Organic and inorganic nanoparticle vaccines for prevention of infectious diseases

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Abstract
Infectious diseases remain a leading cause of concern worldwide. Conventional vaccine methods to elicit immune responses have limitations in effectively controlling new and re-merging pathogens. Nanoparticle-based vaccines show promise in overcoming these limitations due to their versatility and tunability to protect antigen from premature degradations, facilitate their intracellular uptakes and elicit prolonged immunity against infectious diseases. Nanoparticle can be categorized as purely organic or inorganic based on the components that construct the structure. Most organic materials are biocompatible, biodegradable, and nontoxic, while most inorganic materials have a smaller particle size, improved stability, controlled tunability, enhanced permeability, high antigen loadings, and a triggered release profile. This review will focus on the different type of organic and inorganic nanoparticles used as vaccine against infectious diseases.

1. Introduction
According to the World Health Organization (WHO), three infectious diseases were found in the top ten leading causes of death worldwide, with approximately 17 million deaths each year [1]. Over the past decades, some major diseases, including malaria and tuberculosis, have re-emerged, while new infectious diseases and recent outbreaks, like HIV/AIDS, Ebola hemorrhagic fever, Zika virus, and Coronavirus disease 2019 (COVID-19), have caused many thousands of casualties, mass social and economic disruptions and widespread fear globally. Many of these diseases lack immediate and effective prevention or treatment. Thus, there is clearly an urgent need to develop novel vaccines to elicit a strong humoral and cellular immune responses against these pathogens. Conventional vaccines, derived from microbial agents, recombinant proteins and synthetic peptides, have many drawbacks from optimal effectiveness against infectious diseases: (1) their low stability in the bloodstream and (2) their inability to provoke prolonged and sufficient immune response [2]. As a result, higher titers of vaccines are needed to elicit therapeutic effects. However, higher doses often lead to greater risk of side effects [3].

Nanoparticle-based vaccines offer an alternative to conventional vaccines, with potential advantages including high payloads, tunable sizes, tailorable surface properties, controllable drug release kinetics, and improved stability [4]. Many nanoparticle vaccine platforms with additional adjuvant properties and targeting ability to antigen-presenting cells (APCs), have been developed to enhance immunity [5–7]. Furthermore, nanoparticles can mimic aspects of the original protein or DNA and promote interactions with host cell receptors for activation of immune response [8, 9]. To maximize the delivery of the antigens, nanoparticles can be tailored with respect to their unique physiochemical properties, such as their size and surface chemistry [10]. For example, nanoparticles consisting of cationic lipids or polymers are commonly used to deliver DNA for enhancing immunogenic response [10, 11]. Likewise, nanoparticles can also be constructed to mimic virus-like properties in order to stimulate the host immune response without introducing the live viral DNA during infection [12].

Nanoparticles can be categorized as purely organic (e.g. polymeric, liposomes, and virus-like particle) or inorganic (e.g. gold nanoparticles, metal oxide, and mesoporous silica nanoparticles) based on the components that construct the structure. Most organic materials are biocompatible, biodegradable, and nontoxic, while most
inorganic materials have a smaller particle size, improved stability, controlled tunability, enhanced permeability, high drug loadings, and a triggered release profile [13–16] (figure 1). In this review, current novel vaccine strategies using nanoparticle are discussed, focusing on recent developments of organic and inorganic nanoparticles for the induction of immune responses against infectious diseases (table 1).

2. Organic nanoparticle

A wide variety of different organic nanoparticles have been developed as vaccine platform because of their biocompatibility, biodegradability, and general lack of toxicity [13]. Purely organic nanoparticles possess many advantages over other existing nanoparticle platforms, including self-assembly of antigens and adjuvants in physiologically mild conditions, and chemical diversity for accommodating a variety of modalities, compositions, sizes, shapes, and surface functionalization [16, 42]. This section will discuss recent developments of organic nanoparticle vaccine delivery platform, including polymeric nanoparticles, liposomes, and virus-like particles (VLPs).

2.1. Polymeric nanoparticle

Over the past few years, polymeric nanoparticles have gained usage in vaccine formulations due to their optimizable properties, including particle size, composition, and surface charge, which allows the development of multifunctional vaccine delivery platform to targeted hosts [43]. Polymeric nanoparticles consist of highly biocompatible polymers, including poly(lactic-co-glycolic acid) (PLGA), polyglycolic acid (PGA), and polylactic acid (PLA). PLA produces dense, flexible structure but degrades slowly, while PGA degrades rapidly but is stiff. PLGA has properties between PGA and PLA, which allows for tunability to combine the beneficial features of these polymers [44]. By changing the composition of co-polymer during polymeric nanoparticle synthesis process, these nanoparticles can function as a depot under physiological conditions for prolonged release and exposure of antigen to APCs, which is essential for mucosal vaccination [45]. Thomas et al synthesized nanoparticles of different ratio of PLA and PLGA to deliver hepatitis B surface antigen through the pulmonary route against hepatitis B virus (HBV) [17]. Higher composition of PLA was associated with larger particle size. Their large particle size offered enhanced uptakes in rat alveolar macrophages over smaller particles, leading to increase of cytokine secretion. PLGA can also be encapsulated by lipid membrane to provide enhanced immunization. Moon et al demonstrated that when PLGA conjugated-malaria antigen, VMP001, was encapsulated within lipid membrane, these PLGA-lipid nanoparticles elicited higher humoral responses in vivo with 10-fold less amount of soluble protein vaccine dose and sustained similar antibody titers for up to 180 days [46]. Similarly, a lipid-polymer hybrid multilamellar vaccine particle (MVP), composed of cationic lipid-hyaluronic acid, crosslinked with Ebola virus (EBOV) glycoprotein, generated long-lasting antigen-specific
CD8+ and CD4+ T cell responses, and a single dose of MVP vaccination protected 80% of mice against EBOV infection [18].

In addition to synthetic polymers, biopolymers, such as chitosan, are commonly used as adjuvants. Chitosan is a cationic polyelectrolyte fabricated from deacetylation of chitin, which is found as byproduct of crab and shrimp processing [47]. Chitosan is nontoxic, biocompatible, and biodegradable. Chitosan can be formed into nanoparticles for controlled release and targeted delivery of antigens and immunoadjuvants in mucosal administration of vaccine [48]. Through the interactions between the positive charges of the chitosan-containing nanovesicles and the negative charged cellular membrane of the epithelium, the adsorption of the polymeric nanoparticles is enhanced from nasal and intestinal mucosa to significantly induce immune response. Furthermore, the bioadhesive properties of chitosan enhance the clearance half-life of the particles [49]. Several chitosan-based polymeric nanoparticles exist as vaccine delivery system. Feng et al developed chitosan-based nanoparticle that delivers T cell epitopes of Esat-6 and FMS-like tyrosine kinase 3 ligands (FL) against Mycobacterium tuberculosis (M.tb) [19]. C57BL/6 mice challenged with M.tb H37Rv were immunized with these chitosan nanoparticles. The levels of IFN-γ and IL-12 were found to be 30%–40% higher compared to those the

| Nanoparticles | Antigens | Diseases | Size (nm) | Shape | References |
|---------------|----------|----------|-----------|-------|------------|
| Polymeric     | Hepatitis B surface antigen | HBV | 474–940 | Spherical | [17] |
|               | VMP001   | Malaria  | 290       | Spherical | [7] |
|               | EBOV glycoprotein | Ebola | 350       | Spherical | [18] |
|               | Esat-6 and fms-like tyrosine T cell epitopes | M. tb | 280–330 | Spherical | [19] |
| Liposome      | Recombinant hepatitis B antigen | HBV | 160–220 | Spherical | [20] |
|               | Deactivated RG-5B5 | HAV | N/A | N/A | [21] |
|               | Haemagglutinin of IAV and IBV | IAV and IBV | 50–400 | Spherical | [22, 23] |
|               | M. tb H37Rv | M. tb | 255–322 | Spherical | [24] |
|               | Membrane-proximal external region (MPER) peptide | HIV | 150       | Spherical | [25] |
|               | BG505 MD39 trimer | HIV | 150       | Spherical | [26] |
| Virus-like particle | HPV16 L1 capsomeres5 | HPV | 10        | Pentameric | [27] |
| Ferritin      | H1 HA    | H1N1 IAV | 20–30 | Spherical | [28] |
|               | HIV-1 envelope and H1 HA | HIV and H1N1 IAV | 20–50 | Spherical | [29] |
|               | H1 HA    | H5N1 IAV | N/A | Spherical | [30] |
|               | H3 and H7 HA | IAV | 17–20 | Spherical | [31] |
| Inorganic     | Gold     | West Nile virus envelope protein | West Nile virus | 20–40 (spherical) | Spherical, rod, and cubic | [32] |
|               | Foot-and-mouth disease virus peptide | Foot-and-mouth | 8–50 | Spherical | [33] |
|               | CpG oligodeoxynucleotide Streptococcus pneumoniae type 14 capsular polysaccharide | H1N1 IAV | 12 | Spherical | [34] |
|               | B. thailandensis E264 lipopolysaccharide with Hc fragment of tetanus toxin | Burkholderia mallei | 30 | Spherical | [36, 37] |
|               | Iron Oxide | M. tb fusion protein | M. tb | <20 | Spherical | [38] |
|               | Merospor surface protein 1 (rMSP1) Mannose and HBsAg | Malaria | | | |
| Mesoporous Silica | Soluble Worm Antigen Preparartion Antigen | HBV | 60 | Spherical | [39] |
|               | Porcine circovirus type 2 opening reading frames (PCV2-ORF2) proteins | Schistosoma mansoni | 39 | Spherical | [40] |
|               | Porcine circovirus type 2 open- | Post-weaning multi-systemic wasting syndrome | 200 | Spherical | [41] |

* Clinical approved nanoparticle vaccine
Esat-6/FL plasmid and 20% higher than commercial tuberculosis vaccine (bacillus Calmette-Guerin, BCG). Moreover, it was demonstrated that bacterial burdens were decreased by almost 2-fold compared to BCG and DNA plasmid-treated mice four weeks post challenge. The author theorized that the chitosan component protected the DNA plasmid from nuclease degradation and improved cellular uptake in circulation, leading to enhanced immune response. Chitosan polymeric nanoparticles have also been developed to prevent HBV infections. Prego et al designed polysaccharide-based nanoparticles, crosslinked chitosan, to deliver recombinant HBV antigen [20]. These nanoparticles were intramuscularly injected in mice challenged with HBV and produced 9-fold higher amount of HBV specific IgG than conventional aluminum-adsorbed vaccine. The tunability and modification of block copolymers will permit advances in polymeric nanoparticles as viable vaccine against infectious disease.

2.2. Liposome

Liposomes are a unique class of organic nanoparticles that have been the most successful nanoparticle platform for biomedical application. These nanoparticles consist of biodegradable phospholipids which self-assemble into a lipid bilayer around an aqueous core upon hydration [50]. The addition of a lipid bilayer to a particle surface can result in enhanced stability as liposomes are mostly impermeable to moieties such as salts and macromolecules that are known to degrade the particles under biological condition [51]. The versatility of liposome can incorporate both hydrophobic and hydrophilic molecules, like antigenic proteins and peptides, within the lipid bilayer and aqueous core, respectively.

Several liposomal platforms have been clinically approved as vaccine for infectious diseases [52]. The Epaxal™ vaccine, which contained deactivated RG-SB strain antigen, was the first approved liposomal vaccine product for the treatment of hepatitis A (HAV) developed by Crucell Berna Biotech [21]. Unlike traditional liposome, Epaxal vaccine contained viral envelope glycoprotein within its phospholipid bilayer. The dioleophosphatidylethanolamine (DOPE) and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) lipid components of Epaxal vaccine facilitated the uptake of HAV antigen to immunocompetent cells and provided immunogenicity from HAV injection for more than 20 years after two booster doses. Inflexal™ V vaccine, another liposomal particle developed by Crucell Berna Biotech, was used to prevent influenzas by incorporating haemagglutinin of influenza A and B virus strains within lecithin-phospholipid. Inflexal V vaccine has been shown to have four-fold higher in immunogenicity than conventional influenza vaccines, like Influvac™ vaccine [22, 23].

A key advantage of liposomal nanoparticle is the tunability of the lipid bilayer, which can further be functionalized with targeting ligands or antigens, allowing for vaccine applications in biomedical imaging and drug delivery. These materials have many characteristics beneficial to drug delivery such as chemical diversity, high loading capacity, and intrinsic biodegradability [53]. Like polymeric nanoparticle, the lipid bilayer of liposome can be functionalized with chitosan. Das et al developed liposomes consisting of antigenic M.tb H37Rv-strained lipids coated with chitosan [24]. Following administration of these chitosan liposome to BALB/c mice, CD1 took up these nanoparticles and induced both pro-and anti-inflammatory cytokines related to Th1 and Th2 immune responses by activating γδ T cells. In addition to the functionality of the lipid bilayer, the physical properties of liposomes can also be modified to modulate the immunogenicity of the vaccines. Hanson et al and Tokalian et al evaluated particle size, lipid composition, and the incorporation of T-cell helper of liposomal vaccines [25, 26]. By anchoring the antigens onto the surface of the liposome, they discovered that particle diameter of 150 nm provided enhanced retention in draining lymph nodes. Furthermore, the inclusion of high melting temperature lipids like DOPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), and 1,2-dioleophosphatidylglycerol (DOPG) was found to elicit 6.2-fold higher titer than DOPC-only liposomes. Finally, they discovered that the incorporation of encapsulated T-cell helper epitopes enhanced humoral responses.

By incorporating other pH-sensitive or thermosensitive linkers, one can trigger release of its payload over time in response to environmental conditions, allowing for prolonged stimulation of immune response. For example, pH-sensitive lipids or polymers, like DOPE, polyoleoylphosphatidylethanolamine (POPE), and diolein, have been used in liposomes to destabilize the endosomal membrane for efficient drug release into the cell cytosol [54–56]. In particular, pH-sensitive liposomes were developed to encapsulate cytotoxic T lymphocyte epitopes and peptide immunogens for prolonged immunization in vivo against HIV and cancer [55, 57–59]. Themosensitive liposomes have also been developed to control drug release at elevated temperature [60]. Radiofrequency ablation increased the local temperature to 42°C, allowing for thermosensitive lipids, like 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1-Myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC), composed within a liposome to undergo gel to liquid transition for easier permeability and drug release. This approach has been shown in cancer therapy and can be applied to vaccine immunization [61].
2.3. Virus-like particles (VLPs)
Another strategy to elicit greater immune response is to design carriers that mimic the natural structure and intrinsic immunogenic property of the virus, also known as VLPs. VLPs are spherical nanoparticles, typically self-assembled to be 20–200 nm in diameter [45]. These particles are generally derived from proteins from bioengineered bacteria, yeast, insect, mammals, or plants [62]. VLPs consist highly purified viral proteins that are free from its host genetic materials to mimic aspects of the original virus [63]. Namely, these particles allow for broad cross-protection against different viruses. VLPs are generally highly thermostable, without the need for cold chains for viability, and suitable for vaccination in developing countries where cold chains are not readily available [27]. The promise of VLPs is validated with the clinical success of Recombivax HB®, Gardasil®, and Cervarix® vaccines [64]. The Recombivax vaccine was the first VLP to be FDA approved for the prevention of HBV, which forever changed the landscape of recombinant DNA in vaccine development. Following soon after, the Gardasil and Cervarix vaccines were the second and third nanoscale vaccine systems to have been approved by the FDA and are currently used to prevent human papillomavirus (HPV).

2.4. Ferritin
Another attractive self-assembly nanoparticle-based vaccine platform for infectious diseases is ferritin, which is produced in a majority of living organisms [65]. Ferritin is composed of 24 alpha helix subunits of 3-folds axis symmetry, and self-assembles into nanoparticles with improved thermal and chemical stability [66]. The conformation of ferritin nanoparticles allows for favorable presentation of trimeric antigens, which improves the likelihood for providing cross-protection against different subtype of influenza virus.

Kanekiyo et al were the first group to report the use of ferritin nanoparticle to display viral glycoprotein by genetically fusing the hemagglutinin (HA) at the interface of the ferritin subunits without compromising the native trimeric confirmation [28]. Typically, antibodies provide strain-specific immunity by targeting the always changing head domain of HA. Compared to current commercial vaccines, these nanoparticles have been shown to enhance the potency of neutralizing antibody responses and provide broad vaccine protection against H1N1 viruses in mice and ferrets.

Georgiev et al developed two-component ferritin nanoparticles to incorporate trimeric antigens derived from HIV-1 envelope (CNE58) and influenza A (IAV) HA (A/California/7/2009) [29]. These dual-antigen ferritin nanoparticles elicited neutralizing antibodies against both HIV and IAV in guinea pigs. The authors also designed dual-flu and dual-HIV ferritin nanoparticles to incorporate two strains of influenza and HIV-specific antigens, respectively. In another example, Yassine et al reported the structure-based development of ferritin nanoparticles consisting of only H1 HA stem region that were able to provide broad heterosubtypic immune-protection against H5N1 virus in mice and ferrets, despite no H5N1 neutralizing activity detected in vitro [30]. This suggested that HA stem-based vaccine can provide broad protection without the need of using the same neutralizing epitope.

The thermostability of ferritin nanoparticles has been studied by Corbet et al using differential scanning calorimetry (DSC) [31]. Uniform ferritin nanoparticles composed of IAV group 2 H3 and H7 HA stem antigens demonstrated thermal melting temperatures ($T_m$) from 56.6 to 66.6 °C with three other transition temperature at 78, 96, and 106 °C. Furthermore, the authors investigated the effect of multiple protein stabilization methods, including optimization of helix, loop, disulfide bond, and side chain, on their ferritin nanoparticle design. The improved thermostability of ferritin nanoparticles provided improved vaccine transport and storage. Furthermore, these Group 2 HA stem ferritin nanoparticles elicited broadly neutralizing antibody responses in mice challenged with lethal dose of IAV. These resulting immunogens could activate B cells expressing inferred unmutated common ancestor versions of human antibody lineages and are currently being developed for clinical evaluation.

3. Inorganic nanoparticle
Inorganic nanoparticles have largely been used as imaging contrast agents or photothermal therapy in cancer. Recent interest has been directed toward the development of inorganic nanoparticles as vaccines in preclinical settings. Most inorganic materials have a smaller particle size, improved stability, controlled tunability, enhanced permeability, high drug loadings, and a triggered release profile, which is ideal for antigen delivery as a vaccine [14, 15]. These newer generations are typically constructed with an inorganic core and an organic outer shell to afford hybrid inorganic nanomaterials [16, 67]. In this section, we briefly review the recent development of these inorganic nanoparticles in vaccines as both carriers and adjuvants.
3.1. Gold nanoparticle
Gold nanoparticles (AuNPs) have been used in a variety of applications, including computing devices, catalysis, sensing probes, and drug delivery [68]. Due to its relatively low toxicity and its chemical diversity for accommodating different compositions, sizes, shapes, and surface functionalization, AuNPs are ideal for vaccine application [69]. AuNPs are prepared ‘in situ’ using the Turkevich-Frens method, which involves citrate ions as both a reducing agent and a capping reagent to produce spherical AuNPs of 10–20 nm in diameter [70]. Recent synthesis methods, such as seed-growth methods, allow for better control of nanoparticle size and shapes by altering the reducing agent, temperature, pH, solvent, and synthesis time to afford rod or cubic shaped particles of 2–150 nm in size [69]. Different shape and size affect the uptake and immune response of the host cells. Niikura et al investigated the effect on immune response of spherical, rod, and cubic shaped AuNPs of around 40 nm in diameter or length coated with West Nile virus envelope protein [32]. Rod-shaped AuNPs were found to be more efficient in macrophage and dendritic cell uptakes than spherical or cubic-shaped AuNPs. However, both spherical and cubic AuNPs induced higher level of inflammatory cytokines, like TNF-α, IL-6, IL-12, and GM-CSF, while rod-shaped AuNPs induced higher secretion of inflammamome-related cytokines, like IL-1β and IL-18. Therefore, antibody production is not dependent on uptake efficacy, and different shape of AuNPs could enhance immune responses of different pathways. Likewise, Chen et al explored different sizes of spherical AuNPs, ranging from 2 to 50 nm in diameter that were conjugated with synthetic foot-and-mouth disease virus peptide [33]. As peptides can be presented on the exterior of nanoparticle, peptide-based nanoparticle vaccines provide greater penetration into cells than whole proteins. They found that AuNPs of diameter 8 to 17 nm had maximal antibody response compared to the synthetic peptide conjugate control.

Another peptide-based AuNP vaccine by Tao et al demonstrated the ability of AuNPs, functionalized with extracellular domain of M2 peptide (M2e), to elicit protective immunity against influenza A [34]. The AuNP was further adjuvanted with soluble CpG oligodeoxynucleotide to stimulate TLR-9, which was critical to provide protection against influenza pneumonia. When incorporated with soluble M2e peptide in the formulation with AuNP, mice challenged with H1N1 influenza virus had a high level of M2e-specific IgG antibody, resulting in complete protection.

Functionalizing AuNPs with carbohydrate conjugates is another common vaccination strategy used to enhance immunogenicity. Safari et al developed AuNPs conjugated to synthetic tetrasaccharide epitopes from Streptococcus pneumoniae type 14 capsular polysaccharide (Pn14PS) [35]. These carbohydrate conjugated AuNPs induced specific anti-Pn14PS IgG antibodies in mice, leading to cytokine production of TNF-α, IL-2, and IL-5 in mice spleen and activation of memory T-cell. Gregory et al also developed AuNPs functionalized with B. thailandensis E264 lipopolysaccharide (LPS) with Hc fragment of tetanus toxin to protect against Burkholderia mallei, a bacterial agent responsible for the infectious disease glanders [36]. These glycoconjugated AuNPs demonstrated increased production of IgG1, IgG2a, and IgM in mice challenged with B. mallei infection compared to LPS only. The author theorized that the elevated immune response was due to the high density of the epitopes localized on the AuNPs, which increased presentation of LPS toward B memory cells. The authors further investigated these particles with another protein carrier, FliC, as adjuvant on a rhesus macaque model of pneumonic glanders [37]. These glycoconjugated AuNPs provided protection in half of the animal challenged with aerosol B. mallei. Although survival benefit was not observed from these AuNPs compared to the control, higher LPS-specific IgG titer was seen in the vaccinated animal who survived than the ones that did not.

3.2. Iron oxide nanoparticle
Iron oxide nanoparticles (IONPs) are most commonly associated with magnetic resonance imaging (MRI) contrast agents that have been used to image a wide variety of diseases, leading to their FDA approval for clinical use in 1996 [71–73]. Recent efforts have been directed toward using IONPs as adjuvants for vaccine development. Iron plays a critical role in the initiation of the inflammatory process. For instance, Roja et al synthesized superparamagnetic iron oxide nanoparticles (SPIONPs) coated with dimercaptosuccinic acid, aminopropyl silane or aminodextran in murine M2 macrophage models [74]. The authors found that the treatment of SPIONPs on M2 macrophages induced reactive oxygen species production, altered the iron metabolism, and promoted immune regulation by producing IL-10. This was further supported in a study by Shen et al in which SPIONPs were intravenously administered in mice sensitized with ovalbumin (OVA) [75]. These SPIONPs reduced T cell-mediated immune reactions, as shown in the reduction of OVA-specific IgG1 and IgG2a antibodies. The cytokine production from splenocytes that was re-stimulated by OVA antigen was also decreased by these SPIONPs. For these reasons, IONPs showed great potential as a vaccine platform against infectious diseases.

IONPs are consisted of γ-Fe₂O₃ and Fe₂O₄ magnetite, most commonly prepared by oxidative coprecipitation or thermal decomposition [76]. Several IONP-based platforms have been developed as vaccine adjuvant. Through coprecipitation, Neto et al synthesized citrate-coated manganese ferrite (MnFe₂O₄)
nanoparticles modified with *Mycobacterium tuberculosis* fusion protein [77]. These nanoparticles were evaluated in subcutaneous and intranasal murine models of tuberculosis. Different immune responses were found with different administration routes. Through subcutaneous vaccination of MnFe₂O₄ particles, specific Th1 and CD8+ responses were induced in mice challenged with tuberculosis. In contrast, mice that were vaccinated intranasally generated Th1, Th17, and Tc1 responses. A mixed vaccination method induced Th1 and Tc1 response but not Th17 response. The authors hypothesized that the DCs in the lung produced higher level of IL-6 in cervical lymph nodes and spleen, leading to preferential Th17 generation in the intranasal administration. In a different study, Pusic *et al* developed IONPs of < 20 nm in diameter, containing recombinant malaria vaccine antigen, merozoite surface protein 1 (mRMSPI), without additional adjuvant [38]. These IONPs demonstrated complete immune response rate via intramuscular and intraperitoneal administration routes in mice challenged with malaria, while only 60% response rate was achieved when administered subcutaneously. Moreover, these IONPs were efficiently internalized in APCs, DCs, and macrophages, leading to increased proinflammatory cytokines and chemokines productions in DCs.

Advances have also been made in incorporating carbohydrate coating of nanovaccines to target receptors on DCs. Rezaei *et al* developed IONPs coated with silica and loaded with mannose and HBSAg, a surface antigen of HBV, on the surface of the particle for targeted delivery to DCs [39]. These IONPs with mannose were successful in selectively targeted DCs, leading to 16-fold increase in IL-6, TNF-α, and IFN-γ gene expression *in vitro* as compared to IONPs without mannose. Furthermore, when these mannose functionalized-IONPs were immunized in BALB/c mice, higher levels of INF-γ, TNF-α, IL-2, IL-4, and IL-12 cytokine levels were observed than nanoparticles without mannose. Another carbohydrate-functionalized strategy by Shen *et al* demonstrated the ability of lactosylated N-alkyl polyethylenimine (PEI) coated SPIONPs to label DCs with high efficiency and low cytotoxicity [78]. The surface of the SPIONPs were lactosylated with PEI to induce autophagy and maturation of DCs, which are essential for migration and antigen presenting abilities to strengthen their vaccine function.

### 3.3. Mesoporous silica nanoparticle

Mesoporous silica nanoparticles (MSNPs) are another attractive vaccine delivery platform due to their biocompatibility, chemical stability, and biodegradability properties [79]. Unlike solid silica nanoparticles, MSNPs contain high surface areas, tunable pore sizes, and large pore volume, which are ideal for incorporating vaccine antigens within the particles [79]. MSNPs are often prepared by the Stöber method, which involves ammonia catalyzed hydrolysis of tetraethylorthosilicate [80]. The thickness of the silica shell could be controlled by changing the base concentration and reaction time. In physiological conditions, the silica coating on the nanoparticles is inert, which improves biocompatibility in tissues and cells [81]. The addition of the silica coating could also control the delivery of antigens with controlled release characteristics and optimal pharmacokinetic profiles.

MSNPs could be functionalized with antigens as a vaccine delivery system by co-condensation or post-synthesis grafting [82]. Many researchers have used aminosilane functionalized ordered silica materials (SBA-15) to deliver vaccine antigens for better understanding of their mechanistic and immunogenic properties. For example, Carvalho *et al* compared the adjuvant effect of SBA-15 by loading bovine serum albumin (BSA) within SBA-15 and an aluminum hydroxide adjuvant approved for human use and delivering subcutaneously in genetically modified mice selected for high or low antibody response [83]. Higher immunogenic response was found in low antibody response mice treated with SBA-15. In addition, BSA-loaded SBA-15 induced both Tc1 and Tc2 responses as compared to BSA-adsorbed by aluminum hydroxide, which only activated the Tc1 pathway. In another example, Mercieri *et al* developed SBA-15 as an adjuvant to deliver bacterial recombinant protein Int1/3 and *Micrurus* snake venom proteins. To compare the ability of SBA-15 adjuvant, these proteins were loaded within SBA-15 nanocarriers or adsorbed on aluminum hydroxide [84]. These SBA-15 nanoparticles induced 2-folds higher immune response than proteins absorbed on aluminum hydroxide in mice challenged with either Int1/3 or snake venom.

Other MSNPs have also been explored for vaccine delivery. Oliveira *et al* synthesized MSNPs loaded with Soluble Worm Antigenic Preparation (SWAP) antigen as a novel vaccine adjuvant against *Schistosoma mansoni* parasite [40]. These SWAP-loaded MSNPs improved immunological potency by 38% compared to conventional SWAP antigen associated with aluminum salt in mice challenged with *Schistosoma mansoni*. Moreover, SWAP-loaded MSNPs showed higher IgG1 level after 112 days of immunization compared to SWAP-associated aluminum salt, which confirmed that MSNPs could improve the immune response of vaccines. In another study, Guo *et al* developed MSNPs loaded with porcine circovirus type 2 opening reading frame (PCV2-ORF2) proteins to induce immune response against post-weaning multi-systemic wasting syndrome (PMWS) [41]. Due to their large surface area and pore size, these nanoparticles demonstrated higher binding capacity and delivery of the PCV2-ORF2 proteins. The slow release enabled by the silica coating
provided long lasting humoral and cellular immunization, as seen in 2-fold higher T-lymphocyte proliferation responses from mice treated with PCV2-ORF2 MSNPs than those treated with only the PCV2-ORF2 protein.

4. Conclusion

The effective delivery of antigen to APCs to elicit prolonged immune response remains a significant challenge for vaccination against infectious diseases. In the last several years, there has been significant progress in the use of nanoparticles as vaccine delivery platforms. Both organic and inorganic nanomaterials offer unique advantageous properties as vaccine carriers. In particular, these nanoparticles prevent premature antigen release while prolonging antigen presentation for potent immunity against infectious diseases. With emergence of new clinical nanoparticle vaccines, we are entering a bright future of translating nanomedicine from the benchtop to the clinic. However, challenges remain in the optimization of high throughput and scale-up synthesis methods to manufacture homogenous, reproducible nanoparticle in a cost-effective way, which hinders clinical translation and industrial production of nanoparticle vaccines [85]. Taken together, we believe nanoparticles offer new strategies for developing vaccine delivery vehicles with clinical potential.

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Conflicts of interest

C.P. and A.P. are employees of Emergent Travel Health Inc. but this conflict does not alter our adherence to policies set forth by Nano Express.

Author contributions

C.P. and A.P. conceived the concept and wrote the review.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

All authors have provided consent for the manuscript to be published.

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