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ADVANCED REVIEW

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Materials-based vaccines for infectious diseases

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Abstract

Infectious diseases that result from pathogen infection are among the leading causes of human death, with pathogens such as human immunodeficiency virus, malaria, influenza, and ongoing SARS-COV-2 viruses constantly threatening the global population. While the mechanisms behind various infectious diseases are not entirely clear and thus retard the development of effective therapeutics, vaccines have served as a universal approach to containing infectious diseases. However, conventional vaccines that solely consist of antigens or simply mix antigens and adjuvants have failed to control various highly infective or deadly pathogens. Biomaterials-based vaccines have provided a promising solution due to their ability to synergize the function of antigens and adjuvants, troubleshoot delivery issues, home and manipulate immune cells in situ. In this review, we will summarize different types of materials-based vaccines for generating cellular and humoral responses against pathogens and discuss the design criteria for amplifying the efficacy of materials-based vaccines against infectious diseases.

This article is categorized under:

Therapeutic Approaches and Drug Discovery > Nanomedicine for Infectious Disease

KEYWORDS

adjuvant, antigen, immune response, infectious disease, pathogen, vaccine

1 | INTRODUCTION

Infectious diseases caused by organisms such as viruses, bacteria, fungi, and parasites are accountable for a rising mortality over decades (Laxminarayan et al., 2020; Rana et al., 2021; Zwizwai, 2016). While the mechanisms for various

types of infectious diseases remain elusive, which poses difficulty for developing effective drugs, vaccines have stood out as a generalizable approach to preventing infectious diseases (Pollard & Bijker, 2021). Vaccines function by delivering antigens derived from the corresponding organism to antigen presenting cells (APCs) in the body. APCs process and present antigens via major histocompatibility complex I (MHCI) or II (MHCII) for subsequent priming of antigen-specific T and B cells, a fraction of which further differentiate into memory phenotypes (Fries et al., 2021). When the same pathogen shows up again, memory B and T cells are able to recognize and quickly respond to it by generating a substantial amount of antibodies that can neutralize the pathogen, and expanding effector T cells that can directly kill the pathogen (Malley et al., 2005; Natoli & Ostuni, 2019). Vaccines against measles (Strebel et al., 2012), chickenpox (Takahashi, 2018), and many other organisms have established long-lasting success. Recently, vaccines have also played a critical role in severe acute containing respiratory syndrome coronavirus 2 (SARS-CoV-2) during the covid-19 pandemic (Krammer, 2020).

Antigen is a central component of vaccines to elicit antigen-specific humoral and cellular responses against antigen-expressing pathogens (Graham et al., 2019). The sources of antigens have varied from attenuated cells (Milligan et al., 2018), toxoids (Havers et al., 2020), purified proteins (Zerbo et al., 2019), to more recent DNAs and mRNAs encoding the antigenic proteins or peptides (Chaudhary et al., 2021). Among them, attenuated cells are the most commonly used antigen source to construct vaccines against infectious diseases, as in the case of measles and chickenpox vaccines. However, these attenuated cell-based vaccines have shown varying degrees of success, with little to no success toward many hard-to-tackle pathogens such as *Mycobacterium tuberculosis* (Hatherill et al., 2020), human immunodeficiency virus (HIV) (Bekker et al., 2020), and drug resistant bacteria (Piddock, 2017). Recent progress in identifying protein and peptide antigens from disease-causing pathogens has greatly facilitated the development of vaccines that can more precisely induce pathogen-specific T and B cell responses. However, antigens alone often failed to provide full protection from pathogens, likely due to the limited potency of generated humoral and cellular responses.

The incorporation of adjuvants that can activate APCs and facilitate the presentation of antigens by APCs has significantly enhanced the potency of generated antigen-specific humoral and cellular responses (Reed et al., 2013). For example, aluminum salt (e.g., alum), a commonly used adjuvant, was able to improve the immunogenicity of attenuated pathogens and contribute to the development of enhanced DTaP vaccines, pneumococcal conjugate vaccines, and hepatitis B virus (HBV) vaccines (Marrack et al., 2009). AS04, a combination of aluminum hydroxide and monophosphoryl lipid A (MPLA), is also incorporated in the Cervarix vaccine that prevents cervical cancers caused by human papillomavirus types 16 and 18 (Keam & Harper, 2008). The AS03 adjuvant made up of D,L-alpha-tocopherol, squalene, and polysorbate 80 is incorporated in the "bird flu" vaccines for the prevention of H5N1 influenza (Garçon et al., 2012). CpG 1018, an oligonucleotide adjuvant, is incorporated in the FLUAD vaccine for the prevention of seasonal influenza in adults 65 years of age or older (Campbell, 2017). These adjuvants demonstrated favorable safety profiles and the ability to amplify immune responses against the target pathogens. However, current formulations of these FDA-approved vaccines are simple mixtures of antigens and adjuvants either in soluble form or in the presence of an emulsifier. Noncontrolled lymphatic drainage, tissue retention, and APC uptake of vaccine components after injection likely result in sub-optimal antigen presentation, and T and B cell priming, thus exhibiting limited efficacy against various hard-to-tackle pathogens and infectious diseases (Reed et al., 2013).

A variety of strategies have been adopted to improve the formulation of vaccines for infectious diseases, and more importantly, facilitate the co-delivery of antigens and adjuvants to lymphatic tissues (e.g., lymph nodes) where T and B cell priming occurs (Roth et al., 2021). For example, antigens and adjuvants were conjugated for concurrent delivery to APCs in the lymph nodes, which resulted in improved antigen-specific humoral and cellular responses (Moyer et al., 2020; Wilson et al., 2019). Biomaterials can also contribute to the development of vaccines by enabling improved delivery of vaccine components to lymphatic tissues, reducing off-target side effects, amplifying the synergistic effect of different molecules, and manipulating immune cells in situ (Fries et al., 2021). For example, nanomaterials enable co-delivery of antigens and adjuvants to APCs in lymph nodes for improved elicitation of T and B cell priming (Ke et al., 2019; Schudel et al., 2019). Porous biomaterial scaffolds loaded with chemokines were also developed to recruit and program dendritic cells (DCs), a prominent type of APCs in the body, in situ for modulation of local and systemic immune responses (Ali et al., 2009; Kim et al., 2015; Super et al., 2021). While biomaterials-based vaccines possess tremendous potential for vaccine development, their application to the field of infectious diseases are still in the early stage. We anticipate the roaring development of material vaccines for the prevention of viruses, bacteria, parasites, and other pathogens in the coming years, as exemplified by the liposomal vaccines developed by Moderna and Pfizer for the prevention of SARS-CoV-2 (Polack et al., 2020). In this review, we will describe the mechanisms of vaccination against infectious diseases and provide an overview of material-based vaccines under development or in the clinic that aim to

improve pathogen-specific humoral and cellular responses and the overall efficacy. We will also discuss the design criteria for future materials-based vaccines against pathogens and infectious diseases.

1.1 | Vaccination against infectious diseases

Vaccination against infectious diseases is aimed at inducing adaptive immune responses, both humoral and cellular responses, against disease-causing pathogens. Administered antigens are taken up and processed by APCs. Antigens entering the endosomes can be directly loaded onto MHCII while antigens entering the cytoplasm are degraded by proteasomes and loaded onto MHCI, prior to presentation on the cell membrane (Figure 1). APCs then traffic to lymphatic tissues (e.g., lymph nodes) to induce the expansion of $CD8^+$ T cells, $CD4^+$ T cells, or B cells that can recognize MHCI-antigen or MHCII-antigen complexes. The presence of adjuvants can facilitate the maturation of APCs and subsequent APC-mediated priming of T and B cells. Cytotoxic $CD8^+$ T cells can directly kill antigen-bearing pathogens, while $CD4^+$ T cells modulate the priming processes and functions of $CD8^+$ T cells and B cells. A fraction of these antigen-specific T and B cells can further differentiate into memory phenotypes for surveillance of re-appeared pathogens (Harty & Badovinac, 2008; Si et al., 2016; Figure 1). Depending on the surrounding cues, $CD4^+$ T helper cells can differentiate into different subtypes including T helper 1 (Th1), T helper 2 (Th2), and T helper 17 (Th17) cells. Th1 cells release interferon-γ (IFN-γ) and interleukin-2 (IL-2) that can activate $CD8^+$ T cells for cytotoxic killing of pathogens and differentiation of memory $CD8^+$ T cells (Schreiner & King, 2018). Th2 subtypes often exhibit a tolerogenic effect, but were also reported to induce the secretion of antibodies from plasma cells via cytokines such as IL-4, IL-5, IL-10, and IL-13 in the presence of intracellular bacteria (Walker & McKenzie, 2018). Tissue-resident Th17 cells can induce affinity maturation of B cells and generate long-lived plasma cells and memory B cells (Stockinger & Veldhoen, 2007).

In addition to the potency of elicited antigen-specific T and B cell responses, the efficacy of vaccines is also dependent on the fatality, proliferation rate, and mutation rate of invading pathogens. On one hand, attenuated pathogens, the easiest form of vaccines, are able to provide full protection from measles and chickenpox. On the other hand, sophisticatedly designed vaccines with incorporation of adjuvants might exhibit minimal protection from some highly transmissible pathogens such as *Haemophilus influenzae* type B (McVernon, Johnson, et al., 2003) and capsular group C meningococcus (McVernon, MacLennan, et al., 2003). The administration of booster vaccines, which can amplify the levels of neutralizing antibodies and antigen-specific T cells, has become a practice of standard for the vast majority of

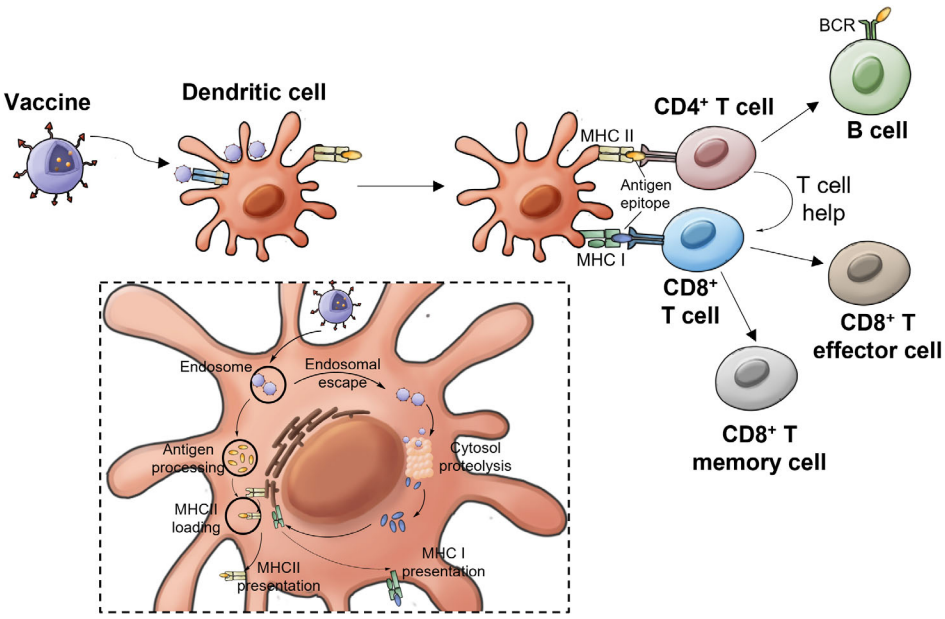

FIGURE 1 Vaccine-elicited adaptive immune responses. Administered antigens can be taken up and presented by APCs (e.g., DCs) via MHCI (antigens in cytosols) or MHCII (antigens in endosomes), for subsequent priming of antigen-specific $CD8^+$ and $CD4^+$ T cells. $CD4^+$ T cells can further induce the proliferation and maturation of B cells, while $CD8^+$ T cells can differentiate into effector and memory phenotypes.

vaccines. However, even with the boosters, the treatment of many pathogens and infectious diseases remains challenging (Zhu et al., 2018). Among the variety of parameters that need to be improved for better vaccination, vaccine formulation could be a critical yet feasible one.

1.2 | Nanomaterial vaccines for infectious diseases

Nanomaterials including liposomes, micelles, polymeric conjugates, and nanoparticles can improve the water-solubility, stability, blood circulation, and tissue accumulation of molecules, and have demonstrated success for systemic delivery of various drugs. The large library of nanomaterials developed in the past three decades enables custom design of nanomaterial vaccines with different sizes, compositions, surface properties, and antigen/adjuvant loading efficiency. Depending on the types and administration routes of nanomaterials, the accumulation of nanovaccines in different tissues can also be adjusted. For example, subcutaneously administered nanomaterial vaccines can traffic to lymph nodes via lymphatic drainage for elicitation of antigen-specific T and B cells (Roth et al., 2021). The retention of nanomaterial vaccines in lymph nodes often dictates the potency of generated humoral and T cell responses, and can be tuned by changing the size, composition, and surface properties of nanovaccines. For example, nanoparticles smaller than 15 nm are rapidly cleared from lymph nodes, while nanovaccines with a size of 20–200 nm could retain in lymph nodes for over 5 weeks and traffic into B cell follicles with the help of subcapsular sinus (SCS) macrophages (Zhang et al., 2019; Figure 2). Large nanovaccines (>200 nm), instead, are typically transported into B cell follicles via migratory DCs (Cyster, 2010; Reddy et al., 2007). The different retention profiles in B cell follicles resulted in distinct humoral responses for nanovaccines with different sizes (Figure 2). In this section, we summarize the main types of nanomaterial vaccines that have been developed for preventing and treating infectious diseases, including liposomal vaccines, nanoparticulate vaccines, extracellular vesicle (EV) vaccines, and glycoconjugate vaccines.

1.3 | Liposomal vaccines

Liposomes are bilayer lipid structures self-assembled from natural or synthetic lipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid,

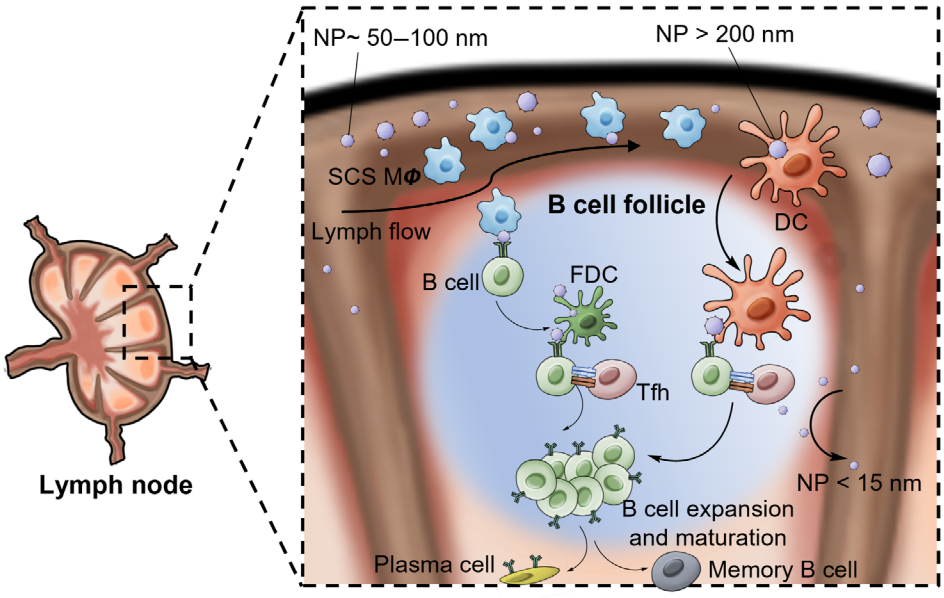

FIGURE 2 Trafficking of nanovaccines in lymphatic tissues and induction of follicle immune responses. Nanovaccines with a diameter of <15 nm are rapidly cleared from the follicle area. Nanovaccines with a diameter of 50–100 nm can migrate into the B cell follicle with the help of subcapsular sinus (SCS) macrophages and B cells. Large nanovaccines (>200 nm) are transported into B cell follicles with the help of migrating DCs. Antigen epitopes are then presented to naïve B cells to induce B cell expansion and maturation with the help of T follicular helper (Tfh) cells.

1,2-dioleoyl3-trimethylammonium propane, 1,2-dimyristoyltrimethylammonium propane (DOTAP), and dimethyldioctadecylammonium bromide, and have been widely used as delivery vehicles for antigens and adjuvants. With an encased hydrophilic core and hydrophobic lipid shell, liposomes are able to incorporate antigens and adjuvants that are either hydrophilic, amphiphilic, or hydrophobic (Nisini et al., 2018). Antigens such as peptides (Ludewig et al., 2000), proteins (Rao et al., 2002), carbohydrates (Kallert et al., 2015), and nucleic acids (Desmet & Ishii, 2012) can be either conjugated to the surface or encapsulated into the core (Watson et al., 2012). The surface-displayed antigens can directly stimulate B cell receptors and induce the expansion and differentiation of B cells. Membrane-mimicking liposomes also enable effective endocytosis of incorporated antigens and adjuvants by APCs, for subsequent antigen presentation and T and B cell priming. The diverse and large library of liposomes with different compositions established in the past decades has enabled custom design of liposomal vaccines for treating different pathogens and infectious diseases (Szoka Jr & Papahadjopoulos, 1980). Recently, liposomal mRNA vaccines against SARS-COV-2 developed by Moderna and Pfizer have played a critical role in containing SARS-COV-2 and set a milestone for clinical translation of liposomal vaccines (Pardi et al., 2018; Sahin et al., 2021). Liposomal vaccines encapsulating irradiated *Ebola Zaire* (EBO-Z) virus also achieved 100% protection of mice from a lethal dose of mouse-adapted EBO-Z virus, in comparison to the bolus vaccine which only resulted in 55% overall protection (Rao et al., 2002). In another design, recombinant trimeric H3 hemagglutinin (HA) was tethered to the surface of liposomes for enhanced APC uptake and improved protection from H3N2 flu virus, in comparison with alum-tethered antigens or soluble antigens (Sia et al., 2021). The same antigen tethering strategy was also utilized to develop liposomal vaccines against malaria, which outperformed alum-based formulations in triggering IgG responses (Huang et al., 2018).

Beyond serving as a building block of liposomes, lipids can also function as adjuvants to activate APCs and facilitate antigen presentation (Allison & Gregoriadis, 1974). For example, MPLA is a clinically licensed adjuvant used in vaccines against malaria and HIV (Alving et al., 2012). Liposomal vaccines containing MPLA induced higher cytotoxic T lymphocyte and antibody responses against HBV than MPLA-free formulations (Richards et al., 1998). Cationic lipids can also interact with cell membranes, stimulate APCs, and induce the secretion of inflammatory cytokines (Lonez et al., 2012). For example, DOTAP-based liposomes were shown to promote the immune responses by upregulating monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, and macrophage inflammatory protein-1 beta transcription factors (Yan et al., 2007).

While the vast majority of vaccines are administered via injection, liposomal vaccines have also been attempted for mucosal vaccination such as intranasal or oral vaccination which could be especially effective against certain invading pathogens (Levine, 2003; Lycke, 2012). Mucus layers serve as the first barrier to defend against pathogens, and APCs frequently patrol and sample antigens from pathogens or administered vaccines in these areas and traffic to the draining lymph nodes to prime antigen-specific T and B cells. As a result, mucosal vaccination can initiate local antigen-specific IgA and IgG responses along with the systemic humoral and cellular responses (Kozlowski et al., 2002). The stability, retention, and APC uptake of vaccine components in the mucus layers are inevitably critical for the generation of potent humoral and cellular responses. The stability of liposomes has been well demonstrated and can be further improved with refined choices of lipid building blocks (Aramaki et al., 1994). The mucosal retention of liposomal vaccines can be tuned by adjusting the surface charge of liposomes or modifying liposomes with targeting ligands. For example, cationic liposomes composed of DOTAP/cholesterol can adhere to the mucus layer with a prolonged retention and result in robust efficacy against influenza viruses (Guy et al., 2001). The uptake of liposomal vaccines by APCs is also dependent on the surface charge, size, and morphology of liposomes, and further efforts to optimize the design of liposomal vaccines for intranasal or oral vaccinations are needed.

1.4 | Nanoparticulate vaccines

In addition to liposomal vaccines, nanoparticulate vaccines based on nanoparticles, nanogels, micelles, and polymeric conjugates have also been widely explored in preclinical and clinical settings for preventing and treating Zika virus (Wu et al., 2020), HIV (Li et al., 2016), *M. tuberculosis* (Chen et al., 2019), and influenza virus, among many others. The diverse library of nanoparticles with varied compositions, size, morphology, and physicochemical and pharmacokinetic properties enables custom-design of nanoparticulate vaccines that can elicit potent immune responses against different pathogens. For example, poly (lactic-co-glycolic acid) (PLGA) nanoparticulate vaccines loaded with simian immunodeficiency virus (SIV) antigens and TLR7/8 and TLR4 agonists were developed to induce long-lasting humoral responses against SIV in macaques and outperformed the mixture of SIV antigens and alum (Kasturi et al., 2011). Similarly, poly(ε-caprolactone)

(PCL) nanovaccines encapsulating HBV antigens were able to generate robust humoral responses with one single oral dose (Dinda et al., 2016). Cationic polymers such as polyethylenimine (PEI) could form polyplexes with negatively charged antigens (e.g., mRNAs or DNAs) via electrostatic interactions, and facilitate their cellular uptake and endosomal escape in APCs (Boussif et al., 1995). As a result, antigen-specific cellular and humoral responses were amplified, resulting in the enhanced efficacy against H1N1 influenza, *Toxoplasma gondii*, and Ebola virus (Chahal et al., 2016).

Inorganic nanoparticle-based vaccines have also been developed to combat infectious diseases in view of their excellent stability, facile functionalization, and self-adjuvanting effect (Turner et al., 2015). Indeed, alum, a type of inorganic particle, has been widely used as the adjuvant in various vaccines. Other inorganic particles such as iron oxide nanoparticles have also demonstrated promise to induce robust pathogen-specific immune responses. For example, iron oxide nanoparticles tethered with tuberculosis-specific DNA antigens induced significantly improved humoral and cellular responses in a mouse infection model compared to bolus DNA vaccines or clinical available BCG vaccines (Yu et al., 2012), resulting in a much lower *M. tuberculosis* burden after pathogen challenge. The composition, size, and morphology inevitably dictate the physicochemical and pharmacokinetic properties of inorganic particles. Inorganic nanoparticles can be further functionalized to tune their biocompatibility, cellular uptake rate, and lymphatic drainage efficiency (Poon et al., 2018). For example, surface modification of gold nanoparticles with glycans was able to improve the internalization of particles by human patient-derived DCs and resulted in improved presentation of HIV gag p17 antigen and subsequent priming of autologous cytotoxic T cells, in comparison with unmodified particles (Climent et al., 2018).

Recent advances also uncovered the ability of particulate immunogens with multivalency to elicit enhanced follicular helper T (T_{fh}) cell and germinal center maturation (Abbott et al., 2018; Ingale et al., 2016; Jardine et al., 2013). Using the HIV envelop gp-120 60-mer (eOD-60mer) and gp-140-trimer 8-mer (MD39-8mer) complexes as models of antigens, it was shown that nanosized antigens generated a significantly improved humoral responses than monomeric antigens. Compared to MD39-8mer that mostly accumulated in SCS macrophages, MD39-8mer nanoparticles better accumulated in the B cell follicles in lymph nodes, generated much higher IgG titers, and increased the numbers of antigen-specific follicular T helper cells and germinal center B cells (Figure 3). Mechanistic studies demonstrated that multivalent antigens were able to bind to the complement system via mannose binding lectin to facilitate their trafficking into follicular DCs (Phan et al., 2007; Phan et al., 2009). These studies also indicated that glycosylation of nanovaccines could redirect the lymphatic trafficking paths and tune the overall immune responses.

1.5 | EV vaccines

Pathogens such as bacteria can secrete nano-sized EVs (20–500 nm) as the mediator of intercellular communication (Kaparakis-Liaskos & Ferrero, 2015). These EVs share various constituents (e.g., proteins, saccharides, RNAs, and DNAs) with their parent pathogens, some of which can function as pathogen-associated antigens (Fuhrmann et al., 2017). The antigen-encased EVs can be endocytosed by APCs for antigen presentation and subsequent priming of antigen-specific T and B cells. Compared to pathogens, EVs exhibit excellent safety profiles and desired physicochemical and pharmacokinetic properties (Bitto & Kaparakis-Liaskos, 2017; Théry et al., 2002). Beyond the role of antigen carriers, EVs can also induce the secretion of cytokines from pathogens (Alaniz et al., 2007; Ismail et al., 2003; Lee et al., 2012) and effectively cross cell membrane barriers (Nakao et al., 2014), for the development of potent vaccines against pathogens. To date, various EV-based vaccines have been developed to contain pathogens such as gram-negative bacteria. For example, EVs derived from gram-negative *Bordetella pertussis* enabled improved protection of mice compared to whole-cell vaccines in a lung infection model (Bottero et al., 2016). Immunization of mice with *Vibrio cholerae*-derived EVs also induced potent humoral responses and conferred protection of their offspring from *Vibrio cholerae* rechallenge (Schild et al., 2008). EV vaccines generated by gram-negative *Shigella flexneri* successfully protected mice from a lethal dose of bacteria (Camacho et al., 2011).

Due to the presence of a thick cell wall, gram-positive bacteria show a lower tendency to secrete EVs compared to gram-negative bacteria. Nevertheless, EVs were also successfully isolated from gram-positive bacteria such as *Staphylococcus aureus* (Mehanny et al., 2021). A mutant detoxified *S. aureus* with decreased peptidoglycan crosslinking was shown to generate a significantly higher number of EVs than the wild type bacteria. The resultant EV vaccines significantly improved the protection of mice from lethal sepsis (Wang et al., 2018). EVs from another gram-positive bacteria, *Streptococcus pneumoniae*, could also be rapidly internalized by DCs, trigger the release of tumor necrosis factor-α, and result in robust humoral responses against *S. pneumoniae* (Mehanny et al., 2020).

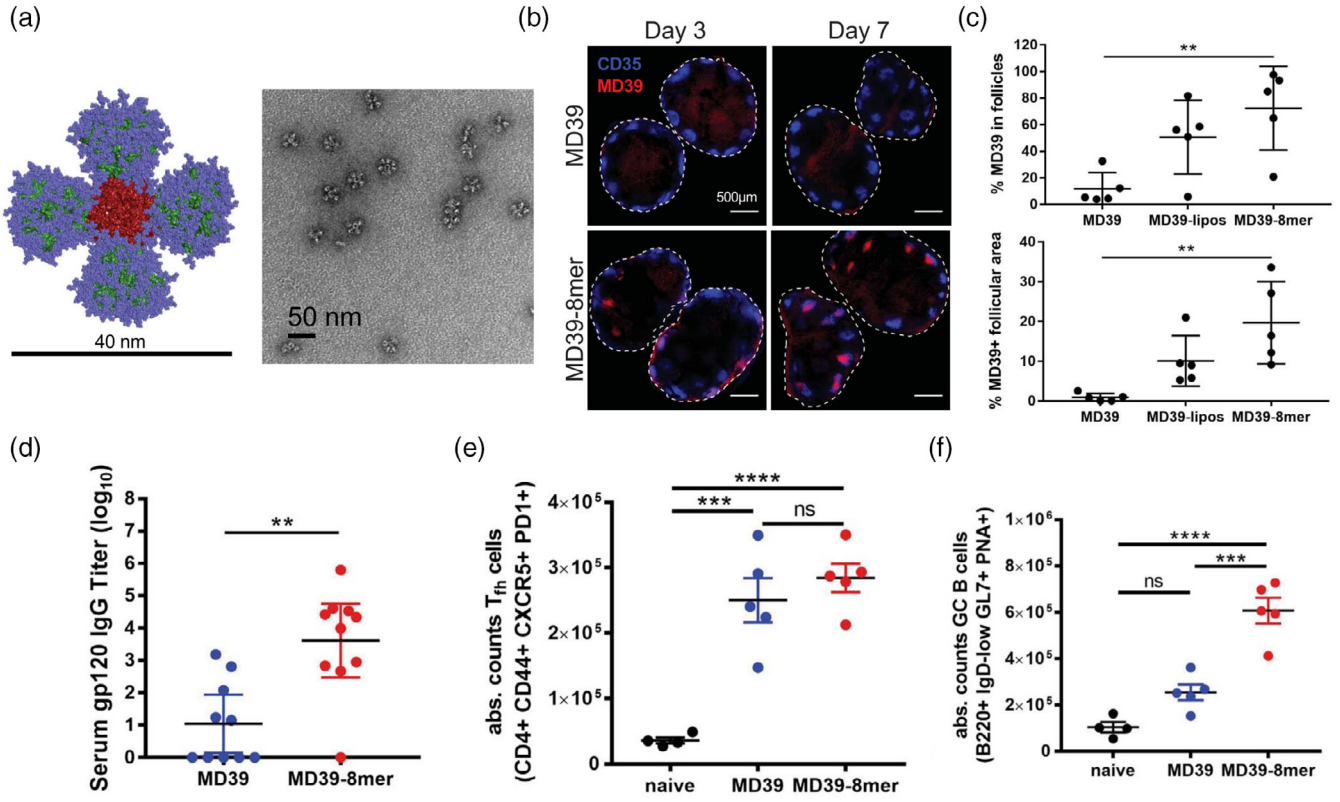

FIGURE 3 Multivalent nanovaccines show enhanced trafficking into B cell follicles and result in improved humoral responses. (a) Model representation and TEM image of MD39-8mer nanoparticle. (b) Localization of MD39 or MD39-8mer in lymph nodes of mice at 3 or 7 days post immunization, as determined by confocal imaging. (c) Percentages of MD39 in follicles and $MD39^+$ follicular area in lymph nodes at 7 days post immunization. Lipos, liposomes. (d–f) Balb/c mice ($n = 5$/group) were immunized with 1 μg MD39 or ~1.3 μg MD39-8mer containing the same moles of adjuvant and boosted at 6 weeks. (d) Gp120-specific IgG titers at 3 weeks post boost. Also shown are absolute (abs.) counts of antigen-specific (e) T_{fh} cells and (f) GC B cells at 7 days post the primary dose. Reprinted from Tokatlian et al. (2019) with permission from AAAS.

Different from bacteria, viruses lack the vesicle secretion machinery for direct production of EVs. However, EVs generated from host cells infected by viruses often carry viral antigens and have been utilized to develop antiviral vaccines (Martins & Alves, 2020). For example, EV-based HIV vaccines were developed by isolating EVs from DCs which were pre-transfected with HIV-specific envelope glycoprotein Gp120. Such EV vaccines managed to induce HIV-1- specific $CD8^+$ CTL responses in the absence of DCs and $CD4^+$ T cells, and could be especially valuable for patients with a compromised immune system (Nanjundappa et al., 2011). EV vaccines derived from infected host cells may also carry adjuvant components for elicitation of enhanced innate immune responses. For example, EVs isolated from the lung and serum of influenza virus-infected mice contain enriched miR-483-3p which is known to induce an inflammatory cytokine response. Such EVs managed to induce strong protection from flu viruses in vivo (Maemura et al., 2018).

While EVs exhibit a much better safety profile than pathogens in general, the inheritance of cytotoxic molecules from the parent pathogens could still pose safety concerns. For example, lipopolysaccharide (LPS) on the surface of vesicles is inherited from the outer membrane of gram-negative bacteria, and could provoke gram-negative septic shock in the host if not properly controlled (Simpson & Trent, 2019). Mutational depletion of lipid A acyltransferase can reduce the toxicity of LPS while maintaining the immunogenic potential of EVs (Kim et al., 2009). Similarly, EVs generated from a mutant *S. aureus* strain with detoxified cytolysin exhibited reduced toxicity compared to those secreted from the wild type strain (Wang et al., 2018).

1.6 | Polysaccharide and glycoconjugate vaccines

Pathogens often express unique carbohydrates on the outer surface that can be recognized by the immune system. These macromolecular carbohydrates, also known as capsular polysaccharides, have been utilized to formulate vaccines

against specific pathogens and diseases. To date, polysaccharide vaccines have been successfully applied to control *Neisseria meningitidis* (Brundage et al., 2002), *H. influenzae* (Peltola et al., 1977), *S. pneumoniae*, and others (Butler et al., 1993). However, the immune responses induced by polysaccharide vaccines among the infants or people with a compromised immune system are relatively weak, likely due to the defective maturation of B cells and lack of memory B cells (Pollard et al., 2009). The absence of T helper cells during B cell maturation often limits the potency and persistence of memory responses elicited by polysaccharide vaccines. To further amplify the elicited humoral and cellular responses of polysaccharide vaccines, the conjugation of polysaccharides with additional immunomodulatory agents has been explored (Rappuoli, 2018). For example, by conjugating tetanus toxoid or diphtheria toxoid (Sun et al., 2019) that can activate T helper cells to polysaccharides, memory B cell differentiation was improved in the presence of activated T helper cells, resulting in enhanced efficacy of vaccines in immune-compromised patients (Pollard et al., 2009). Glycoconjugate vaccines also showed improved protection from pneumonia and meningitis caused by *S. pneumoniae* (Robbins et al., 1989).

1.7 | Broad and heterotypic protection by nanovaccines

The rapid mutation of infective pathogens (e.g., influenza virus) often poses a challenge for the development of long-lasting vaccines (Wei et al., 2020). For example, the flu vaccine needs to be updated annually to cover the emerging mutations (Innis et al., 2019). Similarly, the effort to end the ongoing SARS-CoV-2 pandemic is hurdled by the rapidly emerging mutated strains (Planas et al., 2021; Wilhelm et al., 2021), necessitating the injection of boosters or updated vaccines covering the new mutations. Thus, vaccines that can provide protection from divergent pathogens of a same kind are highly demanded. Nanovaccine enables simultaneous delivery of multiple antigens to elicit protection from a broader range of mutations. The display of multiple relevant antigens on the surface of nanovaccines was shown to improve the universal humoral responses (Cohen et al., 2021; Kanekiyo et al., 2013, 2019; Marcandalli et al., 2019). In view of the relatively more conserved stem domain than the highly drifting roundhead domain of HA (Kanekiyo & Graham, 2021), nano-immunogen was designed to amplify immune responses toward the stem domain (Bommakanti et al., 2010; Impagliazzo et al., 2015; Yassine et al., 2015). Recently, computational design of nanovaccines that can potentially cover all the predicted mutations was also attempted (Boyoglu-Barnum et al., 2021). The nanovaccines were developed by fusing I53_dn5B immunogen which carries various HA sequences to the N-terminus of I53_dn5A pentamer protein (Figure 4a). Among them, the mosaic nanovaccine qsMosaicl-I53_ dn5 was able to elicit significant higher levels of HA-specific antibody titers and neutralization titers than commercial quadrivalent influenza vaccines, and enabled broad protection from historical versions of H1N1 influenza viruses. Furthermore, the qsMosaicl-I53_ dn5 also triggered humoral responses against the heterotypic HA antigens from H5N1 and H7N9 virus, which are insensitive to commercial quadrivalent vaccines. In addition to the rational design of immunogens, the incorporation of adjuvants into nanovaccines also showed promise to broaden immune protection (Reed et al., 2013). For example, MF59 adjuvant, a nano emulsion structure with a diameter of ~160 nm, was able to shift the antibody responses of H5N1 vaccines from HA2 sequence to HA1 and neuraminidase (NA) sequences, broadened the repertoire of antibody response, and increased the antibody titres (Khurana et al., 2010, 2011). Pulmonary surfactant–biomimetic nanoparticles encapsulating 2′,3′-cyclicguanosinemonophosphate–adenosine monophosphate (cGAMP) also extended the protection of H1N1 vaccines to heterotypic H3N2, H5N1, and H7N9 viruses, by enabling durable induction of lung resident memory T cells (Wang et al., 2020; Figure 4b).

1.8 | Biomaterial scaffold-based vaccines

Different from nanovaccines that rely on efficient trafficking to and retention in lymph nodes to induce antigen-specific humoral and cellular responses, biomaterial scaffold-based vaccines can recruit the immature DCs for in situ antigen loading. The sustained release of chemokines (e.g., GM-CSF) from materials can lure massive DCs which are then modulated by a pool of antigens and adjuvants in situ (Ali et al., 2009). The mature, antigen-presenting DCs can then migrate into lymph nodes to prime antigen-specific T and B cells and thus elicit antigen-specific humoral and cellular responses. For example, mesoporous silica rods loaded with carbohydrate antigens, GM-CSF, and CpG, after subcutaneous injection, induced improved humoral and cellular responses toward bacteria than the bolus vaccine (Cartwright et al., 2016; Figure 5). These biomaterial scaffold-based vaccines could increase the number of antigen-presenting DCs

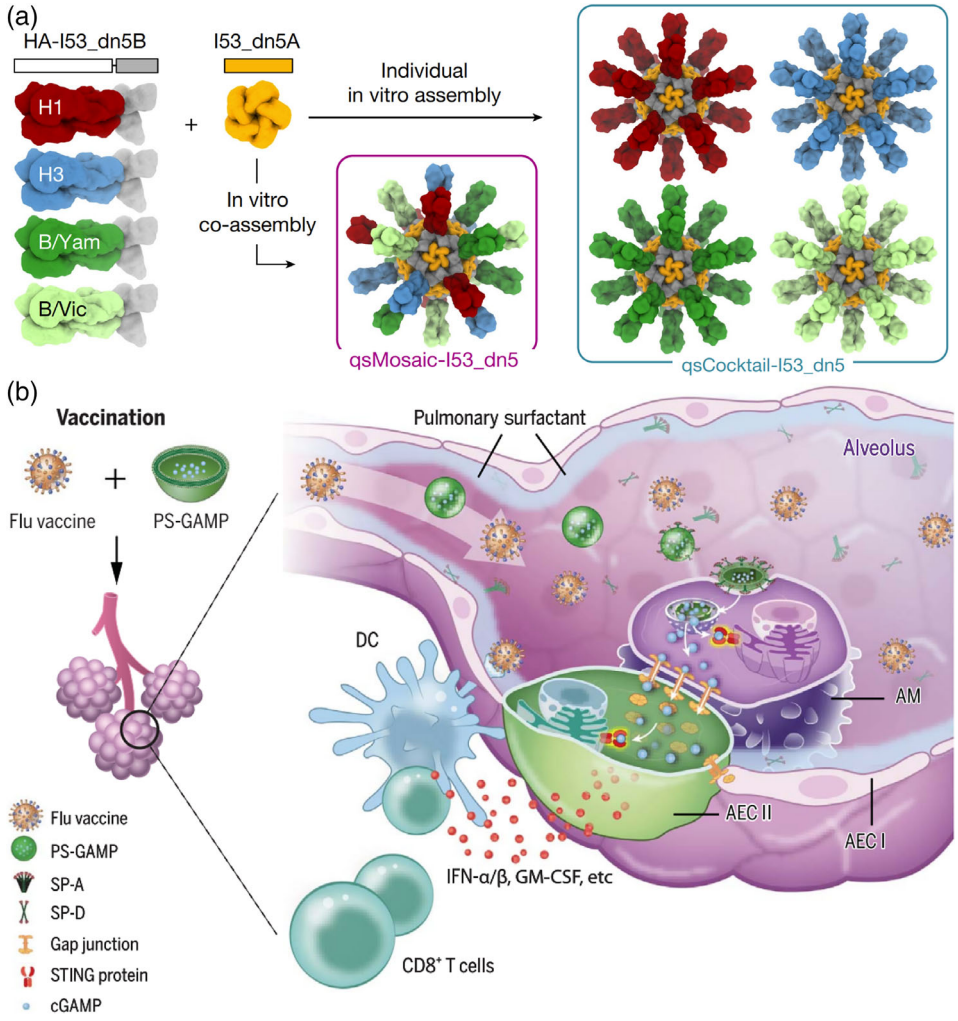

FIGURE 4 Two representative strategies for inducing broad protection from pathogens. (a) Rational design of mosaic immunogens by fusing I53_dn5B immunogen which carries various HA sequences to the N-terminus of I53_dn5A pentamer protein. Reprinted from (Boyoglu-Barnum et al., 2021) with permission from Nature Publishing Group. (b) Incorporation of cGAMP into the flu vaccine extended the protection to heterotypic H3N2, H5N1, and H7N9 viruses, by enabling durable induction of lung-resident memory T cells. Reprinted from Wang et al. (2020) with permission from AAAS.

in both the vaccination site and draining lymph nodes, and amplify the systemic antigen-specific $CD4^+$ T cell and humoral responses (Super et al., 2021). As a result of the biomaterial scaffold vaccines, better protection of pigs from gram-negative septic shock and reduced skin abscess formation by gram-positive methicillin-resistant *S. aureus* (MRSA) were achieved. The modular design of the biomaterial scaffold vaccine can be easily adapted for any type of antigens and pathogens.

2 | OUTLOOK

Recent advance in the development of material-based vaccines has shed light on strategies to enhance the synergistic effect of antigens and adjuvants, in order to optimize pathogen-specific humoral and T cell responses (Boyoglu-Barnum et al., 2021). Antigens and adjuvants can be co-incorporated into materials with precisely tunable release kinetics, co-delivered to APCs for improved antigen presentation and subsequent T and B cell priming, and eventually result in improved humoral and cellular responses against pathogens and infectious diseases. Thus far, various types of material vaccines including liposomal vaccines, nanoparticulate vaccines, EV vaccines, glycoconjugate vaccines, and biomaterial scaffold-based vaccines and others have been developed to combat highly infective and deadly pathogens. Nevertheless,

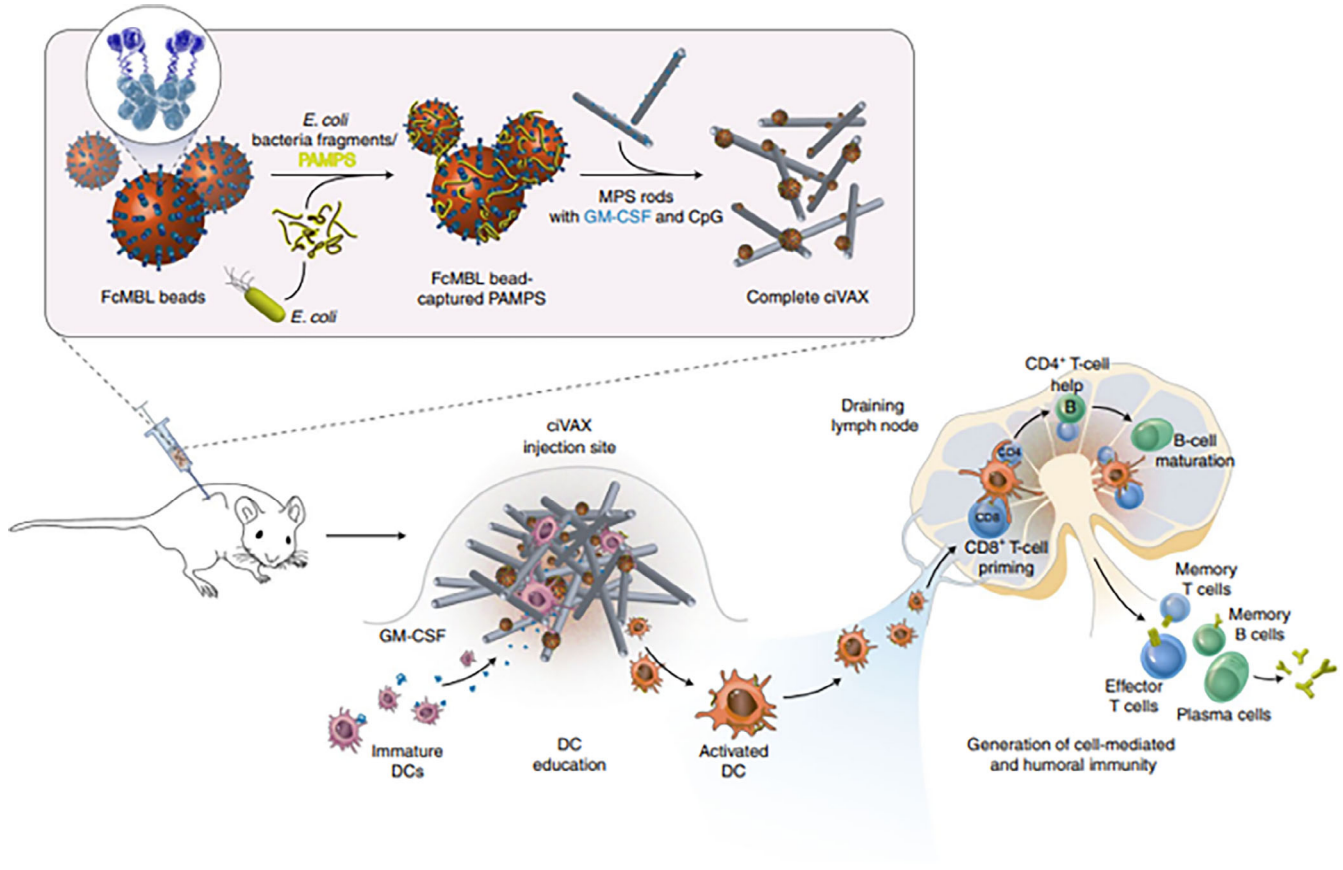

FIGURE 5 Biomaterial scaffold-based vaccines against pathogens. Three-dimensional, porous biomaterial scaffolds can slowly release chemokines such as GM-CSF to recruit a large number of DCs. The pathogen associated molecular patterns (PAMPs) captured by Fc-mannose-binding lectin, together with adjuvants, can activate and program the DCs in situ. The activated DCs then migrate into the lymphatic tissue to induce pathogen-specific humoral and cellular responses. Reprinted from Super et al. (2021) with permission from Nature Publishing Group.

the application of materials-based vaccines to the field of infectious diseases is still in an early stage, with the impact of material composition, size, charge, surface properties on the immunomodulatory effect in the context of different infectious diseases remaining poorly understood. For example, the lymphatic trafficking of nanovaccines into lymph nodes and their internalization by different types of resident APCs are critical for the ultimate T and B cell responses, but advance in fundamental knowledge about the desired distribution and retention profiles of nanovaccines within the lymphatic tissues (e.g., T and B cell zones) is needed to rationally design more potent vaccines (Phan et al., 2007, 2009; Tokatlian et al., 2019). Future efforts on the profiling of immune cell phenotypic changes in response to material vaccines will also facilitate rational design of more potent vaccines that can systemically modulate the phenotypes and activation status of different immune cells (Lindquist et al., 2004). With an increasing number of clinical trials on biomaterials-based vaccines (Curtiss, 2002; Lipsitch & Eyal, 2017), the safety profile and reproducibility of material platforms have also emerged as important factors impacting the eventual clinical translation. The extensive experience we have accumulated in the fields of nanomedicines, drug delivery, and cancer therapy regarding the design of different materials systems would greatly facilitate the development of material vaccines against infectious diseases. Nevertheless, each type of material system should have to be carefully examined in the context of the specific infectious disease to understand the underlying mechanisms and further improve the design of vaccines.

The ability to provide broad protection from mutated strains of pathogens will be a critical requirement for future vaccines, which could be a unique advantage of biomaterial-based vaccines. We summarized some recent efforts in the development of nanovaccines with broadened protection from pathogens such as flu viruses. In these efforts, multivalent immunogens were designed to amplify the immunogenic effect of subdominant yet conservative epitopes (Boyoglu-Barnum et al., 2021), and adjuvants were integrated to drift the immune responses toward similar pathogens

(Wang et al., 2020). While these approaches have shown some success for the development of broadly-protecting vaccines, further mechanistic studies on how nanovaccines could expand the breadth of protection over different strains such as rapidly mutating SARS-CoV-2 viruses and bacteria are needed.

It is noteworthy that a variety of pathogens and infectious diseases remain incurable so far as a result of the failure in developing effective vaccines. For example, FDA-approved vaccines for some sepsis-causing pathogens, which remain to be the main danger of clinical infection, still do not exist (Cecconi et al., 2018). Similarly, no vaccines against the highly dynamic and infectious HIV have been approved by the FDA (Hraber et al., 2014). While the first malaria vaccine (Mosquirix) was approved in 2021, 30% protection of among youngsters with severe cases is far from satisfactory (Maxmen, 2021). The identification of key pathogen-associated antigens is always the first step to design effective vaccines, which remains a challenge for some pathogens, especially those highly mutable ones. The ability to magnify the immunogenic effect of few identified antigens, which by themselves fail to elicit potent humoral and cellular responses, via the design of advanced vaccines is crucial. Biomaterials-based vaccines possess tremendous potential to amplify the pathogen-specific humoral and cellular responses, improve the prophylactic and therapeutic treatment of disease-causing pathogens, and further provide broad protection from mutated pathogens.

AUTHOR CONTRIBUTIONS

Hua Wang: Writing – original draft (equal); writing – review and editing (lead). **Yang Bo:** Writing – original draft (lead); writing – review and editing (supporting).

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created.

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RELATED WIREs ARTICLES

Biomaterials and nanomaterials for sustained release vaccine delivery

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