Published in final edited form as:

ACS Biomater Sci Eng. 2020 February 10; 6(2): 759–778. doi:10.1021/acsbiomaterials.9b01255.

Integrating Biomaterials and Immunology to Improve Vaccines Against Infectious Diseases

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Abstract

Despite the success of vaccines in preventing many infectious diseases, effective vaccines against pathogens with ongoing challenges – such as HIV, malaria, and tuberculosis – remain unavailable. The emergence of new pathogen variants, the continued prevalence of existing pathogens, and the resurgence of yet other infectious agents motivate the need for new, interdisciplinary approaches to direct immune responses. Many current and candidate vaccines, for example, are poorly immunogenic, provide only transient protection, or create risks of regaining pathogenicity in certain immune-compromised conditions. Recent advances in biomaterials research are creating new potential to overcome these challenges through improved formulation, delivery, and control of immune signaling. At the same time, many of these materials systems – such as polymers, lipids, and self-assembly technologies – may achieve this goal while maintaining favorable safety profiles. This review highlights ways in which biomaterials can advance existing vaccines to safer, more efficacious technologies, and support new vaccines for pathogens that do not yet have vaccines. Biomaterials that have not yet been applied to vaccines for infectious disease are also discussed, and their potential in this area is highlighted

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Author Contributions

All authors contributed to the planning and writing of the manuscript. All approve the final version of the manuscript.

Disclosures

C.M.J. is an employee of the VA Maryland Health Care System. The views reported in this paper do not reflect the views of the Department of Veterans Affairs or the United States Government. C.M.J. has an equity position in Cellth Systems, LLC.

Graphical Abstract

Keywords

infectious disease; vaccine; biomaterial; immunology; nanotechnology; clinical trial

1. Introduction

Vaccines protect individuals by “training” the immune system to generate adaptive immune responses, which are divided into two major classes: cellular responses – characterized primarily by CD4+ and CD8+ T-cells, and antibody-mediated immunity – characterized by secreted antibodies generated by B-cells. These responses prepare the immune system to rapidly neutralize or eliminate pathogens during a future encounter with the same antigen. Since the first widely-recognized vaccine example – noted by Edward Jenner in 1796 for smallpox – vaccines have greatly decreased the incidence or nearly-eradicate several diseases, including diphtheria, tetanus, and poliovirus.¹ Despite those successes, the development of vaccines against prevalent infectious pathogens, such as human immunodeficient virus (HIV), tuberculosis (TB), and malaria have been challenging;^{2,3} maintaining efficacy against some viral and bacterial pathogens over time is also challenging due to mutation. Conventional vaccines are typically comprised of either attenuated live pathogens, inactivated pathogens, or purified proteins. Live-attenuated and inactivated vaccines contain whole pathogens that have been weakened through selective propagation, or toxins that are inactivated by heat or chemical treatment. Much of the early successes of vaccines are attributed to live-attenuated and heat-inactivated vaccines; however, the clinical translation of some of these vaccine types creates safety concerns, including the potential to revert into virulent forms that cause disease.³ Subunit vaccines, on the other hand, contain purified antigens (e.g., well-defined protein or peptide) from pathogens that are the target of the specific, protective immune responses that vaccines are designed to elicit. These vaccines are safer to administer. However, they are poorly immunogenic; that is, immunization generally does not induce immune responses that are strong enough to prevent infection.^{4,5} To address that limitation, subunit vaccines are often formulated with immune-stimulating adjuvants - a compound that mimic “danger signals” displayed by pathogens - to

activate the immune system and drive a potent immune response to the antigen.^{6–9} Several classes of adjuvants have been safely used in the clinic to enhance the potency of subunit vaccines. These include inorganic compounds (e.g., aluminium salts or alum), organic molecules such as squalene (e.g., QS21), emulsion-based products (e.g., MF59), and Toll-like receptors agonists (e.g., viral or bacterial nucleic acids).⁸ The benefits of adjuvants, however, are sometimes limited by degradation of vaccine components at the injection site and toxicity associated with systemic distribution.^{10–13} These synthetic or molecularly-specific components are also generally much less potent in generating immune responses relative to live vaccines. Additionally, a growing body of literature supports the idea that vaccines against some pathogens will require careful activation of multiple immune pathways to drive synergistic responses.^{14–16} Therefore, vaccine delivery systems that combine the safety of subunit vaccines, the potency of attenuated or inactivated vaccines, and more precise control over immune signaling are needed to address infectious diseases.

Through recent advances in biotechnology and a better understanding of the immunological basis for effective vaccination, biomaterials have emerged as an innovative strategy to improve the formulation, delivery, and efficacy of vaccines. Biomaterials offer multifaceted advantages that can be customized to address the significant health challenges posed by infectious diseases. For example, these technologies can be designed on size scales (e.g., nanoparticles (NP), microparticles (MP)) and with morphologies that mimic pathogen features, loaded with antigens and adjuvants, provide control molecular features such as antigen display density (i.e., multivalency), and increase immune stimulation (“adjuvanticity”). Compared with live-attenuated and inactivated vaccines, NPs and MPs often allow improved pre-clinical safety profiles because of their non-replicating nature, as well as modularity to apply a particular materials platform to multiple pathogen targets. Biomaterials also offer other key advantages that can be leveraged for vaccines, including co-encapsulation of antigen and immune-stimulatory agents, protection of cargo from enzymatic degradation, targeting of specific immune cells, and control over vaccine release kinetics.^{17–20} Together, these features enable more precise control over immune processing of vaccines on both physiological and cellular levels, while potentially reducing toxicity compared to conventional vaccines. Owing to this potential, many biomaterials – including polymers, lipid, self-assembled proteins, and inorganic materials – are being explored for vaccines against numerous infectious diseases, though the majority of this work is thus far primarily in pre-clinical animal models.^{3,4}

In this review, we first briefly review several key classes of pathogens and the current state of vaccines for each class to illustrate ongoing clinical challenges in the broader vaccine field (Section 2). We then discuss how biomaterials are being explored to improve vaccine delivery, potency, and safety (Section 3). Finally, we highlight recent breakthroughs in the design of carriers not yet applied to infectious disease, creating future opportunities to further enhance the outcome of vaccines against the most pressing infectious diseases (Section 4). We also note that while biomaterials are being studied in an array of immunological application (e.g., cancer, autoimmunity, diagnostics), this perspective paper focuses only on their application to prophylactic (i.e., preventive) vaccines against infectious diseases.^{21–23}

2. Several key classes of pathogen characterize most infectious diseases in human

Infectious diseases are caused by different classes of microorganisms, spanning viruses, bacteria, parasites, and fungi (Table 1). The human immune system has naturally evolved to recognize and eliminate a vast number of these pathogens; however, other pathogens have developed the ability to escape immune response. In the following sections, we introduce three common classes of pathogens – viruses, bacteria, and parasites – using a key pathogen in each category to highlight some of the existing strategies toward vaccines, and the ongoing challenges facing the field. We begin with viral pathogens (Section 2.1), using HIV as an example. The subsequent two sections focus on bacteria and parasites, using tuberculosis and malaria as case studies. Research on vaccines for fungal infections – which is much less developed in the biomaterials space – is outside the scope of this review.

2.1. Viruses

Viruses are small biological assemblies that reproduce inside the cells of living hosts. HIV, for example, achieves replication and infection by invading CD4⁺ T-cells - an immune cell population important in generating adaptive immunity.^{25,26} As HIV virus destroys and impairs the function of CD4⁺ T-cells, infected individuals gradually become immunodeficient and susceptible to other infections. According to the UN Joint Program on HIV/AIDS, there were approximately 37 million people living with HIV at the end of 2017, and 940 000 people died from HIV-related illnesses the same year.²⁷ Dramatic successes have been achieved for vaccines against prevalent viral pathogens, such as smallpox, yellow fever, and poliovirus; these were live-attenuated or inactivated vaccines.^{28,29} Preclinical and clinical studies in other challenging pathogens do reveal some promise. Some examples include vaccine against dengue,³⁰ Ebola,^{31–33} and Zika viruses.^{34–39} However, vaccine candidates have been unsuccessful thus far for HIV and other pathogens. Initial attempts to develop HIV vaccines, for example, focused on eliciting antibodies that bind directly to the virus to prevent viral particle entry into host cells.^{41–46} Additional vaccine efforts have been directed towards stimulating CD8⁺ cytotoxic T lymphocyte (CTL) responses to detect and kill infected cells.^{47,48} In each of these strategies, the vaccines failed or provided very limited protection. This failure resulted because vaccination elicited immune responses that could prevent virus variants similar to the ones in the vaccine, but were ineffective against mutant strains.⁴⁹ The common feature of viral pathogens for which vaccines have failed is their antigenic variability caused by a high mutation rate and/or genetic instability, a particular problem in HIV, which exhibits very high mutation rates.⁴⁰ Therefore, an important consideration for vaccines to confer protective effects against challenging viral pathogens is the need to include antigens. Antigens are peptide or protein fragments of pathogens that enable pathogen-specific immune response to be generated. In addition, vaccines must generate immune responses that are broad enough to provide protection against multiple viral strains.^{40,50}

2.2. Bacteria

Unlike viruses, bacteria are complex microbes that span pathogens able to replicate in the extracellular environments of the body (e.g., *Pseudomonas aeruginosa*), or inside host cells (e.g., *Chlamydia trachomatis*). Bacteria can cause infection ranging from mild skin irritation to lethal pneumonia.³ For example, *Mycobacterium tuberculosis* - the microbial agent responsible for TB - is an airborne bacterium that primarily attacks immune cells in the lungs, but can cause disease throughout the body.⁵¹ TB has been estimated to infect more than 10 million people globally in 2017.⁵² Among those infected, 1.3 million have died; about a quarter of these patients were also HIV positive, demonstrating the susceptibility one pathogen can cause to another.⁵² Early successes in preventing and controlling bacterial infection were marked by the introduction of a combined vaccine against diphtheria, tetanus, and pertussis (DTaP).^{53–55} This vaccine is based on a combination of inactivated toxins, also called toxoids, from each pathogen and worked by inducing antibody responses against the targeted bacteria.⁵⁵ This approach was followed by the discovery that the injection of small doses of live-attenuated *Mycobacterium bovis* – a bacterial strain that causes TB in cattle – could be used to protect against TB in human; this vaccine was later called Bacillus Calmette-Guérin (BCG).^{56,57} BCG partially protects against disseminated forms of TB in infants, but does not adequately protect against pulmonary infection.⁵⁶ Thus, a new vaccine that could enhance protection in infants, or extend protection into adulthood, would have a significant impact globally. Very few pre-clinical vaccine candidates have entered the TB vaccine pipeline and those in the pipeline have moved slowly through the stages of clinical trials or have not progressed at all.^{58–64} One interesting candidate - VPM1002 - is a recombinant vaccine that was engineered to increase the capacity of the conventional BCG vaccine to promote CD8+ T-cell responses.^{57,65,66} VPM1002 expresses an enzyme that acts within infected macrophages to allow translocation of antigens into the cytoplasm, thus increase antigen presentation to CD8+ T-cells. Three doses of the vaccine demonstrated increased safety, immunogenicity, and efficacy in early phase clinical studies when compared to one dose of conventional BCG, and recently entered Phase II/III trials.^{57,67} This vaccine highlights the value of exploring new strategies in TB vaccine design, but also the challenge of multiple booster immunization during implementation. It also underscores the need to understand the clinical requirements for protective immunity, the immune mechanisms for bacterial containment, and to identify the key immunogens that provide protective immunity against challenging bacterial pathogens. In addition, based on the pathogenesis of the targeted bacteria, activating multiple immune pathways (e.g., antibody or cellular) may be necessary to clear the pathogens.

2.3. Parasites

Parasites are more complex than viruses and bacteria; their cells share some features with human cells, including a defined nucleus. Similar to bacteria, parasites can replicate in intracellular (e.g., *Toxoplasma gondii*) or extracellular (e.g., *Trypanosoma cruzi*) environments within the host.⁶⁸ Unlike bacteria and viruses, parasites have a more complicated life cycle that often involves more than one host, and they exhibit various forms at different stages of their life cycle.⁶⁹ For example, Malaria is caused by single-celled *Plasmodium* parasites that are transmitted to human or animal hosts through the bite of an infected female *Anopheles* mosquito. *Plasmodium* exists in multiple forms (e.g., sporozoites

– the form of *Plasmodium* injected during mosquito bite), and it requires both the human and mosquito hosts to complete its life cycle.⁷⁰ In 2017, approximately 219 million malaria cases resulting in 435,000 deaths were reported.⁷¹ While successful vaccines exist for some classes of viral and bacterial pathogens, no safe and widely-approved vaccine against parasitic infection are licensed for human use. Both live-attenuated and inactivated vaccines have been tested in humans against a range of parasitic diseases, including leishmaniasis and malaria but have not yielded encouraging results.⁷² For example, a live-attenuated malaria vaccine has been developed by exposing mosquitoes infected with *Plasmodium falciparum* – the strain of *Plasmodium* that cause the majority of malaria burden – sporozoites to gamma radiation.⁷³ Malaria-naïve human volunteers were immunized through the inoculation of parasites by the irradiated mosquitoes. This vaccination strategy elicited almost complete protection after challenge with homologous (i.e., the same parasite strain in the vaccine) and heterologous (i.e., different parasite strain from the one in the vaccine) parasites.⁷⁴ However, while promising, immunizing large susceptible populations via mosquito bites (>1000 per subject) is clinically and logistically impractical. Thus, a team led by Hoffman revisited this vaccine and developed an injectable radiation-attenuated malaria vaccine, called PfSPZ.^{75,76} In clinical trials, PfSPZ was safe and well tolerated by humans and conferred greater than 90% protection against controlled human malaria infection with homologous parasites.^{74,77–79} This approach, however, only induced modest protective efficacy (~44%) in naturally-exposed individuals.⁷⁷ Although encouraging, the high parasite doses (5 doses of 2.7×10^5 parasites) and route of immunization (intravenous) pose substantial challenges to move PfSPZ forward. Therefore, newer studies are evaluating the potential of other vaccines strategies.^{80–89} Among them, the most advanced candidate, RTS/S – a subunit vaccine, demonstrated 35.9% efficacy in the first year after vaccination in a phase III human trials, but efficacy fell to 2.5% in the fourth year.^{90,91} Albeit the low efficacy, this vaccine has recently been included in the national immunization programs of three African countries as a complement to existing control approaches.⁹² Similar to other parasites, the complex make-up of *Plasmodium* – over 5000 genes encoding hundreds of potential targets during distinct pathogen life stages – has greatly hindered vaccine design.^{93–96} Current hypotheses posit that achieving greater efficacy against parasitic diseases may require the inclusion of multiple antigens of the same or multiple parasite stages and strains. In addition, developing vaccine delivery systems that induce sufficient immune responses are needed to provide full protection.

3. Vaccine delivery using biomaterials offers new capabilities for vaccination

As discussed in Section 2, infectious diseases continue to pose substantial health concerns. A key issue in creating new vaccines is the balance between safety and efficacy. Effective vaccines (e.g., live-attenuated or inactivated vaccines) are associated with safety concerns, while safe vaccines (e.g., subunit vaccines) often fail to effectively prevent infection. To add more value to the already established safety of subunit vaccines, novel platforms that improve potency are needed. Through recent advances across the fields of materials science, biotechnology, and immunology, biomaterials have emerged as a new tool to improve the efficacy of subunit and other vaccine classes. Biomaterials possess unique physical (e.g.,

size, shape) and chemical (e.g., surface chemistry) properties that provide the basis for conjugating or encapsulating cargo of interest. Moreover, biomaterials allow the co-delivery of both antigen and molecular adjuvants to the same immune cells or tissues, which is important in potent activation of specific types of immune responses.^{17,19} This feature has a distinct advantage compared to the delivery of soluble antigens and adjuvants in conventional soluble vaccines. Not surprisingly, a variety of biomaterials have been developed and tested for infectious disease vaccination. Some of the ubiquitously used biomaterial classes include polymers, lipids, protein or peptide-based materials with self-assembling properties, and inorganic materials. This section highlights examples of the major categories of biomaterials that are being investigated for vaccines against infectious disease. Before diving into these discussions, we first provide some immunological background.

3.1. The immune system is a balanced and multifaceted defense network

The immune system includes an array of cells that survey the body in search of invading pathogens: antigen presenting cells (APCs). After detection and uptake of invading pathogens using surface receptors and other cues, APCs – such as dendritic cells (DCs), actively migrate from the peripheral tissues into specialized immune sites; these include the spleen and lymph nodes.⁹⁷ The activation of APCs is marked by upregulation of costimulatory surface receptors including CD40, CD80, and CD86. In the lymph nodes, APCs process and present fragments of the pathogen (i.e., antigen) to lymphocytes, including B-cells and T-cells, to initiate pathogen-specific immune responses.⁹⁸ Activated B-cells secrete antibodies that can bind extracellular pathogens or prevent viruses from entering host cells. Activated T-cells, on the other hand, differentiate into CD4+ helper T-cells and CD8+ cytotoxic T-cells. CD8+ T-cells recognize and destroy infected cells whereas CD4+ helper T-cells further differentiate into T-cells subsets (e.g., Th1, Th2) that produce cytokines to initiate distinct types of immune responses.⁹⁹ For example, Th1 cells produce interferon gamma (IFN- γ) to limit spread of active intracellular pathogens (e.g., virus), whereas Th2 cells produce signaling molecules called cytokines (e.g., IL-4, IL-13), important in generating immune responses against certain types of extracellular infections (e.g., parasite).¹⁰⁰ The T-cell commitment to differentiate into one of these subsets is strongly influenced by inflammatory signals provided by APCs. Upon future exposure, the T and B-cells that have been previously trained to recognize a particular pathogen (i.e., memory cells) rapidly expand to eliminate the pathogen before extensive propagation and dissemination in the host (i.e., infection). The next section discusses the exploitation of the unique properties of biomaterials to improve the efficacy of vaccine against infectious diseases by directing immune function.

3.2. Polymeric biomaterials

Polymers have received significant attention for vaccine delivery applications due to their ease of preparation, biodegradability, reduced systemic toxicity, and the possibility to engineer or finetune their surface properties. Polymers also offer flexible control over their degradation profile and the release rate of vaccine cargos such as antigens or adjuvants.^{101,102} Moreover, polymers offer the potential to co-deliver antigens and immunostimulants, which can increase potency and minimize dose, as well as the associated off-target effects.

Many synthetic polymers have been studied for vaccine application, including poly (lactic-co-glycolic acid) (PLGA),^{103–109} polyethylene-imine,¹¹⁰ and polystyrenes.¹¹¹ Substantial works have also been carried out with natural polymers and polysaccharides, such as chitosan,^{112–115} inulin,^{116–118} and alginate.¹¹⁹

Among synthetic polymers, PLGA is the most explored for vaccine applications. This polymer has been approved by the FDA in a number of applications. Using techniques including sonication or homogenization, PLGA polymers can be formulated into nanoparticles (NPs) or microparticles (MPs),¹²⁰ and these diverse size scales influence vaccine trafficking, uptake by APCs, and the subsequent immune response.^{101,102,111,121} For example, MPs (> 500 nm) tend to accumulate at the injection sites and prolong the stimulation and antigen presentation by APCs. This antigen depot effect has been shown to strongly elicit antibody- and cell-mediated responses against *Toxoplasma gondii* infection.¹⁰⁴ NPs (< 30 nm), on the other hand, efficiently drain to and accumulate in the lymph node and are easily taken up by APCs at these sites.⁶ These factors benefit antigen presentation to T-cells and B-cells, consequently, amplifying the strength of immune response. Thompson et al. recently encapsulated a malaria antigen and a Toll-like receptor (TLR)-based adjuvants in PLGA NPs and reported that the vaccine effectively stimulated innate immunity. This activation promoted CD4+ T-cell responses that increased the overall strength of antibody binding and the duration for which these responses persisted.¹²² In addition to size, other physicochemical properties of polymers – such as surface charge and shape – can be modified to alter immune cell recognition and the quality of immune response to vaccines. This was exemplified in a recent study where cationic polystyrene NPs were internalized and processed more efficiently by APCs relative to neutral-surface NPs. In addition, these vaccine particles induced a more robust response consisting of both T-cell and antibody function.¹¹¹

Synthetic polymers can also be formulated to engineer devices such as microneedles¹²³ and microdisks¹²⁴ for vaccine delivery. Microneedles, for example, are micron-scale structures that efficiently deliver vaccines to skin-resident APCs. These devices have been used to deliver a range of antigens in pre-clinical animal models.^{125–127} For example, Zaric et al. developed a thermostable microneedle vaccine to deliver a recombinant candidate HIV antigen (Figure 1A). The needles were fabricated with sodium carboxy-methylcellulose – a highly water-soluble material – and sucrose. The investigators reported that the microneedles rapidly dissolved following application into mice skin (Figure 1B) and generated robust antigen-specific CD8+ T-cells in the blood and mucosal tissues (Figure 1C). Moreover, the elicited CD8+ memory T-cells remained in peripheral tissues for at least one-year after vaccination, also retaining their functional capacity (Figure 1D).¹²⁸ This long-lasting presence of CD8+ memory T-cells was later reported to be driven by the activation of a subset of immune cell populations that are essential for recruiting CD8+ T-cells.¹²⁷ The clinical potential of microneedle was also recently tested in a first-in-human trial to deliver influenza vaccination. The microneedle vaccine was shown to generate antibody titers similar to those of existing injectable vaccines even when self-administered by recipients.^{129,130} Of note, these technologies do not require refrigeration and offer the potential for self-administration of the simple patch.

In addition to synthetic polymers, natural biopolymers have also been used for vaccine delivery. Chitosan, for example, has been used to improve the delivery of DNA plasmids encoding the polypeptide sequence of candidate antigens. DNA molecules are easy to produce, stable in ambient temperature, and possess the ability to induce both antibody and cellular immune responses. Therefore, the delivery of DNA as vaccine poses as an intriguing alternative to induce immune responses against antigens which are difficult to produce.¹³¹ However, the delivery of naked DNA into host cells suffer from several drawbacks, such as enzymatic degradation and the inability to cross cellular membranes; these features both limit the level of protein antigen expression and the resulting immune response.¹³² Enhanced delivery technologies, such as electroporation, have increased the efficacy of DNA vaccines in humans,¹³³ but have not reduced the risk of degradation of delivered DNA material. The use of chitosan for DNA vaccines is supported by the cationic nature of the polymer, which allows for electrostatic interaction with negatively charged DNA molecules. DNA plasmid can be either bound to the cationic surface or loaded within the core of polymer particles, which help protect DNA from degradation by extracellular nucleases. For example, Zhao et al. encapsulated Newcastle Disease Virus F gene plasmid DNA along with a molecular adjuvant in a chitosan-based nanosystem by polyelectrolyte complexation. After complexation, the NPs efficiently encapsulated the plasmid DNA and protected the DNA from enzymatic (DNase) degradation. Intranasal immunization of the chitosan DNA NPs vaccine in chickens led not only to higher antibodies levels, but also improved lymphocyte maturation.¹¹⁴ Another study later showed that this improved immune cell activation was caused by the ability of chitosan to serve as an immune potentiating signal via the DNA-sensing cGAS-STING pathway. The STING pathway detects the presence of DNA in the cytosol and plays a key role in the activation of both innate and adaptive immunity.¹³⁴ Upon interaction with APCs, chitosan induces type I interferons in a cGAS and STING-dependent fashion, driving cellular maturation and the promotion of Th1 responses.^{135,136} In addition to DNA vaccine delivery, natural polymers have been used to encapsulate and deliver recombinant proteins and peptides. For example, Dacoba et al. showed that the immunogenicity of subunit vaccines could be improved following the chemical linkage of targeted peptides to natural polymers (e.g., chitosan and hyaluronic acid) in the presence of adjuvants. The group engineered NPs HIV vaccines via covalent attachment of an HIV peptide antigen to chitosan and hyaluronic acid-based nanoparticles. The TLR3 agonist polyIC was also incorporated in the NPs to increase their immunostimulatory properties (Figure 1E). Following immunizations in mice, the NP vaccine induced strong activation of antigen-presenting cells (Figure 1F) and T-cell response.¹³⁷

Some other natural polymers explored for vaccines against infectious diseases involve advax, an adjuvant based on delta inulin microparticles, and alginate. Advax is a novel adjuvant that has recently entered human trials.¹³⁸ One group has shown that the formulation of a TB antigen with Advax provides significant protection in the lungs of *M. tuberculosis*-infected mice. The protection was associated with the generation of antigen-specific multifunctional CD4+ T-cells, and addition of the TLR9 agonist, CpG, further improved both the immunogenicity and protective efficacy of the vaccine.¹¹⁷

3.3. Lipid biomaterials

Lipid biomaterials – formulated in structures such as liposomes, lipid-polymer hybrids, and emulsions, are another important class of vaccine delivery system. Lipid materials have been used clinically in vaccines such as Epaxal (Hepatitis A) and Inflexal V (influenza).^{139,140} Their synthesis involves a spontaneous process, where hydration of lipids induces lipid bilayer formation in an aqueous environment.^{141,142} Lipid can also be artificially synthesized^{143,144} or secreted by cells (e.g., exosomes) and isolated.¹⁴⁵ The versatility of lipid biomaterials can be exploited to allow the encapsulation of both hydrophilic and hydrophobic substances, the integration of charged moieties to promote antigen encapsulation (e.g., DNA/RNA), and the inclusion of targeting ligands that promote uptake by APCs.

As a first example, liposomes are self-assembled dispersions composed of phospholipids, such as phosphatidylserine, phosphatidylcholine, and cholesterol. The size of these structures varies from smaller unilamellar vesicles (30 – 100 nm) to larger multilamellar vesicles (>400 nm).¹³⁹ As with polymer particles, size plays an important role in how these carriers will be recognized and processed by the immune system, and thus on the type and magnitude of immune response. Smaller vesicles (<100nm) tend to skew responses toward Th2 function, while larger vesicles (>400 nm) tend to skew responses toward Th1 response characterized by IFN- γ production.^{146,147} Tokatlian et al. recently developed a strategy to covalently anchor an HIV antigen on the surface of synthetic liposomes to form unilamellar vesicles for HIV vaccination (Figure 2A). The group demonstrated that during immunization of mice, antigen-specific helper T-cells and antibody responses increased compared to immunization with soluble antigen (Figure 2B–C).¹⁴⁸

A potential factor influencing the potency of unilamellar lipid vesicles in vaccine delivery is their limited stability in the presence of serum components. Along these lines, stability of liposomes has been improved by developing multilamellar vesicles stabilized via inter-bilayer cross-linking (ICMV).¹⁴⁹ The robustness of this technology has been tested in several pathogen settings using pre-clinical models of malaria,¹⁵⁰ Hepatitis C,¹⁵¹ and Ebola.¹⁵² The investigators found that the multilayer structure of the ICMVs facilitated a stable entrapment of antigens both in the aqueous core and the lipid bilayer surfaces compared to unilamellar liposomes. Mice immunization with ICMVs along with MPLA - TLR4 agonist, promoted strong antibody responses at lower dose of antigen compared to soluble antigen mixed with conventional adjuvants, such as MPLA, alum, or Montanide. This strong immune response was mediated by the enhanced antigen delivery and persistence in draining lymph nodes and the efficient cross-presentation of ICMV-associated antigen by lymph node-resident DCs. Targeting ICMVs to APC-rich pulmonary mucosa was also shown to promote robust T-cell responses and provide enhanced protection to both local and systemic viral challenges compared to nonparticulate pulmonary vaccination.¹⁵³

Recently, Huang et al. reported on a new strategy to incorporate multiple pathogen-derived antigens into liposome NPs. The group designed liposomes containing cobalt porphyrin-phospholipid - with or without a synthetic TLR4 agonist - that can be stably functionalized by mixing with polyhistidine-tagged proteins through a process termed “spontaneous nanoliposome-antigen particleization” (SNAP). In preliminary studies, they showed that

immunization with SNAP NPs containing a malaria antigen and a TLR4 agonist resulted in orders-of-magnitude higher functional antibody generation compared with a mix-and-inject soluble vaccine. The liposomes efficiently drained into the lymph nodes following intramuscular injection and increased accumulation and uptake by antigen-presenting cells. To add value to the SNAP liposomes technology, the group also examined their ability to deliver a panel of his-tagged *P. falciparum* antigens expressed at distinct stages of the parasite life cycle (Figure 2D, **left**). The binding of each his-tagged protein antigen, as well as the multiplexed combination, was assessed using native polyacrylamide gel electrophoresis (Figure 2D, **right**). Following mice immunization, the multiplexed SNAP vaccine resulted in high IgG production against all the antigens (Figure 2E).¹⁵⁴ This study illustrated the possibility of developing polymer-enabled vaccines that generate responses against multiple stages of a pathogen lifecycle.

Lipid biomaterials can also be complexed with synthetic polymers to form lipid-polymer hybrids for surface adsorption of proteins and immune signals. Liu et al. used this strategy to adsorb Hepatitis B antigen on the surface of biodegradable poly (lactic acid) (PLA) microparticles modified with a cationic surfactant, didodecyldimethylammonium bromide (DDAB). After immunization, DDAB-PLA MPs enhanced the expression of co-stimulatory molecules and activated bone-marrow-derived dendritic cells (BMDCs) *in vitro*. The vaccine formulations also efficiently induced antibody production more potently than aluminum-based vaccines and empty PLA MP-based formulation in animal studies.¹⁵⁵

Similar to polymers, such as chitosan, cationic lipids have been used for the targeted and controlled delivery of negatively-charged cargo, including DNA (as plasmid) or RNA (as mRNA). Lipid-DNA or lipid-RNA complex formation is enhanced by electrostatic interactions between materials.¹⁵⁶ For example, Fotoran et al. showed that cationic liposome efficiently encapsulated DNA, using plasmids encoding malaria antigens as a model, and reported that the liposome-based vaccine generated strong immune responses.¹⁵⁷ Unlike DNA vaccines, which have to overcome cellular and nuclear membranes before protein expression, target antigens can be directly translated from RNA vaccines as soon as they enter the cytoplasm, without transport to the nucleus.^{158,159} However, the delivery of large amounts of mRNA can trigger innate immune receptors (e.g., Toll-like receptors and/or RIG-I-like receptors), which can restrain certain cell functions and result in limited production of the protein antigen.¹⁶⁰ Therefore, effective cytoplasmic delivery of RNA and prevention of both toxicity and immune stimulation are important steps for RNA vaccine efficacy. To address these challenges, lipid NPs based on cationic lipid or lipid-polymer complexes have been used to facilitate the delivery of RNA and enhance antigen expression. For example, Zhao et al. used a self-assembled cationic micelle based on polyethylene-imine stearic acid (PSA) copolymer to deliver mRNA encoding HIV-1 gag to DCs. After sub-cutaneous administration of the gag mRNA to BALB/c mice, antigen-specific immune responses were notably higher with the nanomicelle formulation compared with naked gag mRNA.¹⁶¹ Pardi et al. developed cationic lipid NPs encapsulating nucleoside modified mRNA encoding the pre-membrane and envelope glycoproteins of a Zika virus strain. The mRNA was encapsulated in the lipid NPs using a self-assembly process in which an aqueous solution of mRNA was rapidly mixed with a solution of lipids containing a cationic lipid,

phosphatidylcholine and cholesterol. The group showed that intradermal immunization with a single low-dose vaccine elicited potent and durable neutralizing antibody responses in mice and non-human primates.¹⁶² Lipid NPs have also been used to develop multi-valent vaccines by delivering mRNAs encoding multiple target antigens;^{163,164} these vaccines are being tested in both preclinical and clinical settings against Zika¹⁶⁵ and influenza.¹⁶⁶

Lipid biomaterials can also be formulated with immune-stimulating adjuvants to form nanosized emulsions. These emulsions can carry antigens along with targeting ligands that promote uptake by professional APCs inside their core to increase the efficiency of vaccines.¹⁶⁷ The emulsions can also simply be mixed with antigen, creating modularity for application to multiple pathogens. One commonly used emulsion is MF59, an emulsion that has been licensed as a safe and potent vaccine adjuvant for influenza. Another emulsion adjuvant that has been recently developed and used in vaccine trials is the Toll-like receptor 4 agonist glucopyranosyl lipid adjuvant-stable emulsion (GLA-SE).^{168–170} GLA-SE has been shown to be safe in human, to enhance antigen delivery, and to elicit a robust immune response by stimulating immune cells via TLR4 engagement in rhesus macaques.¹⁶⁸

3.3. Self-assembled biomaterials

In Sections 3.2 and 3.3, we discussed the attractive properties of two classes of biomaterials, including delivery of multiple types of cargo and protection of payloads from enzymatic degradation. Although promising, several challenges including the lack of control over the physical arrangement of molecules inside the materials have limited the wide use of these biomaterials in the clinics.¹⁷¹ Recently, self-assembled systems have gained interest in the context of generating well-controlled structures in an attempt to drive higher levels of protein interaction with specific immune cells and receptors. The most commonly used systems in this area are protein assembly and protein-TLR assembly.

Protein assemblies include recombinant virus-like particles (VLPs) and naturally occurring recombinant proteins that possess self-assembly properties. VLPs are recombinant proteins designed to self-assemble into particulate structures after expression.¹⁷² These particles mimic native viruses, but cannot replicate, thus, pose lower safety risks compared with live or attenuated vaccines.^{173,174} VLPs offers distinct advantages that can be exploited to enhance vaccine potency. For example, VLPs have the unique ability to present vaccine antigens in the same physical conformations that is found on native pathogens to maximize immunogenicity and vaccine efficacy.^{175–180} This key feature is often lost when fragment of pathogens (i.e., epitopes) are expressed in recombinant systems (e.g., bacteria) or when pathogens are rendered inert through chemical or heat inactivation. Another attractive advantage of VLPs is their particulate structure (ranging from 20–200nm), which allows them to be efficiently taken up by antigen-presenting cells (APCs).¹⁸¹ In addition, VLPs are composed of self-assembled viral membranes that display a high density of antigens. Display of antigens on recombinant VLPs can be achieved by either chemical conjugation or genetic fusion to the viral coat protein. One well-tested example of chemical conjugation of a recombinant antigen to the surface of a preassembled particle is the VLP formed from the capsid protein of the bacteriophage Q β .^{181–183} The amino group of the surface-exposed lysine residues on Q β are modified with a bi-functional chemical cross-linker and

subsequently reacted with a target antigen engineered to contain a reactive cysteine residue.¹⁸² The resulting VLP products present repetitive arrays of the target epitope on the particle surface. Basu et al. recently used this approach to conjugate Zika virus envelope B-cell epitopes to Q β VLPs. The authors showed that immunization with VLPs displaying a single B-cell epitope minimally reduces Zika virus infection, whereas immunization with a mixture of VLPs displaying a combination of B-cell epitopes elicited antibodies that neutralized infections.¹⁸² Hong et al. later described the mechanism of this strong antibody response. The group found that the repetitive display of antigens on VLPs enhance vaccine interaction with B-cell receptors. This interaction enhances B-cell signaling and facilitates the generation of high-affinity antibodies by the B-cells (Figure 3A).¹⁸⁴ VLP-based vaccines are among the first nanoparticle class to reach the market. Some of the key examples include Engerix® and RECOMBIVAX®HB against Hepatitis B.¹⁷³ VLP vaccines targeting other infectious pathogens are currently under clinical investigation.^{33,185–189} These clinical uses highlight the potential of the VLP platform.

Kanekiyo et al. developed another modular self-assembling nanoparticle system based on the ferritin nanoparticle scaffold. Through this system, antigens of interest are expressed as a fusion construct linked to an engineered ferritin sequence.¹⁹⁰ The expressed product spontaneously self-assembles to form particles that are secreted into the culture supernatant. This system enables the production of homogeneously assembled NPs (building blocks with a single sequence) as well as heterogeneously co-assembled mosaic NPs (building blocks with multiple sequences). The group used H1N1 influenza virus hemagglutinin as a model antigen and developed a mosaic array by co-localizing antigens from multiple strains across time on a single NP. One advantage of this system is to diminish or avoid activation of strain-specific B-cells and allow selective engagement of B-cells that tolerate antigenic variability, thus, promote cross-reactive antibody responses by adaptively targeting conserved antigenic surfaces. The group found that the heterotypic mosaic NPs elicited B-cell responses quantitatively and qualitatively superior to those elicited by antigenically homotypic NPs. This modular strategy could improve vaccine efficacy by addressing the discordance between structure of vaccine antigens and that of circulating strains.¹⁹¹

Like polymer and lipids, viruses have also been used as backbone to deliver genetic materials (e.g., DNA or mRNA) that encode for immunity-inducing antigens to target cells. Viruses are naturally very efficient at transducing their own genetic information into host cells for their own replication. By replacing non-essential viral genes with genes of interest, recombinant viral vectors can be used to transduce the cell type that they would normally infect. Once inside the cells, the proteins are co-expressed in cells and assemble into virus-like particles. Replication deficient viruses, such as adenoviruses and modified vaccinia virus, are widely-used vectors for this strategy because they can be easily produced at high quantity and can deliver large transgene sequences.^{39,192–194} Another key advantage is their capability to promote long-term transgene expression without causing toxicity *in vivo*.^{192,195,196} For example, Yusuf et al. recently developed a series of recombinant adenovirus virus expressing two *Plasmodium falciparum* proteins that are major malaria vaccine targets. They showed that mice immunization with both adenovirus elicited robust and durable antigen-specific antibodies that lasted over 280 days.^{192,197–201}

Co-administration of antigens with particle-based carriers of TLRs have been shown to markedly improve vaccine performance for both T-cell and antibody responses. However, recent studies reveal many biomaterials (e.g., PLGA, chitosan, VLPs) can activate inflammatory pathways even in the absence of antigens and adjuvants or elicit immune responses to the carriers.^{197–201} To minimize off-target immune responses, there is a growing interest to directly link protein antigens to immune signals (e.g., TLRs) to form self-assembled particles. Kaba et al. recently tested that idea and developed a self-assembled protein nanoparticle containing epitopes from the *Plasmodium falciparum* surface protein and portions of the TLR5 agonist, flagellin (Figure 3B). By combining different molar ratios of the individual components, they found that only a very low dose of flagellin per particle is needed to enhance both antibody titers and protection.²⁰² A similar strategy was used by the Burkhard lab to provide protection against lethal influenza challenge. The group also found that the self-assemble nanoparticles stimulated TLR5 receptor in a dose-dependent manner. Of note, the adjuvanted particles generated significantly higher levels of antibodies and led to higher cross-neutralizing activity compared to those induced by unadjuvanted nanoparticles.²⁰³ Together, these two studies showed the versatility of the platform.

3.4. Inorganic biomaterials

Inorganic materials can be designed with some of the same physical properties (e.g., size, shape), as polymers, lipid, and self-assembled materials, but they also offer distinct capabilities. These materials are often structurally stable and non-biodegradable, but can be engineered to promote biocompatibility.^{205,206} A major advantage of inorganic materials over other classes of materials is that many of these materials do not elicit immune response against the carrier itself.²⁰⁷ In the following section, the use of inorganic materials – including gold, silica, calcium carbonate, and calcium phosphate are discussed as vaccine delivery systems to elicit responses in a variety of infectious disease models.

Gold nanoparticles (AuNPs) are one the most widely studied inorganic materials for vaccines. AuNPs do not induce an antibody response to the vehicle itself, and acute cytotoxicity has rarely been observed to date.²⁰⁸ AuNPs can be synthesized in different sizes and shapes (e.g., nanospheres, nanorods). As with other materials, the size of AuNPs has been shown to influence the efficacy of vaccine draining into the lymph nodes and the robustness of elicited immune responses.^{209,210} The surface of AuNPs can be functionalized with stabilizing agents to provide an anchor point for ligands or other biological molecules.^{211,212} For example, sulfhydryl groups in thiol moieties bind with high affinity to the surface of gold particles; therefore, thiol-modified oligonucleotides, peptides, or proteins can be readily coupled with AuNPs. This strategy was recently used by Vetro et al. to develop a candidate Pneumococcal vaccine. The group prepared gold glyco-nanoparticles bearing two synthetic carbohydrate antigens of *Streptococcus pneumoniae* and evaluated their immunogenicity *in vivo*. Following mice immunization, they found that the AuNPs vaccine elicited antibodies against the displayed antigens at the same order of magnitude seen in the currently used human vaccine.²¹³

Gold nanoparticles have also been used to harness natural cell functions toward the development of novel vaccines. For example, in a study by Gao et al. AuNPs were coated

with bacterial outer membrane vesicles (OMVs) to modulate immunity against *E. coli* (Figure 4A). The goal was to preserve the native cell membrane of bacteria. These membranes contain a range of antigens and danger signals capable of stimulating innate immune cells through multiple pathways that naturally recognize bacteria. Following vaccination of mice, these coated NPs traveled to draining lymph nodes in a size dependent manner. As expected, small particles (30nm in diameter) significantly accumulated in the lymph nodes as compared to larger particles (90 nm in diameter). It was further shown that the uptake of the membrane-coated NPs drove an enhanced maturation of dendritic cells in vaccinated mice compared to OMVs alone. In addition, vaccination with the NPs elicited antibody responses that were durable and high avidity (i.e., high antibody binding strength), (Figure 4B) along with a strong T-cell response (Figure 4C).²¹⁴

Silica nanoparticles (SNPs) have recently gained attraction for vaccine delivery because the abundant silanol groups on the surface of SNPs can facilitate functionalization to introduce specific molecules on their surface. These studies demonstrate SNPs can be synthesized in a range of shapes, sizes, surface chemistry; their morphologies can also be tuned to create mesoporous silica nanoparticles (MSNs) with variable pore size and payload capacity.^{215–218} These features are useful for cargo transport and release to drive both antibody and cellular immune responses. Whereas surface coating with various molecules allows enhanced cellular targeting and uptake, the porous spaces of mesoporous NPs can also be loaded with active biomolecules. As with polymers, lipids, and self-assembled biomaterials, inorganic materials can also be used for gene delivery. For example, the surface of mesoporous silica NPs has been modified with a cationic polymer to bind DNA and RNA.¹¹⁰ Complexing polymers with the MSNs have the potential advantage of facilitating gene delivery by a multifunctional platform that could also allow for imaging, targeting, and concurrent delivery of therapeutic agents. These added values pose inorganic materials as a useful alternative of traditional viral vectors for gene delivery.

Other types of inorganic particles have also been tested for vaccine applications. For example, calcium phosphate nanoparticles (CaPs) have been explored as carriers for peptides and DNA vaccines.^{219,220} Knuschke et al. recently reported a CaPs vaccine that delivered a TLR9 agonist (CpG) and an influenza A virus antigen. Following immunization of mice, functionalized CaPs were effectively taken up by APCs *in vivo* and induced a strong immune cells activation. This led to high numbers of IFN- γ -producing, antigen-specific T-cells. Most importantly, this vaccination strategy was effective at preventing virus replication when administered via multiple injection routes.²²⁰ Recently, Wang et al. demonstrated the ability of titanium oxide (TiO₂) microparticles decorated with nanospikes to activate and amplify immune response *in vitro* and *in vivo*. The spiky MPs were fabricated from TiO₂ powders that were assembled into bundles of spiky microparticles with an average particle diameter of 2 μ m and a spike length of 400 nm (Figure 4D). The potential of this carrier for vaccination was tested in a pre-clinical model of influenza. The group found that macrophages actively take up spiky particles without the loss of cell viability. The spiky particles specifically activated inflammasomes due to a spike-mediated mechanical stress on the cell membrane. The injected spiky particle vaccine significantly upregulated the expression of co-stimulatory molecules on dendritic cells and bolstered antigen-specific immune responses when combined with monophosphoryl lipid A, an

agonist of TLR4 (Figure 4E–F).²²¹ Overall, the study sheds light on the significance of mechanical roles in the generation of innate immunity, and provides motivation for engineering more potent vaccines and adjuvants with physical cues for immune cell activation.

4. Learning from cancer immunotherapy to improve vaccine against infectious diseases

The recent introduction of biomaterials in the delivery of vaccines against infectious diseases has offered new opportunities to address challenges in the field. As discussed in Section 3, vaccine delivery via biomaterials provide the capability to more precisely manipulate immune responses. In addition to the delivery systems discussed above, there are many other exciting nanotechnology platforms being used in other areas of immune study that could be applied to future vaccines against infectious diseases. One of these approaches is the use of cell membrane-coated polymeric nanoparticles being developed for cancer vaccination.^{222,223} As discussed in Section 4.1, these particles are attractive because their surfaces preserve the natural structures of cell membranes and the tunable physicochemical properties of polymers to further enhance immune response. Another major benefit of these materials is the ability to further functionalize their surfaces with moieties, such as targeting ligands, to increase the chance for delivering the vaccine to desired immune locations. This aspect will be discussed in Section 4.2. In both sections, the discussions draw on insights from cancer immunotherapy that could be relevant for the design of future multi-antigenic vaccines against infectious diseases.

4.1. Cell membrane-coated polymeric particles induce potent immune responses

Similar to infectious pathogens, cancer vaccines seek to target antigens overexpressed on tumors. Therefore, researchers have been exploring the direct use of cancer cell membranes as materials for enhancing nanoparticle vaccine functionality. This strategy leverages natural interactions that have evolved between pathogens and immune cells over millions of years and offers unique advantages, including the ability to present multiple functional moieties in their native conformation without the complication associated with identifying, synthesizing, and conjugating individual components.²²⁴ The application of cancer membrane coating nanoparticle vaccine has been demonstrated in multiple pre-clinical instances.^{225,226} In one recent example, membrane derived from cancer cells – displaying the associated tumor antigens – were coated onto CpG-loaded PLGA NPs (Figure 5A). When administered subcutaneously to mice, fluorescent imaging indicated that both tumor antigens and CpG adjuvant were delivered concurrently to dendritic cells within the lymph node. The CpG immunostimulatory property was shown to remain active after loading into the nanoparticles as indicated by the upregulation of maturation markers CD40, CD80, CD86 (Figure 5B). In addition, both membrane-coated and uncoated CpG nanoparticles equivalently activated DCs, indicating that the coating of the cancer cell membrane onto NPs does not affect the immunostimulatory property of the adjuvant inside the nanoparticle. To further confirm the antitumor benefit of the vaccine, the ability to generate antigen-specific T-cells was examined. These studies revealed immunization with membrane-coated particles promoted native generation of T-cells with a specificity for a range of tumor antigens. This highlights

the ability of the cell membrane-coated nanoparticles to train the immune system against a multitude of antigens. The protective effects of the vaccine were tested by challenging mice after immunization with the particles. Mice vaccinated with the NPs were able to reject the tumor cells significantly better than any other formulation tested, with 86% of mice remaining tumor free for over 150 days after challenge.²²⁷

Additional studies further expanded upon this concept to show that microparticles could also serve as core materials for the delivery of immune stimulators and antigens to APCs. These studies revealed that MPLA-loaded PLGA MPs coated with cancer cells form cancer cell-derived vesicles (MS-VEs) that were more efficiently engulfed by APCs compared with non-coated microspheres. In addition, incorporation of MPLA within MS-VEs triggered elevated release of immune stimulating cytokines from macrophages and dendritic cells compared to free MPLA.²²⁸ Together, these studies suggest that polymer particles coated with cancer-derived cell membranes can induce efficient immune responses, and this response could be further amplified by incorporating immune signals in the core material. Because microbial membranes contain multiple immunogenic antigens, this strategy could be adapted to develop potent multi-valent vaccines against infectious diseases.

4.2. Functionalizing cell membrane-coated particles with targeting ligands further enhances immune response

In addition to delivering native antigens to APCs, another opportunity to learn from cancer vaccines is the ability to improve intracellular trafficking of vaccine by adding surface ligands on the surface of cell membrane-coated particles. This feature is important because stable protection against chronic infections such as HIV, malaria, and tuberculosis require both antibody and cellular immunities.^{9,229} Current vaccine candidates often lack the potential to promote cellular immune responses as a result of the poor presentation of antigens to CD8⁺ T-cells (cross-presentation). To improve the CD8⁺ T-cell response, vaccines that target DCs via cross-linking to receptors that facilitate intracellular trafficking of endocytosed antigens through pathways known to promote cross-presentation are under investigation.²³⁰ To improve targeting of APCs, Yang and co-workers developed a new cell membrane-coated particle by coating adjuvant-loaded NPs with mannose-modified tumor cell membranes (Figure 6A). Mannose is a glycan that is known to target DCs via mannose-binding receptors.^{231,232} The vaccine NPs are loaded with a TLR7 agonist to activate endosomal ligand once internalized. The mannose-modified particles were shown to be more readily engulfed by immune cells *in vitro* and *in vivo* compared to particle without mannose modification (Figure 6B–C). This enhanced vaccine uptake also correlated with an upregulation of INF- γ cytokine levels.²³³ Other biomolecules have been recently reported for their potential to improve intracellular trafficking of endocytosed vaccine.^{234,235} Although they are yet to be tested in membrane-coated vaccines, the results suggest that they have potential to elicit immune responses needed to effectively address current limitations of vaccine against infectious diseases.

5. Perspectives/Conclusion

Infectious diseases have for centuries been among the leading causes of death worldwide and continue to pose a significant burden on public health. The challenge is further deepened by the innate heterogeneity of infectious pathogens, the continued re-emergence and rapid spread of established disease, and the emergence of new diseases. Because of our incomplete understanding of the type of immune response (e.g., cellular, humoral immunity, and/or mucosal) that would give the best long-term protection, rational design of safe vaccines against many prevalent infectious diseases have been challenging. Current efforts to develop vaccines that meet safety standards, while remaining effective are focused on developing subunit vaccines composed of molecularly defined antigens combined with immune-stimulatory adjuvants. Though this approach has led to several vaccines that are currently in clinical trials, recent advances in biomaterials offer new opportunities to improve vaccine effectiveness. These benefits include improved antigen uptake by APCs, as well as enhanced immunogenicity stemming from either immunostimulatory features of the biomaterials themselves or of co-delivered adjuvant molecules. A variety of biomaterial formulations differing in physical and chemical composition have been shown to play crucial roles in vaccine protection, cellular trafficking, and overall immune response with minimal toxicity. Newer biomaterials with improved properties are also being engineered, but their application to infectious diseases is still in its infancy and will require strong collaborative efforts between researchers in diverse fields. As existing materials are refined, the field of biomaterials offers new knowledge and exciting ideas that could be leveraged in the future to develop improved vaccines against infectious diseases.

Acknowledgments

Funding Sources

This work was supported in part by the National Institutes of Health (Award # R01EB027143) and the United States Department of Veterans Affairs (Award # 1I01BX003690).

ABBREVIATIONS

HIV	human immunodeficient virus
TB	tuberculosis
NPs	nanoparticles
MPs	microparticles
AIDS	acquired immune deficiency syndrome
BCG	Bacille Calmette-Guérin
APCs	antigen presenting cells
DCs	dendritic cells
INF	Interferon

TNF	tumor necrosis factor
IL	interleukin
CTL	cytotoxic T lymphocyte
PLGA	poly (lactic and glycolic) acid
PolyIC	poly (polyinosinic:polycytidylic acid)
TLR	Toll-like receptor
MPLA	monophosphoryl lipid A
ICMVs	interbilayer-crosslinked multilamellar vesicles
SNAP	spontaneous nanoliposome-antigen particleization
STING	stimulator of interferon genes
cGAS	cyclic GMP-AMP synthase
BDMCs	bone-marrow-derived dendritic cells
CCMF	cancer cell membrane fractions
VLP	virus-like particles

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Figure 1.

Polymeric biomaterial platforms for vaccination against infectious diseases. Microneedle array (MA) fabricated to deliver a live recombinant human adenovirus vector encoding HIV-1 gag antigen pre-(**A**) and post-(**B**) application. (**C**) Following intra-vaginal antigen boost of vaccinated mice, a significant increase in the frequency of CD8⁺ T-cells was detected in genital track tissue of boosted mice when cross compared with non-boosted mice. (**D**) Antigen-specific memory CD8⁺ T-cells, CN54 gag_{308–318}, were also detected in the blood and genital tract of immunized female mice after 365 days. Reproduced with permission from ref ¹²⁸. Copyright 2017 Elsevier. (**E**) Schematic representation of the preparation process for chitosan NPs. (**Top**) CS–PCS5/DS/pIC NPs, and (**Bottom**) CS/HA–PCS5/pIC NPs. Key: CS, chitosan; DS, dextran sulfate; PCS5, protease cleavage site 5; pIC, poly(I:C) (polyinosinic:polycytidylic acid); HA, hyaluronic acid. NPs increase costimulatory factors CD40+ (**F-top**) and CD86+ (**F-bottom**) expression in macrophages of vaccinated mice CS/DS + PCS5 (black bars, G2), CS–PCS5/DS/pIC (white bars, G3), or CS/HA–PCS5/ pIC (gray bars, G4) compared to non-treated naive (red bars, G1) at 9 weeks post prime. Reproduced with permission from ref ¹³⁷. Copyright 2019 American Chemical Society.

Figure 2.

Lipid biomaterial platforms for vaccination against infectious diseases. **(A)** HIV trimers, MD39, were modified to introduce a single free cysteine residue at the C-terminus and covalently-anchored on liposomes prepared with maleimide-functionalized lipids (MBP) and Ni-NTA lipids. **(B)** Increasing the stability of the liposomes by incorporating sphingomyelin improved early germinal center responses *in vivo* marked by a significant increase in the frequencies of trimer-specific T helper cells. **(C)** This was associated with significantly higher titers antibodies production compared to soluble trimers 3 weeks post-boost. Reproduced with permission from ref ¹⁴⁸. Copyright 2018 Springer Nature. **(D-left)** Schematic representation of multivalent SNAP particle displaying various *P. falciparum* antigens. **(D-right)** Native PAGE demonstrating effective single and multiplexed antigen binding to CoPoP/PHAD liposomes. **(E)** Mice immunized with individual antigens or a multivalent particle elicited similar antibodies levels. Reproduced with permission from ref ¹⁵⁴. Copyright 2018 Springer Nature.

Figure 3. Self-assembly polymer vaccines exhibit unique features that can be harnessed to program the assembly of a wide array of particle. **(A)** Virus-like particles induce antigen-presentation through B-cells in to promote an immunogenic germinal center. Cognate antigen presented by B-cells enhance the proliferation of CD4+ T-cells, and the cytokine milieu generated by B-cells in response to TLR signaling play a role in the differentiation of CD4+ T-cells. Reproduced with permission from ref ¹⁸⁴. Copyright 2018 Elsevier. **(B)** Computer schematic showing the generation of a self-assembled nanoparticle composed of a flagellin-derived adjuvant, a *Plasmodium falciparum* antigen (Left), and the generated co-assembly particle (Right). Reproduced with permission from ref ²⁰⁴. Copyright 2018 Elsevier.

Figure 4.

Inorganic biomaterial platforms for vaccination against infectious diseases. **(A)** Schematic illustration describing the modulation of antibacterial immunity via bacterial membrane vesicles (OMVs) coated on gold NPs (BM-AuNPs). Following mice immunization, the BM-AuNPs induced significantly higher **(B)** *E. coli*-specific antibody titers and **(C)** bacterium-specific T-cell response in comparison to OMVs alone. Reproduced with permission from ref ²¹⁴. Copyright 2015 American Chemical Society. Titanium oxide spiky nanoparticles designed to activate immune cells and amplify immune responses against influenza challenge. **(D)** SEM image of particles. Mice immunization showed the superior adjuvant effect of spiky+ MPL and was evidenced by the highest level of **(E)** IFN- γ -producing CD4⁺ T-cells and **(F)** IFN- γ -producing CD8⁺ T-cells among all the adjuvants tested either alone or in combination. Reproduced with permission from ²²¹. Copyright 2018 Springer Nature.

Figure 5.

Characterization of PLGA nanoparticles coated with cancer cell membranes designed for antitumor vaccination. (A) Cancer cell membrane-coated on polymeric PLGA nanoparticles encapsulating CpG adjuvant (CCNPs) constitute a rich source of multivalent antigen presentation. These particles can facilitate the delivery of encapsulated adjuvant to its receptor, thus, enhancing immune cell maturation. The co-delivered membrane provides cancer antigens for presentation. (B) Characterization of dendritic cell activation markers (left) CD40; (middle), CD80; and (right) CD86 in the draining lymph nodes after administration with CpG-CCNPs and various control formulations, including whole cell lysate with free CpG (WC + fCpG), CCNPs with free CpG (CCNP + fCpG), CCNPs, CpG-NPs, and blank solution. Reproduced with permission from ref ²²⁷. Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 6.

Preparation and characterization of cancer cell coated nanovaccine modified with binding moieties to enhance targeting. **(A)** (PLGA) NPs loaded with a TLR7 agonist were coated with membranes from B16-OVA cancer cells. The derived nanovaccine, NP-R@M, is further modified with mannose by a lipid-anchoring method to improve specific binding between mannose and its receptors on APCs such as dendritic cells, NP-R@M-M. The incorporation of mannose in the particle was shown to increase **(B)** the mean fluorescence intensity of the cell uptake capability when compared to particles without mannose modification *in vitro*. **(C)** The benefit was further confirmed in *ex vivo* fluorescence imaging of isolated draining lymph nodes taken at 6 h after intradermal injection of NPs. Reproduced with permission from ref ²³³. Copyright 2018 American Chemical Society.

Table 1.

A variety of pathogens can cause infection in human. Key characteristics of the four main class of infectious pathogens including viruses, bacteria, parasites, and fungi are listed. Representative pathogens in each group are also listed.²⁴

Key Characteristic	Viruses	Bacteria	Parasites	Fungi
Structure/type	Essentially spherical	Rod-shape, spherical, helical	Protozoa, helminth, ectoparasites	Yeast, mold
Approximate diameter (µm)	0.02–0.2	1–5	3–25	3–10
Genetic content	Either DNA or RNA	Both DNA and RNA	Both DNA and RNA	Both DNA and RNA
Type of nucleus	None	Prokaryotic	Eukaryotic	Eukaryotic
Nature of outer surface	Protein capsid and lipoprotein envelope	Rigid wall containing peptidoglycan	Rigid wall containing chitin or flexible membrane	Rigid wall containing chitin
Replication	Lytic or lysogenic cycles	Binary fission	Budding or mitosis	Budding or mitosis
Representative examples	HIV, Ebola virus, Zika virus, Dengue fever, Hepatitis virus	Mycobacterium tuberculosis, Shigella, Staphylococcus pneumoniae, Pseudomonas, Chlamydia trachomatis	Plasmodium, Leishmania, Giardia, Toxoplasma gondii, Trypanosoma cruzi	Candida albicans, Candida auris, Aspergillus, Trichophyton, Histoplasma capsulatum,