced the antitumor immunity[73]. This immunotherapy strategy promoted the infiltration of CTLs and inhibited local recurrence and pulmonary metastasis. In another study, an implantable 3D porous scaffold was designed to deplete myeloid-derived suppressor cells and present whole tumor lysates with nanogel-based adjuvants for promoting CTLs[74]. This immune niche strategy modulated the immunosuppressive environment and prevented postoperative tumor recurrence and metastasis. Autologous tumor cells are an excellent source for personalized postoperative nanovaccine development. Li and colleagues[75] developed a hydrogel matrix loaded with JQ1, a PD-L1 checkpoint blockade inhibitor, and indocyanine green (ICG). This immunotherapy strategy combined with PDT effectively inhibited tumor relapse and metastasis. Further, they design a PDT-motivated nanovaccine composed of autologous cancer cells and Fmoc-KCRGDK−phenylboronic acid hydrogel. This nanomedicine can be prepared feasible to boost personalized immunotherapy[76]. Besides, specific autologous cancer cells can be combined with non-specific immune activation such as bacterial-derived membranes[77]. Postoperative nanovaccines are rising for the treatment of cancer.

3.2. *Intradermal/subcutaneous administration*

Intradermal/subcutaneous administration is a common route of immunization for DNA vaccines. Both epidermis and dermis layers of the skin contain resident APCs that are targeted for immunization. As the skin is painless, intradermal/subcutaneous administration has been widely applied for prophylactic vaccination.

In recent years, this administration strategy was also explored for anticancer therapy. It has been reported that subcutaneous immunizations using VLPs conjugated with human EGFR 2 epitopes induced elevated HER2-specific antibody titers against the HER2 positive malignancies[78]. For advanced intradermal administration, versatile microneedle systems have also been explored for tumor and infectious diseases vaccination. A transdermal vaccine may be applied for topical and intratumoral immunotherapy against melanoma. Autonomous active microneedle-mediated propulsive delivery of cowpea mosaic virus nanoparticles and magnesium (Mg) microparticles enhanced the antitumor immunity and greatly suppressed tumor progression[79]. Microneedles can also be dissolvable for vaccine delivery. Plasmodium falciparum surface protein P47 and CpG were loaded into microneedles and showed potent activation of TLR9 signaling for malaria vaccine[80]. Recently, a vaccine core and PLGA shell microneedle patch was developed for the long-last and programmed burst release of the vaccine[81]. This strategy may be used for both prophylactic and therapeutic purposes without repeated vaccination.

3.3. *Intranasal administration*

Intranasal administration is an important route for respiratory infectious diseases[82]. Nasal immunization *via* nanovaccines is promising for preventing diseases through mainly affecting infected respiratory tracts such as TB and for the treatment of cancers.

Chitosan nanoparticles are water-soluble platforms that can be explored for intranasal delivery of antigen for TB vaccination. Thiolated OVA conjugated to *N*-trimethylaminoethylmethacrylate chitosan showed elevated cellular uptake, deep cervical lymph nodes transport efficiency, and immune responses after intranasal administration[83]. Recently, inulin acetate, a natural polymer, was developed as an intranasal nanovaccine delivery system for its inherent adjuvant (TLR4 activation) ability[84]. This nanocarrier has the potential for mucosal vaccination *via* intranasal administration. For synthetic nanoparticles, a "self-healing microencapsulation" technology has been developed by Bailey and colleagues for the stable loading of antigens in PLGA particles. They used calcium phosphate adjuvant gel as a trapping agent for antigen encapsulation, leading to sustained release of OVA antigen and proliferation of $CD8^+$ T cell *via* intranasal delivery[85] and could be used as a single-dose vaccination platform[86]. More recently, for the controllable particle size, PLGA nanoparticle was used for intranasal delivery of all *trans*-Retinoic acid and prolonged the drug release for targeted treatment of TB in the lung[87]. For intranasal cancer nanovaccine delivery, a recent study developed a self-assembled nanovaccine loaded with multiple OVA peptide antigens. This nanovaccine is safe through nasal administration and prolonged residence time and increased the antigen uptake efficiency, which led to enhanced antigen-specific immune response[88].

3.4. *Inhalation administration*

Inhalation administration is also a promising vaccination route for pulmonary infectious diseases such as TB. Synthetic nanoparticles are useful tools for inhalation formulations.

Polymeric nanocapsules with oily core and polymer shell have been developed for pulmonary delivery of imiquimod, a TLR-7 agonist, and a fusion antigen protein[89]. Vaccination of this

polymeric nanocapsule induced strong immune responses. The development of biomimetic nanotechnology offered strategies for developing nanovaccines by imitating respiratory droplets. In a recent study, a bionic-virus nanovaccine that mimics the structure of SARS-CoV-2 was developed by using liposomes as capsid structure and the receptor binding domains as "spike"[90]. This inhalable nanovaccine induced strong mucosal immunity and this nanovaccine strategy can also be used for other respiratory infectious diseases.

In addition, inhalation administration can also be applied for cancer nanovaccines such as lung metastasis. It has been reported that inhalation of the VLPs can facilitate the neutrophils infiltration in tumor, and increase cytokines and chemokines production and macrophage inflammatory protein 1α in tumor-bearing mice[91]. This nanovaccine treatment significantly reduced metastatic tumor burden for various tumor types.

3.5. *Oral administration*

Oral administration is a noninvasive route with excellent compliance[92]. Oral vaccines are optimal formulations for administration, immunization, safety, and storage. Despite the existence of lymphatic tissues under the mucous, the intestine forms a barrier for antigens. To develop a vaccine for oral administration, antigens are uptake and transported by epithelial cells and then recognized by immune cells for responses. During the process, antigens may degrade in the gastrointestinal tract resulting in a small number of antigens exposed to the mucosal tissue and limited intestinal uptake.

Several nanocarriers have been developed as TB vaccines that can be orally administrated. Liposome-encapsulated DNA vaccines can induce effective immune responses against TB[93]. VLP can also be used to carry HIV envelope cDNA with enhanced stability in the gastric environment. This strategy leads to high antigen concentration across intestinal lumen after oral administration[94]. In another example, polyethyleneimine-coated SPIONs loaded with malarial DNA showed high DNA binding and transfection efficiency even in the acidic environment[95].

Oral administration strategy may also be used for cancer vaccines. It has been reported that nanoemulsions have high encapsulation capacity for co-delivery of melanoma antigen, heal shock protein, and staphylococcal toxin A for oral administration. This oral delivery strategy showed comparable immune responses to subcutaneous immunization[96].

4. Type of nanomaterial-based vaccines

Recently, various nanomaterials for developing vaccines have been explored, including lipid-based nanoparticles, protein nanoparticles, polymeric nanoparticles, inorganic nanocarriers, and biomimetic nanoparticles. Different types of nanocarriers have distinct physicochemical profiles and behaviors *in vivo*, that influence vaccination accordingly. Here, we will briefly discuss the different types of nanomaterials for nanovaccines and their features.

4.1. *Self-assembled protein nanoparticles*

Natural nanomaterials have excellent biocompatibility and biodegradability. Several types of protein nanoparticles made of natural source proteins have been utilized for the delivery of antigens[97]. Self-assembled protein nanoparticles are promising candidates for nanovaccines. Typical examples of self-assembled protein nanoparticles include ferritin family proteins, pyruvate dehydrogenase (E2), and virus-like particles (VLPs) which have shown potentials in the development of nanovaccines.

VLPs are self-assembled complexes composed of viral proteins, which are supposed to be safe and highly efficient delivery platforms for antigen delivery without genetic components and replication ability[98]. VLPs have favorable immunological properties as they are self-adjuvants and can be immunologically recognized for the virus size and repetitive surface geometry. VLPs-form polydispersed systems can be efficiently uptaken by APCs and induce immune responses[99]. Antigens can be chemically coupled or genetically modified to VLPs with high density. VLPs-based vaccines have resulted in successful immunization programs as they are currently available in the market such as Cervarix® and Gardasil® against human papillomavirus virus (HPV) and Sci-B-Vac™ against hepatitis virus.

In contrast to exogenous viral proteins, several endogenous self-assembled proteins can also be explored as nanovaccine platforms, those protein nanoparticles are also called caged protein nanoparticles for their highly organized structures[100]. Ferritin is a typically caged protein nanoparticle that has widely been used for antigen delivery, drug delivery, imaging, and diagnostic applications[101]. Classical ferritin is comprised of 24 subunits, forming a central hollow cavity structure (12 nm $\times$ 8 nm) that stores iron. Antigen proteins can be genetically modified as subunits to form ferritins or can be incorporated onto ferritins to be efficiently phagocytosed by APCs. It has been reported that ferritin can passively target lymph nodes with a high retention time and induce strong immune responses[79].

4.2. *Polymeric nanoparticles*

Polymeric nanoparticles are colloidal systems with a wide size range (10−1000 nm)[102]. Polymeric nanoparticles have high immunogenicity and stability for efficient encapsulation and display of antigen, which can be loaded within the core and conjugated to the surface. While polymeric nanoparticles are generally solid, they have controllable size and can be self-adjuvant[103]. Polymeric nanoparticles can improve the efficiency of antigen uptake by APCs by phagocytosis or endocytosis[104].

For the development of nanovaccines, natural polymeric nanomaterials such as chitosan and dextran and synthetic polymeric nanomaterials such as PLA and PLGA are both useful tools. Polymeric nanoparticles from natural sources are highly biocompatible, water-soluble, and cost-saving. For example, chitosan, a typical natural polymer derived from chitin, is a linear cationic polysaccharide that can be used for vaccine delivery. Owing to its cationic charge and bioadhesive properties, chitosan is a competitive candidate for gene delivery and coating other polymeric nanoparticles to improve adherence and immunogenicity[105]. Moreover, chitosan can be customized depending on purpose by introducing functional groups[106].

Compared to natural polymers, synthetic polymeric nanoparticles generally have higher reproducibility and are more controllable for molecular weight compositions and degradation rates[107]. For example, PLGA nanoparticle is highly biodegradable and its properties can be fine-tuned. PLGA can be coupled with PEG and then self-assembled into a polymeric micelle for hydrophobic peptide antigens delivery with better T cell responses[108].

4.3. Lipid-based nanoparticles

Lipid nanoparticles (LNPs) are nanoscale lipid vesicles formed by amphipathic phospholipid molecules through self-assembling. LNPs are promising nanocarriers for nucleic acid delivery with low toxicity, high biocompatibility and controlled release properties[109].

LNPs are also vital components for mRNA drugs and vaccines. LNPs have controllable size, shape and charge which are important properties that may affect the efficacy of immune activation. Modification of LNPs can achieve optimal immune responses[110]. As nanovaccines, LNPs can achieve co-delivery of multiple antigens and adjuvants. Besides, the membrane surface of LNPs can display antigen with enhanced representation of native conformations.

LNPs has shown great potentials for nanovaccine development in a number of preclinical and clinical applications. As mentioned earlier, the lipid nanoparticles play a vital role in protecting mRNA vaccines from nuclease for effective delivery. LNPs have successfully been translated for the delivery of mRNA against COVID-19 recently (mRNA-1273[111] and BNT162b2[112]). There are many other LNP−mRNA formulations that are under ongoing clinical trials for the prevention and treatment of major human health threats including virus infections, cancers and genetic diseases as summarized in a recent review[113]. Cationic lipids, ionizable lipids and other types of lipids are all suitable components of LNPs. Besides, lipids can be functionalized by modification such as PEGlyation, making LNPs more versatile and powerful for vaccine development[114].

4.4. Inorganic nanomaterials

Commonly used inorganic materials in nanomedicine include metals and oxides, non-metal oxides, and inorganic salts. Inorganic materials have low biodegradability but are stable in structure. Many inorganic nanoformulations have inherent adjuvant activity[115]. However, for nanovaccine application, the physicochemical properties of inorganic nanomaterials need to be modified to improve their biocompatibility. The most widely used inorganic materials for antigen delivery include gold[116], iron[117], and silica nanoparticles[118].

Gold nanoparticles (GNPs) are spherical and positively charged. GNPs have good biocompatibility, low immunogenicity, and high antigen loading capacity. GNPs have size-dependent toxicity[119]; however, GNPs also have a high affinity to sulfhydryl groups[120], which can be utilized for surface engineering to couple with cysteine residues to produce polypeptide antigens with improved safety and pharmacokinetic profiles. In addition, GNPs have intrinsic immunostimulatory effects to induce inflammatory cytokines production[121]. Therefore, GNPs can be used not only as a transport carrier for antigens but also for stimulating immune responses[122]. Silica nanoparticles are also potent candidates for nanovaccine carrier materials[123]. Recent studies have shown that controlling the morphology[124] and pore size[118,125] of silicon particles can make them have variable porosity, thereby increasing their effective load capacity for different antigens and adjuvants. Their porous structure of silicon particles can fill various active biomolecules or directly wrap on the surface, thereby enhancing the targeting and uptake of the nano-vaccine. Silica nanoparticles have been used to target lymph nodes and accumulate in APCs to deliver antigens and adjuvants[126].

4.5. Biomimetic nanomaterials

Biomimetic nanomaterials are emerging for nanovaccine development for their effective and complex biofunctions[127,128]. Biomimetic nanomaterials are multifunctional and can achieve efficient delivery to the target site or effective interaction with biological systems. Bioinspired nanoparticles have also produced high biocompatibility, extended circulation and unique antigenic properties for the development of effective vaccine formulations.

A simple biomimetic design uses natural ligands or peptides, such as arginylglycylaspartic acid (RGD) and candoxin (CDX) peptides, to modify nanoparticles and enhance binding to improve targeting for efficient delivery[129]. In addition, molecularly imprinted polymers can also be used to mimic antibodies for developing biomimetic nanoparticles[130]. The decoration of nanoparticles with an individual natural ligand can endow specific functions, but multiple decorations would be rather difficult and can hardly replicate biological complexity. An emerging biomimetic strategy is to employ biomembranes to fabricate membrane-coated nanoparticles for enhancing biointerfacing[131]. Cell membrane−coating nanotechnology has been employed widely for improving circulation, targeted delivery, and imaging of nanoparticles[132]. For vaccine development, camouflaging with cell membrane may help nanoparticles to stay unnoticed in the immune system and target the lesion[133]. For example, the red blood cell (RBC) membrane can extend circulation and improve the bioavailability of nanoparticles[134]; platelet membranes can achieve targeting to the damaged vasculature and certain pathogens[135]; nanoparticles coated with cancer cell membranes have shown autologous targeting to cancer cells[136]; immune cell membrane-coating can endow the nanoparticle the ability to interaction with tumor tissues[137]. In addition to cell membranes, intracellular membranes such as outer mitochondrial membrane can also be utilized for specific targeting and detection[138]. Besides, biomimetic nanoparticles may be exploited as cancer nanovaccines with combined photothermal (PTT) and photodynamic therapy (PDT) against metastasis[139,140].

Several other biomimetic strategies are emerging in nanovaccines design for combating infection and cancer. Virosome is a lipidic unilamerllar nanocarriers (60−200 nm) utilized the liposome concept but has structure similar to an enveloped virus with removed nucleocapsid[141]. Virosome is an emerging biomimetic nanoparticle for the development of nanovaccine against viral infections. Virosome can be developed by different antigen epitope to target host cells of interest and can be modified by polymers for enhanced pharmacokinetic profiles[142]. Outer membrane vesicles (OMVs) are bacterial-derived nanovesicles carrying various proteins similar to bacterial outer membranes. OMVs are natural antibacterial vaccination for their multi-antigen features[143]. In addition, OMVs have shown the ability of lymph node entry and can be take up efficiently by APC, making them attractive candidates for antigen delivery and vaccination. Antigenic OMVs can be explored as adjuvant delivery systems to improve vaccine efficacy[144].

5. Nanovaccines for diseases prevention and treatments

Nanovaccines have been developed for various diseases. Here, we provide examples of how nanovaccines are being employed against cancers and infectious diseases, including HIV/AIDS, malaria and tuberculosis (TB). The most cutting-edge strategies of developing nanovaccines and their design aspects are included and discussed.

5.1. *The prevention and treatment of worldwide infectious disease*

HIV/AIDS, malaria, and TB are impacting global health and causing millions of deaths worldwide, highlighting the need for prevention and treatment strategies[145], but vaccine strategies can hardly generate protective immunity in the population. HIV has a highly dynamic genome and unclear clear immune protection; malaria is complex for life cycles and there are multiple infection forms (sporozoites, merozoites, and gametocytes); patients with TB infection could be co-infected by HIV and bacteria that are multi-drug resistant. Despite dissimilar pathogens, the development of vaccines for these diseases shares some similarities and antigen delivery remains a key for vaccination[146].

Self-assembled protein nanoparticles are useful platforms for antigen delivery. RTS,S, the first and currently the only malaria vaccine in the market[147], uses VLP to deliver antigen. VLP has been tested to display HIV envelope proteins such as V1V2 loop for vaccination and generated specific IgG in mice (Fig. 2A)[148]. Ferritin nanoparticles have also been employed to display HIV envelope trimers on particle surfaces to increase immunogenicity[148,149]. Other larger proteins such as dihydrolipoyl acetyltransferase (E2)[150] and lumazine synthase[151] are also useful for HIV vaccination. A two-component protein nanoparticle[152] was recently developed for enhancing the immunogenicity of HIV envelope (SOSIP) trimers by incorporating well-folded trimers into self-assembled nanoparticles. Further studies are exploring how spacing, antigens, and particle (size, shape, and charge) factors are involved in the protective immune responses.

Polymeric nanomaterials have received great interest as vaccine platforms for their synthetic feasibility, low immunogenicity, and high biodegradability. Recently, HIV-1-derived gp140 immunogen with 3M-052 (a TLR-7/8 agonist) were incorporated in PLGA nanoparticles and induced high and persistent frequencies of HIV envelope-specific immune responses in rhesus macaques[153]. Besides, self-encapsulating PLGA microspheres loaded with calcium phosphate adjuvant gel and ovalbumin (OVA) antigen achieved the sustained release of antigen for more than seven weeks. Administration of OVA-loaded nanoparticles induced strong Th2-type response[85].

LNPs can stably carry multiple antigens. It has been reported that cobalt porphyrin-phospholide can be loaded into LNP nanovaccine to express antigens coupled to the liposomal surface[154]. More recently, a heterologous trimer-liposome primer was performed by presenting well-ordered native flexible linked trimers on liposomes with high density and elicited cross-neutralizing antibodies (Fig. 3)[155].

Inorganic nanoparticles are also interesting platforms for developing anti-infection nanovaccines. GNPs-mediated antigen delivery can facilitate the presentation, thus inducing potent immunity. For example, gag p17 of HIV increased proliferation of $CD8^+$ T cells *via* conjugating onto high-mannoside-modified GNPs (Fig. 4A)[156]. Fe_2O_3 nanoparticle containing plasmid DNA TB vaccine induced significant humoral and cellular immune responses[157]. Enhanced vaccination was recently reported by amine functionalized silica nanoparticles-mediated delivery of antigen in combination with mincle agonist[158].

Biomimetic nanoparticles are powerful platforms against infectious diseases. Virosomal vaccine developed by HIV-1 gp41 subunit induced strong mucosal antibodies against HIV challenges[159]. In another study, Shao et al.[160] developed membrane proximal external region (MPER) peptide fragments-bounded liposomes-containing cobalt porphyrin-phospholipid (CoPoP) and a synthetic monophosphoryl lipid A (MPLA) to generate immunogenicity in mice. Immunization with the lipid-presented MPER elicited antibody responses recognizing recombinant HIV gp41 and gp140 proteins. As HIV attack explicitly T cells, Wei et al.[161] developed T cell membrane-coated PLGA nanoparticles to neutralize the HIV infection. Membranes of T cells inherit retained antigens of CD4 receptor, C–C chemokine receptor 5 (CCR5) or C–X–C chemokine receptor type 4 (CXCR4) for HIV envelope glycoprotein 120 binding. This biomimetic nanovaccine strategy effectively inhibited viral killing and neutralized HIV infection.

5.2. *Suppressing tumor recurrence and metastasis*

Cancer remains a leading cause of human death. Developing an anticancer vaccine is a vital step in reaching personalized medicine to treat this prolific disease. Despite tremendous efforts, full elucidation of the cancer pathogenesis is challenging[162]. Generally, cancerous cells result from the mutation of healthy cells involving multiple environmental and genetic factors. Therefore, unlike infectious diseases, cancer is highly heterologous in cases and the prevention of cancer is extremely difficult[163]. As small amounts of malignant cells can lead to relapse, the development of vaccines is of significance for the elimination of residual malignant cells and suppression of tumor recurrence and metastasis. Nanomedicine provided opportunities against tumors by using the above-mentioned nanomaterials to enhance either tumor vaccine delivery, *in situ* tumor antigen exposure, or presentation of the immune activation program.

A variety of nanomaterials have been explored as efficient platforms for the delivery of tumor vaccines. VLPs have been used directly for tumor-associated antigens delivery, and vaccination with VLPs could be used in combination with radiation therapy[164], chemotherapy[165] or immune therapy[166]. For general stimulation of antitumor immune responses, Kuai and colleagues[167] designed nanodiscs mimicking high-density lipoprotein for advanced delivery of antigens and adjuvants to lymphoid organs. The nanodiscs treatment exhibited substantially higher production of neoantigen-specific CTLs control formulations and eliminated tumors in combined immune checkpoint blockade therapy (Fig. 2B)[167]. Traditional LNPs are also highly effective platforms for tumor vaccine delivery. In a recent study, mRNA encoding tumor antigens were incorporated into cationic C1 LNP, which has adjuvant properties, for efficient delivery and presentation to dendritic cells (Fig. 4B and C)[168]. The C1 mRNA nanovaccine showed significant prevention and therapeutic effects on tumors.

Membrane-coating technology has been extensively explored for nanovaccine development. RBC-NPs with mannose modification and MPLA as the adjuvant were used to deliver B16F10 melanoma-associated antigen glycoprotein 100 to dendritic cells and inhibited significantly tumor growth[169]. Cancer cell membranes may be employed as antigens to coat nanoparticles as cancer vaccines. B16F10 cancer cell membrane coating of CpG-loaded emulsion nanoparticles increased significant CTLs levels[170]. Similarly, the B16-OVA cancer cell membrane modified with mannose coating of polymeric nanoparticles loaded with the TLR7 agonist R837 showed improved APC delivery[54]. In another study, membrane vesicles from cancer cells was used to coat spermine-modified acetylated dextran that loaded with thermally oxidized porous silicon[171]. This biomimetic nanoparticle with the

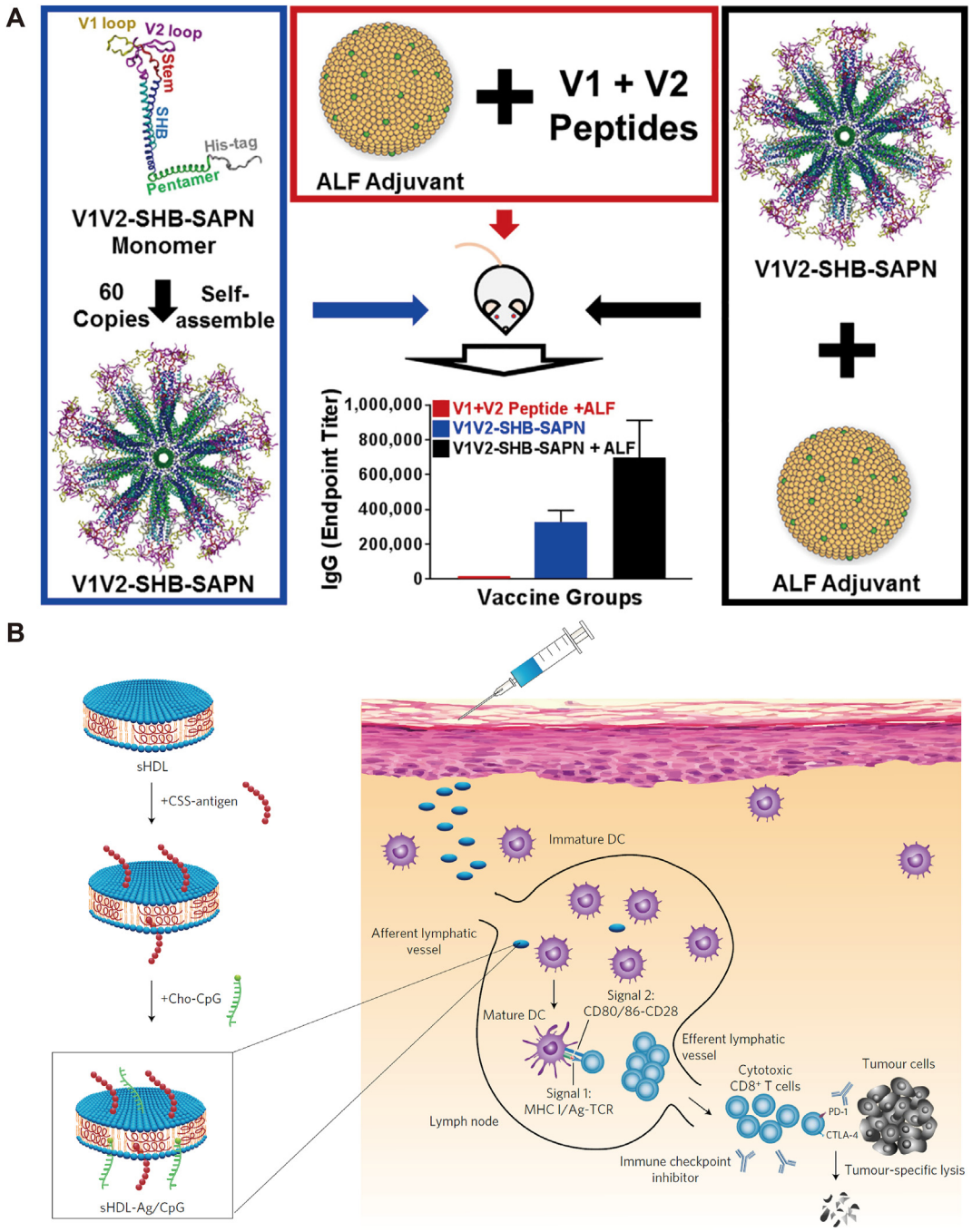

Figure 2 (A) Self-assembled protein nanoparticles as HIV vaccines. Fully assembled protein nanoparticles display 20 copies of trimers. The protein nanovaccine induces specific IgG in mice and the immune response can be enhanced with army liposome formulation (ALF) as adjuvant. Reprinted with permission from Ref. 148. Copyright © 2019. Elsevier. (B) Design and application of high-density lipoprotein-mimicking nanodisc platform composed of lipids and peptides for co-delivery of Ag and CpG for as cancer vaccine. Subcutaneous injection of the nanovaccine induce DC maturation and elite robust Ag-specific $CD8^+$ T cell responses, killing target cancer cells. This nanovaccine can be used in combination immunotherapy with immune checkpoint blockade. Reprinted with permission from Ref. 167. Copyright © 2017 Springer Nature.

immunostimulatory core inhibited the proliferation of autologous cancer cells by inducing potent immunostimulatory response.

In situ exposing tumor antigens is a promising vaccine strategy for preventing recurrence and metastasis. Most *in situ* tumor vaccinations utilized the ICD[172] for activating antitumor immune programs by killing tumor cells and exposing DAMPs to recruit and activate APCs for processing the antigens and activate tumor-specific T cells. Fan and colleagues[173] used mitoxantrone to induce ICD and conjugated the dying cells with multilamellar lipid-polymer nanoparticles loaded with CpG. Biomimetic nanoparticles are also useful tools for *in situ* tumor nanovaccine. Natural killer (NK) cell membrane[119] and myeloid-derived suppressor cell membrane[174] are useful to coat nanoparticles for enhanced PDT to promote ICD and activate immune responses

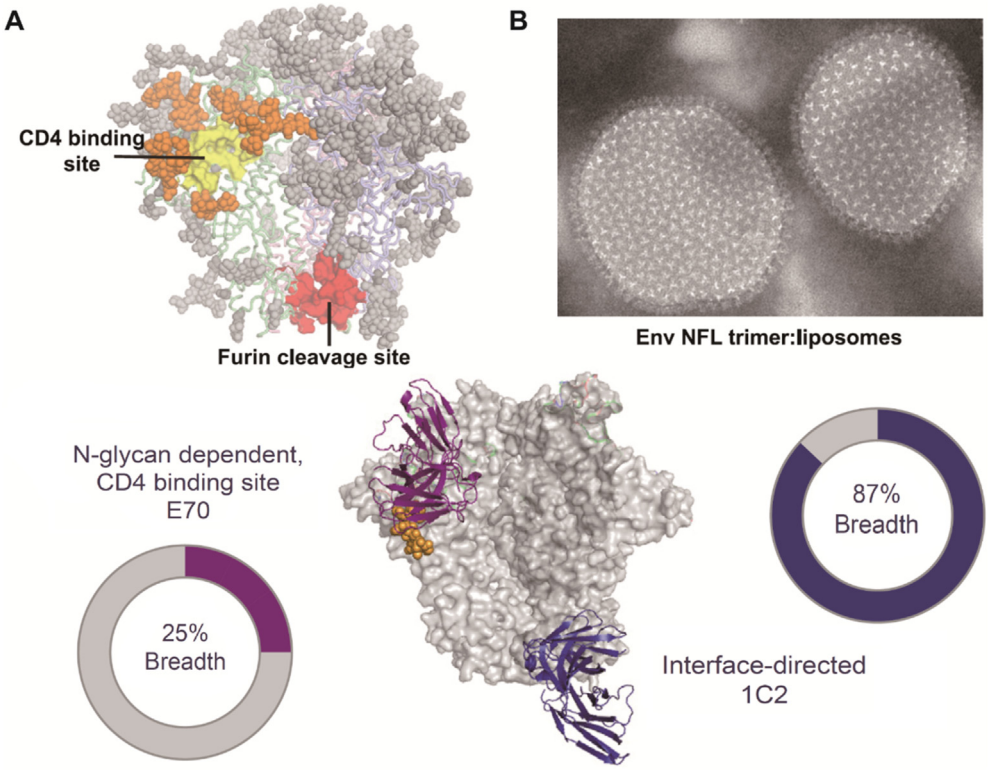

Figure 3 (A) HIV envelope trimer model. Conserved sites of vulnerability were highlighted as CD4bs (yellow) ringed with N-glycans (orange). The interface-directed antibody (1C2) showed significantly higher HIV neutralization breadth (87%) than N-glycan-dependent CD4-binding site E70 (25% HIV neutralization breadth) when vaccinating against a panel of clinical isolates. (B) Morphology of HIV envelope native flexibly linked trimer coupled to liposomes by negative stain electronic microscope. Reprinted with permission from Ref. 155. Copyright © 2019 Cell press.

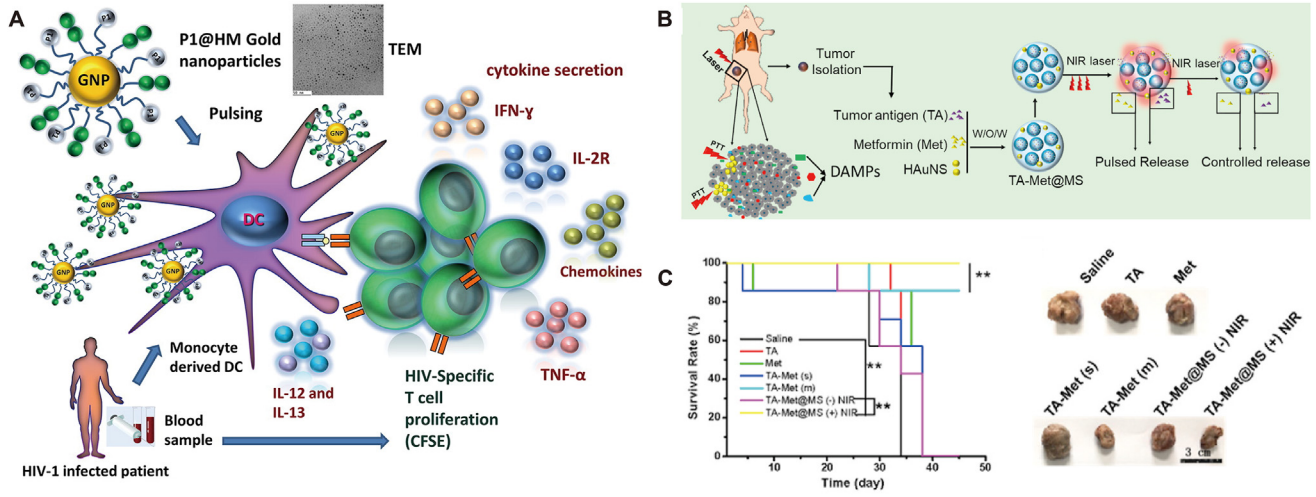

Figure 4 (A) Gold nanoparticle (GNP) decorated with high-mannoside-type oligosaccharides (P1@HM) and HIV-1-peptides-pulsed DC for HIV-specific T cell immunity. Reprinted with permission from Ref. 156 © Copyright 2018. Elsevier. (B) Fabrication of PLGA nanoparticle loaded with tumor antigen, metformin and hollow gold nanospheres (TA-Met@MS) as tumor vaccines. Photothermal therapy (PTT) stimulate the nanoparticle to release antigen and drug for inducing immunogenicity. (C) TA-Met@MS treatment prolonged the survival of tumor bearing mice and suppressed tumor progression. Reprinted with permission from Ref. 168. Copyright © 2021 Elsevier.

that suppress significantly both *in situ* and metastatic tumors. *In situ* immunotherapy requires multiple steps, to address this issue, a recent study reported a nanomedicine strategy for programmable immune activation driven by the high level of reactive oxygen species induced by supramolecular assembled nanoparticle in the tumor microenvironment[175]. Release of drug and CpG/PAMAM led to the exposure of tumor antigen and APC activation, and subsequent antitumor immune responses.

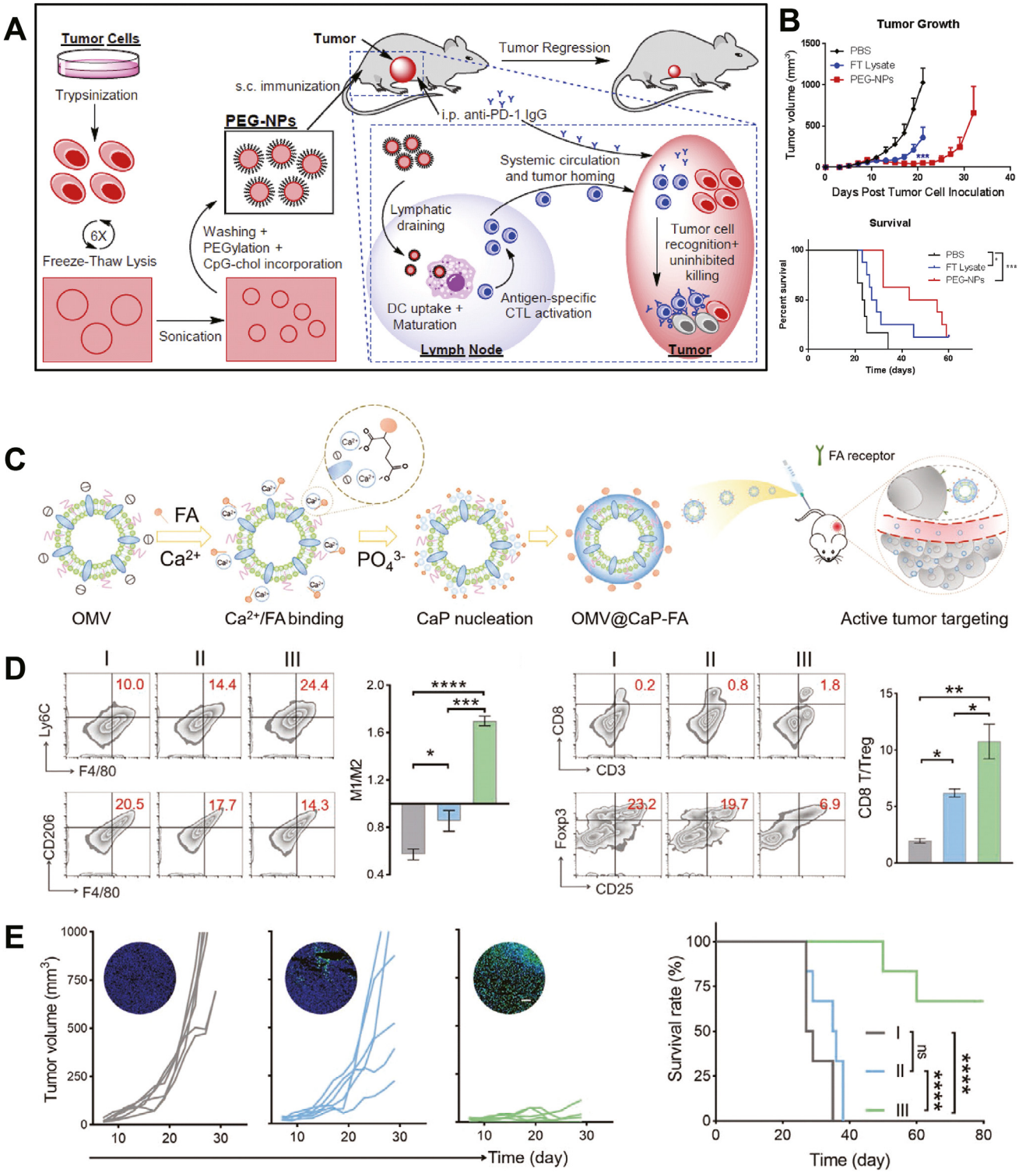

Figure 5 (A) Nanovesicles derived from tumor cell membrane as vaccine platform for cancer therapy. B16F10-OVA cell-derived nanovesicles (PEG-NPs) were obtain by freeze-thawing lysis, sonication, calcium-mediated aggregation, PEGylation, and cholesterol-linked CpG incorporation. Subcutaneous administrated PEG-NPs are taken up by DCs to activate antigen-specific cytotoxic $CD8^+$ T lymphocytes, which recognize and kill cancer cells in synergy with immune checkpoint blockade. (B) PEG-NPs nanovaccines suppressed tumor growth and prolonged survival of tumor bearing mice. Reprinted with permission from Ref. 178. Copyright © 2018 Elsevier. (C) Fabrication of biomineralized OMVs (OMV@CaPs) by Ca^{2+} binding, CaP nucleation, crystal growth and folic acid modification as targeted tumor vaccines. (D) Flow cytometry analysis showing OMV@CaPs shifted the macrophages polarization from M2 to M1, and increased $CD8^+$ T cell infiltration and decreased Treg in tumors. (E) OMV@CaPs suppressed tumor growth and prolonged survival of tumor bearing mice. Reprinted with permission from Ref. 187. Copyright © 2020 Wiley-VCH.

Table 1 Typical clinical approved vaccines and candidates using nanotechnology for addressing infectious disease or cancer.

Name	Formulation	Indication	Administration	Trial ID	Ref.
Mosquirix (RTS,S/AS01E)	Liposomal (AS01) adjuvant and recombinant Plasmodium, Hepatitis B protein	Malaria and hepatitis B	Intramuscular	NCT03162614, NCT02992119	190
M72/AS01E	Liposomal (AS01) adjuvant and mycobacterial 'M72' recombinant fusion antigen	Tuberculosis	Intramuscular	NCT01755598	191
HIV-1 gp-41 liposome vaccine	HIV-1 gp-41 MPER peptide 656 liposomes	HIV	Intramuscular	NCT03934541	NA
Lipo-MERIT	RNA formulated with liposomes (RNA-lipoplexes)	Melanoma	Intravenous	NCT02410733	192
mRNA-2752	Lipid nanoparticle encapsulating mRNAs encoding human OX40L, IL-23, and IL-36γ	Solid tumors or lymphoma	Intratumoral	NCT03739931	193
mRNA-4157	Lipid nanoparticle encapsulating mRNAs encoding multiple neoantigens	Solid tumors	Intramuscular	NCT03313778	194

NA, not available.

As tumor cells are highly heterologous, a single tumor antigen vaccine may have insufficient immune responses to eliminate tumors[176]. Therefore, the whole tumor cell lysate may be loaded into nanoparticles such as chitosan[177] and nanovesicles (Fig. 5A and B)[178] for enhanced antigens presentation. Besides, native tumor antigens may have low immunogenicity and induce limited immune responses to combat the tumor. In recent years, artificial antigen-presenting cells (aAPC) technology[179] has emerged to stimulate tumor-specific T cells by engineering nanomaterials equipped with peptide epitope and costimulatory molecules, replicating the immune-activation functions of APCs. Nanoscale aAPCs may have core material such as iron oxide[180]. It has been reported that iron-dextran aAPCs can induce great expansion of T lymphocytes expressing the cognate TCR. Membrane coating has also been used in the development of aAPCs[181]. The efficacy of aAPCs could be improved by modifying the nanoparticle morphology[182], signal coupling[183], and fluidity[136]. Further exploration and establishment of protocols of aAPCs with personalized neoantigens may generate highly effective and personalized tumor vaccines[184,185]. In a recent study, the immune response of autologous tumor antigen was enhanced by a hybrid membrane delivery strategy[77]. Bacterial cytoplasmic membrane and tumor cell membranes were used to form a nanoparticle for loading antigen and adjuvant to induce dendritic cell maturation, cytotoxic T cell activation, tumor growth suppression, and recurrence prevention.

Non-specific immune activation is another emerging strategy for developing cancer nanovaccines. OMV can induce systemic immune responses and recruit nonspecifically activated immune cells to initiate APC processing and CTLs generation. Intravenous injection of OMVs derived from *Escherichia coli* into CT26 tumor-bearing mice eradicated tumor cells[186]; moreover, the growth of re-challenged tumors in mice was suppressed significantly. In a recent study, OMVs were encapsulated into calcium phosphate shells and lead to M2-to-M1 polarization of macrophages in the tumor microenvironment and eliminated *in situ* tumor, and prevented metastasis with reduced side effects (Fig. 5C–E)[187].

6. Conclusions and perspectives

In the past decades, the rapid development of nanotechnology provided avenues for nanomedicine and vaccine development. Compared to traditional vaccines, nanovaccines utilized a variety of nanoparticles with essential advantages for delivery efficiency, dose regimens, administration route, adjuvants, and vaccination effects. In this review, we summarized major types of nanomaterials for vaccines and discussed cutting-edge examples, highlighting worldwide infectious diseases and cancers. In addition to the nanomaterial design, the development of novel immunogens is of importance toward a desirable prophylactic immune response for infectious diseases; while for cancer nanovaccines development, the safety, targeting ability and efficient whole vaccination cascade is vital for treatment immune response. In regards to the safety of nanovaccine, immunogenicity and toxicity are two major issues. Nanoparticles may activate host immune responses after administration. In addition, nanoparticle-derived products can cause unexpected nonspecific immune responses after biodegradation. Cationic and ionizable nanoparticles may have immunogenicity by increasing proinflammatory cytokine levels[188]. Cytotoxicity of nanoparticles is closely related to the type of nanomaterials and the dose. Biodegradable components are highly encouraged for developing nanovaccines with improved biocompatibility[189].

Focus on the typical clinical approved nanovaccines and vaccine nanotechnology under clinical development, we would get inspirations to find out the direction of next-generation vaccine nanotechnology. As shown in Table 1[190–194], liposomes and lipid nanoparticles have played dominant roles in nanovaccine clinical application, suggesting excellent biocompatibility and biosafety of nanomaterials would still be nonnegligible index in next-generation nanovaccine competition. It is also worth mentioning that the diseases with different underlying immune mechanisms would further push the development of nanovaccine subtypes. Take a panoramic view of current vaccine nanotechnology under clinical development, mRNA-based nanovaccine would have great promise in cancer treatment and infectious disease prevention. Furthermore,

many issues, including physicochemical properties, biointerfacing, and quality control remain to be addressed toward successful clinical translation of nanovaccines. The population implementation and the cost-effectiveness of nanovaccines should be considered; while for cancer nanovaccines, the patient-specific antigen is a challenge for personalized vaccination. Taken together, vaccine nanotechnology has shown promising results in experimental studies, and further joint efforts of nanomaterials, immunology, virology, oncology, and pharmaceutical industries will promote the clinical translation and application of nanovaccines for the management of devastating infectious diseases and cancers.

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Author contributions

Wei Tao and Chan Feng conceived the manuscript. Chan Feng, Yongjiang Li, Bijan Emiliano Ferdows, Dylan Neal Patel, Jiang Ouyang, Zhongmin Tang, and Na Kong co-wrote the draft. Wei Tao and Enguo Chen refined the draft. All authors discussed and edited the manuscript at all stages. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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