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An overview of the use of nanoparticles in vaccine development

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Abstract

Nanotechnology is revolutionizing vaccine development by addressing the limitations of traditional vaccines, including inefficacy against complex diseases like HIV, tuberculosis, and cancer. Nanoparticles, such as lipid nanoparticles, polymeric carriers, and virus-like particles (VLPs), mimic pathogens and enhance antigen delivery, triggering robust immune responses. These nano systems improve vaccine efficacy, stability, and safety by enabling targeted and controlled antigen release.

Notably, lipid nanoparticles have enabled mRNA vaccines for COVID-19, as demonstrated by the success of Moderna and Pfizer-BioNTech vaccines. Advanced delivery methods such as viral vectors, virosomes, and polymeric particles show promise for cancer immunotherapy and combating intracellular infections. Nanoparticle-based platforms also provide versatility across different administration routes, including oral, intranasal, and injectable formats, enhancing accessibility and compliance.

Despite promising advances, challenges like toxicity, regulatory standards, and large-scale manufacturing persist. Future prospects highlight nanotechnology's potential to develop next-generation vaccines capable of combating infectious diseases, cancer, and complex conditions effectively.

Keywords: Nanotechnology; Vaccines; Nanoparticles; Immunity; Delivery

1. Introduction

Vaccination has revolutionized public health by preventing millions of infections and saving countless lives. Despite remarkable progress in vaccine science, some infectious diseases, such as HIV, tuberculosis, and malaria, remain significant health threats, especially in low-resource regions. Additionally, emerging viral pathogens, such as SARS-CoV-2, highlight the need for rapid, effective vaccine platforms [1-4]. Conventional vaccines, including live-attenuated, inactivated, and subunit types, are effective against many diseases but often come with limitations, such as potential risks to immunocompromised individuals, the need for multiple doses, or reliance on adjuvants to achieve a robust immune response. These challenges drive the search for innovative approaches to vaccine development.

Nanotechnology has become a promising solution to overcome these limitations by introducing nanoscale materials that can improve vaccine efficacy, safety, and delivery accuracy. Nanoparticles, including lipid nanoparticles, polymeric particles, virus-like particles (VLPs), and outer membrane vesicles (OMVs), have unique properties making them ideal for developing next-generation vaccines. These nanomaterials can mimic pathogen structures, efficiently deliver antigens to immune cells, and activate immune pathways in ways that traditional vaccines cannot. The recent success of lipid nanoparticle-based mRNA vaccines against COVID-19, developed by Pfizer-BioNTech and Moderna, has further proven nanotechnology's potential to revolutionize vaccine science.

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This article provides an overview of nanoparticles in vaccine development, focusing on their roles in enhancing immune response, the design of novel vaccine platforms, and the potential applications in complex disease settings such as cancer[8-9]. It also discusses the current challenges and future prospects of integrating nanotechnology with immunology to create more effective vaccines. By exploring the structural advantages and versatility of nanoparticles, we aim to highlight their transformative potential in addressing global health needs and advancing the field of vaccinology.

2. Conventional vaccines

As expressed by the WHO, antibodies are drugs that create protective insusceptibility against an illness by initiating the creation of explicit antibodies by the invulnerable framework against a microbe[10]. Antibodies are viewed as the best strategy to control pestilences, like measles, diphtheria, and, in the long run, SARS-CoV-2. The first antibody utilized in the Western world was found by E. Jenner toward the end of the eighteenth century against smallpox, a horrendous cause for mortality at the time[11]. This immunization was in view of the cowpox infection. E. Jenner was a provincial doctor who understood that steers laborers who had recovered from cowpox infection were safeguarded against smallpox. Nonetheless, he didn't realize that the illness was brought about by an infection; an irresistible specialist that was not found furthermore, depicted until the 20th 100 years. According to a logical perspective, traditional immunizations are an immediate result of the revelation by Evon Behring and S. Kitasato, toward the finish of the nineteenth 100 years, of the presence of defensive particles, begat antibodies, in the plasma of patients who recovered from contaminations brought about by microbes, infection, or parasites[12]. These particles additionally secured patients from future assaults by a similar microbe. This revelation created a rush among microbiologists to recognize the microorganisms responsible for normal irresistible illnesses at the time, including diphtheria, measles, and poliomyelitis, and so forth, to acquire in this manner defensive immunizations. Antigens used to secure insurance incorporate weakened microbes which lost the capacity to contaminate after monotonous societies in the lab (lessened vaccines, for example, the Calmette-Guerin antibody in view of M. Bovis, against tuberculosis, and microbes inactivated by intensity or synthetic specialists (inactivated antibodies)[12,13]. In numerous cases, practical antigens for antibodies were made out of cleansed pieces of microbes that induced an immune reaction against the whole microbes or infection. Conventionally, these antigens were obtained by DNA recombinant processes in other organisms, mainly bacteria or cultured cells that produce high quantities of the selected antigen from its encoding gene, which can be easily purified[14]. These biological preparations used in vaccinations were called second-generation vaccines. This generation is based on subunit elements, recombinant or synthetic proteins, non-protein antigens, and expressed bacterial or viral immunogens, which may include numerous molecules and epitopes of different strains or even species of pathogens[15].

3. Nanoparticles Employed in Vaccine Technologies

While nanoparticles have great potential to carry and release drugs, they also have the potential to act as antigens themselves[16]. In this sense, nanoparticles could be specifically engineered to interact with the immune system, which could be desirable when leading to certain beneficial biomedical applications, such as vaccine development of certain therapies for inflammatory and autoimmune disorders. This technology makes it possible to add a series of agents that direct the nanoparticle towards a specific target, or that enhance the immune response to the antigen. On the other hand, it was also shown that, in some cases, the nanoparticle itself is able to enhance the immune response induced by the antigen[17]. In fact, the most important NPs-based drug delivery systems used in vaccines are those capable of providing a potent and antigen-specific immune response. Certain parameters are crucial for nanoparticle immunogenicity, such as size, shape, and surface charge of the nanoparticles themselves[18]. The reason for that relies on their importance to improve antigen delivery and presentation. In this regard, they have a strong influence on NP circulation, biodistribution, bioavailability, and capacity to cross certain biological barriers. Nanoparticle size was found to determine the way of cellular uptake, together with the cellular specificity and migration, so they can reach antigen-presenting cells to activate the immune response[19]. The particle size can significantly contribute to the efficiency of vaccine formulations, since it was reported as one of the most important factors in determining if the loaded antigens induce type I (interferon-gamma) or type II (IL-4) cytokines, which would ultimately determine the immune response[20,21]. Examples of how nanoparticle size might be a leading parameter to determine the potential to induce cytokine responses are the length of CNTs, which was observed to correlate with the induced subcutaneous inflammation in an in vivo model[22]. An important consideration is that the immune system recognizes foreign bodies based on their size, among other properties. Large NPs normally interact with APCs present in many tissues, while NPs smaller than 200 nm could circulate for longer through the venous system and lymphatic drainage, which increases the antigen presentation[23]. Interestingly, nanoparticles with size 50 nm were found to increase the expression of certain cell markers and inflammatory cytokines that are responsible for the immune system[24]. The shape of the NPs also has a strong influence in the cellular interaction, intracellular trafficking, and the release kinetics of the antigen into de-targeted cells. Nanoparticle shape can also determine the localization of nanoparticles inside the cells, as it happened

with nano rods vs. nano sheets. The former was delivered to the nucleus while the latter were retained into the cytoplasm[19]. Therefore, nanoparticle shape would also control the immune response of the NPs. There are reports showing that rod-shaped NPs that might present higher surface area than spherical NPs are more likely to be internalized by macrophages, enhancing the production of certain inflammatory markers[25]. The surface charge of the NPs is responsible for the interaction with the molecules the membranes of the targeted cells. In this sense, positive NPs would be more efficiently internalized by the antigen-presenting cells than neural or negatively-surface charged might help to generate a stronger immunological response[26].

4. Nanomaterial-based vaccine delivery systems

Recent advancements in vaccine development have increasingly explored the use of nanomaterials, including lipid-based nanoparticles, protein nanoparticles, polymeric nanoparticles, inorganic nanocarriers, and biomimetic nanoparticles. Each type of nanocarrier possesses unique physicochemical properties and biological behaviours, which influence vaccine efficacy and delivery mechanisms.

Classical vaccines such as those for tetanus and diphtheria often utilize particulate adjuvants like alum to enhance immunogenicity. Nanoparticles offer a similar advantage; their size is comparable to many pathogens, which optimizes immune system recognition and activation. This similarity has inspired the development of particulate delivery systems, aimed at improving the immunogenicity of novel vaccines. These systems include lipid emulsions, biodegradable polymers, virus-like particles (VLPs), virosomes, and immunostimulatory complexes, which serve dual roles: they deliver antigens to targeted sites and act as immune stimulants[27-30].

Nanoparticle-based vaccine delivery systems show particular promise due to their ability to facilitate intracellular antigen delivery, eliciting T-cell responses necessary for combating intracellular infections. These systems enable controlled antigen release over extended periods, ensuring sustained antigen presence in antigen-presenting cells (APCs) and enhancing immune response duration.

The materials used for these nanocarriers are diverse spanning lipids, polymers, proteins, carbohydrates, metals, and even non-infectious viral and bacterial components. Key characteristics for effective nanocarrier materials include biocompatibility, biodegradability, stability, and the ability to deliver an adequate antigen load to targeted cells. Furthermore, the route of administration significantly impacts immune response, underscoring the importance of versatile delivery mechanisms.

Innovative nanocarrier systems for vaccine delivery continue to be developed, including viral vector-based vaccines, bacterial ghost particles, and VLPs. These developments underscore the versatility and potential of nanoparticle-based systems as pivotal tools in next-generation vaccine technology.

4.1. Viral-Vector Based Antigen Delivery System

Viral vectors consist of both replicating and non-replicating viruses that deliver the vaccine antigen to target cells to induce an immune response[31]. Most of the time vaccine antigen is the genetic material from the pathogen against which immunity is desired. Since the immune system has evolved to respond to viruses, viral vector-based vaccine using a virus provides the most ideal way to deliver vaccine antigen[27]. Many viruses like vaccinia virus, adenoviruses, and alpha viruses have been successfully used to develop a delivery system for vaccines[32]. Among all the viral vector-based vaccines, adenoviruses have been most extensively used as a delivery platform for many vaccines. Safety and efficacy of adenovirus-based vaccine delivery have been shown in humans using the intranasal and percutaneous route[33]. Advantages of virally-vectored vaccines include their ease of production and ability to produce both humoral and cellular responses. These viral vectors can be used for nasal, percutaneous delivery or mucosal immunization and have been reported to improve the immunogenicity of DNA vaccines. Immune response generated by a virally vectored vaccine is further increased by the use of a prime-boost approach, where the primary immunization is carried out by DNA, followed by boosting with protein antigen[34]. Such a prime boost immunization modality has resulted in elicitation of strong T cell response in many cases[34-36]. Generation of antibody response along with strong T cell response makes this prime boost approach most suitable for the development of a vaccine against intracellular infection.

4.2. VLPs, Virosomes and Bacterial Ghosts

VLPs are non-infective viruses consisting of self-assembled viral envelope proteins without the genetic material[37]. They mimic certain virus properties like size and conformation, which help them to elicit a strong immune response. Virosomes are a liposome-like structure using viral coat protein, where the envelope of one virus is used as a platform[27]. To this viral coat, components of the virus or another virus or pathogen are attached or entrapped[27,38].

Both VLPs and virosomes have morphology and cell penetrating ability similar to an infective viral particle to trigger the immune system. Both types of particles have been shown to elicit both cellular and humoral immunity[39,40]. VLPs are generally produced in vitro by transfecting a cell line with a plasmid encoding only the viral structural protein, followed by entrapment of the candidate vaccine antigen. Recombinant Hepatitis B vaccine and the human papillomavirus vaccine are the two successful examples of VLP-based vaccines[41]. VLPs are easy to make and can be produced either in bacteria, plants, insects, animals, and yeast cells; however, the insect cell system has been most widely used to produce VLPs[42]. VLPs provide improved immune response in comparison to that achieved from vector-based as well as virosome-based immunization. Because of these reasons, VLP and virosome-based vaccine delivery systems are currently under evaluation for the development of influenza vaccine[43,44]. Another system which is being used to deliver an antigen to a cell is the bacterial ghost system, where the non-living bacterial cell without the genetic component is used for immunization, carrying the protein antigen[45]. Like VLPs, bacterial ghosts are made up of non-living envelope of the cells having native antigenic structure including its bio-adhesive properties. Escherichia coli, Salmonella typhimurium, BCG, V. cholerae, and many other gram-negative bacteria have been used as bacterial ghosts for gene delivery[46]. Bacterial cell walls promote T cell activation, induce systemic, cellular, and mucosal immunity to target antigens, and thus provide a model platform for vaccine delivery.

4.3. Immunostimulant Complexes (ISCOMs)

The ISCOMs are novel vaccine delivery vehicles with potent adjuvant activity[47]. ISCOMs are lipid particles comprising of cholesterol, phospholipids, and protein antigens formulated by incorporating saponin Quill A from the soapbark tree Quillaja Saponaria[48]. These are cage-like structures with having size of around 40–50 nm. Antigens are trapped within ISCOMs through apolar interaction[49]. ISCOMs are described as a novel structure for the presentation of membrane proteins from a virus to APCs to elicit an immune response[50]. These particles, due to their lipophilic nature, are preferentially taken up by APCs such as DCs, monocytes, and macrophages. Immune responses observed by ISCOMs are mostly due to antigen presentation by both MHC class I and class II pathways, resulting in the elicitation of both cellular and humoral immune responses[51]. The immunomodulatory capability of the saponin helps in further augmentation of the immune response using ISCOMs. Smaller size of ISCOMs and their negative surface ensures colloidal nature of the adjuvant and thus makes them a very stable preparation for vaccine delivery purposes. ISCOMATRIX is another delivery system without an antigen[52]. Antigen is added to the is comatrix during formulation for improved immunogenicity. When administered in mice, ISCOMs elicit strong mucosal, systemic as well as CTL responses[49]. Even though ISCOMs have been used for improved immunogenicity of different antigens, the toxicity of saponin is one of the major concerns for human application. Currently, ISCOMs and ISCOMATRIX-based delivery systems are only registered for veterinary applications.

4.4. Polymeric Nanoparticles

Polymeric particles are well well-established system for the delivery of vaccines[53,54]. These are essentially solid particles made of polymers either derived from natural source or from synthetic origin entrapping/encapsulating the candidate antigen. These particles offer advantages in terms of size, load and release profile of antigen and thus are preferred over other carrier systems. The most important role of polymeric nanoparticles in terms of vaccine development are, modulation of immune response, enhanced uptake of antigen, targeting to particular APCs depending on size and surface chemistry and, more importantly, protecting the antigen inside the polymer matrix for a longer period of time in vivo. Because of these advantages, polymeric nanoparticle-based formulations have been extensively explored for vaccine development. A variety of polymers have been used for nanoparticle formulations for drug/vaccine delivery. However, the most commonly studied polymers are poly D L lactide-co-glycolide (PLGA) and polylactide (PLA)[55]. These biodegradable, biocompatible polymers have been approved by the FDA for use in humans and have been extensively used for the development of single-dose vaccine delivery system[56]. In polymeric particle formulations, antigens are either entrapped or adsorbed to the surface of the polymer particles. These can act as a depot from which antigen is released in a controlled manner. Most of these polymers induce inflammation thus providing an adjuvant effect. Apart from this, polymeric nanoparticles can elicit an innate immune response. Multiple antigen delivery in the same particle and co-delivery of antigen and adjuvant can also be achieved with polymeric nanocarrier systems. Chitosan has been widely used for the delivery of antigens[57,58]. Because of its bio-adhesiveness, it has been tried mostly for mucosal delivery of antigens[59]. Different-sized particles with varying load of antigen could be formulated for the delivery of antigen to achieve the desired immune response. Highly cationic charges of chitosan make it particularly suitable for genetic immunization as the formulation of particle with plasmid DNA is easily achieved through electrostatic attraction. Varieties of nanocarrier systems can be formulated using a chitosan-based formulation for immunization. These include chitosan-coated PLGA particles, electrostatic chitosan DNA complexes, nanoparticles made from chitosan and its derivatives and finally chitosan-coated nanoemulsion. These coatings are particularly suitable for the mucosal delivery of vaccines due to the adhesive properties of the chitosan[60]. Nanoparticles made from amphiphilic polyamino acid derivates have also been reported for the delivery of antigens[61]. Polyglutamic acid-based

nanoparticles have been extensively used for the delivery of antigens[62-64]. Using polyglutamic acid-based nanoparticle systems, both humoral and cellular response has been observed. Polyglutamic acid-based nanoparticles have been used as a delivery system for an AIDS vaccine as well as a tumor vaccine[62,63].Polyethyleneimine amine (PEI) based nanoparticle systems have been successfully used for the delivery of nucleic acid[65,66]. Efficient transfection ability of such polymeric nano system provided a viable alternative for genetic immunization to combat many intracellular infections.

4.5. Solid Nanoparticles (SNPs) are Vaccine Carriers

SNPs are made of biodegradable materials, such as proteins, fats, lipids, polystyrene, and other polymers, and are the most commonly used nanocarrier systems[67]. These particles may be solid lipid nanoparticles (SLNs), lipospheres, and particles made from polystyrene and other materials. Ranging in size from 10 to 1,000 nm, SNPs can be used simultaneously for imaging and drug delivery. A major advantage of these particles is that they release the entrapped drug in a controlled manner. Masamune is the first nanoparticle-mediated medicine used as an immunosuppressant to prevent organ transplant rejection, approved by the US FDA in 2000. Albumin nanoparticle entrapping paclitaxel is the most successful nano formulation. SLNs, because of their physical stability and controlled release characteristics, are an excellent drug delivery platform[68]. SLNs, because of their versatility and stability, can be administered by most of the routes generally used for drug delivery[69]. Topical application using SLN is already in the market for therapeutic and cosmetic applications[70]. SLNs have been used for vaccine delivery systems as they release the antigen in a controlled manner and provide an adjuvant effect. Lipid particles have been reported to trigger internalization of BSA by the APCs[71]. Solid lipid nanoparticles have been explored for the delivery of the Hepatitis B vaccine[72]. Mucosal immunization of HBsAg-loaded SLNs has been reported to elicit a higher IgA response.

5. Type of nanomaterial-based vaccine

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

5.1. Self-assembled protein nanoparticles

Natural nanomaterials have excellent biocompatibility and biodegradability. Several types of protein nanoparticles made of natural source proteins have been utilized for the delivery of antigens[73]. Self-assembled protein nanoparticles are promising candidates for nano-vaccines. Typical examples of self-assembled protein nanoparticles include ferritin family proteins, pyruvate dehydrogenase (E2), and virus-like particles (VLPs), which have shown potential in the development of nano vaccines. VLPs are self-assembled complexes composed of viral proteins, which are supposed to be safe and highly efficient delivery platforms for antigen delivery without genetic components and replication ability[74]. VLPs have favorable immunological properties as they are self-adjuvants and can be immunologically recognized for the virus size and repetitive surface geometry. VLPs-form polydisperse systems can be efficiently uptaken by APCs and induce immune responses[75]. Antigens can be chemically coupled or genetically modified to VLPs with high density. VLPs-based vaccines have resulted in successful immunization programs as they are currently available in the market, such as Cervix# and Gardasil# against the human papillomavirus (HPV) and Sci-B-Vac™ against the hepatitis virus. In contrast to exogenous viral proteins, several endogenous self-assembled proteins can also be explored as nano vaccine platforms; those protein nanoparticles are also called caged protein nanoparticles for their highly organized structures[76]. Ferritin is a typically caged protein nanoparticle that has been widely used for antigen delivery, drug delivery, imaging, and diagnostic applications[77]. Classical ferritin is comprised of 24 subunits, forming a central hollow cavity structure (12 nm # 8 nm) that stores iron. Antigen proteins can be genetically modified as subunits to form ferritins or can be incorporated onto ferritins to be efficiently phagocytosed by APCs. It has been reported that ferritin can passively target lymph nodes with a high retention time and induce strong immune responses.

5.2. Polymeric nanoparticles

Polymeric nanoparticles are colloidal systems with a wide size range (10e1000 nm)[78]. Polymeric nanoparticles have high immunogenicity and stability for efficient encapsulation and display of antigen, which can be loaded within the core and conjugated to the surface. While polymeric nanoparticles are generally solid, they have controllable size and can be self-adjuvant[103]. Polymeric nanoparticles can improve the efficiency of antigen uptake by APCs by phagocytosis or endocytosis[79]. For the development of nano vaccines, natural polymeric nanomaterials such as chitosan and dextran, and synthetic polymeric nanomaterials such as PLA and PLGA are both useful tools. Polymeric nanoparticles from natural sources are highly biocompatible, water-soluble, and cost-saving. For example, chitosan, a typical natural

polymer derived from chitin, is a linear cationic polysaccharide that can be used for vaccine delivery. Owing to its cationic charge and bioadhesive properties, chitosan is a competitive candidate for gene delivery and coating other polymeric nanoparticles to improve adherence and immunogenicity[80]. Moreover, chitosan can be customized depending on the purpose by introducing functional groups[81]. Compared to natural polymers, synthetic polymeric nanoparticles generally have higher reproducibility and are more controllable for molecular weight compositions and degradation rates[82]. For example, PLGA nanoparticle is highly biodegradable and its properties can be fine-tuned. PLGA can be coupled with PEG and then self-assembled into a polymeric micelle for hydrophobic peptide antigens with better T cell responses[83].

5.3. Lipid-based nanoparticles

Lipid nanoparticles (LNPs) are nanoscale lipid vesicles formed by amphipathic phospholipid molecules through self-assembling. LNPs are promising nanocarriers for nucleic acid delivery with low toxicity, high biocompatibility and controlled release properties[84]. LNPs are also vital components for mRNA drugs and vaccines. LNPs have controllable size, shape and charge which are important properties that may affect the efficacy of immune activation. Modification of LNPs can achieve optimal immune responses[85]. As nano vaccines, LNPs can achieve co-delivery of multiple antigens and adjuvants. Besides, the membrane surface of LNPs can display antigen with enhanced representation of native conformations. LNPs has shown great potential for nano vaccine development in a number of preclinical and clinical applications. As mentioned earlier, the lipid nanoparticles play a vital role in protecting mRNA vaccines from nuclease for effective delivery. LNPs have successfully been translated for the delivery of mRNA against COVID-19 recently (mRNA-1273[86] and BNT162b2[87]). There are many other Lopera formulations that are under ongoing clinical trials for the prevention and treatment of major human health threats, including virus infections, cancers and genetic diseases as summarized in a recent review[88]. Cationic lipids, ionizable lipids and other types of lipids are all suitable components of LNPs. Besides, lipids can be functionalized by modification such as PEGylation, making LNPs more versatile and powerful for vaccine development[89].

5.4. Inorganic nanomaterials

Commonly used inorganic materials in nanomedicine include metals and oxides, non-metal oxides, and inorganic salts. Inorganic materials have low biodegradability but are stable in structure. Many inorganic nanoformulations have inherent adjuvant activity[90]. However, for nano vaccine application, the physicochemical properties of inorganic nanomaterials need to be modified to improve their biocompatibility. The most widely used inorganic materials for antigen delivery include gold[91], iron[92] and silica nanoparticles[93]. Gold nanoparticles (GNPs) are spherical and positively charged. GNPs have good biocompatibility, low immunogenicity, and high antigen loading capacity. GNPs have size-dependent toxicity[94]; however, GNPs also have a high affinity to sulfhydryl groups[95], which can be utilized for surface engineering to couple with cysteine residues to produce polypeptide antigens with improved safety and pharmacokinetic profiles. In addition, GNPs have intrinsic immunostimulatory effects to induce inflammatory cytokines production[96]. Therefore, GNPs can be used not only as a transport carrier for antigens but also for stimulating immune responses[97]. Silica nanoparticles are also potent candidates for nanovaccine carrier materials[98]. Recent studies have shown that controlling the morphology[99] and pore size [100] of silicon particles can make them have variable porosity, thereby increasing their effective load capacity for different antigens and adjuvants. Their porous structure of silicon particles can fill various active biomolecules or directly wrap on the surface, thereby enhancing the targeting and uptake of the nano-vaccine. Silica nanoparticles have been used to target lymph nodes and accumulate in APCs to deliver antigens and adjuvants[101].

5.5. Biomimetic nanomaterials

Biomimetic nanomaterials are emerging for nano vaccine development for their effective and complex biofunctions[102,103]. Biomimetic nanomaterials are multifunctional and can achieve efficient delivery to the target site or effective interaction with biological systems. Bioinspired nanoparticles have also produced high biocompatibility, extended circulation and unique antigenic properties for the development of effective vaccine formulations. A simple biomimetic design uses natural ligands or peptides, such as arginylglycylaspartic acid (RGD) and acedoxin (CDX) peptides, to modify nanoparticles and enhance binding to improve targeting for efficient delivery[104]. In addition, molecularly imprinted polymers can also be used to mimic antibodies for developing biomimetic nanoparticles[105]. The decoration of nanoparticles with an individual natural ligand can endow specific functions, but multiple decorations would be rather difficult and can hardly replicate biological complexity. An emerging biomimetic strategy is to employ bio membranes to fabricate membrane-coated nanoparticles for enhancing bio-interfacing[106]. Cell membrane coating nanotechnology has been employed widely for improving circulation, targeted delivery, and imaging of nanoparticles[107]. For vaccine development, camouflaging with a cell membrane may help nanoparticles to stay unnoticed in the immune system and target the lesion[108]. For example, the red blood cell (RBC) membrane can extend

circulation and improve the bioavailability of nano particles[109]; platelet membranes can achieve targeting to the damaged vasculature and certain pathogens[110]; nanoparticles coated with cancer cell membranes have shown autologous targeting to cancer cells[111]; immune cell membrane-coating can endow the nanoparticle the ability to interaction with tumor tissues[112].In addition to cell membranes, intracellular membranes such as the outer mitochondrial membrane can also be utilized for specific targeting and detection[113]. Besides, biomimetic nanoparticles may be exploited as cancer nano vaccines with combined photothermal (PTT) and photodynamic therapy (PDT) against metastasis[114,115]. Several other biomimetic strategies are emerging in nano vaccine design for combating infection and cancer. Virosome is a lipidic uniflagellar nanocarrier (60e200 nm) utilizes the liposome concept but has a structure similar to an enveloped virus with removed nucleocapsid[116]. Virosome is an emerging biomimetic nanoparticle for the development of a nano vaccine against viral infections. Virosomes can be developed with different antigen epitopes to target host cells of interest and can be modified by polymers for enhanced pharmacokinetic profiles[117]. Outer membrane vesicles (OMVs) are bacterial-derived nanovesicles carrying various proteins similar to bacterial outer membranes. OMVs are a natural antibacterial vaccination for their multi-antigen features[118]. In addition, OMVs have shown the ability to enter of lymph node and can be taken up efficiently by APC, making them attractive candidates for antigen delivery and vaccination. Antigenic OMVs can be explored as adjuvant delivery systems to improve vaccine efficacy[119].

6. Administration strategies

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

6.1. Postoperative administration

Currently, surgery remains the primary option for solid tumour treatment. However, tumour recurrence remains a challenge as residual tumour cells can be a risk that leads to fast relapse and metastasis. Strategies of nanomedicine are emerging for postoperative tumour drug delivery and immunotherapy[120]. To increase the efficiency of postoperative T-cell immunity, a thermo-responsive, curcumin-loaded polymer nanoparticles assembled hydrogel with an antigenic peptide and CpG-ODN was developed. This strategy can induce ICD and consequently enhance the antitumor immunity[121]. This immunotherapy strategy promoted the infiltration of CTLs and inhibited local recurrence and pulmonary metastasis. In another study, an implantable 3D porous scaffold was designed to deplete myeloid-derived suppressor cells and present whole tumour lysates with nanogel-based adjuvants for promoting CTLs[122]. This immune niche strategy modulated the immunosuppressive environment and prevented postoperative tumour recurrence and metastasis. Autologous tumour cells are an excellent source for personalized postoperative nano vaccine development. Li and colleagues [123]developed a hydrogel matrix loaded with JQ1, a PD-L1 checkpoint blockade inhibitor, and indocyanine green (ICG). This immunotherapy strategy combined with PDT effectively inhibited tumour relapse and metastasis. Further, they design a PDT-motivated nano vaccine composed of autologous cancer cells and Fmoc-KCRGDK phenylboronic acid hydrogel. This nanomedicine can be prepared to boost personalized immunotherapy[124]. Besides, specific autologous cancer cells can be combined with non-specific immune activation such as bacterial-derived membranes[125]. Postoperative nano vaccines are rising for the treatment of cancer.

6.2. Intradermal/subcutaneous administration

Intradermal/subcutaneous administration is a common route of immunization for DNA vaccines. Both the epidermis and dermis layers of the skin contain resident APCs that are targeted for immunization. As the skin is painless, intradermal/subcutaneous administration has been widely applied for prophylactic vaccination. In recent years, this administration strategy was also explored for anticancer therapy. It has been reported that subcutaneous immunizations using VLPs conjugated with human EGFR 2 epitopes induced elevated HER2-specific antibody titers against the HER2-positive malignancies[126]. For advanced intradermal administration, versatile microneedle systems have also been explored for tumor and infectious disease vaccination. A transdermal vaccine may be applied for topical and intratumorally immunotherapy against melanoma. Autonomous active microneedle-mediated propulsive delivery of cowpea mosaic virus nanoparticles and magnesium (Mg) microparticles enhanced the antitumor immunity and greatly suppressed tumor progression[127]. Microneedles can also be dissolvable for vaccine delivery. Plasmodium falciparum surface protein P47 and CpG were loaded into microneedles and showed potent activation of TLR9 signaling for malaria vaccine[128]. Recently, a vaccine core and PLGA shell microneedle patch were developed for the long-lasting and programmed burst release of the vaccine[129]. This strategy may be used for both prophylactic and therapeutic purposes without repeated vaccination.

6.3. Intranasal administration

Intranasal administration is an important route for respiratory infectious diseases[130]. Nasal immunization via nano vaccines is promising for preventing diseases through mainly affecting infected respiratory tracts such as TB, and for the treatment of cancers. Chitosan nanoparticles are water-soluble platforms that can be explored for intranasal delivery of an antigen for TB vaccination. Thiolate OVA conjugated to N-trimethyl aminoethyl methacrylate chitosan showed elevated cellular uptake, deep cervical lymph nodes transport efficiency, and immune responses after intranasal administration[131]. Recently, inulin acetate, a natural polymer, was developed as an intranasal nano vaccine delivery system for its inherent adjuvant (TLR4 activation) ability[84]. This nanocarrier has the potential for mucosal vaccination via intranasal administration. For synthetic nanoparticles, a "self-healing microencapsulation "technology has been developed by Bailey and colleagues for the stable loading of antigens in PLGA particles. They used calcium phosphate adjuvant gel as a trapping agent for antigen encapsulation, leading to sustained release of OVA antigen and proliferation of CD8þ T cell via intranasal delivery [132]and could be used as a single-dose vaccination platform[133]. More recently, for the controllable particle size, PLGA nanoparticle was used for intranasal delivery of all-trans-retinoic acid and prolonged the drug release for targeted treatment of TB in the lung[134]. For intranasal cancer Nano vaccine delivery, a recent study developed a self-assembled nonvaccine loaded with multiple OVA peptide antigens. This Nano vaccine is safe through nasal administration and prolonged residence time and increased antigen uptake efficiency, which led to enhanced antigen-specific immune response[135].

6.4. Inhalation administration

Inhalation administration is also a promising vaccination route for pulmonary infectious diseases such as TB. Synthetic nanoparticles are useful tools for inhalation formulations. Polymeric nano capsules with oily core and polymer shell have been developed for pulmonary delivery of imiquimod, a TLR-7 agonist, and a fusion antigen protein[136]. Vaccination of this polymeric nano capsule induced strong immune responses. The development of biomimetic nanotechnology offered strategies for developing nano vaccines by imitating respiratory droplets. In a recent study, a bionic-virus nano vaccine that mimics the structure of SARS-CoV-2 was developed by using liposomes as a capsid structure and the receptor binding domains as "spike"[137]. This inhalable nano vaccine induced strong mucosal immunity, and this nano vaccine strategy can also be used for other respiratory infectious diseases. In addition, inhalation administration can also be applied for cancer nano vaccines, such as for lung metastasis. It has been reported that inhalation of the VLPs can facilitate the neutrophils infiltration in tumor, and increase cytokines and chemokines production and macrophage inflammatory protein 1a in tumor-bearing mice[138]. This nano vaccine treatment significantly reduced metastatic tumor burden for various tumor types.

6.5. Oral administration

Oral administration is a non-invasive route with excellent compliance[139]. Oral vaccines are optimal formulations for administration, immunization, safety, and storage. Despite the existence of lymphatic tissues under the mucosa, the intestine forms a barrier for antigens. To develop a vaccine for oral administration, antigens are taken up and transported by epithelial cells and then recognized by immune cells for responses. During the process, antigens may degrade in the gastrointestinal tract, resulting in a small number of antigens exposed to the mucosal tissue and limited intestinal uptake. Several nanocarriers have been developed as TB vaccines that can be orally administered. Liposome-encapsulated DNA vaccines can induce effective immune responses against TB[140]. VLP can also be used to carry HIV envelope cDNA with enhanced stability in the gastric environment. This strategy leads to high antigen concentration across the intestinal lumen after oral administration[141]. In another example, polyethyleneimine-coated SPIONs loaded with malarial DNA showed high DNA binding and transfection efficiency even in the acidic environment[142]. Oral administration strategy may also be used for cancer vaccines. It has been reported that nano emulsions have high encapsulation capacity for the co-delivery of melanoma antigen, heal shock protein, and staphylococcal toxin A for oral administration. This oral delivery strategy showed comparable immune responses to subcutaneous immunization[143].

7. Nano vaccines for diseases prevention and treatments

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

7.1. The prevention and treatment of worldwide infectious diseases

HIV/AIDS, malaria, and TB are impacting global health and causing millions of deaths worldwide, highlighting the need for prevention and treatment strategies[144], but vaccine strategies can hardly generate protective immunity in the population. HIV has a highly dynamic genome and unclear immune protection; malaria is complex for life cycles, and

there are multiple infection forms (sporozoites, merozoites, and gametocytes); patients with TB infection could be co-infected by HIV and bacteria that are multi-drug resistant. Despite dissimilar pathogens, the development of vaccines for these diseases shares some similarities, and antigen delivery remains a key for vaccination[145].

Self-assembled protein nanoparticles are useful platforms for antigen delivery. RTS, S, the first and currently the only malaria vaccine in the market[146], uses VLP to deliver antigen. VLP has been tested to display HIV envelope proteins such as the V1V2 loop for vaccination and generated specific IgG in mice[147]. Ferritin nanoparticles have also been employed to display HIV envelope trimers on particle surfaces to increase immunogenicity[148]. Other larger proteins, such as day dioleoyl acetyl-transferase (E2)[149]and lumazine synthase[150], are also useful for HIV vaccination. A two-component protein nanoparticle[151] was recently developed for enhancing the immunogenicity of HIV envelope (SOSIP) trimers by incorporating well-folded trimers into self-assembled nanoparticles. Further studies are exploring how spacing, antigens, and particle (size, shape, and charge) factors are involved in the protective immune responses. Polymeric nanomaterials have received great interest as vaccine platforms for their synthetic feasibility, low immunogenicity, and high biodegradability. Recently, HIV-1-derived gp140 immunogen with 3M-052 (a TLR-7/8 agonist) was incorporated in PLGA nanoparticles and induced high and persistent frequencies of HIV envelope-specific immune responses in rhesus macaques[152]. Besides, self-encapsulating PLGA microspheres loaded with calcium phosphate adjuvant gel and ovalbumin (OVA)antigen achieved the sustained release of antigen for more than seven weeks. Administration of OVA-loaded nanoparticles induced strong Th2-type responsiveness and can stably carry multiple antigens. It has been reported that cobalt porphyrin-phosphide can be loaded into an LNP Nano vaccine to express antigens coupled to the liposomal surface[153]. More recently, a heterologous trimer-liposome primer was performed by presenting well-ordered native flexible-linked trimers on liposomes with high density and elicited cross-neutralizing antibodies[154]. Inorganic nanoparticles are also interesting platforms for developing anti-infection nano-vaccines. GNPs-mediated antigen delivery can facilitate the presentation, thus inducing potent immunity. For example, gag p17 of HIV increased the proliferation of CD8þ T cells via conjugating onto high-mannosidic-modified GNPs[155]. Fe2O3 nanoparticle containing plasmid DNA TB vaccine induced significant humoral and cellular immune responses[156]. Enhanced vaccination was recently reported by amine functionalized silica nanoparticles-mediated delivery of antigen in combination with mince agonist[157]. Biomimetic nanoparticles are powerful platforms against infectious diseases. A virosomal vaccine developed by the HIV-1 gp41 subunit induced strong mucosal antibodies against HIV challenges[158]. In another study, Shao *et al.*,[159] developed membrane proximal external region (MPER) peptide fragments-bounded 2213 liposomes-containing cobalt porphyrin-phospholipid (Coop) and a synthetic monophosphorylate lipid A (MPLA) to generate immunogenicity in mice. Immunization with the lipid-presented MPER elicited antibody responses recognizing recombinant HIV gp41 and gp140 proteins. As HIV attacks T cells explicitly, Wei *et al*.,[160] developed T cell membrane-coated PLGA nanoparticles to neutralize the HIV infection. Membranes of T cells inherit retained antigens of CD4 receptor, C–C chemokine receptor 5 (CCR5) or C–X–C chemokine receptor type 4 (CXCR4) for HIV envelope glycoprotein 120 binding. This biomimetic Nano vaccine strategy effectively inhibited viral killing and neutralized HIV infection.

7.2. Suppressing tumor recurrence and metastasis

Cancer remains a leading cause of human death. Developing an anticancer vaccine is a vital step in reaching personalized medicine to treat this prolific disease. Despite tremendous efforts, full elucidation of the cancer pathogenesis is challenging[161,162]. Generally, cancerous cells result from the mutation of healthy cells involving multiple environmental and genetic factors. Therefore, unlike infectious diseases, cancer is highly heterogeneous in cases and the prevention of cancer is extremely difficult[163]. As small amounts of malignant cells can lead to relapse, the development of vaccines is of significance for the elimination of residual malignant cells and suppression of tumor recurrence and metastasis. Nanomedicine provided opportunities against tumours by using the above-mentioned nanomaterials to enhance either tumor vaccine delivery, in situ tumor antigen exposure, or presentation of the immune activation program. A variety of nanomaterials have been explored as efficient platforms for the delivery of tumor vaccines. VLPs have been used directly for tumor-associated antigens delivery, and vaccination with VLPs could be used in combination with radiation therapy[164], chemotherapy[165], or immune therapy[166]. For general stimulation of antitumor immune responses, Kuai and colleagues[167] designed nanodiscs mimicking high-density lipoprotein for advanced delivery of antigens and adjuvants to lymphoid organs. The nanodiscs treatment exhibited substantially higher production of neoantigen-specific CTLs control formulations and eliminated tumours in combined immune checkpoint blockade therapy[167]. Traditional LNPs are also highly effective platforms for tumor vaccine delivery. In a recent study, mRNA encoding tumor antigens was incorporated into cationic C1 LNP, which has adjuvant properties, for efficient delivery and presentation to dendritic cells[168]. The C1 mRNA nanovaccine showed significant prevention and therapeutic effects on tumors. Membrane-coating technology has been extensively explored for nanovaccine development. RBC-NPs with mannose modification and MPLA as the adjuvant were used to deliver B16F10 melanoma-associated antigen glycoprotein 100 to dendritic cells and significantly inhibited tumor growth[169]. Cancer cell membranes may be employed as antigens to

coat nanoparticles as cancer vaccines. B16F10 cancer cell membrane coating of CpG-loaded emulsion nanoparticles increased significant CTLs levels[170]. Similarly, the B16-OVA cancer cell membrane modified with mannose coating of polymeric nanoparticles loaded with the TLR7 agonist R837 showed improved APC delivery. In another study, membrane vesicles from cancer cells were used to coat spermine-modified acetylated dextran that was loaded with thermally oxidized porous silicon[171]. This biomimetic nanoparticle with the immunostimulatory core inhibited the proliferation of autologous cancer cells by inducing a potent immunostimulatory response. In situ exposure of tumor antigens is a promising vaccine strategy for preventing recurrence and metastasis. Most in situ tumor vaccinations utilized the ICD[172] for activating antitumor immune programs by killing tumor cells and exposing DAMPs to recruit and activate APCs for processing the antigens and activate tumor-specific T cells. Fan and colleagues[173] used mitoxantrone to induce ICD and conjugated the dying cells with multilamellar lipid-polymer nanoparticles loaded with CpG. Biomimetic nanoparticles are also useful tools for an in situ tumor nanovaccine. Natural killer (NK) cell membrane and myeloid-derived suppressor cell membrane [174]are useful to coat nanoparticles for enhanced PDT to promote ICD and activate immune responses that suppress significantly both in situ and metastatic tumours. In situ immunotherapy requires multiple steps; to address this issue, a recent study reported a nanomedicine strategy for programmable immune activation driven by the high level of reactive oxygen species induced by a supramolecular assembled nanoparticle in the tumor microenvironment[175]. Release of drug and CpG/PAMAM led to the exposure of tumor antigen and APC activation, and subsequent antitumor immune responses. As tumor cells are highly heterogeneous, a single tumor antigen vaccine may have insufficient immune responses to eliminate tumors[176]. Therefore, the whole tumor cell lysate may be loaded into nanoparticles such as chitosan [177]and nanovesicles [178]for enhanced antigens presentation. Besides, native tumor antigens may have low immunogenicity and induce limited immune responses to combat the tumor. In recent years, artificial antigen-presenting cells (aAPC) technology [179] has emerged to stimulate tumor-specific T cells by engineering nanomaterials equipped with peptide epitope and costimulatory molecules, replicating the immune-activation functions of APCs. Nanoscale aAPCs may have core material such as iron oxide[180]. It has been reported that iron-dextran aAPCs can induce great expansion of T lymphocytes expressing the cognate TCR. Membrane coating has also been used in the development of aAPCs[181]. The efficacy of aAPCs could be improved by modifying the nanoparticle morphology[182], signal coupling[183], and fluidity. Further exploration and establishment of protocols of aAPCs with personalized neoantigens may generate highly effective and personalized tumor vaccines[184,185]. In a recent study, the immune response of autologous tumor antigen was enhanced by a hybrid membrane delivery strategy. Bacterial cytoplasmic membrane and tumor cell membranes were used to form a nanoparticle for loading antigen and adjuvant to induce dendritic cell maturation, cytotoxic T cell activation, tumor growth suppression, and recurrence prevention. On-specific immune activation is another emerging strategy for developing cancer nanovaccines. OMV can induce systemic immune responses and recruit non-specifically activated immune cells to initiate APC processing and CTLs generation. Intravenous injection of OMVs derived from Escherichia coli into CT26 tumor-bearing mice eradicated tumor cells[186]; moreover, the growth of re-challenged tumours in mice was suppressed significantly. In a recent study, OMVs were encapsulated into calcium phosphate shells and lead to M2-to-M1 polarization of macrophages in the tumor microenvironment and eliminated in situ tumor, and prevented metastasis with reduced side effects[187].

8. Application of Nanotechnology in COVID-19 Therapeutics

As we already know, there are no therapeutic drugs available for the management of COVID-19 that are approved by the FDA. Hence, a rapid and point-of-care diagnosis of coronavirus is very significant and helpful in the timely management of coronavirus infection. In the diagnosis of coronavirus disease, nanotechnology-based methodologies play an important role so that the spreading of coronavirus can be stopped. Researchers working in the biomedical field have been investigating the relationships between high infection rates as well as the capacity of distinct nanostructured materials and viral vectors to deliver genes. In COVID-19 management, the nanotechnology-based approach has a wide range of uses and can act at various phases of the disease. It has the potential to block virus–cell contact, lipid bilayer blending, the endocytosis of cells, transcription, translation, and viral reproducibility in addition to stimulating subcellular processes that inflict irreparable harm on viruses. To create delivery methods that may be applied in several disciplines, nanotechnology scientists have investigated the biological mechanisms of gene

carriers[188,189].Since viral particles and nanostructures operate in a similar dimension, developing vaccines and performing immune engineering relies heavily on this strategy Nano pharmaceuticals may be the ideal substitute for cutting-edge vaccine development technologies since nanoparticles (NPs) are tools that may mimic the functional and structural characteristics of viral infectious particles[190-192].Nano sensors and medication delivery for various diseases have already demonstrated the value of nanotechnology and nanoparticles. Additionally, nanotechnology can give a more comprehensive perspective of new vaccine design approaches. For example, a unique nanoparticle-based vaccine metastatic platform, helpful nanomedicines for treating SARS-CoV-2 infections, and a nano-based formulation for SARS-CoV-2 therapies are all being produced. To quickly identify and create suitable nano vaccines and therapeutic options,

including novel nano-based technologies, scientists have been working hard up to this point. We will talk about COVID-19 management alternatives in nanomedicine in this review. To do this, we will first look at the pathology of COVID-19 to provide the groundwork for uncovering any openings or loopholes in the pathology of this virus where the application of nanotechnology can be useful. In the current tragic condition wherein coronaviruses and their sub-strains are major challenges to researchers and scientists, especially in vaccine development, and nanomedicine development provide good and comparable techniques[193,194].

9. Nanoparticle as a Tool for Immunotherapy of Cancer

Nanoparticle-based vaccine delivery systems have the capacity to deliver the antigen intracellularly, thus they can be used for eliciting an immune response against cancer through the generation of cell-mediated immune response. This involves antigen-specific lymphocyte priming in vivo or stimulation and expansion of antigen-specific T cells ex vivo, and their subsequent retransfer into patients. The former process is called active immunotherapy, whereas the latter is known as adoptive immune therapy. Success of these cancer therapies requires expansion of antigen-specific T cells[195,196].In such a scenario, a polymer particle improves the performance related to both active and adoptive immunotherapy. Entrapment of the cancer antigen in polymer particles not only improves its immunogenicity but also activates T cell response to the cancer antigens[197]. Cancer antigen entrapped in nanoparticles helps in introducing the antigen in an immunogenic form, either to break tolerance or to activate the T cell repertoire[198]. This helps in the generation of a CD8 T cell response against the tumor and helps in clearing them. Numerous cancer antigens have been entrapped in polymer particles and have shown improved performance for cancer treatment. These nanoparticles deliver the antigens to APCs with high efficiency; induce effector T cell responses for tumor clearance. Even cancer antigens, along with TLR ligands, co-entrapped in the same polymer particles, have been reported to elicit potent CD8 T cell-mediated anti-tumor immunity. Polyethylenimine (PEI) based nanoparticles have been successfully used for tumor targeting and tumor gene therapy[199,200]. Chondroitin and hyaluronic acid-based composite PEI particles have been used to deliver DNA to solid tumours, thus opening an exciting possibility of tumor targeting using a nanoparticle-based system.

10. Success Case of Vaccines Based on Nanoparticles

A notable success case of vaccines based on nanoparticles is the development and approval of mRNA COVID-19 vaccines, such as

10.1. Johnson and Johnson/Jansen and Oxford/Astra Zeneca Vaccines

The development of these vaccines was based on using a known DNA technology, where an adenovirus vector was engineered to carry the DNA with the information to produce the surface spike protein of the COVID-19 virus. Concretely, the Johnson and Johnson vaccine is based on an adenovirus type 26 modified to produce the SARS-CoV-2 Spike protein. This adenovirus vaccine was designed to be employed as a single intramuscular injection—the first of this type available that comes in a single dose and when it enters a cell, it produces the vaccine protein but cannot replicate inside the cell or cause illness. This vaccine was shown to provide an average of 66% protection against moderate or severe COVID-19, but more importantly, this vaccine showed 85% protection against severe disease, with no differences across countries or age groups. The Oxford/AstraZeneca vaccine is also based on DNA transported by an adenovirus vector—a modified version of a chimpanzee adenovirus, known as ChAdOx1—to transport the genetic information to produce the surface spike protein of the virus. One of the benefits of this type of vaccines is that they are more rugged than the mRNA vaccines. This is because DNA is not as fragile as RNA, and the adenovirus's tough protein coat helps protect the genetic material inside. Consequently, the Oxford/AstraZeneca vaccine does not have to be stored frozen. In fact, this vaccine was expected to last for at least six months when refrigerated at ca. 4 ◦ C. In 2020, it was shown that the efficacy of the vaccine was ca. 76% at preventing COVID-19 following the first dose and ca. 81% after the second dose[201].

10.2. Moderna and Pfizer Vaccines

The development of SARS-CoV-2 vaccines based on the use of messenger RNA technology encapsulated in lipid nanoparticles was a success case in the use of nanoparticles for vaccine manufacture[202]. Messenger RNA is the key intermediary in protein synthesis, but it is a very large and negatively charged molecule, so it cannot cross cell membranes on its own. Thus, messenger RNA needs a vehicle to cross these cellular barriers, and this is where LNPs played a major role. While it is true that over the past few years, we had the misfortune of experiencing a pandemic first-hand, it is also true that we were fortunate to witness in real time how we came out of this pandemic, thanks, among other things, to the extraordinarily rapid development of SARS-CoV-2 vaccines[203]. In the case of Moderna's vaccine,

development was truly rapid; from 11 January 2020, when Chinese scientists published the genetic sequence of the virus, it took just a couple of days for materials scientists to design a messenger RNA vaccine, encapsulate it in nanoparticles, and send it to the NIH in February to begin trials. The first patient was injected with the first prototype vaccine on 16 March 2020, the start of human clinical trials. Two months later, in May 2020, Phase I results were published, and then, 6 months later, Phase II and III results were presented, with 94–95% effectiveness (as a reference, the flu vaccine should be around 45% effective), in what was a giant victory for science and for nanoparticle technology[204,205].On the other hand, Pfizer signed a letter of intent with BioNTech to co-develop a potential COVID-19 vaccine just six days later than the World Health Organization declared the pandemic on 11 March 2020. By that time, BioNTech, a German immunotherapy company, had pioneered a novel genetic technology based on mRNA to prompt cells to fabricate antibodies to fight off that virus. Although mRNA technology was out there for decades, problems related to the structure and stability of mRNA prevented its translation to the clinic. In this sense, BioNTech had a great success stabilizing mRNA thanks to the use of lipid nanoparticles. Over the next nine months, Pfizer and BioNTech worked together to develop a vaccine across companies and across countries to set a record in any previous vaccine development program. All this was possible thanks to the research work of many people over a long period of time, both from the point of view of messenger RNA technology and the point of view of nanoparticle technology. Many people were involved in the whole process of generating the knowledge and basic science necessary for its application in a specific case such as this. Among them, it is worth mentioning the pair of Turkish doctors who founded BioNTech, Türeci and Sahin, the great messenger RNA specialist, Kariko, the founders of Moderna, Rossi and Langer, and, of course, Pieter Cullis, a pioneer in the use of lipid nanoparticles to transport messenger RNA into cells[206,207].

10.3. Future Prospects

Vaccines provide the most wonderful strategy to activate the immune response to combat infection. Most successful vaccines work by generating of neutralizing antibodies through an adaptive immune response. However, many intracellular pathogens and cancer treatments require activation of the cytotoxic T cell response to combat infection. Normal vaccine, which consists of live/attenuated or subunits of antigens fail to elicit a T cell response. Apart from this, many times it is necessary to activate the innate immune response along with the adaptive response to protect against infection. In these scenarios, nanoparticle-based vaccine delivery system provides a viable solution and offer tremendous opportunity to fine-tune tune immune response. Many recombinant protein candidate vaccines are poorly immunogenic and have stability problems. This is taken care of by a nanoparticle-based delivery system. Apart from this, a nanoparticle-based delivery system can deliver an antigen to a particular site to promote antigen presentation and processing according to the need. Modulation of immune response and generation of cytotoxic T cell response are the most attractive benefits of a nanoparticle-based vaccine delivery system. It is expected that novel candidate vaccines, particularly for malaria and tuberculosis, with the aid of a nanotechnology-based delivery system, will be able to elicit both humoral and cellular responses, which are necessary to provide immunity for combating intracellular infections. Nanotechnology-based formulations are being investigated as vaccine carriers, adjuvants, and drug delivery systems to target infection. Liposomes, polymeric particle-based systems, have shown novel applications in terms of the development of allergy vaccines, mucosal vaccines, and most importantly, for adoptive immunotherapy. The use of nanoparticle systems as adaptors provided an exciting area of research, particularly for cancer immunotherapy. Some polymeric nanoparticle-based formulations are in clinical development for infectious diseases. Although understanding of nanoparticles and their use on activating the immune system has been explored fairly, the molecular interaction of these particles with cells[208], toxicity, safety[209], and, more importantly, regulatory issues need detailed exploration. Pharmacokinetics and anatomical distribution of nanoparticle-based vaccine delivery system and its interaction with all types of APC need careful analysis[210-212]. Finally, there is a need to establish the production of such nanoparticle-based antigen delivery systems using good manufacturing practices (GMP). Very little is reported on clinical-grade manufacturing of nanoparticle-based vaccine delivery systems. This needs careful monitoring to produce reproducible batches of nanoparticle-based stable delivery systems. Once these issues are addressed, the full potential of this technology can be realized and put to use for human welfare. Pathogens continuously develop a number of strategies to evade the immune system to cause infection. In such a scenario delivering the vaccine with nanotechnology offers a counterattack strategy to combat infection. It is expected that with the advancement of nanotechnology, a new generation of vaccine formulations will be developed for controlling infection, cancer, metabolic, and complex diseases[213,214].

11. Conclusion

Nanotechnology has emerged as a transformative tool in vaccine development, addressing limitations of traditional approaches and enabling new frontiers in combating infectious diseases, cancer, and complex medical challenges. By utilizing nanoparticles, such as lipid-based carriers, polymeric particles, and biomimetic nanostructures, vaccines can

achieve enhanced efficacy, targeted delivery, and prolonged immune responses. Success stories like the mRNA vaccines for COVID-19 underscore the potential of this technology to deliver rapid and effective solutions.

However, challenges such as regulatory hurdles, toxicity concerns, and scalable manufacturing remain to be addressed. As advancements continue, nanoparticle-based systems are poised to revolutionize medicine, offering hope for novel therapies and preventive measures against a wide range of diseases. With further innovation and exploration, nanotechnology promises a future of personalized, efficient, and robust healthcare solutions.

Compliance with ethical standards

Disclosure of conflict of interest

The author reports no conflicts of interest in this work.

References

[1] Eppler HB, Jewell CM. Biomaterials as tools to decode immunity.Adv Mater 2020; 32:1903367.

[2] Shields Iv CW, Wang LL-W, Evans MA, Mitragotri S. Materials for immunotherapy. Adv Mater 2020; 32:1901633.

[3] Tang ZM, Xiao YF, Kong N, Liu C, Chen W, Huang XG, et al. Nanobio interfaces effect of two dimensional nanomaterials and them applications in cancer immunotherapy. Acta Pharm Sin B 2021;11:3447e64.

[4] Tang ZM, Zhang XC, Shu YQ, Guo M, Zhang H, Tao W. Insights from nanotechnology in COVID-19 treatment. Nano Today 2021;36:101019.

[5] Tang ZM, Kong N, Zhang XC, Liu Y, Hu P, Mou S, et al. A materials-science perspective on tackling COVID-19. Nat Rev Mater 2020; 5:847e60

[6] Khurana A, Allawadhi P, Khurana I, Allwadhi S, Weiskirchen R,Banothu AK, et al. Role of nanotechnology behind the success of mRNA vaccines for COVID-19. Nano Today 2021; 38:101142.

[7] Kingwell K. Uncoupling resistance to cancer immunotherapy. Nat Rev Drug Discov 2019; 18:171.Chan Feng et al.

[8] McLeod HL, Mariam A, Schveder KA, Rotroff DM. Assessment of adverse events and their ability to discriminate response to anti-PD-1/PD-L1 antibody immunotherapy. J Clin Oncol 2019;38:103e4.

[9] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39:1e10

[10] Pollard, A.J.; Bijker, E.M. A Guide to Vaccinology: From Basic Principles to New Developments. Nat. Rev. Immunol. 2021, 21,83–100. [CrossRef] [PubMed]

[11] Riedel, S. Edward Jenner and the History of Smallpox and Vaccination. In Baylor University Medical Center Proceedings; Taylor & Francis: Oxfordshire, UK, 2005; Volume 18, pp. 21–25. [CrossRef]

[12] Hajj Hussein, I.; Chams, N.; Chams, S.; El Sayegh, S.; Badran, R.; Raad, M.; Gerges-Geagea, A.; Leone, A.; Jurjus, A. Vaccines Through Centuries: Major Cornerstones of Global Health. Front. Public Health 2015, 3, 269. [CrossRef] [PubMed]

[13] Khan, Y.H.; Saifullah, A.; Mallhi, T.H. Bacterial Vaccines. In Encyclopaedia of Infection and Immunity; Rezaei, N., Ed.; Elsevier:Oxford, UK, 2022; pp. 530–544. [CrossRef]

[14] Nascimento, I.P.; Leite, L.C.C. Recombinant Vaccines and the Development of New Vaccine Strategies. Braz. J. Med. Biol. Res.2012, 45, 1102–1111. [CrossRef]

[15] Coler, R.N.; Reed, S.G. Second-Generation Vaccines against Leishmaniasis. Trends Parasitol. 2005, 21, 244–249. [CrossRef]

[16] Peek, L.J.; Middaugh, C.R.; Berkland, C. Nanotechnology in Vaccine Delivery. Adv. Drug Deliv. Rev. 2008, 60, 915–928. [CrossRef]

[17] Diaz-Arévalo, D.; Zeng, M. Nanoparticle-Based Vaccines: Opportunities and Limitations. In Nanopharmaceuticals; Elsevier:Amsterdam, The Netherlands, 2020; pp. 135–150. [CrossRef]

[18] Pati, R.; Shevtsov, M.; Sonawane, A. Nanoparticle Vaccines Against Infectious Diseases. Front. Immunol. 2018, 9, 2224. [CrossRef]

[19] Dobrovolskaia, M.A.; Aggarwal, P.; Hall, J.B.; McNeil, S.E. Preclinical Studies To Understand Nanoparticle Interaction with the Immune System and Its Potential Effects on Nanoparticle Biodistribution. Mol. Pharm. 2008, 5, 487–495. [CrossRef]

[20] Zolnik, B.S.; González-Fernández, A.; Sadrieh, N.; Dobrovolskaia, M.A. Nanoparticles and the Immune System. Endocrinology 2010, 151, 458–465. [CrossRef]

[21] Mottram, P.L.; Leong, D.; Crimeen-Irwin, B.; Gloster, S.; Xiang, S.D.; Meanger, J.; Ghildyal, R.; Vardaxis, N.; Plebanski, M. Type 1 and 2 Immunity Following Vaccination Is Influenced by Nanoparticle Size: Formulation of a Model Vaccine for Respiratory Syncytial Virus. Mol. Pharm. 2007, 4, 73–84. [CrossRef]

[22] Sato, Y.; Yokoyama, A.; Shibata, K.; Akimoto, Y.; Ogino, S.; Nodasaka, Y.; Kohgo, T.; Tamura, K.; Akasaka, T.; Uo, M. Influence of Length on Cytotoxicity of Multi-Walled Carbon Nanotubes against Human Acute Monocytic Leukemia Cell Line THP-1 In Vitro and Subcutaneous Tissue of Rats In Vivo. Mol. Biosyst. 2005, 1, 176–182. [CrossRef]

[23] Oh, N.; Park, J.-H. Endocytosis and Exocytosis of Nanoparticles in Mammalian Cells. Int. J. Nanomed. 2014, 9 (Suppl. S1), 51–63.[CrossRef]

[24] Kim, S.; Oh, W.-K.; Jeong, Y.S.; Hong, J.-Y.; Cho, B.-R.; Hahn, J.-S.; Jang, J. Cytotoxicity of, and Innate Immune Response to,Size-Controlled Polypyrrole Nanoparticles in Mammalian Cells. Biomaterials 2011, 32, 2342–2350. [CrossRef]

[25] Son, Y.J.; Kim, H.; Leong, K.W.; Yoo, H.S. Multifunctional Nanorods Serving as Nanobridges to Modulate T Cell-Mediated Immunity. ACS Nano 2013, 7, 9771–9779. [CrossRef]

[26] oged, C.; Brodin, B.; Frokjaer, S.; Sundblad, A. Particle Size and Surface Charge Affect Particle Uptake by Human Dendritic Cells in an In Vitro Model. Int. J. Pharm. 2005, 298, 315–322. [CrossRef]

[27] Peek LJ, Middaugh CR, Berkland C (2008) Nanotechnology in vaccine delivery. Adv Drug Deliv Rev 60:915–928

[28] Look M, Bandyopadhyay A, Blum JS, Fahmy TM (2010) Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Adv Drug Deiv Rev 62:378–393

[29] Lu JM, Wang X, Marin-Muller C, Wang H, Lin PH, Yao Q,Chen C (2009) Current advances in research and clinical applications of PLGA-based nanotechnology. Expert Rev Mol Diagn 9:325–341

[30] ouvreur P, Vauthier C (2006) Nanotechnology: intelligent design to treat complex disease. Pharm Res 23:1417–1450

[31] Liniger M, Zuniga A, Naim HY (2007) Use of viral vectors for the development of vaccines. Expert Rev Vaccines 6:255–266

[32] Robert-Guroff M (2007) Replicating and non-replicating viral vectors for vaccine development. Curr Opin Biotechnol 18:546–556

[33] Barouch DH, Nabel GJ (2005) Adenovirus vector-based vaccines for human immunodeficiency virus type 1. Hum Gene Ther 16:149–156

[34] Draper SJ, Heeney JL (2010) Viruses as vaccine vectors for infectious diseases and cancer. Nat Rev Microbiol 8:62–73

[35] Moore AC, Hill AV (2004) Progress in DNA-based heterologous prime-boost immunization strategies for malaria. Immunol Rev 199:126–143

[36] Liu J, O'Brien KL, Lynch DM, Simmons NL, La Porte A, Riggs AM, Abbink P, Coffey RT, Grandpre LE, Seaman MS, Landucci G, Forthal DN, Montefiori DC, Carville A, Mansfield KG,

[37] Havenga MJ, Pau MG, Goudsmit J, Barouch DH (2009)Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys. Nature 457:87–91

[38] Roy P, Noad R (2008) Virus-like particles as a vaccine delivery system: myths and facts. Hum Vaccine 4:5–12

[39] Gluck R, Burri KG, Metcalfe I (2005) Adjuvant and antigen delivery properties of virosomes. Curr Drug Deliv 2:395–400

[40] Huckriede A, Bungener L, Stegmann T, Daemen T, Medema J, Palache AM, Wilschut J (2005) The virosome concept for influenza vaccines. Vaccine 23(Suppl 1):S26–S38

[41] Grgacic EV, Anderson DA (2006) Virus-like particles: passport to immune recognition. Methods 40:60–65

[42] Buckland BC (2005) The process development challenge for a new vaccine. Nat Med 11:S16–S19

[43] Krammer F, Grabherr R (2010) Alternative influenza vaccines made by insect cells. Trends Mol Med 16:313–320

[44] Wilschut J (2009) Influenza vaccines: the virosome concept.Immunol Lett 122:118–121

[45] Kang SM, Song JM, Quan FS, Compans RW (2009) Influenza vaccines based on virus-like particles. Virus Res 143:140–146

[46] Mayr UB, Walcher P, Azimpour C, Riedmann E, Haller C,Lubitz W (2005) Bacterial ghosts as antigen delivery vehicles.Adv Drug Deliv Rev 57:1381–1391

[47] Seow Y, Wood MJ (2009) Biological gene delivery vehicles:beyond viral vectors. Mol Ther 17:767–777

[48] Cox JC, Sjolander A, Barr IG (1998) ISCOMs and other saponin based adjuvants. Adv Drug Deliv Rev 32:247–271

[49] Skene CD, Sutton P (2006) Saponin-adjuvanted particulate vaccines for clinical use. Methods 40:53–59

[50] Sun HX, Xie Y, Ye YP (2009) ISCOMs and ISCOMATRIX.Vaccine 27:4388–4401

[51] Morein B, Sundquist B, Hoglund S, Dalsgaard K, Osterhaus A (1984) ISCOM, a novel structure for antigenic presentation of membrane proteins from enveloped viruses. Nature 308:457–460

[52] Hu KF, Lovgren-Bengtsson K, Morein B (2001) Immunostimulating complexes (ISCOMs) for nasal vaccination. Adv Drug Deliv Rev 51:149–159

[53] Pearse MJ, Drane D (2005) ISCOMATRIX adjuvant for antigen delivery. Adv Drug Deliv Rev 57:465–474

[54] O'Hagan DT, Singh M, Ulmer JB (2006) Microparticle-based technologies for vaccines. Methods 40:10–19

[55] Langer R, Cleland JL, Hanes J (1997) New advances in microsphere-based single-dose vaccines. Adv Drug Deliv Rev 28:97–119

[56] Gupta RK, Chang AC, Siber GR (1998) Biodegradable polymer microspheres as vaccine adjuvants and delivery systems. Dev Biol Stand 92:63–78

[57] Jiang W, Gupta RK, Deshpande MC, Schwendeman SP (2005) Biodegradable poly(lactic-co-glycolic acid) microparticles for injectable delivery of vaccine antigens. Adv Drug Deliv Rev 57:391–410

[58] Langer R, Cleland JL, Hanes J (1997) New advances in microsphere-based single-dose vaccines. Adv Drug Deliv Rev 28:97–119

[59] Johansen P, Men Y, Merkle HP, Gander B (2000) Revisiting PLA/PLGA microspheres: an analysis of their potential in parenteral vaccination. Eur J Pharm Biopharm 50:129–146

[60] Waeckerle-Men Y, Groettrup M (2005) PLGA microspheres for improved antigen delivery to dendritic cells as cellular vaccines.Adv Drug Deliv Rev 57:475–482

[61] Illum L, Jabbal-Gill I, Hinchcliffe M, Fisher AN, Davis SS (2001) Chitosan as a novel nasal delivery system for vaccines.Adv Drug Deliv Rev 51:81–96

[62] Kang ML, Cho CS, Yoo HS (2009) Application of chitosan microspheres for nasal delivery of vaccines. Biotechnol Adv 27:857–865

[63] Alpar HO, Somavarapu S, Atuah KN, Bramwell VW (2005) Biodegradable mucoadhesive particulates for nasal and pulmonary antigen and DNA delivery. Adv Drug Deliv Rev 57:411–430

[64] Akagi T, Wang X, Uto T, Baba M, Akashi M (2007) Protein direct delivery to dendritic cells using nanoparticles based on amphiphilic poly(amino acid) derivatives. Biomaterials 28:3427–3436

[65] Yoshikawa T, Okada N, Oda A, Matsuo K, Matsuo K, Kayamuro H, Ishii Y, Yoshinaga T, Akagi T, Akashi M, NakagawaS (2008) Nanoparticles built by self-assembly of amphiphilic gamma-PGA can deliver antigens to antigen-presenting cells with high efficiency: a new tumor-vaccine carrier for eliciting effector T cells. Vaccine 26:1303–1313

[66] Wang X, Uto T, Akagi T, Akashi M, Baba M (2008) Poly(gamma-glutamic acid) nanoparticles as an efficient antigen delivery and adjuvant system: potential for an AIDS vaccine.J Med Virol 80:11–19

[67] Uto T, Wang X, Sato K, Haraguchi M, Akagi T, Akashi M, Baba M (2007) Targeting of antigen to dendritic cells with poly(gamma-glutamic acid) nanoparticles induces antigen-specific humoral and cellular immunity. J Immunol 178:2979–2986

[68] Almeida AJ, Souto E (2007) Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv Drug Deliv Rev 59:478–490

[69] Joshi MD, Muller RH (2009) Lipid nanoparticles for parenteral delivery of actives. Eur J Pharm Biopharm 71:161–172

[70] Muller RH, Mader K, Gohla S (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery: a review of the state of the art. Eur J Pharm Biopharm 50:161–177

[71] Souto EB, Muller RH (2005) SLN and NLC for topical delivery of ketoconazole. J Microencapsul 22:501–510

[72] Erni C, Suard C, Freitas S, Dreher D, Merkle HP, Walter E (2002) Evaluation of cationic solid lipid microparticles as synthetic carriers for the targeted delivery of macromolecules to phagocytic antigen-presenting cells. Biomaterials 23:4667–4676

[73] Saraf S, Mishra D, Asthana A, Jain R, Singh S, Jain NK (2006) Lipid microparticles for mucosal immunization against hepatitis B. Vaccine 24:45–56

[74] O'Neill CL, Shrimali PC, Clapacs ZP, Files MA, Rudra JS. Peptide-based supramolecular vaccine systems. Acta Biomater 2021;133:153e67.

[75] rietze KM, Peabody DS, Chackerian B. Engineering virus-like particles as vaccine platforms. Curr Opin Virol 2016;18:44e9.

[76] Mohsen MO, Zha L, Cabral-Miranda G, Bachmann MF. Major findings and recent advances in virus-like particle (VLP)-based vaccines. Semin Immunol 2017;34:123e32.

[77] Neek M, Kim TI, Wang SW. Protein-based nanoparticles in cancer vaccine development. Nanomedicine 2019;15:164e74.

[78] Tesarova B, Musilek K, Rex S, Heger Z. Taking advantage of cellular uptake of ferritin nanocages for targeted drug delivery. J Control Release 2020;325:176e90.

[79] Kang H, Rho S, Stiles WR, Hu S, Baek Y, Hwang DW, et al. Size-dependent EPR effect of polymeric nanoparticles on tumor targeting.Adv Healthc Mater 2020;9:e1901223.

[80] Simon-Vazquez R, Peleteiro M, Gonzalez-Fernandez A. Polymeric nanostructure vaccines: applications and challenges. Expert Opin Drug Del 2020;17:1007e23.

[81] Das A, Ali N. Nanovaccine: an emerging strategy. Expert Rev Vaccines 2021;20:1273e90.

[82] Wu DJ, Zhu LX, Li Y, Zhang XL, Xu SM, Yang GS, et al. Chitosan-based colloidal polyelectrolyte complexes for drug delivery: a review. Carbohydr Polym 2020;238:116126.

[83] Butkovich N, Li E, Ramirez A, Burkhardt AM, Wang SW. Advancements in protein nanoparticle vaccine platforms to combat infectious disease. Wiley interdiscip 2021;13:e1681.

[84] Karlsson J, Vaughan HJ, Green JJ. Biodegradable polymeric nanoparticles for therapeutic cancer treatments. Annu Rev Cell Biol 2018;9:105e27.

[85] Rietscher R, Schröder M, Janke J, Czaplewska J, Gottschaldt M,Scherließ R, et al. Antigen delivery via hydrophilic PEG-b-PAGE-b-PLGA nanoparticles boosts vaccination induced T cell immunity.Eur J Pharm Biopharm 2016;102:20e31.

[86] Samaridou E, Heyes J, Lutwyche P. Lipid nanoparticles for nucleic acid delivery: current perspectives. Adv Drug Deliv Rev 2020;154:37e63.

[87] achmann MF, Jennings GT. Vaccine delivery: a matter of size,geometry, kinetics and molecular patterns. Nat Rev Immunol 2010;10:787e96.

[88] Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC,Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383: 2427e38.

[89] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A,Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383:2603e15.

[90] Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater 2021;6:1078e94.

[91] ajj KA, Whitehead KA. Tools for translation: non-viral materials for therapeutic mRNA delivery. Nat Rev Mater 2017;2:17056.

[92] Dykman LA. Gold nanoparticles for preparation of antibodies and vaccines against infectious diseases. Expert Rev Vaccines 2020;19:465e77.

[93] Zhao Y, Zhao XT, Cheng Y, Guo XS, Yuan WE. Iron oxide nanoparticles-based vaccine delivery for cancer treatment. Mol Pharmaceut 2018;15:1791e9.

[94] Hong XY, Zhong XF, Du GS, Hou YY, Zhang YT, Zhang ZR, et al.The pore size of mesoporous silica nanoparticles regulates their antigen delivery efficiency. Sci Adv 2020;6:eaaz4462

[95] Deng GJ, Sun ZH, Li SP, Peng XH, Li WJ, Zhou LH, et al. Cell-membrane immunotherapy based on natural killer cell membrane coated nanoparticles for the effective inhibition of primary and abscopal tumor growth. ACS Nano 2018;12:12096e108.

[96] Sharma M, Salisbury RL, Maurer EI, Hussain SM, Sulentic CE. Gold nanoparticles induce transcriptional activity of NF-kappaB in a B-lymphocyte cell line. Nanoscale 2013;5:3747e56.

[97] Gonzalez-Ballesteros N, Diego-Gonzalez L, Lastra-Valdor M,Rodriguez-Arguelles MC, Grimaldi M, Cavazza A, et al. Immunostimulant and biocompatible gold and silver nanoparticles synthesized using the Ulva intestinalis L. aqueous extract. J Mater Chem B 2019;7:4677e91.

[98] Ferrando RM, Lay L, Polito L. Gold nanoparticle-based platforms for vaccine development. Drug Discov Today Technol 2020;38:57e67.

[99] Mody KT, Popat A, Mahony D, Cavallaro AS, Yu C, Mitter N.Mesoporous silica nanoparticles as antigen carriers and adjuvants for vaccine delivery. Nanoscale 2013;5:5167e79.

[100] Lee JY, Kim MK, Nguyen TL, Kim J. Hollow mesoporous silica nanoparticles with extra-large mesopores for enhanced cancer vaccine. ACS Appl Mater Interfaces 2020;12:34658e66.

[101] Maria de Souza Morais S, Ferreira Rodigues N, Ingrid Oliveira da Silva N, Aparecido Salvador E, Rodrigues Franco I, Augusto Pires de Souza G, et al. Serum albumin nanoparticles vaccine provides protection against a lethal Pseudomonas aeruginosa challenge. Vaccine 2018;36:6408e15.

[102] An M, Li M, Xi J, Liu H. Silica nanoparticle as a lymph node targeting platform for vaccine delivery. ACS Appl Mater Interfaces 2017;9:23466e75.

[103] Yang JL, Zhang XC, Liu C, Wang Z, Deng LF, Feng C, et al. Biologically modified nanoparticles as theranostic bionanomaterials.Prog Mater Sci 2021;118:100768.

[104] ehaini D, Fang RH, Zhang L. Biomimetic strategies for targeted nanoparticle delivery. Bioeng Transl Med 2016;1:30e46.

[105] Xu SX, Wang LS, Liu Z. Molecularly imprinted polymer nanoparticles: an emerging versatile platform for cancer therapy. Angew Chem Int Ed 2021;60:3858e69.

[106] Wang J, Zhu MT, Nie GJ. Biomembrane-based nanostructures for cancer targeting and therapy: from synthetic liposomes to natural biomembranes and membrane-vesicles. Adv Drug Deliv Rev 2021;178:113974.

[107] Fang RH, Kroll AV, Gao W, Zhang L. Cell membrane coating nanotechnology. Adv Mater 2018;30:e1706759.

[108] Zhou JR, Kroll AV, Holay M, Fang RH, Zhang LF. Biomimetic nanotechnology toward personalized vaccines. Adv Mater 2020;32:e1901255.

[109] Rao L, Bu LL, Xu JH, Cai B, Yu GT, Yu X, et al. Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance. Small 2015;11:6225e36.

[110] Ho W, Gao MZ, Li FQ, Li ZY, Zhang XQ, Xu XY. Next-generation vaccines: nanoparticle-mediated DNA and mRNA delivery. Adv Healthc Mater 2021;10:e2001812.

[111] Rao L, Yu GT, Meng QF, Bu LL, Tian R, Lin LS, et al. Cancer cell membrane-coated nanoparticles for personalized therapy in patient-derived xenograft models. Adv Funct Mater 2019;29:1905671.

[112] Oroojalian F, Beygi M, Baradaran B, Mokhtarzadeh A, Shahbazi MA. Immune cell membrane-coated biomimetic nanoparticles for targeted cancer therapy. Small 2021;17:2006484.

[113] Gong H, Zhang Q, Komarla A, Wang S, Duan Y, Zhou Z, et al.Nanomaterial biointerfacing via mitochondrial membrane coating for targeted detoxification and molecular detection. Nano Lett 2021;21:2603e9.

[114] Ouyang X, Wang X, Kraatz H-B, Ahmadi S, Gao J, Lv Y, et al. A Trojan horse biomimetic delivery strategy using mesenchymal stem cells for PDT/PTT therapy against lung melanoma metastasis. Biomater Sci 2020;8:1160e70.

[115] Shi SR, Wang Y, Wang BB, Chen Q, Wan GY, Yang XY, et al.Homologous-targeting biomimetic nanoparticles for photothermal therapy and Nrf2-siRNA amplified photodynamic therapy against oral tongue squamous cell carcinoma. Chem Eng J 2020;388:124268.

[116] Asadi K, Gholami A. Virosome-based nanovaccines; a promising bioinspiration and biomimetic approach for preventing viral diseases:a review. Int J Biol Macromol 2021;182:648e58.

[117] Felnerova D, Viret J-F, Glück R, Moser C. Liposomes and virosomes as delivery systems for antigens, nucleic acids and drugs. Curr Opin Biotechnol 2004;15:518e29.

[118] Gnopo YMD, Watkins HC, Stevenson TC, DeLisa MP, Putnam D.Designer outer membrane vesicles as immunomodulatory systems dreprogramming bacteria for vaccine delivery. Adv Drug Deliv Rev 2017;114:132e42.

[119] Irene C, Fantappie L, Caproni E, Zerbini F, Anesi A, Tomasi M, et al.Bacterial outer membrane vesicles engineered with lipidated antigens as a platform for Staphylococcus aureus vaccine. Proc Natl Acad Sci U S A 2019;116:21780e8.

[120] irtane AR, Verma M, Karandikar P, Furin J, Langer R, Traverso G.Nanotechnology approaches for global infectious diseases. Nat Nanotechnol 2021;16:369e84.

[121] Zhang YW, Jiang C. Postoperative cancer treatments: in-situ delivery system designed on demand. J Control Release 2021;330:554e64.

[122] Liu X, Feng ZJ, Wang CR, Su Q, Song HJ, Zhang CN, et al. Colocalized delivery of nanomedicine and nanovaccine augments the postoperative cancer immunotherapy by amplifying T-cell responses.Biomaterials 2020;230:119649.

[123] Phuengkham H, Song C, Um SH, Lim YT. Implantable synthetic immune niche for spatiotemporal modulation of tumor-derived immunosuppression and systemic antitumor immunity: post-operative immunotherapy. Adv Mater 2018;30:e1706719.

[124] Li XM, Hu ZP, Ma JL, Wang XY, Zhang YP, Wang W, et al. The systematic evaluation of size-dependent toxicity and multi-time biodistribution of gold nanoparticles. Colloids Surf, B 2018;167: 260e6.

[125] Fang L, Zhao ZT, Wang J, Zhang PC, Ding YP, Jiang YY, et al.Engineering autologous tumor cell vaccine to locally mobilize antitumor immunity in tumor surgical bed. Sci Adv 2020;6: eaba4024.

[126] Chen L, Qin H, Zhao RF, Zhao X, Lin LR, Chen Y, et al. Bacterial cytoplasmic membranes synergistically enhance the antitumor activity of autologous cancer vaccines. Sci Transl Med 2021;13:eabc2816.

[127] hukla S, Myers JT, Woods SE, Gong X, Czapar AE,Commandeur U, et al. Plant viral nanoparticles-based HER2 vaccine:immune response influenced by differential transport, localization and cellular interactions of particulate carriers. Biomaterials 2017;121:15e27.

[128] oone CE, Wang C, Lopez-Ramirez MA, Beiss V, Shukla S,Chariou PL, et al. Active microneedle administration of plant virus nanoparticles for cancer in situ vaccination improves immunotherapeutic efficacy. ACS Appl Nano Mater 2020;3:8037e51.

[129] Yenkoidiok-Douti L, Barillas-Mury C, Jewell CM. Design of Dissolvable microneedles for delivery of a Pfs47-based malaria transmission-blocking vaccine. ACS Biomater Sci Eng 2021;7:1854e62.

[130] Tran KTM, Gavitt TD, Farrell NJ, Curry EJ, Mara AB, Patel A, et al.Transdermal microneedles for the programmable burst release of multiple vaccine payloads. Nat Biomed Eng 2021;5:998e1007.

[131] Bernocchi B, Carpentier R, Betbeder D. Nasal nanovaccines. Int J Pharm 2017;530:128e38.

[132] iu QF, Zhang C, Zheng XY, Shao XY, Zhang X, Zhang QZ, et al.Preparation and evaluation of antigen/N-trimethylaminoethylmethacrylate chitosan conjugates for nasal immunization.Vaccine 2014;32:2582e90.

[133] Bakkari MA, Valiveti CK, Kaushik RS, Tummala H. Toll-like receptor-4 (TLR4) agonist-based intranasal nanovaccine delivery system for inducing systemic and mucosal immunity. Mol Pharm 2021;18:2233e41.

[134] ailey BA, Desai KH, Ochyl LJ, Ciotti SM, Moon JJ,Schwendeman SP. Self-encapsulating poly(lactic-co-glycolic acid) A) microspheres for intranasal vaccine delivery. Mol Pharm 2017;14:3228e37.

[135] ailey BA, Ochyl LJ, Schwendeman SP, Moon JJ. Toward a single-dose vaccination strategy with self-encapsulating plga microspheres.Adv Healthc Mater 2017;6:1601418.Chan Feng et al.

[136] 'Connor G, Krishnan N, Fagan-Murphy A, Cassidy J, O'Leary S,Robertson BD, et al. Inhalable poly(lactic-co-glycolic acid) (PLGA)microparticles encapsulating all-trans-Retinoic acid (ATRA) as a host-directed, adjunctive treatment for Mycobacterium tuberculosis infection. Eur J Pharm Biopharm 2019;134:153e65.

[137] Yang Y, Ge S, Song Z, Zhao A, Zhao LQ, Hu ZM, et al. A novel self-assembled epitope peptide nanoemulsion vaccine targeting nasal mucosal epithelial cell for reinvigorating CD8þ T cell immune activity and inhibiting tumor progression. Int J Biol Macromol 2021;183:1891e902.

[138] Diego-Gonzalez L, Crecente-Campo J, Paul MJ, Singh M, Reljic R,Alonso MJ, et al. Design of polymeric nanocapsules for intranasal vaccination against mycobacterium tuberculosis: influence of the polymeric shell and antigen positioning. Pharmaceutics 2020;12:489.

[139] ng B, Peng WC, Guo MM, Huang MQ, Gu YX, Wang T, et al.Inhalable nanovaccine with biomimetic coronavirus structure to trigger mucosal immunity of respiratory tract against COVID-19.Chem Eng J 2021;418:129392.

[140] Lizotte PH, Wen AM, Sheen MR, Fields J, Rojanasopondist P,Steinmetz NF, et al. In situ vaccination with cowpea mosaic virus nanoparticles suppresses metastatic cancer. Nat Nanotechnol 2016;11:295e303.

[141] iao YF, Tang ZM, Wang JQ, Liu C, Kong N, Farokhzad OC, et al.Oral insulin delivery platforms: strategies to address the biological barriers. Angew Chem Int Ed Engl 2020;59:19787e95.

[142] ang D, Xu J, Feng YH, Liu Y, McHenga SS, Shan FP, et al.Liposomal oral DNA vaccine (mycobacterium DNA) elicits immune response. Vaccine 2010;28:3134e42.

[143] Takamura S, Niikura M, Li TC, Takeda N, Kusagawa S, Takebe Y, et al. DNA vaccine-encapsulated virus-like particles derived from an orally transmissible virus stimulate mucosal and systemic immune responses by oral administration. Gene Ther 2004;11:628e35.

[144] Al-Deen FN, Ho J, Selomulya C, Ma C, Coppel R. Super-paramagnetic nanoparticles for effective delivery of malaria DNA vaccine. Langmuir 2011;27:3703e12.

[145] Ge W, Li Y, Li ZS, Zhang SH, Sun YJ, Hu PZ, et al. The antitumor immune responses induced by nanoemulsion-encapsulated MAGE1-HSP70/SEA complex protein vaccine following peroral administration route. Cancer Immunol Immunother 2009;58:201e8.

[146] irtane AR, Verma M, Karandikar P, Furin J, Langer R, Traverso G.Nanotechnology approaches for global infectious diseases. Nat Nanotechnol 2021;16:369e84.

[147] ries CN, Curvino EJ, Chen J-L, Permar SR, Fouda GG, Collier JH.Advances in nanomaterial vaccine strategies to address infectious diseases impacting global health. Nat Nanotechnol 2021;16:1e14.

[148] Adepoju P. RTS, S malaria vaccine pilots in three African countries.Lancet 2019;393:1685.

[149] Karch CP, Bai H, Torres OB, Tucker CA, Michael NL, Matyas GR,et al. Design and characterization of a self-assembling protein nanoparticle displaying HIV-1 Env V1V2 loop in a native-liketrimeric conformation as vaccine antigen. Nanomedicine: NBM 2019;16:206e16.

[150] Sliepen K, Ozorowski G, Burger JA, van Montfort T, Stunnenberg M, LaBranche C, et al. Presenting native-like HIV-1 envelope trimers on ferritin nanoparticles improves their immunogenicity. Retrovirology 2015;12:1e5.

[151] Molino NM, Neek M, Tucker JA, Nelson EL, Wang SW. Viral-mimicking protein nanoparticle vaccine for eliciting anti-tumor responses. Biomaterials 2016;86:83e91.151. Jardine J, Julien J-P, Menis S, Ota T, Kalyuzhniy O, McGuire A,et al. Rational HIV immunogen design to target specific germline B cell receptors. Science 2013;340:711e6.

[152] Brouwer PJ, Antanasijevic A, Berndsen Z, Yasmeen A, Fiala B,Bijl TP, et al. Enhancing and shaping the immunogenicity of native-like HIV-1 envelope trimers with a two-component protein nanoparticle. Nat Commun 2019;10:1e17.

[153] asturi SP, Rasheed MAU, Havenar-Daughton C, Pham M, Legere T,Sher ZJ, et al. 3M-052, a synthetic TLR-7/8 agonist, induces durable HIV-1 envelope-specific plasma cells and humoral immunity innonhuman primates. Sci Immunol 2020;5:eabb1025.

[154] Huang WC, Deng B, Lin C, Carter KA, Geng J, Razi A, et al. A malaria vaccine adjuvant based on recombinant antigen binding to liposomes. Nat Nanotechnol 2018;13:1174e81.

[155] Dubrovskaya V, Tran K, Ozorowski G, Guenaga J, Wilson R, Bale S,et al. Vaccination with glycan-modified HIV NFL envelope trimer-liposomes elicits broadly neutralizing antibodies to multiple sites of vulnerability. Immunity 2019;51:915e29.

[156] Climent N, García I, Marradi M, Chiodo F, Miralles L, Maleno MJ, et al. Loading dendritic cells with gold nanoparticles (GNPs) bearing HIV-peptides and mannosides enhance HIV-specific T cell responses.Nanomedicine: NBM 2018;14:339e51.

[157] Yu FL, Wang J, Dou J, Yang HT, He XF, Xu WG, et al. Nanoparticle based adjuvant for enhanced protective efficacy of DNA vaccine Ag85A-ESAT-6-IL-21 against Mycobacterium tuberculosis infection.Nanomedicine: NBM 2012;8:1337e44.

[158] Abdelwahab WM, Riffey A, Buhl C, Johnson C, Ryter K, Evans JT,et al. Co-adsorption of synthetic Mincle agonists and antigen to silica nanoparticles for enhanced vaccine activity: a formulation approach to co-delivery. Int J Pharmaceut 2021;593:120119.

[159] Bomsel M, Tudor D, Drillet AS, Alfsen A, Ganor Y, Roger MG, et al.Immunization with HIV-1 gp41 subunit virosomes induces mucosal antibodies protecting nonhuman primates against vaginal SHIV challenges. Immunity 2011;34:269e80.

[160] Shao S, Huang WC, Lin C, Hicar MD, LaBranche CC,Montefiori DC, et al. An Engineered biomimetic mper peptide vaccine induces weakly hiv neutralizing antibodies in mice. Ann Biomed Eng 2020;48:1991e2001.

[161] Wei XL, Zhang G, Ran D, Krishnan N, Fang RH, Gao WW, et al. T-Cell-Mimicking nanoparticles can neutralize hiv infectivity. Adv mater 2018;30:e1802233.

[162] Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol 2021;18:215e29.

[163] Turajlic S, Sottoriva A, Graham T, Swanton C. Resolving genetic heterogeneity in cancer. Nat Rev Genet 2019;20:404e16.

[164] Patel R, Czapar AE, Fiering S, Oleinick NL, Steinmetz NF. Radiation therapy combined with cowpea mosaic virus nanoparticle in situ vaccination initiates immune-mediated tumor regression. ACS Omega 2018;3:3702e7.

[165] Lee KL, Murray AA, Le DHT, Sheen MR, Shukla S, Commandeur U, et al. Combination of plant virus nanoparticle-based in situ vaccination with chemotherapy potentiates antitumor response. Nano Lett 2017;17:4019e28.

[166] Lebel ME, Chartrand K, Tarrab E, Savard P, Leclerc D, Lamarre A. Potentiating cancer immunotherapy using papaya mosaic virus-derived nanoparticles. Nano Lett 2016;16:1826e32.

[167] Kuai R, Ochyl LJ, Bahjat KS, Schwendeman A, Moon JJ. Designer vaccine nanodiscs for personalized cancer immunotherapy. Nat Mater 2017;16:489e96.Chan Feng et al.

[168] Luo LH, Li X, Zhang JL, Zhu CQ, Jiang MS, Luo ZY, et al.Enhanced immune memory through a constant photothermal-metabolism regulation for cancer prevention and treatment. Bio-materials 2021;270:120678.

[169] Guo YY, Wang D, Song QL, Wu TT, Zhuang XT, Bao YL, et al.Erythrocyte membrane-enveloped polymeric nanoparticles as nano-vaccine for induction of antitumor immunity against melanoma. ACS Nano 2015;9:6918e33.

[170] Kroll AV, Fang RH, Jiang Y, Zhou J, Wei X, Yu CL, et al. Nano-particulate delivery of cancer cell membrane elicits multiantigenic antitumor immunity. Adv Mater 2017;29:1703969.

[171] Fontana F, Shahbazi MA, Liu D, Zhang H, Makila E, Salonen J, et al.Multistaged nanovaccines based on porous silicon@acetalated dextran@cancer cell membrane for cancer immunotherapy. Adv Mater 2017;29:201603239.

[172] Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol 2017;17:97e111.

[173] Fan Y, Kuai R, Xu Y, Ochyl LJ, Irvine DJ, Moon JJ. Immunogenic cell death amplified by co-localized adjuvant delivery for cancer immunotherapy. Nano Lett 2017;17:7387e93.

[174] Yu GT, Rao L, Wu H, Yang LL, Bu LL, Deng WW, et al. Myeloid-derived suppressor cell membrane-coated magnetic nanoparticles for cancer theranostics by inducing macrophage polarization and synergizing immunogenic cell death. Adv Funct Mater 2018;28:1801389.

[175] Zhang Y, Ma S, Liu XM, Xu YD, Zhao JY, Si XH, et al. Supramolecular assembled programmable nanomedicine as in situ cancer vaccine for cancer immunotherapy. Adv Mater 2021;33:e2007293.

[176] Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 2018;15:81e94.

[177] Shi GN, Zhang CN, Xu R, Niu JF, Song HJ, Zhang XY, et al. Enhanced antitumor immunity by targeting dendritic cells with tumor cell lysate-loaded chitosan nanoparticles vaccine. Biomaterials 2017;113:191e202.

[178] Ochyl LJ, Bazzill JD, Park C, Xu Y, Kuai R, Moon JJ. PEGylated tumor cell membrane vesicles as a new vaccine platform for cancer immunotherapy. Biomaterials 2018;182:157e66.

[179] Eggermont LJ, Paulis LE, Tel J, Figdor CG. Towards efficient cancer immunotherapy: advances in developing artificial antigen-presenting cells. Trends Biotechnol 2014;32:456e65.

[180] Perica K, De Leon Medero A, Durai M, Chiu YL, Bieler JG,Sibener L, et al. Nanoscale artificial antigen presenting cells for T cell immunotherapy. Nanomedicine 2014;10:119e29.

[181] Zhang QM, Wei W, Wang PL, Zuo LP, Li F, Xu J, et al. Biomimetic magnetosomes as versatile artificial antigen-presenting cells to potentiate T-cell-based anticancer therapy. ACS Nano 2017;11:10724e32.

[182] Meyer RA, Sunshine JC, Perica K, Kosmides AK, Aje K, Schneck JP,et al. Biodegradable nanoellipsoidal artificial antigen presenting cells for antigen specific T-cell activation. Small 2015;11:1519e25.

[183] Kosmides AK, Necochea K, Hickey JW, Schneck JP. Separating T cell targeting components onto magnetically clustered nanoparticles boosts activation. Nano Lett 2018;18:1916e24.

[184] Zhang DKY, Cheung AS, Mooney DJ. Activation and expansion of human T cells using artificial antigen-presenting cell scaffolds. Nat Protoc 2020;15:773e98.

[185] chikawa J, Yoshida T, Isser A, Laino AS, Vassallo M, Woods D,et al. Rapid Expansion of highly functional antigen-specific T cells from patients with melanoma by nanoscale artificial antigen-presenting cells. Clin Cancer Res 2020;26:3384e96.

[186] Kim OY, Park HT, Dinh NTH, Choi SJ, Lee J, Kim JH, et al. Bacterial outer membrane vesicles suppress tumor by interferon-gamma-mediated antitumor response. Nat Commun 2017;8:626.

[187] Qing S, Lyu CL, Zhu L, Pan C, Wang S, Li F, et al. Biomineralized bacterial outer membrane vesicles potentiate safe and efficient tumor microenvironment reprogramming for anticancer therapy. Adv Mater 2020;32:e2002085.

[188] incent, M.; de Lázaro, I.; Kostarelos, K. Graphene Materials as 2D Non-Viral Gene Transfer Vector Platforms. Gene Ther. 2016, 24,123–132. [CrossRef]

[189] Yin, H.; Kanasty, R.L.; Eltoukhy, A.A.; Vegas, A.J.; Dorkin, J.R.; Anderson, D.G. Non-Viral Vectors for Gene-Based Therapy. Nat.Rev. Genet. 2014, 15, 541–555. [CrossRef] [PubMed]

[190] Gregory, A.E.; Titball, R.; Williamson, D. Vaccine Delivery Using Nanoparticles. Front. Cell Infect. Microbiol. 2013, 4, 13. [CrossRef]

[191] Panyam, J.; Labhasetwar, V. Biodegradable Nanoparticles for Drug and Gene Delivery to Cells and Tissue. Adv. Drug Deliv. Rev.2003, 55, 329–347. [CrossRef] [PubMed]

[192] Shen, Y.; Hao, T.; Ou, S.; Hu, C.; Chen, L. Applications and Perspectives of Nanomaterials in Novel Vaccine Development.MedChemComm 2018, 9, 226–238. [CrossRef] [PubMed]

[193] Bonam, S.R.; Kotla, N.G.; Bohara, R.A.; Rochev, Y.; Webster, T.J.; Bayry, J. Potential Immuno-Nanomedicine Strategies to Fight COVID-19 like Pulmonary Infections. Nano Today 2021, 36, 101051. [CrossRef]

[194] Fengi qi.; Jei Wu.; Li, H.; Ma, G. Recent Research and Development of PLGA/PLA Microspheres/Nanoparticles: A Review in Scientific and Industrial Aspects. Front. Chem. Sci. Eng. 2018, 13, 14–27. [CrossRef]

[195] Ho WY, Blattman JN, Dossett ML, Yee C, Greenberg PD (2003) Adoptive immunotherapy: engineering T cell responses as biologic weapons for tumor mass destruction. Cancer Cell 3:431–437

[196] Paulos CM, Suhoski MM, Plesa G, Jiang T, Basu S, Golovina TN, Jiang S, Aqui NA, Powell DJ Jr, Levine BL, Carroll RG,Riley JL, June CH (2008) Adoptive immunotherapy: good

[197] habits instilled at youth have long-term benefits. Immunol Res 42:182–196

[198] Hamdy S, Molavi O, Ma Z, Haddadi A, Alshamsan A, Gobti Z,Elhasi S, Samuel J, Lavasanifar A (2008) Co-delivery of cancer-associated antigen and Toll-like receptor 4 ligand in PLGA nanoparticles induces potent CD8 ? T cell-mediated anti-tumor immunity. Vaccine 26:5046–5057

[199] Goforth R, Salem AK, Zhu X, Miles S, Zhang XQ, Lee JH,Sandler AD (2009) Immune stimulatory antigen loaded particles combined with depletion of regulatory T-cells induce potent

[200] tumor specific immunity in a mouse model of melanoma. Cancer Immunol Immunother 58:517–530

[201] Pathak A, Swami A, Patnaik S, Jain S, Chuttani K, Mishra AK,Vyas SP, Kumar P, Gupta KC (2009) Efficient tumor targeting by polysaccharide decked polyethylenimine based nanocomposites. J Biomed Nanotechnol 5:264–277

[202] Pathak A, Kumar P, Chuttani K, Jain S, Mishra AK, Vyas SP,Gupta KC (2009) Gene expression, bio-distribution, and pharmacoscintigraphic evaluation of chondroitin sulfate-PEI nano-constructs mediated tumor gene therapy. ACS Nano 3:1493-1505

[203] Voysey, M.; Costa Clemens, S.A.; Madhi, S.A.; Weckx, L.Y.; Folegatti, P.M.; Aley, P.K.; Angus, B.; Baillie, V.L.; Barnabas, S.L.;Bhorat, Q.E.; et al. Single-Dose Administration and the Influence of the Timing of the Booster Dose on Immunogenicity and Efficacy of ChAdOx1 NCoV-19 (AZD1222) Vaccine: A Pooled Analysis of Four Randomised Trials. Lancet 2021, 397, 881–891.[CrossRef] [PubMed]

[204] Wiersinga, W.J.; Rhodes, A.; Cheng, A.C.; Peacock, S.J.; Prescott, H.C. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19) A Review. JAMA—J. Am. Med. Assoc. 2020, 324, 782–793. [CrossRef] [PubMed]

[205] Horejs, C. From Lipids to Lipid Nanoparticles to MRNA Vaccines. Nat. Rev. Mater. 2021, 6, 1075–1076. [CrossRef] [PubMed]

[206] Dolgin, E. The Tangled History of MRNA Vaccines. Nature 2021, 597, 318–324. [CrossRef] [PubMed]

[207] Diao, B.; Wang, C.; Tan, Y.; Chen, X.; Liu, Y.; Ning, L.; Chen, L.; Li, M.; Liu, Y.; Wang, G.; et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). Front. Immunol. 2020, 11, 827. [CrossRef]

[208] Hellerstein, M. What Are the Roles of Antibodies versus a Durable, High Quality T-Cell Response in Protective Immunity against SARS-CoV-2? Vaccine X 2020, 6, 100076. [CrossRef]

[209] Mayr, L.M.; Su, B.; Moog, C. Non-Neutralizing Antibodies Directed against HIV and Their Functions. Front. Immunol. 2017,8, 1590. [CrossRef]

[210] Nel AE, Madler L, Velegol D, Xia T, Hoek EM, Somasundaran P, Klaessig F, Castranova V, Thompson M (2009) Understanding bio-physicochemical interactions at the nano-biointerface. Nat Mater 8:543–557

[211] Igarashi E (2008) Factors affecting toxicity and efficacy of polymeric nanomedicines. Toxicol Appl Pharmacol 229:121–134

[212] Owens DE III, Peppas NA (2006) Opsonization, bio-distribution, and pharmacokinetics of polymeric nanoparticles. Int J Pharm 307:93–102

[213] Li SD, Huang L (2008) Pharmacokinetics and bio-distribution of nanoparticles. Mol Pharm 5:496–504

[214] Alexis F, Pridgen E, Molnar LK, Farokhzad OC (2008) Factors affecting the clearance and bio-distribution of polymeric nanoparticles. Mol Pharm 5:505–515