Biomaterials and Biosystems 9 (2023) 100073

Contents lists available at ScienceDirect

Biomaterials and Biosystems

journal homepage: www.elsevier.com/locate/bbiosy

Review

Immunomodulatory nanosystems: An emerging strategy to combat viral infections

Sajmina Khatun, Chandra Lekha Putta, Arshadul Hak, Aravind Kumar Rengan*

Department of Biomedical Engineering, IIT Hyderabad, Kandi, Sangareddy, Telangana 502285, India

ARTICLE INFO

Keywords:
Immunomodulatory nanosystems
Viral infections
Antiviral strategies
Immunomodulatory agents
Nanotechnology
Immunomodulation

ABSTRACT

The viral infection spreads with the assistance of a host. Traditional antiviral therapies cannot provide long-term immunity against emerging and drug-resistant viral infections. Immunotherapy has evolved as an efficient approach for disease prevention and treatment, which include cancer, infections, inflammatory, and immune disorders. Immunomodulatory nanosystems can dramatically enhance therapeutic outcomes by combating many therapeutic challenges, such as poor immune stimulation and off-target adverse effects. Recently, immunomodulatory nanosystems have emerged as a potent antiviral strategy to intercept viral infections effectively. This review introduces major viral infections with their primary symptoms, route of transmission & targeted organ, and different stages of the viral life cycle with respective traditional blockers. The IMNs have an exceptional capacity for precisely modulating the immune system for therapeutic applications. The nano sized immunomodulatory systems permit the immune cells to interact with infectious agents enhancing lymphatic drainage and endocytosis by the over-reactive immune cells in the infected areas. Immune cells that can be modulated upon viral infection via various immunomodulatory nanosystems have been discussed. Advancement in theranostics can yield an accurate diagnosis, adequate treatment, and real-time screening of viral infections. Nanosystem-based drug delivery can continue to thrive in diagnosing, treating, and preventing viral infections. The curative medicine for remerging and drug-resistant viruses remains challenging, though certain systems have expanded our perception and initiated a new research domain in antiviral treatments.

1. Introduction

Based on an immunological surveillance process, the immune system can shield us from a wide range of diseases [1]. Ideally, immune cells can identify and kill viruses, bacteria, and cancer cells as foreign antigens and destroy them. The unsettling truth is that effective pathogens have dodged immune approval through various efficient strategies, including obstructing antigen presentation, preventing phagocytosis, and actively inactivating immune cells [2]. Immunotherapy functions by either stimulating or suppressing the human immune system. A range of immune cells, cytokines, and enzymes can influence our immune conditions, which can be explored to minimize potential immune-related conditions or diseases effectively. Several immunotherapeutic approaches have successfully been applied to cure various diseases with spectacular results [3]. However, the actions of some immunomodulatory components can be adversely impacted by their lack of solubility, significant immune-facilitated cytotoxicity, and reduced bioactive properties after prolonged circulation in the blood stream [4]. Over the past 50 years, the concept of influencing immune system activity by nanosystems for therapeutic benefit has greatly revolutionized medical treatment. The idea of "therapeutic immunomodulation," "immunotherapy," or "immuno-engineering" is widely received in extensive biomedical applications like oncology to combat a wide range of metastatic cancers (using cancer therapy vaccines) [5,6]. However, its use in the treatment of viral infections is still advancing notably. The four major categories of immunomodulatory nanosystems explored in the literature are as follows: (1) biodegradable organic nanoparticles such as liposomes and polymeric nanosystems, (2) inorganic nanomaterials, (metallic nanoparticles), (3) biologically active immuno-potent components (exosomes, bilirubin, and rosmarinic acid), (4) hybrid nanomaterials (biocompatible cell membrane-clocked nanoparticles and trigger-responsive immunoregulatory nanostructures). The nanoscale size immunomodulatory nanosystems can effectively interact with receptors on the cell surfaces, followed by intracellular modulation resulting in significant therapeutic benefits [7,8]. The current study offers a broader view of various nanosystems for handling viral diseases. It thoroughly explains their unique immunomodulatory response by targeting immune cells like monocytes, neutrophils, macrophages, T lymphocytes, and dendritic cells.

Worldwide, viral infections are condemned for millions of fatalities each year. Many chronic viral diseases actively endanger human life worldwide, including ebola, zika, dengue, chikungunya, enterovirus,

* Corresponding author.
E-mail address: aravind@bme.iith.ac.in (A.K. Rengan).

https://doi.org/10.1016/j.bbiosy.2023.100073
Received 24 September 2022; Received in revised form 29 December 2022; Accepted 27 January 2023

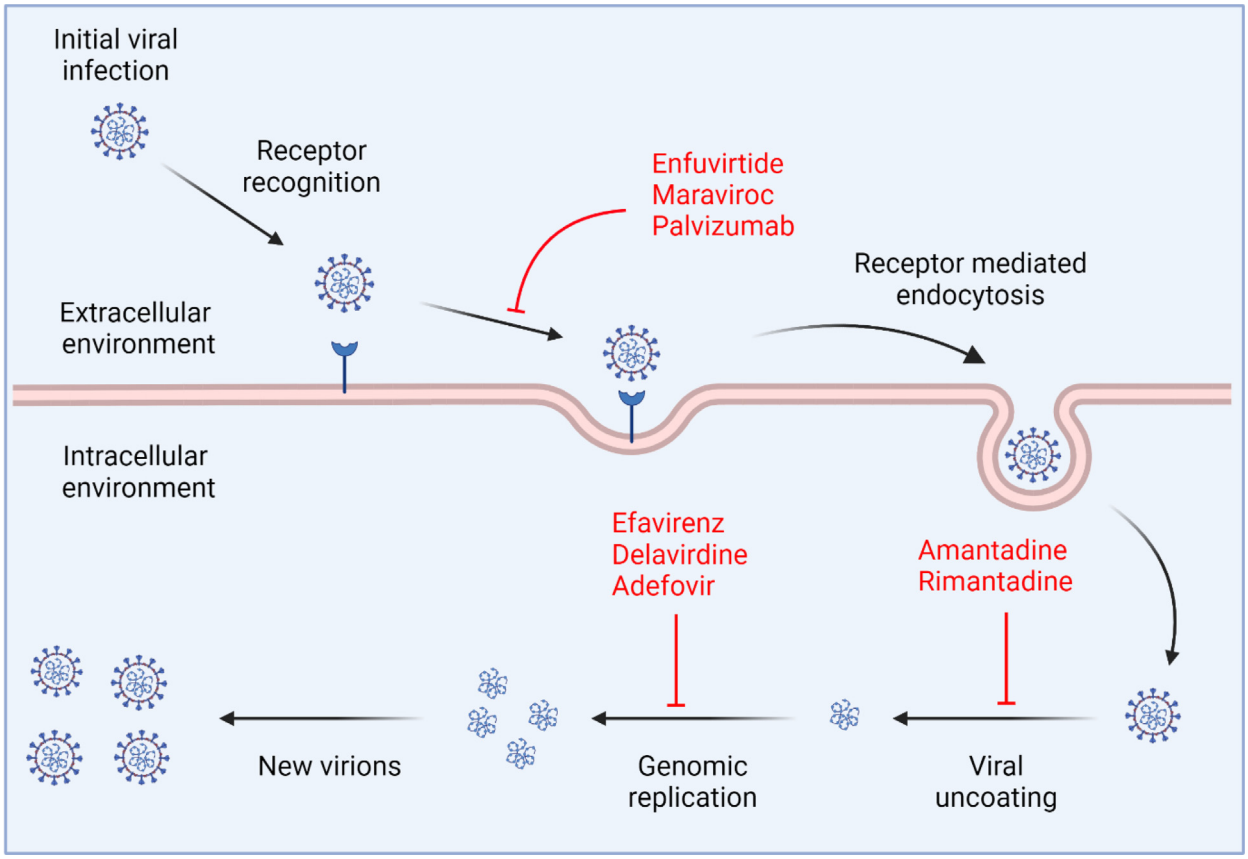

Fig. 1. Schematic presentation of viral infection cycle and different stage/cycle inhibitory conventional antiviral drugs: receptor recognition on the host cells' surface (blocker: enfuvirtide, maraviroc, palvizumab), receptor-mediated endocytosis, uncoating of the viral genome (blocker: amantadine, rimantadine) inside the host cells followed by rapid genomic replications (blocker: efavirenz, delaviridine, adefovir), formations of new virions and spreads to the new host cells.

SARS-COVS, MERS-COV, and SARS-COV2. Unfortunately, the majority of these developing diseases have no viable treatments. Viral diseases can seriously impact public, individual health and cause economic hardship [9,10]. Some of these viral diseases with their significant symptoms, route of transmission, and targeted organs are enlisted in **Supplementary Table 1**. It is quite uncertain when a viral infection might cause a public health emergency to arise. If we stick with current antiviral treatments, novel infections and related disorders are unavoidable.

Additionally, ongoing viral evolution, the reappearance of earlier viruses with increased virulence, and medication resistance are the primary reasons for the current antiviral therapies' failure. Since antiviral medicines/vaccines have previously been effective in treating some of the deadliest viral infections, and most of the treatment depends on antiviral medications once an infection occurs. Anti-viral vaccinations defend against future infections generating or activating specific memory cells. Most currently available antiviral medications, such as inhibitors of viral entrance & uncoating, genetic material synthesis, integration, translation, and release, have been developed based on knowledge of viral surface morphology, invasion, and their development mechanisms inside the host cells [11,12]. The interaction between viral glycoprotein and chemokine receptors on host cells occurs during viral invasion (fusion). Fusion inhibitors include antiviral medications such as enfuvirtide, maraviroc, and palivizumab, which block the fusion glycoproteins (like gp41, and gp140, expressed on the virus envelope) from binding with host cells [13–15]. Once the virus successfully enters the host cells, it uncoils and releases its genetic material. Following uncoating, genetic material is replicated, assisting in the spread of the virus. Drugs including efavirenz, delavirdine, and adefovir, prevent the synthesis of nucleic acids by inhibiting the function of viral RNA-directed DNA polymerase (reverse transcriptase) [16,17]. In contrast, amantadine and rimantadine serve as uncoating inhibitors [18] (Fig. 1). These medications, however, have negative consequences on the host immune system, such as toxicity, resistance, and a delay in immunological recovery.

Similar to antiviral drugs, virucides are the most widely employed substances to prevent the transmission of intact viruses, which can temporarily prevent viral infections. Virucides like peroxides, hypochlorites, cupric, ferric ions, glutaraldehyde, ethanol, and quaternary ammonium salts can damage extracellular viral particles, virion protein capsids, or super capsidal membranes. But, a recent study revealed that prolonged contact with virucidal agents has several undesirable consequences on biological systems. The hazardous consequences of these substances on human health include minor gastrointestinal irritation, portal vein thrombosis, mucosal irritation, and vomiting [19].

Nanotechnology-based immunomodulators have become a more effective alternative treatment option for viral diseases than conventional antiviral therapies [20]. Antiviral substances identified as immunomodulators can enhance host immune responses upon viral infection. Immunomodulators increase innate and cell-mediated immunological responses by enhancing the release of antibodies and interferons secretion to strengthen the host immune system [21,22]. In immunomodulatory nanosystem-based antiviral therapy, customized antigens and adjuvants are chemically or physically conjugated with nanoparticles that stimulate host immune cells. These artificially synthesized nanosystems combined with modified antigens and adjuvants show sustainable release of antigens and long exposure to antigen-presenting cells (APCs) [23,24].

The nanotechnology can handle existing problems of conventional therapy and achieve the effective therapeutic outcome by the following strategies: (a) co-delivery of antigens and targeted therapies to an antigen presenting cells (APCs) [25] (b) extending the half-lives of pharmacologically active cargo components by preventing their enzymatic

degradation in blood circulation; [26] (c) a size-dependent enhanced permeability and retention (EPR) property that leads to massive accumulation in tragted tissues; [27–29] (d) altering the surface to individual tissues or cells; [30,31] (e) stimuli-sensitive response for safe drug distribution and safe trafficking; [32–34] (f) improved tolerance to medication dosages as off-target tissues and organs retain less drug; [35] (g) developing artificial APCs (aAPCs) with surface linking of antigens and costimulatory compounds for enhancing activation of T cell; [36] (h) alternative medication delivery strategies, such as microneedle patches for intranasal delivery or subcutaneous administration; [25,37,38] (i) the installed immunomodulatory properties of nanoparticles [39,40]. Various nanoparticles with target-specific designs and functional capabilities like polymeric nanoparticles, [41,42] liposomes, [43,44] micelles, [45–47] nanogels, [31,48,49] gold nanoparticles (Au NPs), [50,51] and carbon nanomaterials are a few of the most widely observed nanosystems [52]. Among several strategies, targeted delivery of antigen and stimuli-responsive programmed release of adjuvant molecules, chemical modifications of nanoparticles with target-specific functionalities can be potent approaches for improving the localization of encapsulated contents in targeted immune cells or tissues. For instance, dendritic cells (DCs) can selectively uptake nanomaterials labeled with antibodies like DEC-205, CD40, CD11c, or mannose using a receptor-mediated endocytosis mechanism [53–58]. Accelerated uptake by regulatory T lymphocytes (commonly referred to as T_{regs}) was observed by surface pairing with CD3 antibodies or the tLyp1 peptide molecule, respectively [59]. Furthermore, dextran or dextran sulfate-based nanoplatforms have an inherent potential to target macrophages [60,61]. Lately, nanoparticles containing albumin-binding regions have the tendency to leak into lymph nodes (LN) using a technique known as "albumin hitchhiking" [62]. Researchers have also focused extensively on the definitive fabrication of nanoparticles in treating diverse ailments, where nanoparticles function as an essential immunomodulatory component and a delivery system.

This review discusses the key findings on immunomodulatory nanosystems developed to treat viral infections effectively. The latest prominent immunomodulation techniques driven by nanotechnology that were created on engineered-biomaterial platforms have been summarized. To develop a "prudently designed- immunomodulatory nanosystems" for a particular disease, this review emphasizes multiple designing methodologies by highlighting the significance of design variables such as immunomodulator selection, material influence, type of nanosystem, size, shape, and surface morphology. Moreover, we reviewed the clinical development in this field and emphasized current strategies.

A complex series of pathways are involved between virus and host immune cells' interactions that determine the outcomes of infections. Although innate immune response works as a first-line defense, it can not always be protective, especially when the pathological response is uncontrolled. The immune cells with their respective function to kill viral infections were pictorially represented in **Supplementary Fig. 1**. Drugs with immunomodulatory properties have recently emerged as a viable and reliable alternative for the prevention of viral infections [63,64]. Immunomodulation against viral infections has been explored using antibodies, a wide range of receptors/coreceptors, antigen-presenting cells, and cytokines, including interferons and interleukins [65]. Immunoglobulins can eradicate viral infections through their involvement in various intricate pathways, such as complement activation, cytokine networks, idiotype expressions, effector cell differentiation in B and T lymphocytes, and stimulation of antigen-presenting cells [65,66]. Major Histocompatibility Complex (MHC) molecules present foreign particles to effector T and B lymphocytes after being processed and activated by antigen-presenting cells. Recently, DC-based therapies are becoming more significant in antiviral treatments.

Myeloid and plasmacytoid DCs are crucial mediators in generating the antiviral immune response due to their ability to secrete large amounts of IFNs during viral infections. This functions of DCs indirectly link them with high expressions of TLR7/9, which identify the viral RNA/DNA within endosomes [67]. It was observed that immunization with DCs coupled with therapeutic peptides lowered the serum antigen and viral RNA concentration in patients with hepatitis C virus infection by triggering primary T cell responses and synchronizing host defenses against infected viruses. The effective property of DCs to process, present antigens through the MHC complex triggering the T Cells' functions and their modifications have been widely explored for preventing HCV infections [68]. DCs conjugated with C-type lectin, PEG (polyethylene glycol), and IFN/RBV (interferon/ribavirin) for HCV have become better and more effective antiviral therapies in recent years [69–71].

TLRs are among the crucial immunological components in innate immunity, regulate the pro/anti-inflammatory cytokines, and are involved in cross-talking the early innate immune responses and cell-mediated immunity. It can detect invasive foreign microbes based on the features of PAMP (pathogens-associated molecular patterns)- dsRNA (double-stranded ribonucleic acids), ssRNA (single-stranded RNA), and glycoproteins envelopes present on the virus surface. The TLR 3/7/8/9 typically recognizes viruses. These receptors can transmit wake-up signals to specialized cells and protect individuals from viral infections and pro-inflammatory events [72]. TLRs are reported to enhance the secretions of different cytokines, including type 1 and 2 IFNs, activations of enzymatic pathways involved in destroying/ deactivating intracellular pathogens, direct/indirect activations of adaptive immune responses by activating dendritic cells' maturations and antigen presentations [73]. Hence, TLR agonists could be an emerging approach for the robust activations of TLRs on viral infections. A study reported that TLRs agonists like isatoribine and CPG-10,101 are effective against HCV infection by activating the functions of TLRs and expressions of cytokines/IFNs/chemokines [74,75]. HIV-1 derived and artificially synthesized TLR 7/8 agonist 3M-052 formulated in poly(lactic-co-glycolic)acid (PLGA) nanosystem were also observed to induce persistent secretions of antibody, blood monocyte, Th1 cells, and activations of germinal center B cells in rhesus macaques [76].

The ongoing development in antiviral immunity is swifted in the area of cytokine-mediated therapeutic approaches rooted in triggering and mimicking the cytokine networks. Cytokines like IL-12 in combination with IFN-γ decrease the viral pathogenicity. IFNs effector proteins are mainly involved in preventing viral infections. Protein kinase R (PKR) is one of the best known IFN effector molecules, which deals with the prolonged activation of IFNs in the host and the apoptosis of infected cells [77]. A broad-spectrum immunosuppressive cytokine called IL-10 (Interleukin-10) suppresses pro-inflammatory responses by interacting with APC and T cells. Other cytokines, such as GM-CSF (Granulocyte-macrophage colony-stimulating factor) and IL-3, have been employed as adjuvants, either alone or in conjunction with antiviral drugs, to prevent viral infections [78].

2. Immunomodulatory nanosystems (IMNs), their classification, and immunomodulatory effects

Immunomodulatory nanosystems can be classified into 4 categories (Fig. 2) and are developed with immunologically inert and biodegradable components. Polymeric nanostructures, lipids, and carbohydrate-mediated IMNs belong in the 1st category. In 1st category IMNs, polymeric NPs are powerful nano-vehicles that act with dual capacity as adjuvants and delivery systems for diverse payloads (antigens and additional co-adjuvants). These nanoparticles deliver the adjuvants/antigens to the immune cells with sustainable release protecting from the harsh environment (e.g., enzymatic degradation). Polymer-based nanoformulations have been reported to interact with APCs receptors (e.g., Dectin-1) activating multiple cascade mechanisms involving cGAS-STING, a cytosolic DNA sensing pathway, and nucleotide-binding oligomerization domain-like receptors proteins 3 (NLRP3) inflammasome activation. The polymeric NPs-APC receptor interaction results in the induction of DCs, Th1/Th2 mediated immune response, secretion of type 1

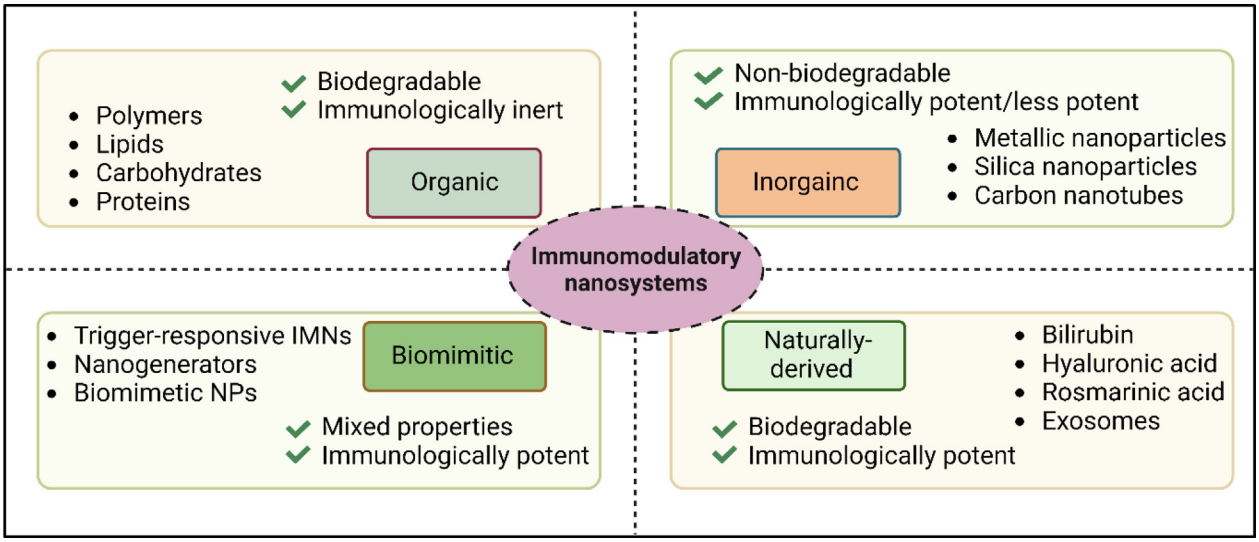

Fig. 2. Types of immunomodulatory nanosystems: organic, inorganic, biomimetic, and naturally derived with their respective inherent characteristics and types of biological compounds used to synthesize them.

IFNs, chemokines (CSCL10/IP-10), and cytokines (IL-12, IL-4, IL-10, and TNF-α) secretion. Polymeric NPs also reported to enhance DCs maturations, macrophage activation, and IgG/IgA antibody-mediated immune response [79–81].

The 2nd category consists of IMNs that are formulated by metallic nanomaterials such as silica, copper (Cu), iron oxide (FeO2), gold (Au), silver (Ag), and carbon nanotubes. Metallic NPs have a higher binding affinity with distinct functional groups and ligands. Large surface area to volume ratio, plasmon excitation, and inherent magnetic and optical properties widen their therapeutic applications. The feasible chemical synthesis process and easy tagging with adjuvants/antigens make them suitable candidates for nano-vehicle formulation. A study reported that metallic NPs (e.g., silica NPs) exert immunomodulatory effects by inducing the secretion of proinflammatory cytokines (IL-1β and IL-18) in the host. The activation of proinflammatory responses is responsible for activating the NLRP3 inflammasome complex, which plays a crucial role in innate immunity via eliciting the alarming signal to TLRs, PAMPs, DAMPs (danger-associated molecular patterns) and recognizing the viral nucleic acids [82,83].

The 3rd category consists of various naturally originated organic substances, such as bilirubin, rosmarinic acid, hyaluronic acid, cell membranes, and extracellular vesicle mediated NPs. This 3rd category of IMNs assists the natural interaction between biological components and NPs mimicking the characteristics and activities of native cells. These NPs also overcome the biological barrier and minimize the rapid clearance from the body before reaching the target site. Chen et al. demonstrated that virus-like NPs loaded with model antigens derived from avian coronavirus spike protein showed immune modulations via accelerating antigen delivery to host lymph nodes, splenic T cell response eliciting strong antibody response [84].

The 4th category consists of hybrid immunomodulatory nanosystems (e.g., polymer-polymer hybrid, hybrid cell membrane coated, protein-polymer hybrid NPs,) generated by cross-linking/coating various components. These nanoplatforms show synergistic properties with excellent therapeutic efficacy. With growing interest, the polymer-hybrid nanosystem became an emerging field in preventing and eradicating viral infections due to novel features like composition, delivery of antigens, biodistribution, and immune responses in the host. Hybrid nanosystems have been reported to elicit robust humoral and cellular antiviral immune responses. These nanosystems were observed to trigger immune response by enhancing antigen delivery and release in targeted areas, availability of antigens in lymph nodes, DCs maturation, and shaping the interaction between APCs and T cells. Antigen-specific CD4+, CD8+ response, and upregulation of CD40 & CD86 markers resulting in clearance of viral infections from the body were also found [79,85].

3. Current progress in nanomedicine for antiviral therapies

Biomaterials are a promising tool in the fight against microbial infections and have been employed to diagnose, treat many infectious diseases, such as COVID-19, AIDS, dengue fever, and influenza. Additionally, biomaterials are utilized in antisepsis, disinfections, and the development of personal protective equipment [86,87]. Nanotechnology is concerned with materials of nanosized level. The US National Nanotechnology Initiative defines nanoparticles as having a size range between 1 and 100 nm. The surface-to-volume ratio of these particles at this scale impacts the material's electrical, magnetic, optical, and structural characteristics [88,89]. Applications of nanotechnology are widely employed in the field of nanomedicine. The major constituents of nanomedicine are nanoparticles, which are used as imaging, diagnostic, and therapeutic agents [90,91]. The early diagnosis of many diseases is largely dependent on medical imaging techniques. Nanoparticle technology has made it feasible to enhance the results of many imaging modalities like CT, MRI, US, PET, and SPECT [92].

In diagnostics, nanoparticles can be utilized as a base to anchor biomarkers like proteins, immunoglobulins, and oligonucleotides. These nanoparticle-based biomolecule-detection assays offer higher selectivity and lower detection limits [93,94]. A major challenge in therapeutics is to deliver the therapeutic agents to the target site, as the therapeutic efficacy of most drugs is limited by poor biodistribution and non-selectivity. Nanoparticle-based drug delivery system is a promising way to overcome these limitations. This approach can deliver a wide range of drug molecules to specific cells/tissues.

Additionally, many hydrophobic drugs are incorporated with nanoparticles to overcome physiological barriers, resulting in increased bioavailability [95]. Passive and active targeting are the two widely used approaches for the discrete localization of nanoparticles to the target site [96]. Passive targeting is based on the enhanced permeability and retention (EPR) effect and mainly targets cancer tissues. Due to higher blood capillary permeability and very low lymphatic drainage of fluid in the tumors, nanoparticles are absorbed easily. They are retained for a longer period in the tumor microenvironment compared to normal tissues [97]. In various pathological conditions, there is no change in

the permeability of blood capillaries; therefore, passive targeting is not applicable. In these cases, an additional molecule called targeting moiety is used, which can specifically recognize and bind to the target site. This approach of targeting is called active targeting [98]. Nanoparticles offer a multifaceted platform for diagnosing, treating, and preventing infectious diseases [99].

It has been reported that nanomaterials can influence the host immunity without affecting the disease condition [100]. Nanoparticles can strengthen the host immunity in different ways to combat viral infections. Nanoparticles can also be used as a nanocarrier system which helps in the co-delivery of drugs and antigens for activating specific immune components. Additionally, the intrinsic properties of nanoparticles, like size, shape, and hydrophobicity, profoundly impact immune activation and deactivation [101]. In recent years, several functional biomaterials have been developed that exhibit inherent antiviral activities and, therefore, can be utilized in antiviral therapies. Their mechanisms of action include virus capturing, blockage of viral entry, destruction of viral structure, and inhibition of viral replication [102]. Therapeutic nanoparticles can be broadly categorized as inorganic and organic nanoparticles. Appreciable efforts and an extensive amount of research have focused on developing metal nanosystems for the prevention of several pathogenic viral diseases. As a result, metallic nanosystems exhibited promising antiviral activities against pathogenic surrogates and clinical isolates. The applications of metallic nanoparticles as antiviral agents have rapidly progressed due to their ability of multitarget attack on viruses, preventing subsequent resistance. Studies have shown promising results against different types of viruses such as human adenoviruses, coronavirus, coxsackievirus, chikungunya virus, dengue virus, herpes simplex virus, HIV, hepatitis, influenza, norovirus, poliovirus, rubeola virus, etc. [103]. In the class of metallic nanoparticles, gold nanoparticles (AuNPs) are well known for their distinctive physio-chemical properties. AuNPs have a high density of free electrons on their surface and exhibit a phenomenon called surface plasmon resonance (SPR). Because of this unique feature, AuNPs are employed for detecting viruses through resonance light-scattering-based techniques like LSPR, DLS, and Raman spectroscopy. Several detection assays based on AuNPs have been designed to detect numerous viruses, including hantaan, rift valley fever, SARS, dengue virus, and Ebola [104]. Similar to AuNPs, silver nanoparticles (AgNPs) are also among the popular metallic nanoparticles, and their antiviral properties have been explored extensively against many viral pathogens [105]. A recent study by Sundararaj et al. demonstrated the antiviral efficacy of AgNPs against SARS-CoV-2. Their study revealed that AgNPs with a concentration of 1–10 ppm could inhibit the extracellular SARS-CoV-2 and prevent the host cells from getting infected [106].

Titanium dioxide nanoparticles (TiO_2 NPs) have chemical and thermal stability and have been well explored in drug delivery systems. Seiko et al. investigated TiO_2 NPs against the respiratory syncytial virus (RSV) using a mouse model. The test animals were exposed to TiO_2 NPs for 5 days after being infected with RSV. The animals unexposed to TiO_2 NPs were considered as the controls. After 5 days of post-treatment, it was found that the levels of IFN-γ, CCL5, and IL-10 were higher in the mouse treated with TiO_2 NPs when compared to the control. These results showed the effect of TiO_2 NPs on the immune response during RSV infection [107]. Another study reveals the antiviral activity of iron oxide nanoparticles against the H1N1 influenza A virus [108].

In addition to metallic nanoparticles, polymeric nanoparticles have also been employed as nanocarriers in several studies. A pharmacokinetic study was performed by Shing et al. on the feline infectious peritonitis (FIP) virus using curcumin as the antiviral agent. Here, curcumin was encapsulated in chitosan nanoparticles. Interestingly, encapsulated curcumin's effectivity was much higher than free curcumin [109]. Irshad et al. employed chitosan nanoparticles in their study to co-deliver mRNA and immunogenic antigens to protect against avian influenza virus (AIV). In this nanoformulation, M2e mRNA molecules were encapsulated in chitosan nanoparticles. After successful encapsulation, the nanoparticle surface was coated with HA2 and M2e proteins. This nanoformulation reported a high immune response in chickens with AIV [110]. A similar study was performed using chitosan nanoparticles to prepare the AIV vaccine [111]. Vacuolar ATPases (V-ATPases), which are present in all eukaryotic cells, play a significant role in viral entry into the host cells. Several pathogens, like the influenza virus, coronavirus, etc., enter host cells with the help of V-ATPase. Different V-ATPase inhibitors containing bafilomycin and diphyllin have been developed to block viral entry, but many of these inhibitors have poor water solubility. In one research investigation conducted against the influenza virus, bafilomycin and diphyllin were encapsulated in PEG-PLGA NPs, increasing their therapeutic index by 3 and 5 times, respectively [112]. Glycyrrhizic acid (GA) is widely employed in Chinese medicine and is effectively used to treat inflammatory disorders and liver diseases. Zhaoyan et al. synthesized glycyrrhizic acid nanoparticles (GANPs) through the hydrothermal process to study the antiviral effects of GANPs against COVID-19. Their study proved that GANPs could reduce severe inflammation caused by SARS-CoV-2. Additionally, GANPs accumulated more in the liver and lungs due to the EPR effect, where inflammation was relatively higher. This specific targeting further improves treatment efficiency [113]. These studies demonstrated the role of nanomaterials in the treatment of viral infections. A wide range of metallic nanoparticles can activate a strong immune response against viral pathogens. In contrast, polymeric nanoparticles can be an effective tool to enhance the effectiveness of treatment by improving drug biodistribution and targetability.

Apart from the pre-clinical studies, nanoparticle-based vaccines have also been explored in phase I/II clinical trials. A study was conducted on 60 people to investigate the immune response of lipid nanoformulation-based mRNA vaccine BNT162b1. This vaccine encodes the receptor binding domain (RBD), situated on the spike protein of SARS-CoV-2, which is a potential target for antibodies. The serum analysis of these candidates showed a dose-dependent production of RBD-binding IgG antibody and RBD-specific CD4+ T cell & CD8+ T cell responses [114]. In a similar study, another lipid nanoparticle based mRNA vaccine BNT162b2 was investigated to explore its effectivity against SARS-CoV-2. Similar to BNT162b1, the BNT162b2 generated a strong IgG antibody response and induced the secretion of cytokines like IFNγ, IL-2, and IL-4 [115]. NVX-CoV2373 is also a nanoparticle based vaccine for recombinant SARS-CoV-2, which contains SARS-CoV-2 spike glycoprotein along with Matrix-M1 adjuvant. Under the phase 1–2 trial on 131 healthy adults, the vaccine-mediated immune activation was observed in the form of anti-spike IgG production and T helper 1 (Th1) response [116]. During viral and bacterial infection, the immune system activates a NETosis process, which forms neutrophil extracellular traps to capture the pathogens. In SARS-CoV-2 infection, the immune responses are impaired, and NETosis is triggered in an uncontrolled manner, which increases the levels of NETosis markers like cell-free DNA in serum, and causes local and systemic tissue damage. In a study by Lee et al., a polymer-based nanoformulation of DNase-1 was synthesized, effectively reducing cell-free DNA levels in the blood samples collected from COVID-19 patients. This nanoformulation showed a great potential for preventing organ failure in COVID-19 patients due to the impaired immune responses [117].

4. Blueprint for immunomodulatory nanosystems

Designing a reasonably constructed immunomodulatory nanosystem to attain optimum therapeutic efficacy with low adverse side effects at the targeted region is challenging. The general effectiveness of an immunomodulatory nanosystem in curing a viral infection was influenced by several interrelated factors, including the type of viral infection (localized or systemic), preference for an immunomodulatory agent & biologically active components, physicochemical characteristics of IMNs and its pharmacokinetics in the body like absorption, distribution,

metabolism, excretion, and toxicity (ADMET). In the following sections, we have discussed the layouts of IMNs, which comprise the basic structural blueprint of IMNs.

4.1. Choice of immunomodulators

An immunomodulator is a substance with recognized immunostimulatory or immunosuppressive properties that could assist in normalizing hyperactive or malfunctioning immune cells. To accomplish desired therapeutic immunomodulation, biologically synthesized immunomodulators have been employed either individually or in combination with traditional immunomodulatory agents [118]. On the contrary, compounds that are immunologically inactive or even less efficient can occasionally be transformed into immunologically potent ones. This transformation is usually mediated by carboxylation, methylation, amination, hydroxylation, acetylation, and conjugation. Immunomodulatory agents like antibodies, cytokines, and growth factors conjugation on the surface of nanocarriers are the most common modifications [119]. The nanostructured carbon nanotubes (CNTs) also achieved tremendous attention for their versatile characteristics and applications in drug delivery. The co-ordination between carbon bonds empower their thermal stability and tensile strength. Large surface area and easy conjugations of therapeutics to their surface assist them in displaying superior efficacy in drug delivery. For instance, single-wall carbon nanotubes intermediate between fullerene cages and flat graphene have been complexed with carboxyl groups, and acids are reported to stimulate monocytes more than non-functionalized CNTs [118–120]. This alteration increased the water solubility of CNTs, reduced their cytotoxicity, and increased their immunological potency. IL-6, CD40, DC-maturation, and TNF-α were successfully stimulated by amine synthesized multiwalled carbon nanotubes (MWCNTs) in monocytes [120].

4.2. Nanoscale size of immunomodulatory nanosystems

Immune cells vary in size from 6 μm to 22 μm. Also, the size varies from species to species. Using a flow cytometer, a study was conducted to evaluate the interspecies distance of pulmonary macrophages and discovered that human alveolar macrophages were the biggest (21.2 0.3 mm), preceded by those from monkeys (15.3 0.5 mm), hamsters (13.6 0.2 mm), and rats (13.1 0.1 mm) [121]. To interact effectively with the surface of HICs and facilitate cellular absorption, the size of nanostructures should be in an optimum range. Most investigations have designed and developed IMNs that are between 10 and 1000 nm in size. Due to their small size, nanosystems can readily enter the lymphatic system and undergo cellular absorption by the targeted immune cells. It has been demonstrated that nanoparticles between 10 and 100 nm can effectively infiltrate the lymphatic drainage network. In contrast, bigger nanoparticles get blocked in the extracellular matrix and interrupt from engaging with immune cells [122]. Immune cells differ in their preferences for various nanosystem sizes. Immune cells selectively absorb nanoparticles more than microparticles, but highly phagocytic macrophages can actively ingest particles up to 2–3 μm in size [123,124].

4.3. Morphological and surface properties of immunomodulatory nanosystems

The biodistribution of IMNs and their efficiency in associating with immune cells are significantly influenced by their morphological characteristics [125]. IMNs with spherical shapes are considered in most investigations owing to their extensively investigated cell absorption and endocytosis technique. According to previous findings, non-spherical morphology, including rod, elliptical, flakes, or needle-shaped nanoparticles effectively interact with the immune cells and cause changes in the immunological reactions. For instance, rod-shaped polystyrene (PS) nanostructures complexed with antibodies could stimulate murine macrophages to enhance the production of TNF-α over spherical PS nanostructures with a similar antibody concentration on their interface [126]. Comparing ellipsoidal (spindle-shaped) and spherical PS nanoparticles, elliptical PS nanoparticles revealed improved adhesion and accelerated internalization by murine macrophages [127]. Similarly, it was discovered that neutrophils preferentially internalized elongated rod-shaped polymeric nanoparticles over spherical ones [128]. The amount of actin cytoskeletal modification necessary for the endocytosis of specific nanoparticles is believed to be a crucial factor of variation in the internalization impact of various morphologies [129]. The surface of IMNs is embellished with ligands that preferentially interact with upregulated cognate receptors on HICs to improve their selective uptake (active targeting) [130]. The resurgence of interest in developing 'biomimetic IMNs' by customizing the NP's surface with constituents like membranes or vesicles derived from the immune cell. These biomimetic IMNs function as pseudo-immune cells when administered in the body, infiltrate deep into the affected regions, and exhibit detoxification by sequestering overproduced cytokines [131,132].

4.4. Immunomodulatory nanosystems with trigger-response properties

Researchers have developed materials that can self-adjust the rate of release of immunomodulant in response to endogenous variables such as acidic pH, enhanced secretion of ROS (reactive oxygen species), or increased enzyme levels in the cells [133–135], or exogenously added trigger points such as light, magnetic force, and ultrasonic radiations. These IMNs are described as trigger-responsive immunomodulatory nanosystems [136,137]. The remarkable potential of these nanosystems' response to a particular stimulation reduces off-target damage. External trigger enables accurate regulation over the immunomodulant's duration of action and potency. Furthermore, extrinsic triggers such as magnetic fields promote increased aggregation of magnetic-immunomodulatory nanosystems at a targeted area under the impact of a magnetic force [138]. The application of an external trigger allows the identification of administered trigger-responsive IMNs into the bloodstream through inbuilt IMNs properties such as photosensitive IMNs imaging by near-infrared, magnetic resonance imaging of nanoparticles, and echogenicity of microbubbles visualized by using ultrasound radiation or by conjugating with an imaging sensor externally. These immunomodulatory nanosystems are regarded as image-guided novel theranostics immunomodulatory nanosystems and provide a facility for accurately monitoring the accumulation of IMNs at the target site [139].

The above discussion showcased that the therapeutic potential of immunomodulatory nanosystems depends upon several factors, such as their ability to induce immune activation, size, shape, surface functionalization, and drug release profile. These factors can be optimized to achieve the desired clinical benefits.

5. Nanosystems-based immunomodulation in viral infections

A wide variety of nanotechnology-based drug-delivery maneuverings have been synthesized and tested in antiviral therapy [140,141]. Some of the clinically investigated antiviral nanomedicines, their antiviral immune response, and mechanism of action are listed in Table 1.

Antigens and adjuvants are highly required to trigger the immune function efficiently, but a lack of safety and effectiveness constrains their role in clinical research. Nanotechnology provides the opportunity to develop a novel class of anti-infective medications. Recently, virosome and liposome-derived nanovaccines targeting viral infections have attracted much attention with excellent potency in the body; a few of them are presented in Table 2. Virosomes are also called non-replicated "artificial viruses" made up of glycoproteins and phospholipids. The cavity-like core of the virosome is loaded with drugs/therapeutics macromolecules. The surface is chemically cross-linked with the targeted pathogen's antigen, which helps them to interact with host cells, transport, and present

Table 1
FDA approved antiviral drugs, their antiviral immune responses, and mechanism of action.

Approved antiviral drugs and their immune responses	Mechanism of drug action	Refs.
Dolutegravir (August 2013) against HIV/AIDS; induces predominant T cells response and cytokine and chemokine secretion by activating macrophages, neutrophils, monocytes, and lymphocytes	Prevents the integration of viral DNA into the host genome of CD4+ cells via inhibiting the integrase enzyme.	[142]
Brincidofobir (October 2014) against HIV-1, HSV-1, HSV-2, Adenovirus, and Ebola virus; triggers the activation and maturation of DCs, leading to INF-dependent cell-mediated immune response	Acts as a nucleotide analog inhibiting viral DNA replication via retarding DNA polymerase resulting in decreased DNA synthesis and chain termination	[143–146]
Peramivir (December 2014) against Influenza and HSV infections; activates PRR receptors, DCs, CD4+, and CD8+ T cells response	Prevents detachment of sialic acid from glycoproteins on the host cell surface, impeding the release and spread of progeny virions.	[147]
Tecovirimat (July 2018) against Smallpox; induces both humoral and cellular immune responses eliciting a strong antibody response	Inhibits p37, a highly conserved protein in the pox virus to communicate with intracellular transport components essential for the synthesis of enveloped virus and spread of virion	[148]

Table 2
Virosome and liposome-derived antiviral nanovaccines and their immune responses.

Nanosystem-based vaccines	Antiviral immune responses	Refs.
Epaxal: Virosome-formulated, aluminum-free hepatitis A vaccine	Boosts the seroprotection rates and geometric mean concentrations (GMCs) of Hepatitis-specific antibodies in pre & post-vaccination and induces T cell proliferation before booster dose in Hepatitis A infected patients.	[151]
Inflexal V: Virosome-based trivalent influenza vaccines	Induces the natural antigen presentation via MHC-1 and MHC-II antigen presentation pathways providing a long-term protective immune response against influenza	[152]
JVRS-100: Cationic lipid/DNA conjugated influenza vaccines	Ensures efficient co-localization of liposomes with antigen and activation of the APCs, interaction of APC to T cells, and triggers of cell-mediated immune responses	[153]
H1/IC31®: Tuberculosis subunit/adjuvants conjugated HIV vaccine	Trigger a persistent Th1-immune response with strong TNF-α and IL-2 co-expressing CD4+ T cells, along with multifunctional TNF-α, IFN-γ and IL-2 expressing CD4+ T cells	[154]
ISCOMATRIX: Liposome-ISCOMATRIX^{TM} adjuvant- complexed influenza vaccines	Elicits strong and long-lived antibody, CD4+, CD8+ T cells mediated immune response in influenza-infected patients	[155]

antigens through the MHC-1 antigen-presenting pathway. Researchers also reported that virosome are non-infectious and biodegradable nanovehicles that activate B cells, CD8+, and CD4+ T cells. Surface modifications of virosome with crucial viral fusion proteins, receptors, or antigens can target host cells triggering immune response through antibody-producing B cells and internalization by endocytosis-mediated pathways. Two nanostructured vaccines, Inflexal V and Epaxal have so far received FDA approval for treating hepatitis A and influenza [149]. Nanoparticles have developed as reservoirs for delayed antigen release enhancing the contact time to APCs and offering a non-viral delivery method for DNA vaccines that provides genomic material to the targeted sites. Numerous studies have supported the positive outcomes of vaccine formulations based on nanotechnology against communicable infections, which benefited from enhanced drug delivery, functional nanoparticle-based technology, and characteristic properties of adjuvant [150].

The combination of immunotherapy with nanomedicine can quickly surpass the setbacks of therapeutic outcomes and emphasize the bioactivity of immunotherapeutic factors. Typically, agents which can either activate or suppress the immune system are widely employed in immunotherapy. However, immunostimulatory agents are used in antiviral therapy to intensify the antiviral immune response by identifying, removing foreign antigens and developing memory-based immune cells for viral diseases [156]. The immunomodulatory nanosystems are devised by coating or conjugating with part of antigens and adjuvants to enhance the immune system function since antigens alone are prone to degradation by enzymes inside the body. The linking of adjuvants may prevent antigens' degradation and escalates the activation of antigen-presenting cells (APCs) more effectively. Immunomodulatory nanoparticles can also stabilize those antigen-adjuvant complexes in circulation and assist in the sustainable release of antigens to target sites. The slow release of the nanosystem can prevent vigorous activation of the immune system intercepting the unwanted immune response and clearing the foreign molecules [156,157]. The modulation of several key players of the host immune system by various nanoformulations regresses viral infections, which are discussed in the following sections.

5.1. Modulation of innate immune components

Communication between innate and adaptive immunity effectively protects the body against foreign invaders. Activation of the innate immune system occurs immediately after encountering the infectious agent and causes the migration of the phagocytic cells toward the infectious site [158]. Recently, innate immune systems and their downstream pathways upon viral infections have been identified. Innate immune system includes individual members like the pathogen recognition receptor (PRR), toll-like receptor (TLR), C-type lectin receptors (CLR), nucleotide-binding oligomerization domain (NOD), and nucleotide-binding oligomerization domain-like receptors (NLR) which are crucial for building up of antiviral innate immune response. These receptors recognize viral DNA and RNA, constitutive to discriminate between self and non-self. After recognizing PAMPs, multiple intracellular signaling cascade mechanisms are initiated, resulting in the secretion of type 1 IFNs, inflammatory cytokines, and DCs maturations which initiate the antiviral response. Cells also produce cytoplasmic RNA helicases, which work as an alternative PRR receptor by recognizing dsRNA, which is synthesized during viral replication. The two PRRs are expressed in separate intracellular compartments and accelerate the type 1 IFNs through different signaling pathways. The antiviral responses also occur by synthesizing genes encoding a complete series of pro-inflammatory agents like chemokines, cytokines, antimicrobial proteins, cell adhesion factors, and immune receptors [159–161]. So, the agonist of the innate immune receptors or the nanoparticles that enhance their signaling pathway would be a powerful source to catalyze a viral-specific immune response.

The preliminary inflammatory response is crucial to determine wake-up signals to innate immune receptors (TLR/PLR). Gomez et al. showed that silica NPs could initiate and enhance the inflammatory cascade mechanism activating an antiviral innate immune response. The pro-inflammatory cytokines IL-1β and IL-18 are the two main components to trigger the downstream inflammatory cascade pathways. A complex inflammasome pathway involves in the maturation and activation of these cytokines. One of the best-known is NLRP3 mediated inflammasome complex pathway. NLRP3 consists of NACHT/NOD domain and

C terminal leucine-rich repeats (LRRs), which trigger a cascade leading to the formation of NLRP3 /pro-caspase-1 complex resulting in the secretion of proinflammatory cytokines [82].

The upper respiratory tract (URT) is the main gateway and provides shelter for the virus. Infections in URT are the most common and serious problems across the globe. Nanoformulation-based therapy can be one of the potential solutions against URT infections. Researchers reported that Liposome-TLRs hybrid nanoformulations (LTR NPs) activate a mucosal innate immune response in the upper respiratory tract. The LTR NPs were synthesized by liposome-TLR ligand complex (LTC) consisting of TLR agonists such as polyinosinic-polycytidylic acid, melanoma differentiation-associated protein 5, a retinoic acid-inducible gene I and noncoding plasmid DNA reach in cytosine and guanine. LTR NPs were observed to activate macrophages rapidly. The presence of LTR NPs inside the macrophage was observed by the emission of bright green fluorescence. It demonstrated that TLR ligands conjugated with liposome NPs could activate the phagocytic cells. The LTR NPs also enhanced the infiltration of neutrophils, T cells (CD5+), and monocytes (CD14+) into the nasal mucosa 6 hr post-administration. In addition to the activation of the costimulatory agents (OX40 and MHC II), LTC was linked with innate immune reactions that induce the release of cytokines which include INF-α, INF-γ, TNF-α, and IL-12. These findings suggested that liposome-based TLR agonists have the potential use to build an immune response against viral infections [162]. Bawage et al. explored gold nanorod (GNR) as a promising nanoparticle to inhibit respiratory syncytial virus (RSV) infections via stimulating the innate immune response. RSV belongs to the pneumoviridae family and causes acute lower respiratory tract infections in immunocompromised patients, fetuses, infants, young children, adults, and older people with cardiovascular morbidity problems. The GNR-RSV treated lung tissues had multiple antiviral gene expression networking profiles belonging to TLR and NLR pathways [163].

Antigen-presenting cells (APCs) are the key linker in crosstalk between innate and adaptive immunity. Dendritic cells and B cells are the primary classical antigen-presenting cells. Modulation of innate immune receptors and antigen-presenting cells by immunomodulatory nanosystems and elicited antiviral immune responses by them are presented in Fig. 3. After recognizing antigens by PRR, APCs internalize their target via phagocytosis, pinocytosis, or clathrin-mediated endocytosis. Antigens are displayed using MHC I/II for T cell recognition, triggering a strong antiviral response [164]. The application of nanotechnology to boost APCs has several specific advantages compared to the systemic loading of immunotherapeutic molecules because of the easy uptake of small-sized NPs by APCs [165]. Nanoparticles can enhance antigen stability and have a high loading efficiency. It has been observed that polymeric NPs prolong the antigen exposure to immune cells, allowing the antigen uptake by DCs and regulating antigen presentation mechanisms within these cells, thereby increasing T cell-mediated immune reactions. Carbohydrate-functionalized nanoparticles in HIV infections are reported to sustain the antigen release kinetics towards the effector immune cells and activate APCs' maturations [166]. Adaptive immune responses are antigen-specific and classified by the production of CD8+ and CD4+ T cells which will further differentiate into effector T cells. It has been reported that the uptake of NPs by DCs is one of the crucial parameters for the stimulation and transformation of T cells [167].

Scheffel et al. reported that calcium phosphate NPs (CaP NPs), a biodegradable nanocarrier, can deliver the immune cell-activating molecules across the biological barrier and provoke the virus-specific CD8+ T cell expansion. A peptide derived from cytomegalovirus (CMV) was used as a classical antigen, and poly (I: C) or CpG functionalized CaP NPs to activate DCs. To determine the uptake of CaP NPs, DCs were isolated from peripheral blood and incubated with CpG-Alexa 488-labeled CaP NPs for 3 h and 24 h, respectively. A distinct increase of green fluorescence inside the cells was observed by the confocal laser scanning microscopy (CLSM), demonstrating that CaP NPs can enter the DCs and cause their maturation. Further studies revealed the uptake of NPs by the cells followed by deep penetration into the nucleus to induce virus-specific CD8+ T cell proliferation [168].

Apart from these NPs, the inorganic NPs also provoke the antigen-presenting cells and trigger effective immune reactions. Orlowski et al. demonstrated tannic acid-modified silver and gold NPs as potent stimulators of DCs activation. Tannic acid-modified silver (Ag) and gold (Au) NPs were pulsed with antigens derived from herpes simplex virus (HSV), followed by incubation with the dendritic cells. The NPs were stained with lysotracker to confirm the degradation of the NPs by lysosome before reaching to DCs. The intense red fluorescence over the green (lysosome) and blue (nucleus) fluorescence depicted the entry of metallic NPs into DCs by overcoming the lysosomal degradation. It has been finally reported that the modified silver and gold NPs are not degraded by lysosome and are internalized by the antigen-presenting cells to induce the maturation of DCs [169].

The above studies delineated that different nanomaterials have different effects on the immune system components, which generate various immunological effects and combat a broad range of viral pathogens.

5.2. Modulation of antibody/immunoglobulin responses

The response of antibodies provides long protection against viral infections. Antiviral antibodies like IgA, IgG, and IgM can reduce the viral burden. The ability of antiviral antibodies to neutralize or inhibit viral infection has been studied extensively [170]. Modulation of antibody response by modified nanoparticles upon viral infections is presented in Fig. 4**.** Antibodies with an antigen-recognition surface are transcribed from a complex and dynamic array of genes. The adaptive and broad binding specificities of immunoglobulins are achieved through allelic combinations and its gene segments' junctional diversity. Repetitive somatic mutation of antibody gene segments and an affinity-based selection process leads to high-affinity binding of immunoglobulins to viral antigens [169]. Viral-neutralizing antibodies can block the viral infection at any stage (attachment to the host cell surface, interaction with receptor and co-receptor, fusion/penetration, and injection of the viral genome) of the viral life cycle. Inhibition of viral infection by blocking cell surface attachment or receptor interaction by causing steric hindrance is an efficient therapeutic approach to clear the viral antigens. However, many antibodies are even reported to block infection at a post-attachment step. These viral neutralizing antibodies inhibit the conformational changes of viral proteins that are required to infect the host cells. The non-neutralizing antibodies provide immunity against viral infection directly by activating Fc (constant/effector region of antibody) -mediated antiviral mechanism, which includes antibody-dependent cell-mediated cytotoxicity (ADCC), mast cell activation, opsonization, and complement activation [171,172]. It has been reported that several nanoparticles induce viral-specific antibodies in both in vitro and *in vivo* [173,173–175]. Wang et al. designed a novel nanosystem using influenza matrix protein 2 ectodomains (M2e). Ethanol desolvation followed by crosslinking M2e with NA (NA-neuraminidase, a membrane glycoprotein of influenza virus) onto the core particle surfaces produces bi-layered protein nanoparticles. The DTSSP (3′-dithiol bis-sulfo-succinimidyl propionate) was used as a coating layer. This nanosystem significantly maintained high levels of M2e and NA-specific IgG antibodies [173]. HIV-1 Env proteins are poorly immunogenic compared to other pathogens, even with adjuvants. Iron nanoparticles and a recombinant envelope protein (SOSIP) of HIV-1 were observed to produce viral-neutralizing antibodies [174].

Researchers also explored the production of viral-specific IgG and IgM antibodies in chronic hepatitis B infection by designing dual-targeting ferritin NPs. The ferritin NPs were designed via self-assembly to deliver preS1 (a major surface protein of HBV that helps in the viral entry) to specific myeloid cells. For dual targeting, ferritin NPs were pulsed with (a) T follicular helper cells activating SIGNR1+ dendritic

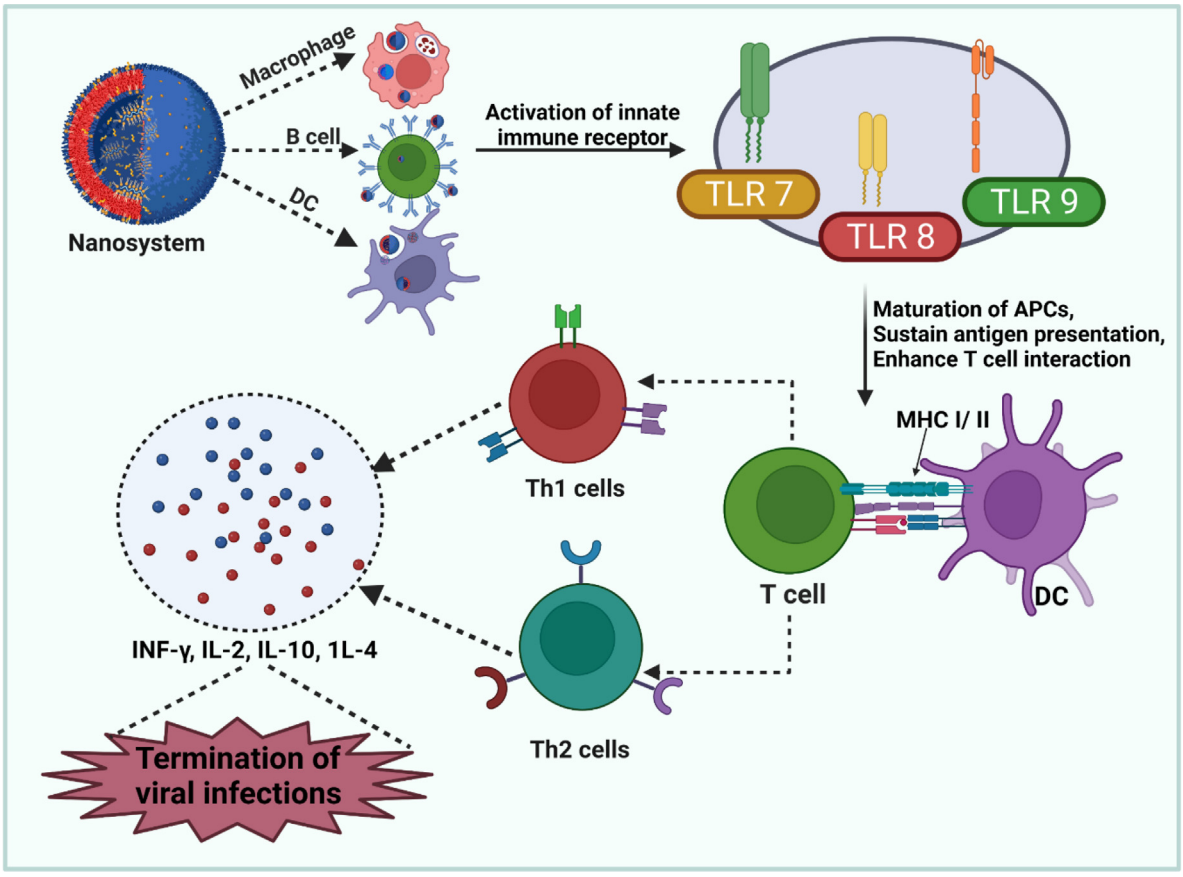

Fig. 3. Modulation of innate immune response by activating the maturations of antigen presenting cells (APCs)-macrophage, B cells, and dendritic cells and expression of innate immune resceptor like toll-like receptors (TLRs). APCs endocytosed the antigens/peptides conjugated NPs gives initial signals to TLR 7/8/9 and procced the active antiviral immune response through mature APCs-T cells interaction involving MHC-1/II. The further proliferated effector T cells and their mediators cause termination of viral infections.

cells and (b) B cells activating lymphatic sinus-associated SIGNR1+ macrophages. This nanoformulation induced a high level of anti-preS1 antibody response by signaling preS1 proteins to particular myeloid cells for the clearance of viral infection. It was observed that the ferritin NPs induced a higher anti-preS1 immune response than the control group (pre S1+CpG), indicating ferritin nanoformulations can elicit a viral-specific high-grade antibody response in chronic HBV infection. The formation of a germinal center (GC) is an essential feature of a strong antibody response. Histological analysis of lymph nodes showed that the treatment of chronic HBV infection with ferritin NP–preS1 significantly enhanced the GC higher than the control group. SIGNR1$^+$ cells are mainly distributed in the medulla and interfollicular regions of lymph nodes which plays a crucial role in early B cell activation and IgG response. The green fluorescence emission from the medullary and interfollicular region was observed upon subcutaneous administration of ferritin NPs, indicating the presence of ferritin NPs in the respective areas and co-localization with SIGNR1$^+$ cells. It is hypothesized that the ferritin NPs triggered the antibody production by activating the SIGNR1$^+$ cells [175].In summary, antibodies can potentially eliminate viral infections by direct viral neutralization or activating viral-specific immune mechanisms. Therefore, inducing high antibody production using immunomodulatory nanosystems is an effective approach in antiviral therapies.

5.3. Modulation of cytokine productions and T-cell responses

The potent antiviral immune response depends on the activation of cytotoxic T cells (CTLs), which release cytokines that lyse the virus-infected cells and thereby clear the infection. The activation of cytotoxic T lymphocytes depends on the activation and maturation of APCs. The activated CD8+ T cells (CTL) release cytotoxic granules such as perforin, granzyme, and granulysin to neutralize the infection. CD4+ T cells provide the necessary co-stimulation to activate CTL [176]. CD4+ and CD8+ T cells play a crucial role in preventing infections caused by viruses like the measles virus, cytomegalovirus (CMV), hepatitis virus (HCV), and HIV [177–180]. The significance of CTL is reported by Sridhar et al. in pandemic H1N1 influenza infection, elucidating that individuals with higher numbers of pre-existing CD8+ T cells prevent severe illness [181]. Wilkinson et al. hypothesized that CD8+ and CD4+ cells protect the host cells from influenza virus. His-research also demonstrated the importance of T cells in preventing viral infections [182]. Previous studies reported that a broad range of cytokines would be secreted by host cells upon viral infection. These cytokines play a significant role in regulating the secretion of interferons (IFNs), inflammatory chemokines (IL8), apoptosis (IL1), and chemotactic growth factors (GC–CSF). The activation of the cytokine profile depends on the nature of invading viruses. Cytokines like IL 6/8, IL α/β and TNF-α works against influenza virus; IL β, IL5/8/18, IP10, MCP-1, and MIP α/β neutralizes the filovirus; IL1/2/6/8/12/18/23, and TNF-α inactivates rotavirus; IL1/6/8, and MIP α/β clears HCV. Cytokines destroy the infected cells by mediating caspase-dependent apoptosis, necrosis, generation of adhesion agents in endothelial cells, and stimulating the extravasation of monocytes, neutrophils, and other immune cells to infection foci [78]. Nanosytem-based activation of cytokines and T cells' network upon viral infections are presented in Fig. 5.

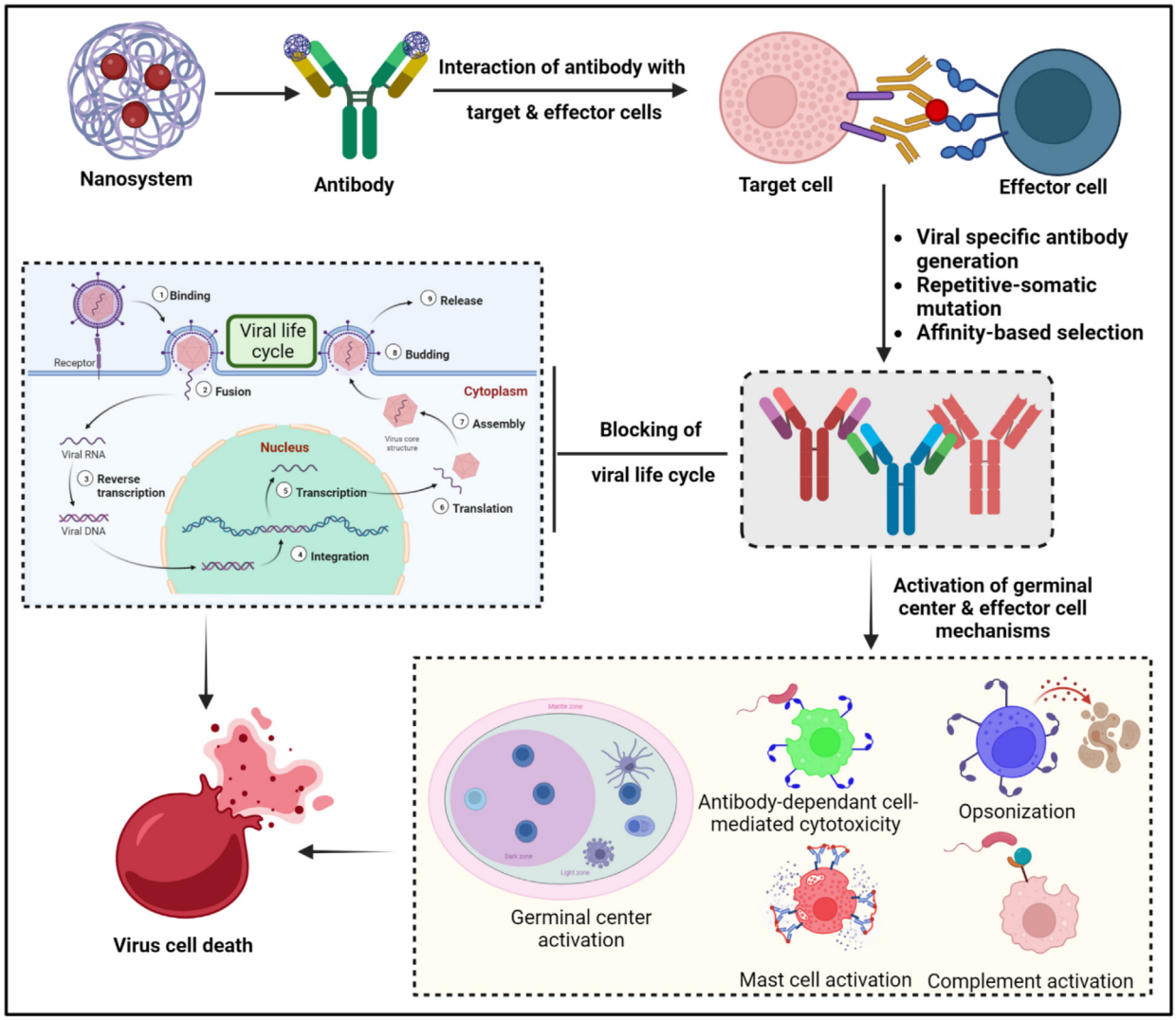

Fig. 4. Modulation of antiviral immunoglobulins response: activation of germinal center, repetitive somatic mutations and enhanced junctional diversity can activate effector cell-mediated mechanisms like antibody-dependent cell-mediated cytotoxicity (ADCC), opsonization, mast cell activation, complement activation, which can block the different stages of viral infections cycle (receptor recognition, interaction with receptor, co-receptor, entry into host cells, injection of the viral genome and replications) and clear the viral infections.

The ability of T cells and cytokines to kill the viral pathogens has motivated researchers to modulate their response in antiviral therapy for clearance of the viral infection. To overcome the adverse effects of conventional agonists or antagonists of cytotoxic T cells and cytokines, the nanoparticle-based approach is one of the potential solutions to modulate the host T cell and cytokine network in various viral diseases like respiratory syncytial virus (RSV), hepatitis B virus, HIV, and influenza [183–186]. Lee et al. synthesized virus-like NPs conjugated with glycoproteins (RSV) consisting of a mixture of fusion glycoproteins (FG-VLPs). RSV increased the levels of CD4+ and CD8+ cells, IL-4 synthesizing cells, Th2 cytokines (IL-5 and IL-13) and reduced the levels of IFN-γ by increasing mucus secretion and excessive lung tissue damage. The FG-VLP NPs were found to reduce T cell infiltration and suppress the production of pro-inflammatory cytokines in the lung tissue. FG-VLP NPs induce long-lasting immunity against RSV by suppressing the pro-inflammatory cytokines and T-cell response without causing overt pulmonary inflammation [183]. Climent et al. synthesized novel nanoparticles by loading dendritic cells into the gold nanoparticles (GNPs) having high-mannoside derivatives and selected HIV peptides. The enhanced proliferation of the HIV-specific effector CD4+ and CD8+ cells were observed. This nanoformulation was also reported to enhance efficient secretion of pro-Th1 cytokines, chemokines with a moderate production of pro-Th2, and significantly higher secretion of pro-inflammatory cytokines like TNFα and IL-1β. This study concluded that modified gold nanoparticles as a promising approach to inducing cellular immunity in HIV infection [185]. The effector T cells provide strong immunity against viral infection in the liver tissues. It has been reported that PD-1, a CD28 family member (highly expressed in liver resident kupffer cells), upon viral infection, suppresses the CD8+ function permitting the virus to infect the liver cells [187,188]. Dolina et al. explored the lipidoid nanoparticles (LNPs) consisting of PD-L1 siRNA for target-specific immune suppression and upregulation of CD8+ cells response. To determine particle uptake, mice were intravenously administered with fluorochrome-labeled siRNA-LNPs on day 5 after infection with adenovirus. Red fluorescence was observed in the fluorescence microscopy images, confirming infiltration of macrophage, DCs, CD4+, CD8+, and NK cells. A histological study of frozen liver cross-sections stained with anti-MHC II subtypes (I-A/I-E), anti-CD4, anti-CD8, and anti-NKp46 revealed a significant number of foci after PD-L1LNP treatment on day 7 post-Ad-Ova infection. All these observations confirmed the target-specific internalization of siRNA-LNP NPs [188].

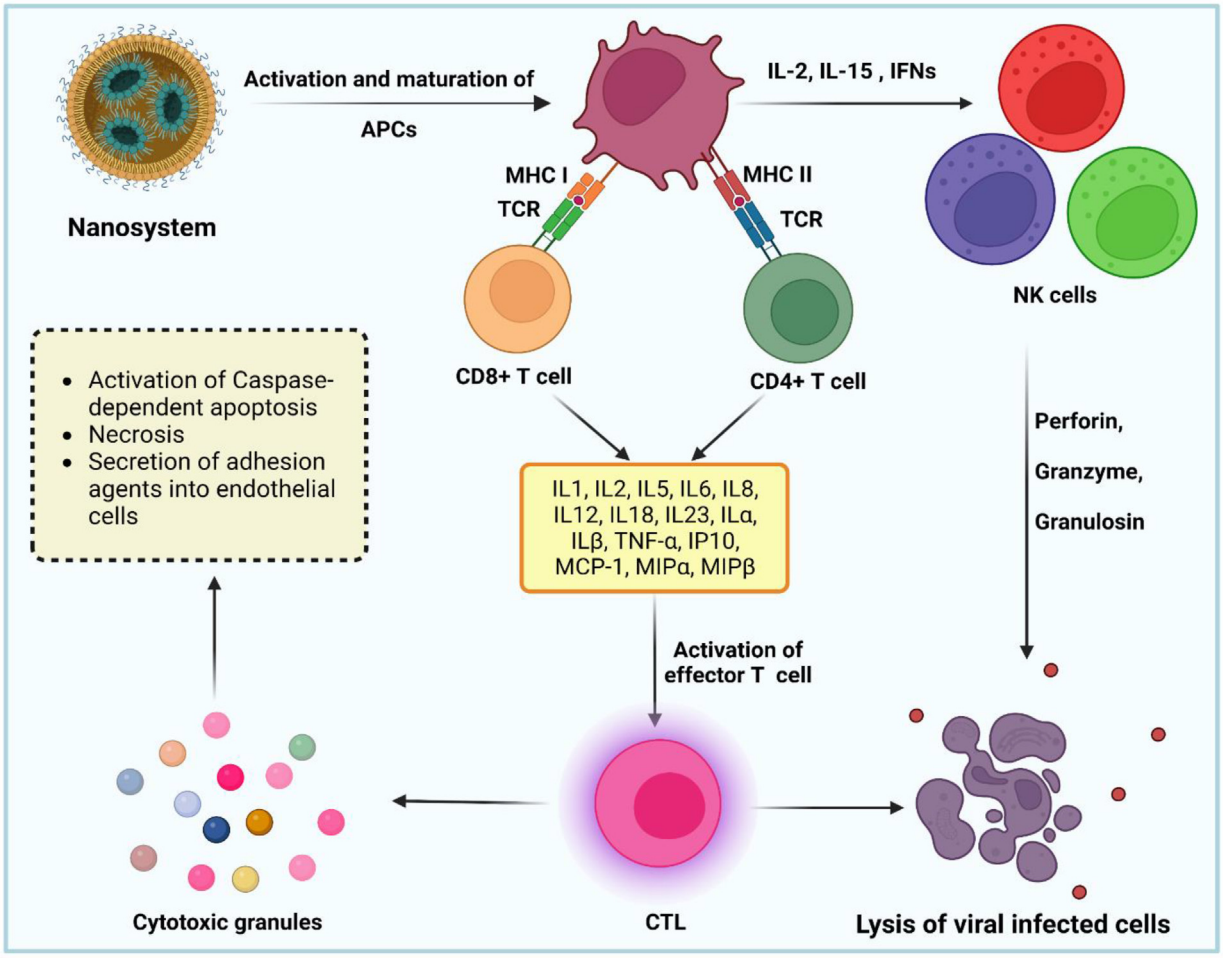

Fig. 5. Modulation of cytokine productions and T cell responses. Surcafe conjugated or modified antigens/adjuvants loaded nanosystem can activate the effector T cells mechasnim by triggring the cytokines response and activating the secretion of cytotoxic granules (perforin, granzyme & granulosin) which induce the different caspase dependent patway leading to lysis of viral infected cells.

6. Conclusion and future prospects

Nanomaterial-based immunotherapy manifests significant potential in the regression of viral infections through the modulation of host immune responses. In the current review, we presented recent progress in immunomodulatory nanosystems, such as modulation of the innate immune responses, activation of antigen-presenting cells, antibody responses, cytokine production, and T-cell response to prevent viral infections. Immune receptors/co-receptors like TLR, NLR, and PLR play a vital role in identifying pathogens and sharpening additional immune responses inside the host body. Functionalized nanoparticles preserve the antigen stability and prolong antigen release towards the APC against viral diseases such as HIV and HSV are discussed in this review. A natural innate immune response is insufficient to provide a robust antiviral response against novel and resistant viral infections. A much better and more efficient immune response is needed to clear these emerging infections. Nanoformulations with viral proteins and ferritin NPs can stimulate viral-neutralizing antibodies like IgG and IgM to reduce HBV and HIV-1 viral infections. The effector T cells and their immune activity, such as CTL and cytokine response, are the major players in the cell-mediated immune response. Various NPs that suppress the pro-inflammatory cytokines, induce the anti-inflammatory cytokines, and enhance the effector CTL response for clearance of the viral infection have been explored well in this study. The immunomodulatory nanosystems reduce viral infections by activating different receptors/co-receptors, APCs, T cells, cytokines, or other immune cells.

Although the application of IMNs showed excellent pre-clinical performance in antiviral therapy, a few challenges need to be addressed. IMNs are mainly designed by activating or suppressing the immune system. However, this strategy can provide short-term protection to the body against other pathological conditions or inflammations. Hyperactivity of immune system can cause inflammations in the body, and suppression of the immune system can cause enhanced sensitivity to several opportunist infections. Though IMNs are designed to target the hyperactive immune cells mainly to kill viral infections, there is a strong chance to induce normal healthy immune cells and can cause immune toxicity. Other unexpected results could also be attributed to the materials used in designing the IMNs can cause adverse side effects in other organs. All these limitations can put IMNs backward from clinical translations. More *in-vitro* and *in-vivo* studies are required to confirm the safety of IMNs before clinical translation. In addition to all these limitations, the exact molecular mechanism of IMNs and cellular pathways involved in activating/suppressing the immune cells is still hidden and needs more detailed explorations in the future. There is no strong evidence about the physiological effects of materials used to design the IMNs. The size, surface morphology, and complex interactions with immune systems must be explored widely. Understanding the detailed mechanism of the effects of IMNs and interactions with immune cells can assist in better designing the IMNs. Combination therapy is an important therapy to

elicit strong therapeutic effects. IMNs can combine with conventional therapy to develop an efficient therapeutic platform. Surface modifications and conjugation with fluorescence tracking agents can also unfold a new domain for IMNs in an image-guided therapy in intracellular and *in-vivo* conditions. Future research can be directed to design a novel immunomodulatory nanosystem with multifunctional possibilities to get target-specific, efficient delivery of more than one drug for broad-spectrum antiviral treatments in mixed populations.

However, curative medicines for novel remerging and drug-resistant viruses remain challenging at large, though these systems have extended our perception and unlocked a whole new ecosystem in the direction of antiviral treatments. Advancements in theranostics might yield precise diagnosis as well as adequate therapeutics and instantaneous screening, which is suitable and necessary in eradicating viral diseases. The apprehension of long-term toxicity must be given the foremost concern in developing the nanosystems. Nevertheless, with active improvements in biology, elemental chemistry, and engineering, one can be confident that the speed at which the development of new viral infections emerges can be restrained, and the overall control of viral epidemics can be more productive in the future. Precisely monitoring, controlling, and multifunctional designing IMNs can untangle a new domain in antiviral therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors would like to thank MHRD IMPRINT (4291), ICMR (No.35/1/2020-GIA/Nano/BMS), DST-Inspire (DST/INSPIRE/04/2015/000377), DST-AMT (DST/TDT/AMT/2017/227), SERB-CRG (CRG/2020/005069) grants. Author SK would like to thank University Grants Commission (UGC), Govt. of India, for UGC-JRF fellowship (18-340769). Schematics were prepared using Biorender.com.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bbiosy.2023.100073.

References

[1] Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3:991–8. doi:10.1038/ni1102-991.

[2] Finlay BB, McFadden G. Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell 2006;124:767–82. doi:10.1016/j.cell.2006.01.034.

[3] Gordon JR, Ma Y, Churchman L, Gordon SA, Dawicki W. Regulatory dendritic cells for immunotherapy in immunologic diseases. Front Immunol 2014;5:1–19. doi:10.3389/fimmu.2014.00007.

[4] Shen Y, Hao T, Ou S, Hu C, Chen L. Applications and perspectives of nanomaterials in novel vaccine development. Medchemcomm 2018;9:226–38. doi:10.1039/c7md00158d.

[5] Van Der Burg SH, Arens R, Ossendorp F, Van Hall T, Melief CJM. Vaccines for established cancer: overcoming the challenges posed by immune evasion. Nat Rev Cancer 2016;16:219–33. doi:10.1038/nrc.2016.16.

[6] Wang H, Mooney DJ. Biomaterial-assisted targeted modulation of immune cells in cancer treatment. Nat Mater 2018;17:761–72. doi:10.1038/s41563-018-0147-9.

[7] Huaux F. Emerging role of immunosuppression in diseases induced by micro-and nano-particles: time to revisit the exclusive inflammatory scenario. Front Immunol 2018;9. doi:10.3389/fimmu.2018.02364.

[8] Cifuentes-Rius A, Desai A, Yuen D, Johnston APR, Voelcker NH. Inducing immune tolerance with dendritic cell-targeting nanomedicines. Nat Nanotechnol 2021;16:37–46. doi:10.1038/s41565-020-00810-2.

[9] Oliver GF, Carr JM, Smith JR. Emerging infectious uveitis: chikungunya, dengue, Zika and Ebola: a review. Clin Exp Ophthalmol 2019;47:372–80. doi:10.1111/ceo.13450.

[10] Zhu Z, Lian X, Su X, Wu W, Marraro GA, Zeng Y. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. Respir Res 2020;21:1–14. doi:10.1186/s12931-020-01479-w.

[11] Strasfeld L, Chou S. Antiviral drug resistance: mechanisms and clinical implications. Infect Dis Clin N Am 2010;24:809–33. doi:10.1016/j.idc.2010.07.001.

[12] Pour PM, Fakhri S, Asgary S, Farzaei MH, Echeverría J. The signaling pathways, and therapeutic targets of antiviral agents: focusing on the antiviral approaches and clinical perspectives of anthocyanins in the management of viral diseases. Front Pharmacol 2019;10:1–23. doi:10.3389/fphar.2019.01207.

[13] Zhu X, Zhu Y, Ye S, Wang Q. Improved pharmacological and structural properties of HIV fusion inhibitor AP3 over enfuvirtide: highlighting advantages of artificial peptide strategy. Sci Rep 2015;5:1–15. doi:10.1038/srep13028.

[14] Dorr P, Westby M, Dobbs S. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrob Agents Chemother 2005;49:4721–32. doi:10.1128/AAC.49.11.4721-4732.2005.

[15] Schepens B, Ibañez LI, De Baets S. Nanobodies® specific for respiratory syncytial virus fusion protein protect against infection by inhibition of fusion. J Infect Dis 2011;204:1692–701. doi:10.1093/infdis/jir622.

[16] Kryst J, Kawalec P, Pilc A. Efavirenz-based regimens in antiretroviral-naive HIV-infected patients: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2015;10:1–23. doi:10.1371/journal.pone.0124279.

[17] Delmas J, Schorr O, Jamard C. Inhibitory effect of adefovir on viral DNA synthesis and covalently closed circular DNA formation in duck hepatitis B virus-infected hepatocytes *in vivo* and *in vitro*. Antimicrob Agents Chemother 2002;46:425–33. doi:10.1128/AAC.46.2.425-433.2002.

[18] Hu Y, Musharrafieh R, Ma C, Zhang J, Smee DF, DeGrado WF, Wang J. An M2-V27A channel blocker demonstrates potent in vitro and *in vivo* antiviral activities against amantadine-sensitive and -resistant influenza A viruses. Antiviral Res 2017;140:45–54. doi:10.1016/j.antiviral.2017.01.006.

[19] Ghafoor D, Khan Z, Khan A, Ualiyeva D, Zaman N. Excessive use of disinfectants against COVID-19 posing a potential threat to living beings. Curr Res Toxicol 2021;2:159–68. doi:10.1016/j.crtox.2021.02.008.

[20] Bowen A, Sweeney EE, Fernandes R. Nanoparticle-based immunoengineered approaches for combating HIV. Front Immunol 2020;11:1–9. doi:10.3389/fimmu.2020.00789.

[21] Gaziano R, Pistoia ES, Campione E, Fontana C, Marino D, Favaro M, Pica F, Francesco PDI. Immunomodulatory agents as potential therapeutic or preventive strategies for COVID-19. Eur Rev Med Pharmacol Sci 2021;25:4174–84. doi:10.26355/eurrev_202106_26061.

[22] Florindo HF, Kleiner R, Vaskovich-Koubi D, Acúrcio RC, Carreira B, Yeini E, Tiram G, Liubomirski Y, Satchi-Fainaro R. Immune-mediated approaches against COVID-19. Nat Nanotechnol 2020;15:630–45. doi:10.1038/s41565-020-0732-3.

[23] Liu Y, Wang H, Li D, Tian Y, Liu W, Zhang L, Zheng W, Hao Y, Liu J, Yang Z, Shao Y, Jiang X. *In situ* formation of peptidic nanofibers can fundamentally optimize the quality of immune responses against HIV vaccine. Nanoscale Horiz 2016;1:135–43. doi:10.1039/c5nh00064e.

[24] Bertoletti A, Bert NLe. Immunotherapy for chronic hepatitis B virus infection. Gut Liver 2018;12:497–507. doi:10.5009/gnl17233.

[25] Tazaki T, Tabata K, Ainai A, Ohara Y, Kobayashi S, Ninomiya T, Orba Y, Mitomo H, Nakano T, Hasegawa H, Ijiro K, Sawa H, Suzuki T, Niikura K. Shape-dependent adjuvanticity of nanoparticle-conjugated RNA adjuvants for intranasal inactivated influenza vaccines. RSC Adv 2018;8:16527–36. doi:10.1039/c8ra01690a.

[26] Kim H, Niu L, Larson P, Kucaba TA, Murphy KA, James BR, Ferguson DM, Griffith TS, Panyam J. Polymeric nanoparticles encapsulating novel TLR7/8 agonists as immunostimulatory adjuvants for enhanced cancer immunotherapy. Biomaterials 2018;164:38–53. doi:10.1016/j.biomaterials.2018.02.034.

[27] Li D, Sun H, Ding J, Tang Z, Zhang Y, Xu W, Zhuang X, Chen X. Polymeric topology and composition constrained polyether-polyester micelles for directional antitumor drug delivery. Acta Biomater 2013;9:8875–84. doi:10.1016/j.actbio.2013.06.041.

[28] Xu W, Ding J, Xiao C, Li L, Zhuang X, Chen X. Versatile preparation of intracellular-acidity-sensitive oxime-linked polysaccharide-doxorubicin conjugate for malignancy therapeutic. Biomaterials 2015;54:72–86. doi:10.1016/j.biomaterials.2015.03.021.

[29] Li D, Xu W, Li P, Ding J, Cheng Z, Chen L, Yan L, Chen X. Self-targeted polysaccharide prodrug suppresses orthotopic hepatoma. Mol Pharm 2016;13:4231–5. doi:10.1021/acs.molpharmaceut.6b00747.

[30] Ding J, Xiao C, Li Y, Cheng Y, Wang N, He C, Zhuang X, Zhu X, Chen X. Efficacious hepatoma-targeted nanomedicine self-assembled from galactopeptide and doxorubicin driven by two-stage physical interactions. J Control Release 2013;169:193–203. doi:10.1016/j.jconrel.2012.12.006.

[31] Chen J, Ding J, Xu W, Sun T, Xiao H, Zhuang X, Chen X. Receptor and microenvironment dual-recognizable nanogel for targeted chemotherapy of highly metastatic malignancy. Nano Lett 2017;17:4526–33. doi:10.1021/acs.nanolett.7b02129.

[32] Xu W, Ding J, Chen X. Reduction-responsive polypeptide micelles for intracellular delivery of antineoplastic agent. Biomacromolecules 2017;18:3291–301. doi:10.1021/acs.biomac.7b00950.

[33] Zhang Y, Cai L, Li D, Lao YH, Liu D, Li M, Ding J, Chen X. Tumor microenvironment-responsive hyaluronate-calcium carbonate hybrid nanoparticle enables effective

chemotherapy for primary and advanced osteosarcomas. Nano Res 2018;11:4806–22. doi:10.1007/s12274-018-2066-0.
[34] Gao S, Tang G, Hua D, Xiong R, Han J, Jiang S, Zhang Q, Huang C. Stimuli-responsive bio-based polymeric systems and their applications. J Mater Chem B 2019;7:709–29. doi:10.1039/c8tb02491j.
[35] Musetti S, Huang L. Nanoparticle-mediated remodeling of the tumor microenvironment to enhance immunotherapy. ACS Nano 2018;12:11740–55. doi:10.1021/acsnano.8b05893.
[36] Steenblock ER, Fahmy TM. A comprehensive platform for *ex vivo* T-cell expansion based on biodegradable polymeric artificial antigen-presenting cells. Mol Ther 2008;16:765–72. doi:10.1038/mt.2008.11.
[37] Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev 2012;64:1547–68. doi:10.1016/j.addr.2012.04.005.
[38] Yang HW, Ye L, Guo XD, Yang C, Compans RW, Prausnitz MR. Ebola vaccination using a DNA vaccine coated on PLGA-PLL/γPGA nanoparticles administered using a microneedle patch. Adv Healthc Mater 2017;6:1–7. doi:10.1002/adhm.201600750.
[39] Chahal JS, Khan OF, Cooper CL, McPartlan JS, Tsosie JK, Tilley LD, Sidik SM, Lourido S, Langer R, Bavari S, Ploegh HL, Anderson DG. Dendrimer-RNA nanoparticles generate protective immunity against lethal ebola, H1N1 influenza, and Toxoplasma gondii challenges with a single dose. Proc Natl Acad Sci U S A 2016;113:E4133–42. doi:10.1073/pnas.1600299113.
[40] Li S, Feng X, Wang J, He L, Wang C, Ding J, Chen X. Polymer nanoparticles as adjuvants in cancer immunotherapy. Nano Res 2018;11:5769–86. doi:10.1007/s12274-018-2124-7.
[41] Xiao H, Yan L, Dempsey EM, Song W, Qi R, Li W, Huang Y, Jing X, Zhou D, Ding J, Chen X. Recent progress in polymer-based platinum drug delivery systems. Prog Polym Sci 2018;87:70–106. doi:10.1016/j.progpolymsci.2018.07.004.
[42] Wang Y, Jiang Z, Xu W, Yang Y, Zhuang X, Ding J, Chen X. Chiral polypeptide thermogels induce controlled inflammatory response as potential immunoadjuvants. ACS Appl Mater Interfaces 2019;11:8725–30. doi:10.1021/acsami.9b01872.
[43] 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;17:7387–93. doi:10.1021/acs.nanolett.7b03218.
[44] Song X, Xu J, Liang C, Chao Y, Jin Q, Wang C, Chen M, Liu Z. Self-supplied tumor oxygenation through separated liposomal delivery of H2O2 and catalase for enhanced radio-immunotherapy of cancer. Nano Lett 2018;18:6360–8. doi:10.1021/acs.nanolett.8b02720.
[45] He L, Xu W, Wang X, Wang C, Ding J, Chen X. Polymer micro/nanocarrier-assisted synergistic chemohormonal therapy for prostate cancer. Biomater Sci 2018;6:1433–44. doi:10.1039/c8bm00190a.
[46] Wang J, Xu W, Li S, Qiu H, Li Z, Wang C, Wang X, Ding J. Polylactide-cholesterol stereocomplex micelle encapsulating chemotherapeutic agent for improved antitumor efficacy and safety. J Biomed Nanotechnol 2018;14:2102–13. doi:10.1166/jbn.2018.2624.
[47] Chen J, Ding J, Zhang Y, Xiao C, Zhuang X, Chen X. Polyion complex micelles with gradient pH-sensitivity for adjustable intracellular drug delivery. Polym Chem 2015;6:397–405. doi:10.1039/c4py01149j.
[48] Guo H, Li F, Xu W, Chen J, Hou Y, Wang C, Ding J, Chen X. Mucoadhesive cationic polypeptide nanogel with enhanced penetration for efficient intravesical chemotherapy of bladder cancer. Adv Sci 2018;5. doi:10.1002/advs.201800004.
[49] Zhang Y, Wang F. Self-stabilized hyaluronate nanogel for intracellular codelivery of doxorubicin and cisplatin to osteosarcoma. Adv Sci 2018;5(5):1700821 (Weinh)Feb 15. doi:10.1002/advs.201700821.
[50] Chen W, Wang Y, Qin M, Zhang X, Zhang Z, Sun X, Gu Z. Bacteria-driven hypoxia targeting for combined biotherapy and photothermal therapy. ACS Nano 2018;12:5995–6005. doi:10.1021/acsnano.8b02235.
[51] Nam J, Son S, Ochyl LJ, Kuai R, Schwendeman A, Moon JJ. Chemo-photothermal therapy combination elicits anti-tumor immunity against advanced metastatic cancer. Nat Commun 2018;9. doi:10.1038/s41467-018-03473-9.
[52] Ye Y, Wang C, Zhang X, Hu Q, Zhang Y, Liu Q, Wen D, Milligan J, Bellotti A, Huang L, Dotti G, Gu Z. Supplementary materials for a melanin-mediated cancer immunotherapy patch. Sci Immunol 2017;2(17):eaan5692 21–13. 10. doi:10.1126/sciimmunol.aan5692.
[53] Stead SO, Kireta S, McInnes SJP, Kette FD, Sivanathan KN, Kim J, Cueto-Diaz EJ, Cunin F, Durand JO, Drogemuller CJ, Carroll RP, Voelcker NH, Coates PT. Murine and non-human primate dendritic cell targeting nanoparticles for *in vivo* generation of regulatory t-cells. ACS Nano 2018;12:6637–47. doi:10.1021/acsnano.8b01625.
[54] Yang R, Xu J, Xu L, Sun X, Chen Q, Zhao Y, Peng R, Liu Z. Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. ACS Nano 2018;12:5121–9. doi:10.1021/acsnano.7b09041.
[55] Shi GN, Zhang CN, Xu R, Niu JF, Song HJ, Zhang XY, Wang WW, Wang YM, Li C, Wei XQ, Kong DL. Enhanced antitumor immunity by targeting dendritic cells with tumor cell lysate-loaded chitosan nanoparticles vaccine. Biomaterials 2017;113:191–202. doi:10.1016/j.biomaterials.2016.10.047.
[56] Heo R, Park JS, Jang HJ, Kim SH, Shin JM, Suh YD, Jeong JH, Jo DG, Park JH. Hyaluronan nanoparticles bearing γ-secretase inhibitor: *in vivo* therapeutic effects on rheumatoid arthritis. J Control Release 2014;192:295–300. doi:10.1016/j.jconrel.2014.07.057.
[57] Yang M, Ding J, Zhang Y, Chang F, Wang J, Gao Z, Zhuang X, Chen X. Activated macrophage-targeted dextran-methotrexate/folate conjugate prevents deterioration of collagen-induced arthritis in mice. J Mater Chem B 2016;4:2102–13. doi:10.1039/c5tb02479j.
[58] Yang M, Ding J, Feng X, Chang F, Wang Y, Gao Z, Zhuang X, Chen X. Scavenger receptor-mediated targeted treatment of collagen-induced arthritis by dextran sulfate-methotrexate prodrug. Theranostics 2017;7:97–105. doi:10.7150/thno.16844.
[59] Bahmani B, Uehara M, Jiang L, Ordikhani F, Banouni N, Ichimura T, Solhjou Z, Furtmüller GJ, Brandacher G, Alvarez D, Von Andrian UH, Uchimura K, Xu Q, Vohra I, Yilmam OA, Haik Y, Azzi J, Kasinath V, Bromberg JS, McGrath MM, Abdi R. Targeted delivery of immune therapeutics to lymph nodes prolongs cardiac allograft survival. J Clin Invest 2018;128:4770–86. doi:10.1172/JCI120923.
[60] Ma L, Liu TW, Wallig MA, Dobrucki IT, Dobrucki LW, Nelson ER, Swanson KS, Smith AM. Efficient targeting of adipose tissue macrophages in obesity with polysaccharide nanocarriers. ACS Nano 2016;10:6952–62. doi:10.1021/acsnano.6b02878.
[61] Heo R, You DG, Um W, Choi KY, Jeon S, Park JS, Choi Y, Kwon S, Kim K, Kwon IC, Jo DG, Kang YM, Park JH. Dextran sulfate nanoparticles as a theranostic nanomedicine for rheumatoid arthritis. Biomaterials 2017;131:15–26. doi:10.1016/j.biomaterials.2017.03.044.
[62] Tsopelas C, Sutton Richard. Why certain dyes are useful for localizing the sentinel lymph node. J Nucl Med 2002;43(10):1377–82 Oct.
[63] van der Burg SH, Arens R, Melief CJM. Immunotherapy for persistent viral infections and associated disease. Trends Immunol 2011;32:97–103. doi:10.1016/j.it.2010.12.006.
[64] Parnham MJ. Immunomodulatory approaches to the treatment of infections. Infektološki glasnik 2011;31(1):15–27. https://hrcak.srce.hr/index.php/66751.
[65] Isorce N, Lucifora J, Zoulim F, Durantel D. Immune-modulators to combat hepatitis B virus infection: from IFN-α to novel investigational immunotherapeutic strategies. Antiviral Res 2015;122:69–81. doi:10.1016/j.antiviral.2015.08.008.
[66] Kreil TR. Treatment of ebola virus infection with antibodies from reconvalescent donors. Emerg Infect Dis 2015;21:521–3. doi:10.3201/eid2103.141838.
[67] Gilliet M, Cao W, Liu Y. Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. Nat Rev Immunol 2008;8(8):594–606 Aug. doi:10.1038/nri2358.
[68] Immunology - 2012Zhou - Dendritic cell-based immunity and vaccination against hepatitis C virus infection. Immunology 2012;136(4):385–96 Aug. doi:10.1111/j.1365-2567.2012.03590.x.
[69] Martin-Gayo E, Yu XG. Role of dendritic cells in natural immune control of HIV-1 infection. Front Immunol 2019;10:1–9. doi:10.3389/fimmu.2019.01306.
[70] Bedoui S, Greyer M. The role of dendritic cells in immunity against primary herpes simplex virus infections. Front Microbiol 2014;5:1–9. doi:10.3389/fmicb.2014.00533.
[71] Alexopoulou A, Karayiannis P. Interferon-based combination treatment for chronic hepatitis C in the era of direct acting antivirals. Ann Gastroenterol 2015;28:55–65.
[72] K. Ramanathan, D. Antognini, A. Combes, M. Paden, B. Zakhary, M. Ogino, G. Maclaren, D. Brodie, Since january 2020 elsevier has created a COVID-19 resource centre with free information in english and mandarin on the novel coronavirus COVID- research that is available on the COVID-19 resource centre - including this for unrestricted research re-use a, (2020) 19–21.
[73] M. Enamul, H. Kayesh, M. Kohara, Recent insights into the molecular mechanism of toll-like receptor response to dengue virus infection, 12 (2021) 1–13. 10.3389/fmicb.2021.744233.
[74] Horsmans Y, Berg T, Desager J, T. Isatoribine, an agonist of TLR7, reduces plasma virus concentration in chronic hepatitis C infection. Hepatology 2005;42(3):724–31 Sep. doi:10.1002/hep.20839.
[75] J.G. Mchutchison, B.R. Bacon, S.C. Gordon, Phase 1B, randomized, double-blind, dose-escalation trial of CPG 10101 in patients with chronic hepatitis C virus, (2007) 1341–9. 10.1002/hep.21773.
[76] S.P. Kasturi, M. Ata, U. Rasheed, C. Havenar-daughton, 3M-052, a synthetic TLR-7 /8 agonist, induces durable HIV-1 envelope – specific plasma cells and humoral immunity in nonhuman primates, 1025 (2020). 26 Jun 2020. Vol 5, Issue 48. 10.1126/sciimmunol.abb1025
[77] Pindel A, Sadler A. The role of protein kinase R in the interferon response. J Interf Cytokine Res 2011;31:59–70. doi:10.1089/jir.2010.0099.
[78] Luis Muñoz-Carrillo J, Francisco Contreras-Cordero J, Gutiérrez-Coronado O, Trinidad Villalobos-Gutiérrez P, Guillermo Ramos-Gracia L, Elizabeth Hernández-Reyes V. Cytokine profiling plays a crucial role in activating immune system to clear infectious pathogens. Immune Response Act Immunomodulation 2019. doi:10.5772/intechopen.80843.
[79] Ahamad N, Kar A, Mehta S, Dewani M, Ravichandran V, Bhardwaj P, Sharma S, Banerjee R. Biomaterials immunomodulatory nanosystems for treating inflammatory diseases. Biomaterials 2021;274:120875. doi:10.1016/j.biomaterials.2021.120875.
[80] Grego EA, Siddoway AC, Uz M, Liu L, Christiansen C, Ross KA, Kelly SM, Mallapragada K, Wannemuehler MJ, Narasimhan B. Polymeric nanoparticle-based vaccine adjuvants and delivery vehicles. Curr Top Microbiol Immunol 2021;433:29–76. doi:10.1007/82_2020_226.
[81] S.C. Svindland, G.K. Pedersen, R.D. Pathirana, G. Bredholt, J.K. Nøstbakken, A study of Chitosan and c-di-GMP as mucosal adjuvants for intranasal influenza H5N1 vaccine, (2012) 1–13. 10.1111/irv.12056.
[82] Gómez DM, UInchima S, Hernandez JC. Silica nanoparticles induce NLRP3 inflammasome activation in human primary immune cells. Innate Immun 2017;23(8):697–708 Nov. doi:10.1177/1753425917738331.
[83] I.C. Allen, M.A. Scull, C.B. Moore, E.K. Holl, E. Mcelvania-, D.J. Taxman, E.H. Guthrie, R.J. Pickles, P. Jenny, NIH Public Access, 30 (2010) 556–65. 10.1016/j.immuni.2009.02.005.The.
[84] Chen H, Huang C, Lin S, Fang Z. Biomaterials Synthetic virus-like particles prepared via protein corona formation enable effective vaccination in an avian model of coronavirus infection. Biomaterials 2016;106:111–18 Nov. doi:10.1016/j.biomaterials.2016.08.018.

[85] Cristian D, Soares F, Poletto F, Eberhardt MJ, Calazans S, De Sousa FB, Luiza M. Polymer-hybrid nanosystems for antiviral applications: current advances. Biomed Pharmacother 2022;146:112249 Feb. doi:10.1016/j.biopha.2021.112249.

[86] Yu Y, Ding J, Zhou Y, Xiao H, Wu G. Biosafety chemistry and biosafety materials: a new perspective to solve biosafety problems. Biosaf Heal 2022;4:15–22. doi:10.1016/j.bsheal.2022.01.001.

[87] Ding J, Xiao H, Chen X. Advanced biosafety materials for prevention and theranostics of biosafety issues. Biosaf Heal 2022;4:59–60. doi:10.1016/j.bsheal.2022.03.011.

[88] Sandhiya S, Dkhar SA, Surendiran A. Emerging trends of nanomedicine - an overview. Fundam Clin Pharmacol 2009;23:263–9. doi:10.1111/j.1472-8206.2009.00692.x.

[89] Grobelny J, DelRio FW, Pradeep N, Kim D-I, Hackley VA, Cook RF. NIST - NCL joint assay protocol, PCC-6 size measurement of nanoparticles using atomic force microscopy. Methods Mol Biol 2011;697:71–82. doi:10.1007/978-1-60327-198-1_7.

[90] Pelaz B, Alexiou C, Alvarez-Puebla RA. Diverse applications of nanomedicine. ACS Nano 2017;11:2313–81. doi:10.1021/acsnano.6b06040.

[91] Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: therapeutic applications and developments. Clin Pharmacol Ther 2008;83:761–9. doi:10.1038/sj.clpt.6100400.

[92] Han X, Xu K, Taratula O, Farsad K. Applications of nanoparticles in biomedical imaging. Nanoscale 2019;11:799–819. doi:10.1039/c8nr07769j.

[93] Yohan D, Chithrani BD. Applications of nanoparticles in nanomedicine. J Biomed Nanotechnol 2014;10:2371–92. doi:10.1166/jbn.2014.2015.

[94] Mieszawska AJ, Mulder WJM, Fayad ZA, Cormode DP. Multifunctional gold nanoparticles for diagnosis and therapy of disease. Mol Pharm 2013;10:831–47. doi:10.1021/mp3005885.

[95] Yetisgin AA, K, Cetinel Sibel, Zuvin Merve, Kosar Ali, Ozlem. Therapeutic nanoparticles and their targeted delivery applications. Molecules 2020;25(9):2193 May 8. doi:10.3390/molecules25092193.

[96] Jahan ST, Sadat SMA, Walliser M, Haddadi A. Targeted therapeutic nanoparticles: an immense promise to fight against cancer. J Drug Deliv 2017;2017:1–24. doi:10.1155/2017/9090325.

[97] Alavi M, Hamidi M. Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles. Drug Metab Pers Ther 2019;34:1–8. doi:10.1515/dmpt-2018-0032.

[98] Torchilin VP. Passive and active drug targeting: drug delivery to tumors as an example. Handb Exp Pharmacol 2010(197):3–53. doi:10.1007/978-3-642-00477-3_1.

[99] Colino CI, Millán CG, Lanao JM. Nanoparticles for signaling in biodiagnosis and treatment of infectious diseases. Int J Mol Sci 2018;19:3–5. doi:10.3390/ijms19061627.

[100] Fang RH, Zhang L. Combatting infections with nanomedicine. Adv Healthc Mater 2018;7:1–2. doi:10.1002/adhm.201800392.

[101] Perciani CT, Liu LY, Wood L, Macparland SA. Enhancing immunity with nanomedicine: employing nanoparticles to harness the immune system. ACS Nano 2021;15:7–20. doi:10.1021/acsnano.0c08913.

[102] Huang X, Xu W, Li M, Zhang P, Zhang YS, Ding J, Chen X. Antiviral biomaterials. Matter 2021;4:1892–918. doi:10.1016/j.matt.2021.03.016.

[103] Maduray K, Parboosing R. Metal nanoparticles: a promising treatment for viral and arboviral infections. Biol Trace Elem Res 2021;199:3159–76. doi:10.1007/s12011-020-02414-2.

[104] Draz MS, Shafiee H. Applications of gold nanoparticles in virus detection. Theranostics 2018;8:1985–2017. doi:10.7150/thno.23856.

[105] Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules 2011;16:8894–918. doi:10.3390/molecules16108894.

[106] Jeremiah SS, Miyakawa K, Morita T, Yamaoka Y, Ryo A. Potent antiviral effect of silver nanoparticles on SARS-CoV-2. Biochem Biophys Res Commun 2020;533:195–200. doi:10.1016/j.bbrc.2020.09.018.

[107] Hashiguchi S, Yoshida H, Akashi T. Titanium dioxide nanoparticles exacerbate pneumonia in respiratory syncytial virus (RSV)-infected mice. Environ Toxicol Pharmacol 2015;39:879–86. doi:10.1016/j.etap.2015.02.017.

[108] Kumar R, Nayak M, Sahoo GC. Iron oxide nanoparticles based antiviral activity of H1N1 influenza A virus. J Infect Chemother 2019;25:325–9. doi:10.1016/j.jiac.2018.12.006.

[109] Ng SW, Selvarajah GT, Hussein MZ, Yeap SK, Omar AR. *In vitro* evaluation of curcumin-encapsulated chitosan nanoparticles against feline infectious peritonitis virus and pharmacokinetics study in cats. Biomed Res Int 2020;2020. doi:10.1155/2020/3012198.

[110] Hajam IA, Senevirathne A, Hewawaduge C, Kim J, Lee JH. Intranasally administered protein coated chitosan nanoparticles encapsulating influenza H9N2 HA2 and M2e mRNA molecules elicit protective immunity against avian influenza viruses in chickens. Vet Res 2020;51:1–17. doi:10.1186/s13567-020-00762-4.

[111] Mohamed SH, Arafa AS, Mady WH, Fahmy HA, Omer LM, Morsi RE. Preparation and immunological evaluation of inactivated avian influenza virus vaccine encapsulated in chitosan nanoparticles. Biologicals 2018;51:46–53. doi:10.1016/j.biologicals.2017.10.004.

[112] Hu CMJ, Chen YT, Fang ZS, Chang WS, Chen HW. Antiviral efficacy of nanoparticulate vacuolar ATPase inhibitors against influenza virus infection. Int J Nanomed 2018;13:8579–93. doi:10.2147/IJN.S185806.

[113] Zhao Z, Xiao Y, Xu L, Liu Y, Jiang G, Wang W, Li B, Zhu T, Tan Q, Tang L, Zhou H, Huang X, Shan H. Glycyrrhizic acid nanoparticles as antiviral and anti-inflammatory agents for COVID-19 treatment. ACS Appl Mater Interfaces 2021;13:20995–1006. doi:10.1021/acsami.1c02755.

[114] Sahin U, Muik A, Derhovanessian E. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 2020;586(7830):594–9 OctEpub 2020 Sep 30. doi:10.1038/s41586-020-2814-7.

[115] Sahin U, Muik A, Vogler I. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 2021;595. doi:10.1038/s41586-021-03653-6.

[116] C. Keech, G. Albert, I. Cho, Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine, (2020) 1–13. 10.1056/NEJMoa2026920.

[117] Young Y, Ho H, Park W. Biomaterials Long-acting nanoparticulate DNase-1 for effective suppression of SARS-CoV-2-mediated neutrophil activities and cytokine storm. Biomaterials 2021;267:120389. doi:10.1016/j.biomaterials.2020.120389.

[118] Sumbayev VV, Yasinska IM, Garcia CP. Gold nanoparticles downregulate interleukin-1β-induced pro-inflammatory responses. Small 2013;9:472–7. doi:10.1002/smll.201201528.

[119] Lappas CM. The immunomodulatory effects of titanium dioxide and silver nanoparticles. Food Chem Toxicol 2015;85:78–83. doi:10.1016/j.fct.2015.05.015.

[120] Pescatori M, Bedognetti D, Venturelli E, Ménard-Moyon C, Bernardini C, Muresu E, Piana A, Maida G, Manetti R, Sgarrella F, Bianco A, Delogu LG. Functionalized carbon nanotubes as immunomodulator systems. Biomaterials 2013;34:4395–403. doi:10.1016/j.biomaterials.2013.02.052.

[121] Krombach F, Münzing S, Allmeling AM, Gerlach JT, Behr J, Dörger M. Cell size of alveolar macrophages: an interspecies comparison. Environ Health Perspect 1997;105(Suppl):1261–3. doi:10.1289/ehp.97105s51261.

[122] Irvine DJ, Swartz MA, Szeto GL. Engineering synthetic vaccines using cues from natural immunity. Nat Mater 2013;12:978–90. doi:10.1038/nmat3775.

[123] Champion JA, Walker A, Mitragotri S. Role of particle size in phagocytosis of polymeric microspheres. Pharm Res 2008;25:1815–21. doi:10.1007/s11095-008-9562-y.

[124] Yu SS, Lau CM, Thomas SN, Jerome WGray, Maron DJ, Dickerson JH, Hubbell JA, Giorgio TD. Size- and charge-dependent non-specific uptake of PEGylated nanoparticles by macrophages. Int J Nanomed 2012;7:799–813. doi:10.2147/IJN.S28531.

[125] Doshi N, Mitragotri S. Macrophages recognize size and shape of their targets. PLoS One 2010;5:1–6. doi:10.1371/journal.pone.0010051.

[126] Garapaty A, Champion JA. Shape of ligand immobilized particles dominates and amplifies the macrophage cytokine response to ligands. PLoS One 2019;14:12–14. doi:10.1371/journal.pone.0217022.

[127] Sharma G, Valenta DT, Altman Y, Harvey S, Xie H, Mitragotri S, Smith JW. Polymer particle shape independently influences binding and internalization by macrophages. J Control Release 2010;147:408–12. doi:10.1016/j.jconrel.2010.07.116.

[128] Safari H, Kelley WJ, Saito E, Kaczorowski N, Carethers L, Shea LD, Eniola-Adefeso O, Eniola-Adefeso O. Neutrophils preferentially phagocytose elongated particles-an opportunity for selective targeting in acute inflammatory diseases. Sci Adv 2020;6:1–10. doi:10.1126/sciadv.aba1474.

[129] Sato M, Suzuki K, Ueki Y, Ohashi T. Microelastic mapping of living endothelial cells exposed to shear stress in relation to three-dimensional distribution of actin filaments. Acta Biomater 2007;3:311–19. doi:10.1016/j.actbio.2006.07.009.

[130] Nogueira E, Gomes AC, Preto A, Cavaco-Paulo A. Folate-targeted nanoparticles for rheumatoid arthritis therapy. Nanomed Nanotechnol Biol Med 2016;12:1113–26. doi:10.1016/j.nano.2015.12.365.

[131] Zhang Q, Dehaini D, Zhang Y, Zhou J, Chen X, Zhang L, Fang RH, Gao W, Zhang L. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. Nat Nanotechnol 2018;13:1182–90. doi:10.1038/s41565-018-0254-4.

[132] Li R, He Y, Zhu Y, Jiang L, Zhang S, Qin J, Wu Q, Dai W, Shen S, Pang Z, Wang J. Route to rheumatoid arthritis by macrophage-derived microvesicle-coated nanoparticles. Nano Lett 2019;19:124–34. doi:10.1021/acs.nanolett.8b03439.

[133] Li Y, Liang Q, Zhou L. An ROS-responsive artesunate prodrug nanosystem co-delivers dexamethasone for rheumatoid arthritis treatment through the HIF-1α/NF-κB cascade regulation of ROS scavenging and macrophage repolarization. Acta Biomater 2022;152:406–24 Oct 15. doi:10.1016/j.actbio.2022.08.054.

[134] Yang B, Chen Y, Shi J. Reactive oxygen species (ROS)-based nanomedicine. Chem Rev 2019;119:4881–985. doi:10.1021/acs.chemrev.8b00626.

[135] Baugh MD, Perry MJ, Hollander AP, Davies DR, Cross SS, Lobo AJ, Taylor CJ, Evans GS. Matrix metalloproteinase levels are elevated in inflammatory bowel disease. Gastroenterology 1999;117:814–22. doi:10.1016/S0016-5085(99)70339-2.

[136] Ahamad N, Prabhakar A, Mehta S, Singh E, Bhatia E, Sharma S, Banerjee R. Trigger-responsive engineered-nanocarriers and image-guided theranostics for rheumatoid arthritis. Nanoscale 2020;12:12673–97. doi:10.1039/d0nr01648a.

[137] Shields CW, Wang LLW, Evans MA, Mitragotri S. Materials for immunotherapy. Adv Mater 2020;32:1–56. doi:10.1002/adma.201901633.

[138] Wu J, Leong-Poi H, Bin J, Yang L, Liao Y, Liu Y, Cai J, Xie J, Liu Y. Efficacy of contrast-enhanced US and magnetic microbubbles targeted to vascular cell adhesion molecule-1 for molecular imaging of atherosclerosis. Radiology 2011;260:463–71. doi:10.1148/radiol.11102251.

[139] A. Manuscript, Trigger-responsive engineered-nanocarriers and image-guided theranostics for Rheumatoid Arthritis, (2020). 10.1039/D0NR01648A.

[140] Milovanovic M, Arsenijevic A, Milovanovic J, Kanjevac T, Arsenijevic N. Nanoparticles in antiviral therapy. Antimicrob Nanoarchitecton From Synth Appl 2017:383–410. doi:10.1016/B978-0-323-52733-0.00014-8.

[141] Cojocaru FD, Botezat D, Gardikiotis I, Uritu CM, Dodi G, Trandafir L, Rezus C, Rezus E, Tamba BI, Mihai CT. Nanomaterials designed for antiviral drug delivery transport across biological barriers. Pharmaceutics 2020;12:1–34. doi:10.3390/pharmaceutics12020171.

[142] Taha H, Das A, Das Satyajit. Clinical effectiveness of dolutegravir in the treatment of HIV /AIDS. Infect Drug Resist 2015;8:339–52 Oct 1. doi:10.2147/IDR.S68396.

[143] Van Genechten T, Van Heerden J, Bauters T. Successful treatment of adenovirus infection with brincidofovir in an immunocompromised patient after hematological stem cell transplantation. Case Rep Infect Dis 2020;2020:5981289 Jan 7. doi:10.1155/2020/5981289.
[144] Dunning J, Kennedy SB, Antierens A. Experimental treatment of ebola virus disease with brincidofovir. PLoS One 2016;11:1–10. doi:10.1371/journal.pone.0162199.
[145] El-haddad D, El Chaer F, Vanichanan J. Brincidofovir (CMX-001) for refractory and resistant CMV and HSV infections in immunocompromised cancer patients: a single-center experience Danielle. Antiviral Res 2016. doi:10.1016/j.antiviral.2016.08.024.
[146] Lee YJ, Neofytos D, Kim SJ. Efficacy of Brincidofovir as prophylaxix against HSV and VZV in hematopoietic cell transplant recipients. Transpl Infect Dis 2018;20(6):e12977 Dec. doi:10.1111/tid.12977.
[147] Alame MM, Massaad E, Zaraket H. Peramivir: a novel intravenous neuraminidase inhibitor for treatment of acute influenza infections. Front Microbiol 2016;7:1–14. doi:10.3389/fmicb.2016.00450.
[148] Russo AT, Grosenbach DW, Chinsangaram J. An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications. Expert Rev Anti Infect Ther 2021;19(3):331–44 Mar. doi:10.1080/14787210.2020.1819791.
[149] Schütz CA, Juillerat-jeanneret L, Mueller H, Lynch I, Riediker M. Therapeutic nanoparticles in clinics and under clinical evaluation. Nanomedicine 2013;8(3):449–67 (Lond)Mar. doi:10.2217/nnm.13.8.
[150] Irvine DJ, Hanson MC, Rakhra K, Tokatlian T. Synthetic nanoparticles for vaccines and immunotherapy. Chem Rev 2015;115:11109–46. doi:10.1021/acs.chemrev.5b00109.
[151] Hatz C, Van Der Ploeg R, Beck BR, Fro G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis a vaccine delayed up to 11 years. Clin Vaccine Immunol 2011;18(5):885–7 May. doi:10.1128/CVI.00358-10.
[152] Mischler R, Metcalfe IC. Inflexal ® V a trivalent virosome subunit influenza vaccine: production. Vaccine 2002;20(Suppl 5):B17–23 Dec 20. doi:10.1016/s0264-410x(02)00512-1.
[153] M. Lay, B. Callejo, S. Chang, Cationic lipid /DNA complexes (JVRS-100) combined with influenza vaccine (Fluzone ®) increases antibody response, cellular immunity, and antigenically drifted protection, 27 (2009) 3811–20. 10.1016/j.vaccine.2009.04.054.
[154] K. Reither, L. Katsoulis, T. Beattie, N. Gardiner, Safety and immunogenicity of H1 /IC31 H, an adjuvanted TB subunit vaccine, in HIV-infected adults with CD4 + lymphocyte counts greater than 350 cells / mm 3 : a phase II, multi-centre, double-blind, randomized, placebo-controlled trial, (2014) 1–19. 10.1371/journal.pone.0114602.
[155] Pearse MJ, Drane D. ISCOMATRIX TM adjuvant : a potent inducer of humoral and cellular immune responses. Vaccine 2004 Jun 23;22(19):2391–5. doi:10.1016/j.vaccine.2003.12.031.
[156] Feng X, Xu W, Li Z, Song W, Ding J, Chen X. Immunomodulatory nanosystems. Adv Sci 2019;6. doi:10.1002/advs.201900101.
[157] Boeckh M, Corey L. Adoptive immunotherapy of viral infections: should infectious disease embrace cellular immunotherapy? J Infect Dis 2017;216:926–8. doi:10.1093/infdis/jix360.
[158] Leleux J, Roy K. Micro and nanoparticle-based delivery systems for vaccine immunotherapy: an immunological and materials perspective. Adv Healthc Mater 2013;2:72–94. doi:10.1002/adhm.201200268.
[159] Amarante-Mendes GP, Adjemian S, Branco LM, Zanetti LC, Weinlich R, Bortoluci KR. Pattern recognition receptors and the host cell death molecular machinery. Front Immunol 2018;9:1–19. doi:10.3389/fimmu.2018.02379.
[160] Mendes AF, Cruz MT, Gualillo O. Editorial: the physiology of inflammation—the final common pathway to disease. Front Physiol 2018;9:1–3. doi:10.3389/fphys.2018.01741.
[161] Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. Int Rev Immunol 2011;30:16–34. doi:10.3109/08830185.2010.529976.
[162] Wheat W, Chow L, Coy J, Contreras E, Lappin M, Dow S. Activation of upper respiratory tract mucosal innate immune responses in cats by liposomal toll-like receptor ligand complexes delivered topically. J Vet Intern Med 2019;33:838–45. doi:10.1111/jvim.15426.
[163] Bawage SS, Tiwari PM, Singh A, Dixit S, Pillai SR, Dennis VA, Singh SR. Gold nanorods inhibit respiratory syncytial virus by stimulating the innate immune response. Nanomed Nanotechnol Biol Med 2016;12:2299–310. doi:10.1016/j.nano.2016.06.006.
[164] Gaudino SJ, Kumar P. Cross-talk between antigen presenting cells and T cells impacts intestinal homeostasis, bacterial infections, and tumorigenesis. Front Immunol 2019;10:1–14. doi:10.3389/fimmu.2019.00360.
[165] Andorko JI, Jewell CM. Designing biomaterials with immunomodulatory properties for tissue engineering and regenerative medicine. Bioeng. Transl Med 2017;2:139–55. doi:10.1002/btm2.10063.
[166] Vela Ramirez JE, Roychoudhury R, Habte HH, Cho MW, Pohl NLB, Narasimhan B. Carbohydrate-functionalized nanovaccines preserve HIV-1 antigen stability and activate antigen presenting cells. J Biomater Sci Polym Ed 2014;25:1387–406. doi:10.1080/09205063.2014.940243.
[167] Silva AL, Rosalia RA, Varypataki E, Sibuea S, Ossendorp F, Jiskoot W. Poly-(lactic-co-glycolic-acid)-based particulate vaccines: particle uptake by dendritic cells is a key parameter for immune activation. Vaccine 2015;33:847–54. doi:10.1016/j.vaccine.2014.12.059.
[168] Scheffel F, Knuschke T, Otto L, Kollenda S, Sokolova V, Cosmovici C, Buer J, Timm J, Epple M, Westendorf AM. Effective activation of human antigen-presenting cells and cytotoxic CD8+ T cells by a calcium phosphate-based nanoparticle vaccine delivery system. Vaccines 2020;8. doi:10.3390/vaccines8010110.
[169] Orlowski P, Tomaszewska E, Ranoszek-Soliwoda K, Gniadek M, Labedz O, Malewski T, Nowakowska J, Chodaczek G, Celichowski G, Grobelny J, Krzyzowska M. Tannic acid-modified silver and gold nanoparticles as novel stimulators of dendritic cells activation. Front Immunol 2018;9:1–23. doi:10.3389/fimmu.2018.01115.
[170] Antia A, Ahmed H, Handel A, Carlson NE, Amanna IJ, Antia R, Slifka M. Heterogeneity and longevity of antibody memory to viruses and vaccines. PLoS Biol 2018;16:1–15. doi:10.1371/journal.pbio.2006601.
[171] Murin CD, Wilson IA, Ward AB. Antibody responses to viral infections: a structural perspective across three different enveloped viruses. Nat Microbiol 2019;4:734–47. doi:10.1038/s41564-019-0392-y.
[172] VanBlargan LA, Goo L, Pierson TC. Deconstructing the antiviral neutralizing-antibody response: implications for vaccine development and immunity. Microbiol Mol Biol Rev 2016;80:989–1010. doi:10.1128/mmbr.00024-15.
[173] Rees HA, Liu DR. Base editing: precision chemistry on the genome and transcriptome of living cells. Nat Rev Genet 2018;19:770–88. doi:10.1038/s41576-018-0059-1.
[174] Ringe RP, Cruz Portillo VM, Dosenovic P. Neutralizing antibody induction by HIV-1 envelope glycoprotein SOSIP trimers on iron oxide nanoparticles may be impaired by mannose binding lectin. J Virol 2019;94:1–32. doi:10.1128/jvi.01883-19.
[175] Wang W, Zhou X, Bian Y. Dual-targeting nanoparticle vaccine elicits a therapeutic antibody response against chronic hepatitis B. Nat Nanotechnol 2020;15:406–16. doi:10.1038/s41565-020-0648-y.
[176] Huber SR, van Beek J, de Jonge J, Luytjes W, van Baarle D. T cell responses to viral infections - opportunities for peptide vaccination. Front Immunol 2014;5:1–13. doi:10.3389/fimmu.2014.00171.
[177] Nelson AN, Putnam N, Hauer D, Baxter VK, Adams RJ, Griffin DE. Evolution of T cell responses during measles virus infection and RNA clearance. Sci Rep 2017;7:1–10. doi:10.1038/s41598-017-10965-z.
[178] Khairallah C, Netzer S, Villacreces A, Juzan M, Rousseau B, Dulanto S, Giese A, Costet P, Praloran V, Moreau JF, Dubus P, Vermijlen D, Déchanet-Merville J, Capone M. $\gamma\delta$ T cells confer protection against murine cytomegalovirus (MCMV). PLoS Pathog 2015;11:1–22. doi:10.1371/journal.ppat.1004702.
[179] Kosinska AD, Sabet LP, Wu W. Low hepatitis B virus-specific T-cell response in males correlates with high regulatory T-cell numbers in murine models. Hepatology 2017;66(1):69–83 JulEpub 2017 May 26. doi:10.1002/hep.29155.
[180] Sáez-Cirión A, Shin SY, Versmisse P. *Ex vivo* T cell-based HIV suppression assay to evaluate HIV-specific CD8+ T-cell responses. Nat Protoc 2010;5:1033–41. doi:10.1038/nprot.2010.73.
[181] Sridhar S, Begom S, Bermingham A. Cellular immune correlates of protection against symptomatic pandemic influenza. Nat Med 2013;19:1305–12. doi:10.1038/nm.3350.
[182] Wilkinson TM, Li CKF, Chui CSC. Preexisting influenza-specific CD4 + T cells correlate with disease protection against influenza challenge in humans. Nat Med 2012;18:274–80. doi:10.1038/nm.2612.
[183] Lee YT, Ko EJ, Hwang HS, Lee JS, Kim KH, Kwon YM, Kang SM. Respiratory syncytial virus-like nanoparticle vaccination induces long-term protection without pulmonary disease by modulating cytokines and T-cells partially through alveolar macrophages. Int J Nanomed 2015;10:4491–505. doi:10.2147/IJN.S83493.
[184] Mahdavi M, Mavandadnejad F, Yazdi MH, Faghfuri E. Oral administration of synthetic selenium nanoparticles induced robust Th1 cytokine pattern after HBs antigen vaccination in mouse model. J Infect Public Health 2017;10:102–9. doi:10.1016/j.jiph.2016.02.006.
[185] Climent N, García I, Marradi M. Loading dendritic cells with gold nanoparticles (GNPs) bearing HIV-peptides and mannosides enhance HIV-specific T cell responses. Nanomed Nanotechnol Biol Med 2018;14:339–51. doi:10.1016/j.nano.2017.11.009.
[186] AbouAitah K, Swiderska-Sroda A, Kandeil A. Virucidal Action against avian influenza H5N1 virus and immunomodulatory effects of nanoformulations consisting of mesoporous silica nanoparticles loaded with natural prodrugs. Int J Nanomed 2020;15:5181–202 Volume. doi:10.2147/ijn.s247692.
[187] Li B, Yan C, Zhu J, Chen X. Anti–PD-1/PD-L1 blockade immunotherapy employed in treating hepatitis B virus infection–related advanced hepatocellular carcinoma: a literature review. Front Immunol 2020;11. doi:10.3389/fimmu.2020.01037.
[188] Dolina JS, Sung SSJ, Novobrantseva TI. Lipidoid nanoparticles containing PD-L1 siRNA delivered *in vivo* enter Kupffer cells and enhance NK and CD8+ T cell-mediated hepatic antiviral immunity. Mol Ther Nucleic Acids 2013;2:e72. doi:10.1038/mtna.2012.63.