Chapter 7
Nanoformulations: A Valuable Tool in the Therapy of Viral Diseases Attacking Humans and Animals

Josef Jampílek and Katarína Kráľová

Abstract Various viruses can be considered as one of the most frequent causes of human diseases, from mild illnesses to really serious sicknesses that end fatally. Numerous viruses are also pathogenic to animals and plants, and many of them, mutating, become pathogenic also to humans. Several cases of affecting humans by originally animal viruses have been confirmed. Viral infections cause significant morbidity and mortality in humans, the increase of which is caused by general immunosuppression of the world population, changes in climate, and overall globalization. In spite of the fact that the pharmaceutical industry pays great attention to human viral infections, many of clinically used antivirals demonstrate also increased toxicity against human cells, limited bioavailability, and thus, not entirely suitable therapeutic profile. In addition, due to resistance, a combination of antivirals is needed for life-threatening infections. Thus, the development of new antiviral agents is of great importance for the control of virus spread. On the other hand, the discovery and development of structurally new antivirals represent risks. Therefore, another strategy is being developed, namely the reformulation of existing antivirals into nanoformulations and investigation of various metal and metalloid nanoparticles with respect to their diagnostic, prophylactic, and therapeutic antiviral applications. This chapter is focused on nanoscale materials/formulations with the potential to be used for the treatment or inhibition of the spread of viral diseases caused by human immunodeficiency virus, influenza A viruses (subtypes H3N2 and H1N1), avian influenza and swine influenza viruses, respiratory syncytial virus, herpes simplex virus, hepatitis B and C viruses, Ebola and Marburg viruses, Newcastle disease virus, dengue and Zika viruses, and pseudorabies virus. Effective antiviral long-lasting and target-selective nanoformulations developed for oral, intravenous, intramuscular, intranasal, intrarectal, intravaginal, and intradermal applications are discussed.

J. Jampílek (✉)
Faculty of Natural Sciences, Department of Analytical Chemistry, Comenius University, Bratislava, Slovakia

K. Kráľová
Faculty of Natural Sciences, Institute of Chemistry, Comenius University, Bratislava, Slovakia

M. Rai, B. Jamil (eds.), *Nanotheranostics*,
https://doi.org/10.1007/978-3-030-29768-8_7

Benefits of nanoparticle-based vaccination formulations with the potential to secure cross protection against divergent viruses are outlined as well.

Keywords Antivirals · Metals · Metal oxides · Nanoformulations · Nanoparticles · Nanoparticle-based vaccines · Viruses

7.1 Introduction

Nanotechnology is a fast-growing field that provides the development of materials that have new dimensions, novel properties, and a broader array of applications. U.S. National Nanotechnology Initiative defines nanoparticles (NPs) in the range 1–100 nm (National Nanotechnology Initiative 2008). Microbial, fungal, and viral infections represent an increasing worldwide threat that is caused by both general immunosuppression of the world population and the growth of resistance of pathogens to clinically used drugs as well as development of cross-resistant or multidrug-resistant strains (Jampílek 2018). In particular, viruses caused a number of diseases worldwide, many of them with fatal termination. Although smallpox has been eradicated and for some of them vaccines were developed, viruses continuously indicate to us that conventional antiviral drugs/strategies directly targeting viral or cellular proteins have been limited, due to frequent virus variation resulting in drug resistance, because many of drugs show high specificity (e.g., De Clercq and Li 2016; Takizawa and Yamasaki 2018; Wang et al. 2018a; Deng and Wang 2018). It can be stated that design and discovery of structurally new anti-infectives with a new/innovative mode of action is time consuming and relatively risky (Jampílek 2016a, b, 2018). Moreover, many of the existing antivirals demonstrate also human toxicity and rapid clearance from the body. Thus, design and development of new safe and potent antivirals with activity against viral infection at multiple points in the viral life cycle remains a major challenge (Al-Ghananeem et al. 2013; Li et al. 2016; Kos et al. 2019).

Strategy based on the reformulation of existing anti-infectives into nanoformulations as well as investigation of various metal and metalloid nanoparticles with respect to their anti-infectious activity and potency is applied more and more frequently (Jampílek and Kráľová 2017; Pisárčik et al. 2017, 2018). In fact, this strategy is not only used for anti-infectious drugs but nanoformulations are also widely used for different classes of drugs, such as antineoplastics (Pentak et al. 2016; Jampílek and Kráľová 2019a), antipsychotics, antidepressants (Jampílek and Kráľová 2019b, c), and nootropics (Jampílek et al. 2015). Nanoscale dimension significantly modifies properties and behavior of all materials (e.g., Dolez 2015), whereby to benefits of pharmaceutical and medical nanoformulations belong primarily sustainable release of drugs, modifications of bioavailability, reduction of the required drug amount, reduction of toxicity of drugs, as well as increasing drug stability (e.g., Jampílek and Kráľová 2018; Patra et al. 2018). Thus in the light of the

above mentioned facts, nanomaterials can constitute a useful tool in combat with viruses as well (Szunerits et al. 2015; Milovanovic et al. 2017; Siddiq et al. 2017; Singh et al. 2017; Zazo et al. 2017).

Recent findings related to development of virus-based nanoparticle (NP) systems as vaccines estimated for the prevention or treatment of infectious diseases, chronic diseases, cancer, and addiction were summarized by Lee et al. (2016), while Jackman et al. (2016) focused their attention on the progress in application of nanomedicine strategies to control critical stages in the virus life cycle through either direct or indirect approaches involving membrane interfaces. For example, diagnostic, prophylactic, and therapeutic applications of metal and metal oxide NPs in human immunodeficiency virus (HIV), hepatitis virus, influenza virus, and herpes simplex virus (HSV) infections were overviewed by Yadavalli and Shukla (2017) and Scherliess (2019). Antiviral activity of the metal NPs, especially the mechanism of action of AgNPs against different viruses (HSV, HIV, hepatitis B virus (HBV), metapneumovirus, respiratory syncytial virus (RSV)), was discussed by Rai et al. (2016).

In the nonviral gene therapy, the use of multifunctional NPs (e.g., lipid-based NPs, quantum dots, carbon nanotubes, magnetic NPs, silica NPs, and polymer-based NPs) is advantageous because these nonviral vectors ensure enhanced gene stability at gene delivery, shielding of cargo from nuclease degradation, and improve passive/active targeting (Lin et al. 2018a; Ariza-Saenz et al. 2018).

At the entry process of viruses into host cells, multivalent interactions with different cell surface receptors occur. Many human viruses attach to the cells through heparan sulfate (HS) proteoglycans and the attachment of the virus to HS on the cell surface start up a cascade of events ending with virus entry. Cagno et al. (2018) designed antiviral NPs having long and flexible linkers mimicking HS proteoglycans, allowing for effective viral association with a binding that was simulated to be strong and multivalent to the viral attachment ligand repeating units, generating forces that eventually lead to irreversible viral deformation and showing nanomolar irreversible activity against HSV, human papilloma virus, RSV, dengue virus, and lentivirus in vitro and were active ex vivo in human cervicovaginal histocultures infected by HSV-2 and in vivo in mice infected with RSV. Nanogels with different degrees of flexibility based on dendritic polyglycerol sulfate to mimic cellular HS designed by Dey et al. (2018) were able to multivalently interact with viral glycoproteins, shield virus surfaces, and efficiently block infection and were found to act as robust inhibitors for human viruses. Dendritic cells are crucial during development of T cell-specific responses against bacterial and viral pathogens.

Surfactant proteins A and D form an important part of the innate immune response in the lung, which can interact with NPs to modulate the cellular uptake of these particles. Unmodified polystyrene NPs of 100 nm were found to modulate surfactant proteins A and D mediated protection against influenza A infection in vitro (McKenzie et al. 2015). Substitution of sulfate groups in cellulose nanocrystals by tyrosine sulfate mimetic groups (i.e., phenyl sulfonates) led to improved viral inhibition indicating that the conjugation of target-specific functionalities to

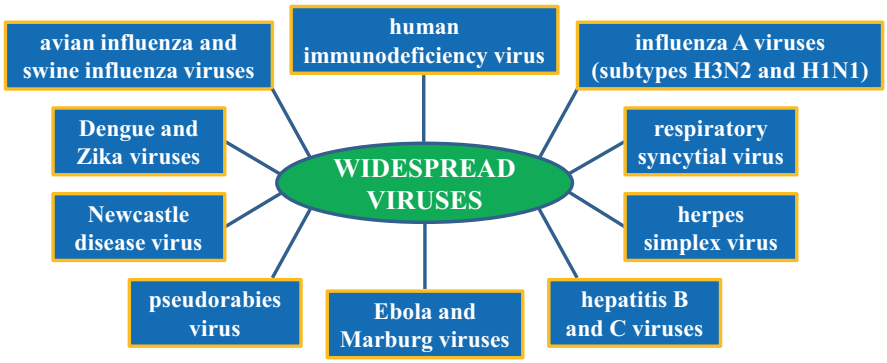

Fig. 7.1 The most common cause of viral diseases

cellulose nanocrystal surfaces provides a mean to control their antiviral activity (Zoppe et al. 2014).

A well-defined structure of virus due to its multifunctional proteinaceous shell (capsid) surrounding genomic material is a promising approach to obtain nanostructured materials, and viruses exhibit an ideal template for the formation of nanoconjugates with noble metal NPs. The interaction of the multifunctional viruses with NPs and other functional additives results in generation of bioconjugates with different properties, including possible antiviral and antibacterial activities (Parboosing et al. 2012; Capek 2015).

This contribution is focused on nanoscale materials/formulations with potential to be used to treat or inhibit the spread of viral diseases caused by human immunodeficiency virus, influenza A viruses (subtypes H3N2 and H1N1), avian influenza and swine influenza viruses, respiratory syncytial virus, herpes simplex virus, hepatitis B and C viruses, Ebola and Marburg viruses, Newcastle disease virus, dengue and Zika viruses, and pseudorabies virus (see Fig. 7.1). Effective antiviral long-lasting and target-selective nanoformulations developed for oral, intravenous, intramuscular, intranasal, intrarectal, intravaginal, and intradermal applications are discussed. Benefits of nanoparticle-based vaccination and nanoformulations with potential to secure cross protection against divergent viruses are outlined as well.

7.2 Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) that causes HIV infection and over time acquired immunodeficiency syndrome (AIDS). HIV is a virus spread through certain body fluids that kills or impairs cells of the immune system, specifically the CD4 T cells, and progressively destroys the body's ability to fight infections and certain cancers (German Advisory Committee Blood 2016).

Based on the investigations of the antiretroviral (ARV) activity of carbon nanotubes (CNTs) using computational molecular approach, the strong molecular interactions suggested the efficacy of CNTs for targeting the HIV-mediated retroviral infections (Krishnaraj et al. 2014). Also, highly hydrophilic and dispersible carboxylated multiwalled carbon nanotubes (MWCNTs) bearing ARV drugs and hydrophilic functionalities were found to exhibit anti-HIV activity (Iannazzo et al. 2015). SiNPs (5–50 nm) prepared by grinding of porous silicon were found to act as efficient scavengers of HIV and RSV (Osminkina et al. 2014).

The production of AgNPs and their use as antiviral therapeutics against pathogenic viruses was reviewed by Galdiero et al. (2011). Ag nanocomplexes with anionic linear globular dendrimers that were assessed against HIV replication pathway in vitro showed also good ARV activity with nonsevere toxic effects in comparison with nevirapine as the standard drug in positive control group (Ardestani et al. 2015). Polyvinylpyrrolidone (PVP)-coated AgNPs were found to be a promising microbicidal candidate for use in topical vaginal/cervical agents to prevent HIV-1 transmission (Lara et al. 2010). Inactivation of microbial infectiousness by AgNPs-coated condom as a new approach to inhibit HIV- and HSV-transmitted infection was proposed by Fayaz et al. (2012). At treatment of HIV-1 infected cells with curcumin-stabilized AgNPs of 45 nm reduced replication of HIV by inhibition of NF-B nuclear translocation and the downstream expression of the pro-inflammatory cytokines interleukin-1β, tumor necrosis factor-α, and interleukin-6 was estimated and no similar biological effects were observed with curcumin alone and conventional AgNPs capped with citric acid (Sharma et al. 2017a). Stable and crystalline AgNPs fabricated using the aqueous leaf extract of mangrove (*Rhizophora lamarckii*) with particle sizes ranging from 12 to 28 nm inhibited HIV type 1 reverse transcriptase activity (IC_{50} of 0.4 μg/mL on the HIV-1) showing the promising potential to be used in the fight against HIV and other viruses of public health importance (Kumar et al. 2017a). AuNPs capped with sulfate-ended ligands that are able to bind HIV envelope glycoprotein gp120 and inhibit in vitro the HIV infection of T cells at nanomolar concentrations were reported by Di Gianvincenzo et al. (2010). AuNPs inhibiting HIV entry by binding with gp120 and preventing CD4 attachment were described by Vijayakumar and Ganesan (2012). HIV-1 peptides loaded onto AuNPs bearing high-mannoside-type oligosaccharides increased HIV-specific $CD4^+$ and $CD8^+$ T cell proliferation and induced highly functional cytokine secretion compared with HIV peptides alone and elicited a highly efficient secretion of pro-Th1 cytokines and chemokines, a moderate production of pro-Th2, and considerably higher secretion of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, suggesting that AuNPs that could simultaneously deliver HIV-1 antigens and high-mannoside-type oligosaccharides could be utilized as a superb vaccine delivery system (Climent et al. 2018).

Nowacek et al. (2011) performed analyses of nanoformulated ARV drugs and found that physical characteristics such as particle size, surfactant coating, surface charge, and most importantly shape are predictors of cell uptake and ARV efficacy. The progress in the development of NP-based drug delivery systems for HIV therapy which focused mainly on injectable nanocarriers enabling delivery of

drug combinations that are long-lasting and target-selective in physiological contexts (in vivo) to provide safe and effective use was summarized by Gao et al. (2018). For example, tenofovir (TFV) alafenamide and elvitegravir (EVG) loaded NPs subcutaneously administered to female humanized $CD34^+$-NSG mice showed long residence time and exposure for both drugs. The $AUC_{(0–14\ day)}$ estimated for TFV and EVG using NPs was 23.1 ± 4.4 and 39.7 ± 6.7 μg h/mL, while with application of drug solutions the observed $AUC_{(0–72\ h)}$ reached 14.1 ± 2.0 and 7.2 ± 1.8 μg h/mL, respectively. Similarly, application of NPs resulted in strong increase of elimination half-life ($t_{1/2}$) that was 5.1 and 3.3 days for TFV and EVG, respectively, while the corresponding $t_{1/2}$ values for free drugs were 14.2 and 10.8 h (Prathipati et al. 2017).

Jiang et al. (2015) incorporated ARV drugs maraviroc, etravirine, and raltegravir into poly(lactic-co-glycolic) acid (PLGA) NPs and found that ARV NPs maintained potent HIV inhibition and were more effective, when used in combinations. Significantly higher antiviral potency and dose-dependent reduction against both cell-free and cell-associated HIV-1 BaL infection in vitro was estimated mainly for ARV NPs combinations involving etravirine NPs, whereby the combinations that showed large dose-reduction were identified to be synergistic. Moreover, ARV NPs combinations inhibited propagation of reverse transcriptase in simian-human immunodeficiency viruses in macaque cervicovaginal tissue and blocked virus transmission by migratory cells emigrating from the tissue. PGLA NPs were also used as a biodegradable carrier for loading with TFV in combination with efavirenz or saquinavir, which resulted in pronounced combination drug effects, and emphasized the potential of NPs for the realization of unique drug-drug activities (Chaowanachan et al. 2013). TFV and EVG-loaded PLGA NPs tested using humanized BLT mouse model were reported to be suitable for long-acting prevention of HIV-1 vaginal transmission (Mandal et al. 2017a). In an in vitro HIV-1 inhibition study, the IC_{50} value observed with emtricitabine-loaded PLGA NPs (size of <200 nm and surface charge −23 mV) was found to be 43-fold lower in TZM-bl cells (0.00043 μg/mL) and approx. fourfold lower (0.009 μg/mL) in peripheral blood mononuclear cells compared with drug solution (0.01861 and 0.033 μg/mL, respectively) and showed comparable activity with emtricitabine solution. Based on prolonged intracellular drug concentration and inhibition of HIV infection, the researchers noted that this long-acting, stable formulation could ensure once-biweekly dosing to prevent or treat HIV infection (Mandal et al. 2017b). PLGA-EVG NPs (~47 nm; zeta potential of approx. 6.74 mV) showed time- and concentration-dependent uptakes in monocytes with an approx. twofold higher drug intracellular internalization of EVG compared to free drug and also exhibited superior viral suppression over control for a prolonged period of time (Gong et al. 2017). Due to the presence of mannose receptors on the surface of macrophages, the mannosylated NPs of anti-HIV drug can target the macrophages, resulting in improvement of the therapeutic outcome and reduced toxicity of ARV bioactives. Surface-functionalized mannosylated-PLGA NPs of lamivudine (LVD) administered by intravenous route in a dose of 10 mg/kg to rats showed pronouncedly higher calculated brain/plasma ratio than PLGA NPs and continuously increased drug concentration up to 12 h (Patel et al. 2018). EFV-loaded PLGA NPs prepared

using microfluidic method with particle size 73 nm, zeta potential −14.1 mV, and 10.8% drug loading showed a sustained in vitro EFV release (50% released within the first 24 h), and NPs functionalization with a transferrin receptor-binding peptide was found to be safe to blood brain barrier (BBB) endothelial and neuron cells (metabolic activity above 70%) and nonhemolytic, whereby functionalized nanosystems exhibited 1.3-fold higher drug permeability through a BBB in vitro model compared to free drug (Martins et al. 2019). EFV-loaded PLGA NPs and PLGA NPs with polyethylene glycol (PEG) coating with particle sizes 200–225 nm also retained native ARV activity of drug in vitro, while showed lower cytotoxicity against different epithelial cell lines and HIV target cells. Both types of NPs were readily taken up by colorectal cell lines and mildly reduced EFV permeation and increased membrane retention in Caco-2 and Caco-2/HT29-MTX cell models monolayer in vitro. At intrarectal administration to CD-1 mice in phosphate-buffered saline (pH 7.4), the coated PLGA NPs encapsulating EFV reached higher drug levels in colorectal tissues and lavages compared to free EFV or EFV-loaded PLGA NPs and they provided enhanced local pharmacokinetics that could be beneficial in preventing rectal HIV transmission (Nunes et al. 2018). TFV and EFV-loaded PLGA NPs incorporated alongside free TFV into fast dissolving films during film manufacturing showed higher retention in vivo in vaginal lavages and tissue when associated to film, and NPs-in-film were still able to enhance drug concentrations of EFV. Film alone also contributed to higher and more prolonged local drug levels as compared to the administration of TFV and EFV in aqueous vehicle, and once daily vaginal administration to mice of this formulation did not cause notable histological changes and major alterations in cytokine/chemokine profiles (Cunha-Reis et al. 2016).

The comparison of EVG-loaded nonadhesive and surface-modified bioadhesive poly(lactic acid)-hyperbranched polyglycerols NP formulations after intravaginal administration showed that bioadhesive NPs markedly improved and prolonged intravaginal delivery of drug and could provide sustained protection over longer durations (Mohideen et al. 2017).

Atripla-trimethyl chitosan (CS) NPs nanoconjugated with particle sizes of 177.2 ± 7.8 nm and zeta potential of −1.35 ± 0.04 mV showed a higher inhibitory effect on HIV replication than atripla alone, and at low doses it could be used for antiviral treatment resulting in reduction of drug resistance and other side effects (Shohani et al. 2017). Spherical intranasal EFV NPs prepared using CS-g-hydroxypropyl-β-cyclodextrin (198 ± 4.4 nm) with 23.28 ± 1.5% drug loading and 38 ± 1.43% entrapment efficiency (EE) exhibited sustained drug release (99.03 ± 0.30% in 8 h), 4.76-fold greater permeability through porcine nasal mucosa than plain drug solution, and 12.40-fold higher central nervous system bioavailability than drug solution administered by i.v. route (Belgamwar et al. 2018). Experiments with NPs coated with glycol chitosan and loaded with a HIV-1 inhibitor peptide tested in vitro and ex vivo using the porcine vaginal mucosa showed that such formulation reached the vaginal tissue and released the peptide within intercellular space without any side effects (Ariza-Saenz et al. 2017).

A novel NP-in-microparticle (MP) delivery system (NiMDS) comprised of pure NPs of the darunavir (DRV) and its boosting agent ritonavir (RTV) encapsulated

within film-coated MPs was reported, in which pure NPs were encapsulated within calcium alginate/CS MPs that were film-coated with a series of poly(methacrylate) copolymers showing differential solubility in the gastrointestinal tract and enabling stability under gastric-like pH and sustained drug release under intestinal one. Using this formulation a 2.3-fold higher oral bioavailability of DRV with respect to both the unprocessed and the nanonized DRV/RTV combinations was estimated in albino Sprague-Dawley rats (Augustine et al. 2018). Enhanced bioavailability of darunavir-loaded lipid nanoemulsion in the brain after oral administration was described by Desai and Thakkar (2019).

Among TFV-loaded HIV-1 g120 targeting mannose responsive particles prepared through the layer-by-layer coating of $CaCO_3$ with concanavalin A (Con A) and glycogen, the one Con A layer containing system showed about twofold increase in drug release vs. control at a concentration of 25 μg/mL HIV gp120 and percent mucoadhesion estimated ex vivo on porcine vaginal tissue, ranged from 10% to 21%, depending on the number of Con A layers in the formulation (Coulibaly et al. 2017).

Hillaireau et al. (2013) referred about the potential of nanoassemblied nucleoside reverse transcriptase inhibitors (NRTIs) delivered as squalenoylated prodrugs to enhance their absorption and improve their biodistribution and also to enhance their intracellular delivery and antiviral efficacy toward HIV-infected cells. Biodegradable cationic cholesterol-ε-polylysine nanogel carriers for delivery of triphosphorylated NRTIs demonstrating high anti-HIV activity along with low neurotoxicity, warranting minimal side effects following systemic administration, were prepared by Warren et al. (2015). Nanogel modification with brain-specific peptide vectors resulted in efficient central nervous system targeting. Senanayake et al. (2015) conjugated succinate derivatives of NRTIs with cholesteryl-ε-polylysine nanogels. Nanogel conjugates of zidovudine (ZDV), LVD, and abacavir demonstrated tenfold suppression of reverse transcriptase activity in HIV-infected macrophages with EC_{90} drug levels of 2–10, 2–4, and 1–2 μM, respectively, for single nanodrugs and dual and triple nanodrug cocktails, conjugate of LVD being the most effective single nanodrugs (EC_{90} 2 μM). NPs of 50–60 nm prepared by encapsulation of ZDV in lactoferrin NPs were found to be stable in simulated gastric and intestinal fluids and the anti-HIV-1 activity of drug remained unaltered in nanoformulation in acute infection, the drug release from NPs was constant up to 96 h and bone marrow micronucleus assay showed that nanoformulation exhibited ca. twofold lower toxicity than soluble form (Kumar et al. 2015). Lactoferrin NPs loaded with a triple drug combination of ZDV, EFV, and LVD showing a diameter of 67 nm and EE >58% for each drug delivered the maximum of its payload at pH 5 with a minimum burst release in vitro, exhibited improved anti-HIV activity, were practically not toxic to the erythrocytes, and reached in in vivo experiment an approx. >4-fold increase in AUC, 30% increase in the C_{max} compared to individual drugs, and >2-fold enhancement in the half-life of each drug. They also showed improved bioavailability of all drugs with less tissue-related inflammation (Kumar et al. 2017b). Improved HIV-microbicide activity through the co-encapsulation of drugs acting as NRTIs

in biocompatible metal organic framework nanocarriers containing iron(III) polycarboxylate NPs was reported by Marcos-Almaraz et al. (2017).

TFV disoproxil fumarate encapsulated in multifunctional magneto-plasmonic liposomes, a hybrid system combining liposomes and magneto-plasmonic NPs, enabled the treatment in the brain microenvironment that is inaccessible to most of the drugs, showed enhanced transmigration across an in vitro BBB model by magnetic targeting, and exhibited desired therapeutic effects against HIV-infected microglia cells, while the gold shell of liposomes showed bright positive contrast in X-ray computed tomography (Tomitaka et al. 2018).

EFV-loaded solid lipid NPs (SLNPs) with mean particle size of 108.5 nm, polydispersity index of 0.172, and 64.9% EE administered intranasally in vivo revealed increased concentration of the drug in brain as desired suggesting their potential to be used for eradication of HIV and cure of HIV-infected patients (Gupta et al. 2017). Endsley and Ho (2012) constructed CD4-targeted SLNPs providing selective binding and efficient delivery of indinavir to $CD4^+$-HIV host cells (whereby inclusion of PEG in SLNPs minimized immune recognition of peptides) that showed enhancement of anti-HIV effects even under limited time exposure. Nanoscaled NRTIs decorated with the peptide-binding brain-specific apolipoprotein E receptor demonstrated low neurotoxicity and high antiviral activity against HIV infection in the brain (Gerson et al. 2014).

A cell surface chemokine receptor CXCR4 targeting peptide 4DV3 acting as an HIV entry inhibitor and a ligand for targeted drug delivery was described by Lee et al. (2019). The use of 4DV3 as the targeting ligand resulted in enhanced endocytosis due to the uptake of 4DV3 functionalized nanocarriers combined with the allosteric interaction with CXCR4, suggesting that 4DV3 peptide could be considered as a dual function ligand.

Bayon et al. (2018) developed vaccine formulations comprising nanostructured lipid carriers (NLC) grafted with p24 antigen, together with cationic NLC optimized for the delivery of immunostimulant CpG, which was able notably enhance immune responses against p24 manifested in specific antibody production and T cell activation in mice as well as in nonhuman primates.

A tissue- and cell-targeted long-acting four-in-one nanosuspension composed of lopinavir, RTV, TFV, and LVD administered as a single injection subcutaneously to four macaques was able to exhibit persistent drug levels in lymph node mononuclear cells and peripheral blood mononuclear cells for 5 weeks and could be proposed for a long-acting treatment with the potential to target residual virus in tissues and improve patient adherence (McConnachie et al. 2018).

Biocompatible ZDV-loaded hybrid core-shell NPs of carboxymethyl cellulose (core) and Compritol®-PEG (shell) for ARV drug delivery with mean size of 161 ± 44.06 nm and 82% drug EE showed controlled drug release and were able effectively enter the brain cells (Joshy et al. 2017). The biocompatible PF-68-coated NPs of amide functionalized alginate prepared by coupling reaction with D,L-glutamic acid encapsulating ZDV with mean size of 432 ± 11.9 nm and a loading efficacy of 29.5 ± 3.2% showed slow and sustained release of drug in phosphate-buffered saline (PBS, pH 7.4) and exhibited significantly higher cellular internalization efficiency

in vitro (Joshy et al. 2018a). Considerable improvement in cellular internalization (murine neuro-2a and HeLa cells) in vitro was observed also with ZDV-loaded PVP/stearic acid (SA)-PEG NPs due to the core-shell NPs prepared from lipid and polymer, suggesting that such NPs have potential to be used for antiviral drug delivery for use in HIV/AIDS therapy (Joshy et al. 2018b). ZDV-loaded core-shell dextran hybrid nanosystem expressed enhanced cellular internalization of drug-loaded hybrid NPs in comparison with free drug (Joshy et al. 2018c).

Retained intracytoplasmic nanoformulations consisting of a hydrophobic and lipophilic modified dolutegravir prodrug encapsulated into poloxamer released the drug from macrophages and suppressed viral replication and spread of virus to $CD4^+$ T cells, while the drug blood and tissue levels in BALB/cJ mice were above 64 ng/mL corresponding to IC_{90} value for 56 and 28 days, respectively (Sillman et al. 2018).

Crystals of myristoylated cabotegravir prodrug that were formulated into NPs facilitated avid monocyte-macrophage entry, retention, and reticuloendothelial system depot formulation, showed sustained protection against HIV-1 challenge, and a single 45 mg/kg intramuscular injection of these NPs at a dose of 45 mg/kg to BALB/cJ mice resulted in fourfold higher pharmacokinetic profiles compared to long-acting parenteral cabotegravir, and similar results were obtained also with rhesus macaques (*Macaca mulatta*); improved viral restriction in human adult lymphocyte-reconstituted NOD/SCID/IL2R$\gamma c^{-/-}$ mice by this nanoformulations was observed as well (Zhou et al. 2018).

7.3 Influenza A Viruses, Subtypes H3N2 and H1N1

Influenza is a respiratory illness caused by a virus. All influenza viruses are negative-sense, single-stranded, segmented RNA viruses. Viruses of influenza A type occur in humans and animals, while types B and C can be found only in humans. Influenza A viruses are classified according to the type of hemagglutinin (H) and the type of neuroaminidase (N) into subtypes H1N1, H1N2, H2N2, H3N2, H5N1, and H8N4. Each virus subtype has mutated into a variety of strains with differing pathogenic profiles using humanized BLT mouse model (Taubenberger and Morens 2010; Takizawa and Yamasaki 2018). Influenza A virus causes influenza in birds and some mammals, and is the only species of the *Alphainfluenzavirus* genus of the *Orthomyxoviridae* family of viruses. Type A influenza is a contagious viral infection that can have life-threatening complications if left untreated. An influenza could be pandemic, when an epidemic of an influenza virus spreads on a worldwide scale, e.g., "Spanish flu" of 1918 (Kuchipudi and Niessly 2018).

Inhibition of A/Human/Hubei/3/2005 (H3N2) influenza virus infection by AgNPs in vitro and in vivo was reported by Xiang et al. (2013). Feng et al. (2013) designed glycosylated metal (Ag and Au) NPs as potent influenza A virus hemagglutinin (HA) blockers. Inhibitory effects of AgNPs with particle size of 10 nm on H1N1 influenza A virus in vitro were also reported by Xiang et al. (2011).

The effect of size dependence of the AgNPs (3.5, 6.5, and 12.9 nm average diameters) that were embedded into the CS matrix on antiviral activity against H1N1 influenza A virus was also observed showing generally stronger antiviral activity with smaller AgNPs in the composites (Mori et al. 2013). Evaluation of the efficacy of AgNP-decorated silica hybrid composite (Ag30-SiO_2) with particle size of 400 nm in diameter for inactivation of influenza A virus showed that even after 1 h of exposure to these NPs >80% of HA damage, 20% of neuraminidase activities, and reduction of the infection caused by the virus in Madin-Darby Canine Kidney (MDCK) cells was observed. The Ag30-SiO_2 NPs were found to interact with viral components situated at the membrane causing them nonspecific damage resulting in virus inactivation (Park et al. 2018).

As the primary mechanism of influenza virus inhibition by AuNPs with different anionic groups blocking of viral attachment to cell surface was suggested, although viral fusion inhibition could not be excluded (Sametband et al. 2011). Li et al. (2016) proposed a new modality to inhibit viral infection by fabricating DNA-conjugated AuNPs networks on cell membranes as a protective barrier, antiviral activity of which may be attributed to steric effects, the disruption of membrane glycoproteins, and limited fusion of cell membrane bilayers. In addition, these DNA-AuNPs beside inhibition of virus attachment and entry could also inhibit viral budding and cell-to-cell spread. Multivalent sialic acid-functionalized AuNPs of 14 nm inhibited influenza virus infection. As the binding of the viral fusion protein HA to the host cell surface is mediated by sialic acid receptors, a multivalent interaction with sialic acid-functionalized AuNPs is expected to competitively inhibit viral infection (Papp et al. 2010). Intranasal immunizations with a mixture of conjugated recombinant trimetric influenza A/Aichi/2/68(H3N2) HA onto functionalized AuNPs surfaces in a repetitive, oriented configuration and AuNPs coupled with Toll-like receptor 5 agonist flagellin as particulate adjuvants resulted in improved mucosal B cell responses (increasing influenza-specific immunoglobulin (Ig) A and IgG l in nasal, tracheal, and lung washes), stimulation of antigen-specific interferon-γ-secreting $CD4^+$ cell proliferation and induced strong effector $CD8^+$ T cell activation suggesting powerful mucosal and systemic immune responses protecting hosts against lethal influenza challenges (Wang et al. 2018b).

CuI NPs of mean size of 160 nm exerted antiviral activity against an influenza A virus of swine origin (pandemic [H1N1] 2009) by generating hydroxyl radicals, suggesting that they could be applied in filters, face masks, protective clothing, and kitchen cloths as a material suitable to protect against viral attacks (Fujimori et al. 2012).

Nanocomposites, in which DNA fragments were electrostatically bound to TiO_2 NPs pre-covered with polylysine, efficiently inhibited human influenza A (subtype H3N2) (Levina et al. 2014). Composites of peptide nucleic acids with TiO_2 NP-containing DNA/peptide nucleic acid duplexes inhibited reproduction of influenza A virus (H3N2 subtype) with an efficiency of 99% and they were shown to not only penetrate through cell membranes, but also exhibit a high specific antisense activity without toxic effects on the living cells (Amirkhanov et al. 2015).

SeNPs decorated by ribavirin (RBV), a broad-spectrum antiviral drug, protected cells during H1N1 infection in vitro, while in in vivo experiments they prevented lung injury in H1N1-infected mice, significantly reduced DNA damage in lung tissue, and restrained activations of caspase-3 and proteins on the apoptosis pathway (Lin et al. 2018b).

Pieler et al. (2016) bound inactivated, concentrated, and diafiltered influenza A virus particles produced in MDCK cell suspension to magnetic sulfated cellulose microparticles (100–250 μm) and directly injected into mice for immunization and observed high anti-influenza A antibody responses and full protection against a lethal challenge with replication-competent influenza A virus, whereby 400-fold reduced number of influenza nucleoprotein gene copies in the lungs of mice immunized with antigen-loaded microparticles compared to mock-treated animals was estimated.

Hybrid inorganic-organic microcapsules obtained by encapsulating siRNA via the combination of layer-by-layer technique and in situ modification by sol-gel chemistry were characterized with high cell uptake efficiency, low toxicity, efficient intracellular delivery of siRNAs and the protection of siRNAs from premature degradation before reaching the target cells, reduced viral nucleoprotein level, and inhibited influenza A virus (H1N1) production in infected MDCK and A549 cells (Timin et al. 2017). CS NPs loaded by siRNA that were efficiently up-taken by Vero cells resulting in the inhibition of influenza virus (strain A/PR/8/34 (H1N1)) replication in vitro showed antiviral effects at nasal administration and considerably protected BALB/c mice from a lethal influenza challenge, suggesting that this nanoformulation is a promising system for controlling influenza virus infection (Jamali et al. 2018).

Figueira et al. (2018) modified the influenza fusion inhibitors by adding a cell-penetrating peptide self-assembling into 15–30 nm NPs and targeting relevant tissues infected with influenza virus A in vivo, causing reduction of viral infectivity upon interaction with the cell membrane, and it was shown that for efficacious biodistribution, fusion inhibition, and efficacy in vivo both the cell-penetrating peptide and the lipid moiety are necessary.

The amino acid sequence of influenza matrix protein 2 ectodomain (M2e) is highly conserved among human seasonal influenza A viruses (Deng et al. 2018a). Multivalent oleanolic acid protein conjugates as nonglycosylated neomucin mimics for the capture and entry inhibition of influenza A viruses (H1N1, H3N2, and H9N2) designed by Yang et al. (2018) were found to be comparable to natural glycosylated mucin, suggesting that this material could potentially be used as anti-infective barriers to prevent virus from invading host cells. Bernasconi et al. (2018) developed a fusion protein with three copies of the ectodomain of matrix protein 2, which is one of the most explored conserved influenza A virus antigens for a broadly protective vaccine and incorporated it into porous maltodextrin NPs to enhance its protective ability and the formulation resulted in broadly protective immunity against a lethal infection with heterosubtypic influenza virus, immune protection being mediated by enhanced levels of lung-resident $CD4^+$ T cells as well as anti-HA and anti-M2e serum IgG and local IgA antibodies.

The initial adhesion of most viruses is quantitatively controlled by multivalent binding of proteins to glycan receptors on the host cell. Lin et al. (2018c) to mimic virus adhesion to cell surfaces attached protein-oligomer-coated NPs to fluidic glycolipid membranes with surface glycan density varying over four orders of magnitude and found that in the binding isotherms two regions could be estimated, which could be attributed to monovalent and multivalent protein/glycan interactions at low and high glycan densities, respectively.

Lauster et al. (2017) designed multivalent peptide-polymer NPs consisting of covalent conjugates of peptidic ligands and a biocompatible polyglycerol-based hydrophilic dendritic scaffold showing binding with nanomolar affinity to the influenza A virus via its spike protein hemagglutinin. A novel seasonal recombinant HA NP influenza vaccine (NIV) formulated with a saponin-based adjuvant, Matrix-M™, induced HA inhibition (HAI) and microneutralizing antibodies against a broad range of influenza A (H3N2) subtypes. HAI-positive and HAI-negative neutralizing monoclonal antibodies derived from mice immunized with NIV were active against homologous and drifted influenza A (H3N2) strains (Smith et al. 2017). Layered protein NPs composed of structure-stabilized HA stalk domains from both HA groups, and constructed M2e, were reported to have potential to be developed into a universal influenza vaccine that could induce broad cross protection against divergent viruses (Deng et al. 2018a).

An intranasally administered biocompatible polyanhydride NP-based influenza A virus (IAV) vaccine (IAV-nanovax) that could provide protection against subsequent homologous and heterologous IAV infections in both inbred and outbred populations, when used for vaccination, resulted in promotion of the induction of germinal center B cells within the lungs, both systemic and lung local IAV-specific antibodies, and IAV-specific lung-resident memory CD4 and CD8 T cells (Zacharias et al. 2018).

Double-layered peptide NPs prepared by desolvating a composite peptide of tandem copies of nucleoprotein epitopes into NPs as cores and cross-linking another composite peptide of four tandem copies of influenza matrix protein 2 ectodomain epitopes to the core surfaces as a coating that were delivered via dissolvable microneedle patch-based skin vaccination, induced robust specific immunity and protected mice against heterosubtypic influenza A virus challenges and demonstrated a strong antigen depot effect resulting in the stronger immune responses, whereby $CD8^+$ T cells were involved in the protection (Deng et al. 2018b).

Intranasal vaccination with NPs formed by 3-sequential repeats of M2e on the self-assembling recombinant human heavy chain ferritin cage could induce robust immune responses such as high titers of sera M2e-specific IgG antibodies, T cell immune responses, and mucosal secretory IgA antibodies in mice in the absence of an adjuvant. These NPs also confer complete protection against a lethal infection of homo-subtypic H1N1 and hetero-subtypic H9N2 virus and could be considered as a promising, needle-free, intranasally administered cross-protective influenza vaccine as being economical and suitable for large-scale production (Qi et al. 2018).

7.4 Avian Influenza and Swine Influenza Viruses

Avian influenza is a variety of influenza caused by viruses adapted to birds. Avian influenza virus (AIV) is an A-type influenza virus belonging to the *Orthomyxoviridae* family, whereby isolated strains of "highly pathogenic avian influenza" inducing intravenous pathogenicity index >1.2 or mortality rate >75% in a defined chicken population during the specified interval of 10 days are of H5 and H7 subtypes (Chatziprodromidou et al. 2018).

Swine influenza is caused by swine influenza viruses (SwIV) that are endemic in pigs. In Europe, swine influenza is considered one of the most important primary pathogens of swine respiratory disease and infection is primarily with H1N1, H1N2, and H3N2 influenza A viruses (Brown 2013).

It was found that dietary supplementation of chromium picolinate (1500 ppb) and chromium NPs (1000 ppb) improved the performance and antibody titers against avian influenza and infectious bronchitis heat stress conditions (36 °C) in broilers (Hajializadeh et al. 2017). Serum samples collected from immunized chickens with formulation consisting of plasmid encoding HA gene of AIV, (A/Ck/Malaysia/5858/04 (H5N1)), formulated using biosynthesized AgNPs (4–18 nm) and PEG showed rapidly increasing antibody responses against H5 on day 14 after immunization and single oral administration of this formulation resulted in the induction of both the antibody and cell-mediated immune responses as well as enhanced cytokine production (Jazayeri et al. 2012). A vaccine formulation consisting of ion channel membrane matrix protein 2 of the extracellular domain of influenza A conjugated to AuNPs with CpG oligodeoxynucleotide as a soluble adjuvant, which was delivered intranasally in mice, resulted in lung B cell activation and robust serum anti-M2e IgG response, with stimulation of both IgG1 and IgG2a subtypes. Lethal challenge of vaccinated mice with A/California/04/2009 (H1N1pdm) pandemic strain, A/Victoria/3/75 (H3N2), and the highly pathogenic AIV A/Vietnam/1203/2004 (H5N1) resulted in 100, 92, and 100% protection (Tao et al. 2017). Considering a very important role of mucosal immunity in the antiviral immune response, AgNPs biofabricated using *Cinnamomum cassia* extract showed enhanced antiviral activity against highly pathogenic AIV subtype H7N3, when incubated with the virus prior to infection as well as introduced to cells after infection, whereby the tested concentrations of extract and AgNPs (up to 500 μg/mL) were found to be nontoxic to Vero cells (Fatima et al. 2016). For complexity, it is necessary to mention (as was discussed above) that Fujimori et al. (2012) described antiviral activity of CuI NPs against influenza A virus of swine origin H1N1.

Formulation using calcium phosphate NPs vaccine adjuvant and delivery platform to formulate an inactivated whole virus pandemic influenza A/CA/04/2009 (H1N1pdm) vaccine as a potential dose-sparing strategy that was intramuscularly administered to BALI/c mice at doses 0.3, 1, or 3 μg (based on HA content) resulted in higher HAI, virus neutralization, and IgG antibody titers compared to the nonadjuvanted vaccine, providing equal protection with one-third of the antigen dose as compared to the nonadjuvanted or alum (hydrated double sulfate salts of aluminum

with potassium, sodium, or ammonium)-adjuvanted vaccine (Morcol et al. 2017). Solution of nanoscale scallop shell powder produced by calcination process showing a size of 500 nm inactivated AIV within 5 s, whereas the solution of greater powder particles (20 μm) could not even after 1 h incubation. Moreover, inactivation of Newcastle disease virus and goose parvovirus solution by nanopowder within 5 and 30 s, respectively, was observed as well (Thammakarn et al. 2014).

Chickens immunized with a low dose (200 μL) of bioadhesive liposomal influenza vaccine using liposomes prepared with tremella or xanthan gum as the bioadhesive polysaccharide showed considerably higher mucosal and serum antibody levels, and low-viscosity gel mixed with liposomes was found to be suitable for nasal delivery and chickens elicited higher mucosal secretory IgA and serum IgG after two vaccinations compared to application of liposome mixture with a high-viscosity gel (Chiou et al. 2009).

Vaccination of chickens with nonencapsulated AIV combined with PLGA-encapsulated CpG oligodeoxynucleotides, CpG 2007, resulted in qualitatively and quantitatively augmented antibody responses manifested as a reduction in virus shedding compared to the encapsulated AIV combined with PLGA-encapsulated CpG 2007 formulation (Singh et al. 2016a). Similarly, nonencapsulated CpG 2007 in inactivated AIV vaccines administered by the intramuscular route generated higher antibody responses compared to the CpG 2007 encapsulated in PLGA, while PLGA-encapsulated CpG 2007 in AIV vaccines administered by the aerosol route elicited higher mucosal responses compared to nonencapsulated CpG 2007 (Singh et al. 2016b). Seok et al. (2017) designed an intradermal pH1N1 DNA vaccine delivery platform using microneedles coated with a polyplex-containing PLGA/polyethyleneimine NPs inducing a greater humoral immune response due to rapid dissolution of the coated polyplex in porcine skin (within 5 min) than that observed at intramuscular polyplex delivery or naked pH1N1 DNA vaccine delivery by a dry-coated microneedles. Consequently, intradermal delivery of DNA vaccines within a cationic polyplex coated on microneedles has potential in skin immunizations. Polyanhydride NPs encapsulating subunit proteins can enhance humoral and cell-mediated immunity and provide protection upon lethal challenge. A robust immunogen, recombinant H5 hemagglutinin trimer ($H5_3$) encapsulated into polyanhydride NPs used to immunizing mice induced high neutralizing antibody titers and enhanced $CD4^+$ T cell recall responses in mice and $H5_3$-based polyanhydride nanovaccine induced protective immunity against a low-pathogenic H5N1 viral challenge (Ross et al. 2015). Similarly, intranasal delivery of nanovaccine consisting of inactivated SwIV encapsulated in polyanhydride NPs enhanced antigen-specific cellular immune response in pigs, with promise to induce cross-protective immunity (Dhakal et al. 2017a), and inactivated SwIV encapsulated in PLGA NPs (200–300 nm diameter) administered via intranasal route reduced the clinical disease and induced cross-protective cell-mediated immune response in a pig model as well (Dhakal et al. 2017b).

As a virus for challenge test Moon et al. (2012) used the HPAI H5N1 virus (A/EM/Korea/W149/06) isolated from fecal specimens collected from wild bird habitats and constructed recombinant HA antigen based on the HA1 head domain of this virus. Intranasal immunization with a mixture of recombinant influenza HA antigen

or inactivated virus and poly-γ-glutamic acid (PGA)/CS NPs induced a high anti-HA IgA response in lung and IgG response in serum, including anti-HA neutralizing antibodies as well as an influenza virus-specific cell-mediated immune response in female BALB/c mice against challenge with a lethal dose of the highly pathogenic influenza A H5N1 virus (Moon et al. 2012). Pigs that were intranasally vaccinated with killed swine influenza A virus H1N2 (δ-lineage) antigens encapsulated in CS polymer-based NPs exhibited an enhanced IgG serum antibody and mucosal secretory IgA antibody responses in nasal swabs, bronchoalveolar lavage fluids, and lung lysates that were reactive against homologous (H1N2), heterologous (H1N1), and heterosubtypic (H3N2) influenza A virus strains (Dhakal et al. 2018).

Mucosal vaccination of conserved matrix protein 2, fusion peptide of hemagglutinin HA_2 and cholera toxin subunit Al (CTAI) fusion protein with poly-γ-glutamate/CS NPs induced protection against divergent influenza subtypes and was found to induce a high degree of systemic immunity (IgG and IgA) at the site of inoculation and in challenge tests in BALI/c mice with several viruses (H5N1, H1N1, H5N2, H7N3, or H9N2) provided cross protection against divergent lethal influenza subtypes up to 6 months after vaccination (Chowdhury et al. 2017). Two immunizations of modified nonreplicating mRNA encoding influenza H10 hemagglutinin and encapsulated in lipid NPs induced protective HA inhibition titers and H10-specific $CD4^+$ T cell responses after intramuscular or intradermal delivery in rhesus macaques (Liang et al. 2017). The results of hemagglutination inhibition and micro-neutralization assays showed that lipid NP-formulated modified mRNA vaccines encoding HA proteins of H10N8 (A/Jiangxi-Donghu/346/2013) or H7N9 (A/Anhui/1/2013) generated rapid and robust immune responses in mice, ferrets, and nonhuman primates, and a single dose of H7N9 mRNA was able to protect mice from a lethal challenge and reduced lung viral titers in ferrets (Bahl et al. 2017).

Coated two-layer protein nanoclusters from recombinant trimeric HA from an avian-origin H7N9 influenza that were evaluated for the virus-specific immune responses and protective efficacy in mice immunized with these nanoclusters were found to be highly immunogenic; they were able to induce protective immunity and long-lasting humoral antibody responses to this virus without the use of adjuvants, suggesting that such coated nanoclusters also have great potential for influenza vaccine production not only in response to an emerging pandemic, but also as a replacement for conventional seasonal influenza vaccines (Wang et al. 2017).

7.5 Respiratory Syncytial Virus

Respiratory syncytial virus (RSV), a negative-sense single-stranded enveloped RNA virus, is a global human pathogen responsible for lower respiratory tract infections and is considered as the major viral pathogen of the lower respiratory tract of infants. Therefore, there are urgent need to utilize convenient strategies to prevent

RSV infection, including beside of live attenuated, chimeric, and subunit vaccines also nanosized particles (Borchers et al. 2013; Clark and Guerrero-Plata 2017).

Au nanorods (AuNRs) were found to inhibit RSV in human epithelial type 2 (HEp-2) cells and in BALB/c mice by 82% and 56%, respectively, whereby the RSV inhibition correlated with marked upregulated antiviral genes due to AuNR-mediated Toll-like receptor, the nucleotide-binding oligomerization domain (NOD)-like receptor, and retinoic acid-inducible gene-I (RIG-I)-like receptor signaling pathways, whereby recruitment of immune cells to counter RSV replication was demonstrated by production of cytokines and chemokines in the lungs (Bawage et al. 2016). Treatment of human dendritic cells with AuNRs conjugated to RSV F formulated as a candidate vaccine preparation for RSV by covalent attachment of viral protein using a layer-by-layer approach induced immune responses in primary human T cells (Stone et al. 2013). Curcumin-modified AgNPs showed strong inhibitory activity against RSV infection resulting in a reduction of viral titers about two orders of magnitude at AgNPs concentration showing no toxicity to the host cells, whereby AgNPs inactivated the virus directly, which resulted in the prevention of RSV to infect the host cells (Yang et al. 2016a).

In BALB/c mice exposed to a single dose of intranasally administered TiO_2 NPs (0.5 mg/kg) that were 5 days later infected intranasally with RSV notably increased levels of interferon-γ and chemokine CCL5 in the bronchoalveolar lavage fluids were estimated compared with the control on day 5 postinfection, but not in uninfected mice. TiO_2 exposure resulted also in an increase in the infiltration of lymphocytes into the alveolar septa in lung tissues, while pulmonary viral titers were not affected. Consequently, it can be stated that the immune system was affected by a single exposure to TiO_2 NPs that exacerbated pneumonia in RSV-infected mice (Hashiguchi et al. 2015).

The curcumin-loaded β-cyclodextrin-functionalized graphene oxide (GO) composite was found to cause highly efficient inhibition of RSV infection, showed great biocompatibility to the host cells, and was able to prevent the host cells from RSV infection by directly inactivating the virus and inhibiting the viral attachment, showing prophylactic and therapeutic effects toward RSV (Yang et al. 2017a).

Recent advances in prophylactic synthetic biodegradable microparticle and nanoparticle vaccines against RSV and the multiple factors that can affect vaccine efficacy were summarized by Jorquera and Tripp (2016). Vaccination with a recombinant RSV F nanoparticle vaccine (60 or 90 g RSV F protein, with or without aluminum phosphate adjuvant) enhanced functional immunity to RSV in older adults (≥60 years), showed an acceptable safety profile, and additional immunogenicity benefit was observed with adjuvanted formulation compared to increasing antigen dose alone. Moreover, the RSV F vaccine co-administered with licensed inactivated trivalent influenza vaccine (TIV) did not impact the serum HAI antibody responses to a standard-dose TIV, and TIV did not affect the immune response to the RSV F vaccine (Fries et al. 2017).

7.6 Herpes Simplex Virus

Double-stranded DNA viruses, *Herpes simplex* virus 1 and 2 (HSV-1 and HSV-2), are members of the α-herpesvirus subfamily of *Herpesviridae* family that infect humans. HSV-1 causes cold sores, while HSV-2 causes genital herpes and these viruses can establish lifelong latent infection within peripheral nervous system (Dai and Zhou 2018).

Size-dependent interactions of AgNPs with HSV-1, HSV-2, and human parainfluenza virus type 3 resulting in reduced viral infectivity or in inhibition of the infectivity of the viruses by smaller-sized NPs that was caused probably by blocking interaction of the virus with the cell was described by Gaikwad et al. (2013). AgNPs applied at nontoxic concentrations administered prior to viral infection or soon after initial virus exposure were capable to inhibit HSV-2 replication, suggesting that the AgNPs acted during the early phases of viral replication (Hu et al. 2014). Tannic acid-modified AgNPs of 13, 33, and 46 nm showed antiviral activity and reduced both infection and inflammatory reaction in the mouse model of HSV-2 infection, when used at infection or for a postinfection treatment (Orlowski et al. 2014), and antiviral activity of such NPs with a size of 33 nm applied upon the mucosal tissues caused activation of immune response in vaginal HSV-2 (Orlowski et al. 2018a). Multifunctional tannic acid/AgNPs-based mucoadhesive hydrogel for effective vaginal treatment of HSV-2 genital infection was also reported (Szymanska et al. 2018). Investigation of the ability of tannic acid-modified Ag and AuNPs to induce dendritic cells maturation and activation in the presence of HSV-2 antigens, when used at nontoxic doses, showed that both types of these metal NPs were good activators of dendritic cells, albeit their final effect upon maturation and activation may be metal and size dependent and can help to overcome virus-induced suppression of dendritic cells activation (Orlowski et al. 2018b). AuNPs of the size of 7.86 nm surface-conjugated with gallic acid showed the antiviral efficacy against HSV infections in Vero cells with EC_{50} of 32.3 μM in HSV-1 and 38.6 μM in HSV-2 (Haider et al. 2018). AuNPs capped with mercaptoethanesulfonate (MES) strongly inhibited HSV-1, whereby they interfered with viral attachment, entry, and cell-to-cell spread, thereby preventing subsequent viral infection in a multimodal manner (Baram-Pinto et al. 2010). However, the antiviral effect of MES-capped AgNPs against HSV-1 was found to be imparted by their multivalent nature and spatially directed MES on the surface (Baram-Pinto et al. 2009). An overview related to application of AgNPs in inhibition of HSV was presented by Akbarzadeh et al. (2018).

ZnO micro-nano structures capped with multiple nanoscopic spikes mimicking cell induced filopodia and showing partially negatively charged oxygen vacancies on their nanoscopic spikes, after trapping the virions rendered them unable to enter into human corneal fibroblasts—a natural target cell for HSV-1 infection and exhibited pronouncedly enhanced anti-HSV-1 effect creating additional oxygen vacancies under UV light illumination (Mishra et al. 2011). Intravaginal ZnO tetrapod NPs with engineered oxygen vacancies, when used intravaginally, acted as a

microbicide and were found to be an effective suppressor of HSV-2 genital infection in female BALB/c mice, suppressing also a reinfection, and exhibited strong adjuvant-like properties as well (Antoine et al. 2016). The antiviral effects of ZnO tetrapods can be enhanced by illuminating with UV light (Antoine et al. 2012).

SnO_2 nanowires working as a carrier of negatively charged structures can compete with HSV-1 attachment to cell-bound HS, resulting in the inhibition of virus entry and subsequent cell-to-cell spread (Trigilio et al. 2012).

Acyclovir (ACV)-loaded glycosaminoglycan-modified mesoporous SiO_2 NPs reduced the viral infection with HSV and such NPs were able to simultaneously inhibit the viral entry and DNA replication (Lee et al. 2018).

Graphene sheets uniformly anchored with spherical sulfonated magnetic NPs were able to capture and photothermally destroy HSV-1 upon irradiation with near-infrared light (808 nm, 7 min) (Deokar et al. 2017). Graphene sheets approx. 300 nm in size and with a degree of sulfation of approx. 10% were found to operate as effective viral inhibitor and inhibited HSV infection at an early stage during entry but did not affect cell-to-cell spread (Ziem et al. 2017). A multivalent 2D flexible carbon architecture fabricated using reduced GO functionalized with sulfated dendritic polyglycerol to mimic the HS-containing surface of cells and to compete with this natural binding site of viruses demonstrated excellent binding as well as efficient inhibition of the infection with orthopoxvirus possessing a HS-dependent cell entry mechanism (Ziem et al. 2016). Carbon nanodots surface-functionalized with 4-aminophenylboronic acid hydrochloride prevented HSV-1 infection on Vero and A549 cells and showed EC_{50} of 80 and 145 ng/mL, respectively, specifically acting on the early stage of virus entry (Barras et al. 2016).

C-Glycosylflavonoid-enriched fraction of *Cecropia glaziovii* encapsulated in PLGA NPs showed antiherpes properties and could be considered as a promising system for the effective drug delivery in the treatment of herpes infections (dos Santos et al. 2017). *Cymbopogon citratus* volatile oil encapsulated in PLGA NPs incorporated in carbomer hydrogels and tested against HSV using Vero cells inhibited virus at 42.2-fold lower concentration than free oil and it was 8.8- and 2.2-fold more efficient than oil-loaded NPs and hydrogel containing free oil, respectively (Almeida et al. 2018). Genistein-loaded cationic nanoemulsions with an average droplet size approx. 200–300 nm containing hydroxyethyl cellulose as a thickening agent showed considerably reduced genistein flux through excised porcine mucosa specimens compared to nanoemulsions before thickening, exhibited notable increase of genistein retention in mucosa compared to the genistein propylene glycol solution, and showed antiherpetic activity in vitro against HSV-1 (strain 29R) (Argenta et al. 2016).

Suspensions of glycyrrhizic acid NPs with particle size approx. 180 nm exhibited better anti-HSV activities compared to glycyrrhizic acid ammonium salt, especially during replication period. Morphology of HSV-1 observed by transmission electron microscopy was found to damage and shed the envelope of HSV-1 (Wang et al. 2015). The antiviral activities against HSV-2 estimated using the cytopathic

effect assay showed also microemulsions with mean nanodroplet diameter of 4.7 ± 1.22 nm consisting of oil, water, surfactants, and cosurfactants that were able to destroy the HSV-2 virus at a 200-fold dilution in Dulbecco's modified eagle medium (Alkhatib et al. 2016). Pentyl gallate nanoemulsions (particle sizes of 124.8–143.7 nm; zeta potential ranging from −50.1 to −66.1 mV) demonstrated anti-HSV-1 activity and the drug reached deeper into the dermis more efficiently from the nanoemulsion as free drug, suggesting that nanoemulsions have potential to be used in topically delivering pentyl gallate in the treatment of human herpes labialis infection affecting primarily the lip (Kelmann et al. 2016).

Enhanced antiviral activity against a clinical isolate of HSV-1 was determined using ACV-loaded spherical carboxylated cyclodextrin-based nanosponges carrying carboxylic groups with the size of about 400 nm that exhibited prolonged release in comparison with that observed with nanosponges, without initial burst effect (Lembo et al. 2013). The formulation of ACV-loaded flexible membrane vesicles with particle size and zeta potential of 453.7 nm and −11.62 mV, respectively, incorporated into a hydrogel enhanced retention of drug deep inside the skin layers indicating potentially reduced need of application frequency resulting in reducing of adverse effects and suitability of such formulation for topical application against HSV-1 infection (Sharma et al. 2017b).

ACV entrapped in nanostructured lipid carriers coated with CS increased the corneal bioavailability in albino rabbits by 4.5-fold when compared to a commercially available ophthalmic ointment of drug, whereby this nanoformulation showed sustained release and improved antiviral properties of ACV through cell internalization (Seyfoddin et al. 2016). The ACV-loaded CS NPs showing a spherical shape, a size approx. 200 nm, and a zeta potential approx. −40.0 mV showed improved in vitro skin permeation and higher antiviral activity than the free drug against both the HSV-1 and the HSV-2 strains (Donalisio et al. 2018). CS as an immunomodulating adjuvant on T cells and antigen-presenting cells in HSV-1 infected mice was reported by Choi et al. (2016). In the dendritic cell-based DNA vaccine (pRSC-NLDC145.gD-IL21) carried by CS NPs, the expressed glycoprotein D in the formulation effectively targeted corneal dendritic cells and significantly alleviated the symptoms of both primary and recurrent HSV keratitis in mice via eliciting strong humoral and cellular immune response suggesting that such vaccine could be successfully used in *Herpes simplex* keratitis treatment (Tang et al. 2018).

Biomimetic supramolecular hexagonal-shaped nanoassemblies composed of chondroitin sulfate formed by mixing hydrophobically modified chondroitin sulfate with α-cyclodextrin in water showed improved antiviral activity against HSV-2 compared to hydrophobically modified chondroitin sulfate (Galus et al. 2016). ACV was found to increasingly permeate through the multilayers of human corneal epithelial cells from the drug-loaded bovine serum albumin NPs (approx. 200 nm) compared to drug solution suggesting potential of such formulation to be used as ocular drug delivery system (Suwannoi et al. 2017).

7.7 Hepatitis B and C Viruses

Hepatitis B virus (HBV), a species of the genus *Orthohepadnavirus* and a member of the *Hepadnaviridae* family of viruses, is a double-stranded DNA virus that replicates by reverse transcription, while hepatitis C virus (HCV) is an enveloped positive-sense single-stranded RNA virus of the family *Flaviviridae* (Zuckerman 1996). HBV and HBC affect the liver and can cause both acute and chronic infections, whereby cirrhosis and liver cancer may eventually develop. Viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV and in 2013 it was the seventh leading cause of death worldwide (Stanaway et al. 2016; World Health Organization 2017). The presence of hepatitis B virus core antigen (HBcAg) that is the major structural protein of hepatitis B virus (HBV) in a blood serum indicates that a person has been exposed to HBV (Liang 2009; Inoue and Tanaka 2016).

Lu et al. (2008) estimated that AgNPs of the size 10 and 50 nm inhibited the in vitro production of HBV RNA and extracellular virions and assumed that the direct interaction between these NPs and HBV double-stranded DNA or viral particles is responsible for their antiviral mechanism. Lee et al. (2012) proposed hyaluronic acid-AuNPs/interferon-α complex for targeted treatment of HCV infection. Antiviral effect of AuNPs showing small particle size (approx. 3.5 nm) organized on the surface of larger layered double hydroxide (LDH) NPs such as MgLDH, ZnLDH, and MgFeLDH (approx. 150 nm) using HBV as a model virus and hepatoma-derived HepG2.2.215 cells for viral replication reduced the amount of viral and subviral particles released from treated cells by up to 80%; in the presence of AuNPs/LDHs the HBV particles were sequestered within the treated cells and the highest antiviral HBV response (>90% inhibition of HBV secretion) was estimated with AuNPs/MgFeLDH (Carja et al. 2015). Cu_2O NPs that were tested on antiviral activity against HCV pronouncedly inhibited the infectivity of HCVcc/Huh7.5.1 at a noncytotoxic concentration, they inhibited the entry of HCV pseudoparticles (HCVpp), including genotypes 1a, 1b, and 2a, while no effect on HCV replication was observed and they were found to stop HCV infection both at the attachment and entry stages suggesting that Cu_2O NPs could be used in the treatment of patients with chronic hepatitis C (Hang et al. 2015).

Multifunctional SeNPs with baicalin and folic acid surface-modifications designed for the targeted treatment of HBV-infected liver cancer primarily targeted lysosomes in HepG2215 cells, induced apoptosis of HepG2215 cell by downregulating the generation of reactive oxygen species (ROS) and the expression of the HBxAg protein, and showed superb ability to inhibit cancer cell migration and invasion (Fang et al. 2017).

Alum-adjuvanted HBV vaccine is considered as the most effective measure to prevent HBV infection; however, it is a frost-sensitive suspension and therefore it would be desirable to use alternative natural adjuvant system strongly immunogenic allowing for a reduction in dose and cost. Therefore, AbdelAllah et al. (2016) subcutaneously immunized mice with HBV surface antigen, HBsAg, adjuvanted with

CS and sodium alginate, either alone or combined with alum, estimated rate of seroconversion, serum HBsAg antibody, interleukin-4, and interferon-γ levels, and compared them with control mice immunized with current vaccine formula or unadjuvanted HBsAg. It was found that the solution formula with CS or sodium alginate exhibited comparable immunogenic responses to alum-adjuvanted suspension and the triple adjuvant application (alum, CS, sodium alginate) resulted in considerably higher immunogenic response than controls. Compared to traditional methods, vaccines prepared from nanoscale materials show appropriate biocompatibility and can secure effective targeting to certain tissue or cells as well as precise stimulation of immune responses (Yang et al. 2016b).

HBsAg-loaded trimethyl CS (TMC)/hydroxypropyl methylcellulose (hypromellose) phthalate (HPMCP) NPs with particle size of 158 nm showing loading capacity and loading efficiency of 76.75% and 86.29%, respectively, at 300 μg/mL concentration of the antigen exhibited improved acid stability and better protection of entrapped HBsAg from gastric destruction in vitro, whereby the antigen showed efficacious activity also after loading. Based on these findings it could be suggested that TMC/HPMCP NPs have potential to be applied in the oral delivery of HBsAg vaccine (Farhadian et al. 2015). Ndeboko et al. (2015) studied the inhibition of the replication of duck hepatitis B virus (DHBV), a reference model for human HBV infection, by peptide nucleic acid (PNA) conjugated to different cell-penetrating peptides (CPPs) and found that the PNA-CPP conjugates administered to neonatal ducklings reached the liver and inhibited DHBV replication, and in mouse model conjugation of HBV DNA vaccine to modified CS ameliorated cellular and humoral responses to plasmid-encoded antigen and plasmid DNA uptake, whereby expression could also be notably increased using gene delivery systems such as CPP-modified CS or cationic NPs.

Biodegradable NPs encapsulating RBV monophosphate prepared from the blend of poly(D,L-lactic acid) homopolymer and arabinogalactan-poly(L-lysine) conjugate were efficiently internalized in cultured HepG2 cells; they ensured sustained release of drug and could be considered as a formulation suitable for the clinical application of RBV as a therapeutic agent for chronic HCV (Ishihara et al. 2014). Liver-specific, sustained drug delivery system prepared by conjugating the liver-targeting peptide to PEGylated cyclosporine A-encapsulated PLGA NPs effectively inhibited viral replication in vitro as well as in a HCV mouse model (Jyothi et al. 2015). Adefovir encapsulated in PLGA microspheres showed sustained release and after intramuscular injection to rats considerable increase in the $t_{max,}$ $AUC_{(0-t)}$, and mean residence time, and a pronounced reduction in the C_{max} was observed, suggesting that the nanoformulation could be used for long-term treatment of chronic hepatitis B instead of the daily dose used by the patient (Ayoub et al. 2018).

Lipid nanocapsules, surface-functionalized with amphiphilic boronic acid through their postinsertion into the semirigid shell of the nanocapsules, were found to be excellent HCV entry inhibitors preventing HCV infection in the micromolar range (Khanal et al. 2015). Phenylboronic-acid-modified NPs as potential antiviral therapeutics were reported previously also by Khanal et al. (2013). siRNA-loaded lipid NPs (LNPs) modified with a hepatocyte-specific ligand, *N*-acetyl-D-galactosamine, showed pronounced improvement of hepatocyte-specificity and

strong reduction in toxicity and further modification of NPs with PEG practically eliminated the LNP-associated toxicity without any detectable loss of gene silencing activity in hepatocytes, whereby a single injection of the LNPs considerably reduced HBV genomic DNA and their antigens without any sign of toxicity in chimeric mice with humanized livers that had been persistently infected with HBV (Sato et al. 2017).

7.8 Ebola and Marburg Virus

Ebola virus disease is caused by Ebola viruses (EBOVs; family *Filoviridae*), members of the group of hemorrhagic fever and it is one of the most dangerous infection diseases with mortality rates up to 90%. The EBOVs do not replicate through cell division, but instead insert their own genetic sequencing into the DNA of the host cell and subsequently hijack all cellular processes, including transcription and translation; thus, the host cell becomes a factory of viral proteins (Gebretadik et al. 2015; Murray 2015).

It was found that graphene sheets associate strongly with the EBOV matrix protein VP40 that is a potential pharmacological target for disrupting the virus life cycle, at various interfaces. Graphene can disrupt the C-terminal domain interface of VP40 hexamers being crucial in forming the Ebola viral matrix, suggesting that graphene or similar NPs-based solutions used as a disinfectant could notably reduce the spread of the disease and prevent an Ebola epidemic (Gc et al. 2017). Rodriguez-Perez et al. (2018) found that MWCNTs functionalized with glycofullerenes can be considered as potent inhibitors of Ebola infection. In two mRNA vaccines based on the EBOV envelope glycoprotein, differing by the nature of signal peptide for improved glycoprotein posttranslational translocation, the mRNAs were formulated with LNPs to facilitate delivery. Vaccination of guinea pigs induced EBOV-specific IgG and neutralizing antibody responses and 100% survival after EBOV infection (Meyer et al. 2018). Adjuvant-free dendrimer NPs vaccine platform wherein antigens are encoded by encapsulated mRNA replicons, able to generate protective immunity against many lethal pathogen challenges, including H1N1 influenza, *Toxoplasma gondii*, and EBOV, that can be formed with multiple antigen-expressing replicons and could elicit both $CD8^+$ T cell and antibody responses was designed by Chahal et al. (2016). Administration of siRNA encapsulated in LNPs able to target Sudan ebolavirus VP35 gene to rhesus monkeys receiving a lethal dose of the virus resulted in up to 100% survival and a reduction of viral replication (up to 4 $\log_{10}$) (Thi et al. 2016). Similar results were received with treatment of Ebola-virus-Makona-infected nonhuman primates following administration of siRNA encapsulated in LNPs suggesting the therapeutic potential of such nanoformulation in combating this lethal disease (Thi et al. 2015). Incorporation of Ebola DNA vaccine into PLGA-poly-L-lysine/poly-γ-glutamic acid increased vaccine thermostability and immunogenicity compared to free vaccine and vaccination performed to skin using a microneedle patch produced stronger immune responses than intramuscular administration (Yang et al. 2017b).

Marburg virus, similarly to Ebola virus, belongs to the family *Filoviridae* and causes severe and often fatal hemorrhagic fever in humans and nonhuman primates with very high mortality rates. The virus is transmitted from animals to humans by contact with bats or monkeys, or their bodily secretions or from person to person, although human-to-human contamination is rare (Sboui and Tabbabi 2017). Formulation of LNPs delivering siRNAs that target the anti-Marburg virus nucleoprotein administered to rhesus monkeys challenged with a lethal dose of Marburg virus-Angola showed excellent therapeutic efficacy and secured survival of infected animals (Thi et al. 2014) and protection against lethal Marburg virus infection mediated by lipid encapsulated siRNA was also observed with virus-infected guinea pigs (Ursic-Bedoya et al. 2014). Blocking of the infection of T-lymphocytes and human dendritic cells by Ebola virus using glyco-dendri-protein-NPs displaying quasi-equivalent nested polyvalency upon glycoprotein platforms, which consist of glyco-dendrimeric constructs (bearing up to 1620 glycans) with diameters up to 32 nm, was observed already at picomolar concentrations (Ribeiro-Viana et al. 2012).

7.9 Newcastle Disease Virus

Newcastle disease, a contagious viral bird disease, is caused by virulent strains of Newcastle disease virus (NDV), that causes substantial morbidity and mortality events worldwide in poultry resulting in devastating economic effects on global domestic poultry production. NDV, a negative-sense, single-stranded RNA virus, is capable of infecting more than 250 species of domestic and wild avian species (Brown and Bevins 2017). NDV is transmissible to humans and the exposure of humans to infected birds can cause mild conjunctivitis and influenza-like symptoms, but the NDV otherwise poses no hazard to human health (Abdisa and Tagesu 2017).

Zhao et al. (2016) designed a NDV F gene-containing DNA vaccine encapsulated in $Ag@SiO_2$ hollow NPs with an average diameter of 500 nm that following intranasal immunization of chickens induced high titers of serum antibody, notably stimulated lymphocyte proliferation and induced higher expression levels of interleukine-2 and interferon-γ, suggesting that $Ag@SiO_2$ hollow NPs could be used as an efficient and safe delivery carrier for NDV DNA vaccine to induce mucosal immunity.

The intranasal administration of quaternized CS (2-hydroxy-*N*,*N*,*N*-trimethyl propan-1-ammonium chloride CS/*N*,*O*-carboxymethyl CS) NPs loaded with the combined attenuated live vaccine against Newcastle disease and infectious bronchitis elicited immune response in chicken and induced higher titers of IgG and IgA antibodies, notably stimulated proliferation of lymphocytes and induced higher levels of interleukine-2, interleukine-4, and interferon-γ than the commercially combined attenuated live vaccine did. Induction of humoral, cellular, and mucosal immune responses protecting animals from the infection of highly virulent NDV and avian infectious bronchitis virus suggested that such CS derivative could be

used as an efficient adjuvant and delivery carrier in mucosal vaccines (Zhao et al. 2017). Quaternized CS NPs loaded with the combined attenuated live vaccine against Newcastle disease and infectious bronchitis elicited immune response in chicken after intranasal administration.

El Naggar et al. (2017) designed preparation of mucosal NPs and polymer-based inactivated vaccine for Newcastle disease and H9N2 AI viruses, which after being delivered via intranasal and spray routes of administration in chickens enhanced the cell-mediated immune response and induced protection against challenge with both abovementioned viruses.

7.10 Dengue Virus and Zika Virus

Dengue is an acute viral illness caused by RNA virus, dengue virus (DENV), a member of the genus *Flavivirus* of the family *Flaviviridae*. DENV is an arthropode-borne virus that includes four different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) and spread by *Aedes* mosquitoes. Its presenting features may range from asymptomatic fever to dreaded complications such as hemorrhagic fever and shock and it is considered as a major global public health challenge in the tropic and sub-tropic nations (Hasan et al. 2016). To achieve durable protective immunity against all four serotypes DENV vaccines must induce balanced, serotype-specific neutralizing antibodies. A tetravalent DENV protein subunit vaccine, based on recombinant envelope protein (rE) adsorbed to the surface of PLGA NPs, was designed. Particulate rE induced higher neutralizing antibody titers compared to the soluble rE antigen alone and stimulated a more balanced serotype-specific antibody response to each DENV serotype compared to soluble antigens, suggesting that such vaccines might overcome unbalanced immunity observed for leading live attenuated vaccine candidates (Metz et al. 2018). AgNPs showed in vitro antiviral activity against dengue serotype DEN-2 infecting Vero cells and the activity of AgNPs against the dengue vector *Aedes aegypti* expressed by IC_{50} values ranged from 10.24 ppm (I instar larvae) to 21.17 ppm (pupae) (Sujitha et al. 2015). AgNPs biosynthesized using the aqueous extract of *Bruguiera cylindrica* leaves significantly inhibited the production of dengue viral envelope E protein in Vero cells and downregulated the expression of dengue viral E gene and they were found to be suitable for application at low doses to reduce larval and pupal population of *Ae. aegypti*, without detrimental effects of predation rates of mosquito predators, such as *Carassius auratus* (Murugan et al. 2015). Stabile AgNPs (particle size from 7 to 32 nm and zeta potential −15.58 mV) biosynthesized using silver nitrate and *Carica papaya* leaf extract demonstrated good binding affinity against dengue type 2 virus nonstructural protein 1 (Renganathan et al. 2019). Treatment with a hybrid consisting of AuNPs functionalized with domain III of envelope glycoprotein derived from serotype 2 of DENV (EDIII) resulted in a high level of antibody, which mediates serotype-specific neutralization of DENV in BALB/c mice, was found to be size-dependent and according to researchers the hybrid concept could also be adopted

for the development of a tetravalent vaccine against four serotypes of DENV (Quach et al. 2018). It is important to note that good antiviral activity against dengue virus exhibited also SeNPs (Ramya et al. 2015).

Zika virus (ZIKV) is a mosquito-borne flavivirus that is the focus of an ongoing pandemic and public health emergency and represents a public health threat due to its teratogenic nature causing microcephaly in babies born to infected mothers and association with the serious neurological condition Guillain-Barre syndrome in adults (Plourde and Bloch 2016). Haque et al. (2018) proposed strategies to design effective and safe vaccines against ZIKV, including Toll-like receptors based NPs vaccines. The development of biomimetic nanodecoy (ND) that traps ZIKV and inhibits ZIKV infection was suggested by Rao et al. (2019). The ND, which is composed of a gelatin nanoparticle core camouflaged by mosquito medium host cell membranes, effectively adsorbs ZIKV and inhibits ZIKV replication in ZIKV-susceptible cells. AgNPs fabricated using leaf extracts of *Cleistanthus collinus* (triangular and pentagonal shape with sizes 66.27–75.09 nm) and *Strychnos nux-vomica* (spherical and round shape with sizes 54.45–60.84 nm) can be applied as a natural biolarvicidal agent to vector control strategy as an eco-friendly approach to prohibit Zika, chikungunya, and dengue fever in the future (Jinu et al. 2018). Insecticidal AgNPs prepared using *Suaeda maritima* were found to be effective against the dengue vector *Ae. aegypti* as well (Suresh et al. 2018). Bacterial exopolysaccharide-coated ZnO NPs nanoparticles showed high antibiofilm activity and larvicidal toxicity against malaria and ZIKV vectors *Anopheles stephensi* and *Ae. aegypti* with 100% mortality against third instars mosquito larvae at very low doses, whereby in the midgut of treated mosquito larvae presence of damaged cells and tissues was observed (Abinaya et al. 2018). Promising toxic and repellent activity against ZIKV mosquito vectors showed also TiO_2 NPs prepared using an extract of *Argemone mexicana* that were capped with poly(styrenesulfonate)/poly(allylamine hydrochloride) (Murugan et al. 2018). Nanoscale silicate platelets modified with anionic sodium dodecyl sulfate significantly suppressed the plaque-forming ability of Japanese encephalitis virus (JEV) at noncytotoxic concentrations and blocked infection with DENV and influenza A virus and also reduced the lethality of JEV and DENV infection in mouse challenge models (Liang et al. 2014).

Efficiency of green-synthesized metal AgNPs and AuNPs used as biopesticides against *Ae. aegypti* that can spread dengue virus and *Culex quinquefasciatus* or *An. stephensi* that transmit Zika virus were presented in several papers (e.g., Jampílek and Kráľová 2019d; Govindarajan and Benelli 2017; Lallawmawma et al. 2015; Pavunraj et al. 2017; Ishwarya et al. 2017; Suganya et al. 2017).

7.11 Pseudorabies Virus

Rabies virus is a neurotropic virus that causes rabies in humans and animals, while pseudorabies virus (PRV) is a herpesvirus of swine, a member of the *Alphaherpesvirinae* subfamily, and the etiological agent of Aujeszky's disease. PRV infection progresses from acute infection of the respiratory epithelium to latent

infection in the peripheral nervous system, whereby sporadic reactivation from latency can transmit PRV to new hosts (Pomeranz et al. 2005).

Au nanoclusters surface-stabilized with histidine that strongly inhibited the proliferation of PRV were found to function via blockage of the viral replication process rather than the processes of attachment, penetration, or release and they were observed to be mainly localized to nucleus (Feng et al. 2018). Both GO and reduced GO showing the nanosheet structure tested against a DNA virus, PRV, and a RNA virus, porcine epidemic diarrhea virus (PEDV), suppressed the infection of these viruses for a 2 log reduction, and their potent antiviral activity can be attributed to the unique single-layer structure and negative charge of GO and reduced GO, whereby GO inactivated both viruses by structural destruction prior to viral entry (Ye et al. 2015).

A nonlinear globular G2 dendrimer comprising citric acid and PEG-600, adjuvanticity effect of which was investigated in veterinary rabies vaccine, did not show significant toxic effect in J774A.1 cells and ensured higher survival rate in the mice after virus challenge in vivo due to adjuvanticity effect of dendrimer resulting in rising of neutralizing antibodies against rabies virus and thus enhancing immune responses (Asgary et al. 2018).

7.12 Other Viruses

AgNPs of 25 nm were found to prevent viral entry of *Vaccinia virus*, an enveloped virus belonging to the poxvirus family, by macropinocytosis-dependent mechanism, which resulted in inhibition of *Vaccinia virus* infection (Trefry and Wooley 2013).

Broglie et al. (2015) tested antiviral activity of Au/CuS core/shell NPs against human Norovirus GI.1 (Norwalk) virus-like particles as a model viral system and found that virucidal efficacy significantly increased with increasing NPs concentration and/or contact time of virus-like particles with NPs.

CuI NPs demonstrated high antiviral activity against the nonenveloped virus feline calicivirus (FCV) as a surrogate for human norovirus (the most common etiological agent of gastroenteritis) that was attributed to Cu^{+} ions, followed by generation of ROS and subsequent capsid protein oxidation (Shionoiri et al. 2012).

The investigation of in vitro antiviral effects of MgO NPs in the foot-and-mouth disease (FMD), an extremely contagious viral disease of cloven-hoofed animals, on Razi Bovine kidney cell line showed that the MgO NPs exhibited virucidal and antiviral activities and they inhibited FMD virus by more than 90% at the early stages of infection such as attachment and penetration but not after penetration (Rafiei et al. 2015).

McGill et al. (2018) developed a mucosal nanovaccine with the post-fusion F and G glycoproteins from bovine respiratory syncytial virus (BRSV) encapsulated in polyanhydride NPs and tested it against BRSV infection using a neonatal calf model. They observed reduced pathology in the lungs, reduced viral burden, and decreased virus shedding compared to unvaccinated control calves showing correlation with BRSV-specific immune responses in the respiratory tract and peripheral blood.

Glutathione-capped Ag_2S nanoclusters showed strong antiviral activity against PEDV used as a model of coronavirus and pronounced reduction of the infection of PEDV by about three orders of magnitude at the noncytotoxic concentration at 12 h post-infection was observed. The Ag_2S nanoclusters inhibited the synthesis of viral negative-strand RNA and viral budding and positively regulated the generation of interferon-stimulating genes and the expression of proinflammation cytokines (Du et al. 2018).

Khandelwal et al. (2014) evaluated antiviral efficacy of AgNPs (5–30 nm) against *Ovine rinderpest* (*Peste des petits ruminants virus*, PPRV), a prototype *Morbillivirus*, causing disease in small ruminants, such as goats and sheep, and estimated significant inhibition of PPRV replication by AgNPs in an experiment using Vero cells already at noncytotoxic concentration, whereby AgNPs blocked the viral entry into the target cells due to interaction of AgNPs with the virion surface as well as with the virion core.

7.13 Conclusions

Nanoscale science and nanotechnology have unambiguously demonstrated to have a great potential in providing novel and improved solutions. Nano-size materials change their physical and chemical properties in comparison with bulk materials and have helped to improve and innovate a variety of pharmaceutical, medical, industrial, and agricultural products. Thus, nanoformulations of antivirotics and antiviral vaccines have become an important tool in the fight against various types of viruses due to modified bioavailability, ability to target viral or cellular proteins and sustainable release of drugs. Also, other nanosized materials were found to exhibit antiviral activity, and their combinations with antivirotics thus could provide remarkable medicines, especially against resistant viral pathogens. However, in spite of these significant benefits of nanomaterials in drug development, an increased attention should be devoted to the potential "intrinsic" toxicity of these nanomedicines caused by particle size that is able, within side effects, to induce various pathological processes in cells/tissues, which can result in various adverse/hazardous effects on animals and humans.

Acknowledgements This study was supported by the Slovak Research and Development Agency (projects APVV-17-0373 and APVV-17-0318).

References

AbdelAllah NH, Abdeltawab NF, Boseila AA, Amin MA. Chitosan and sodium alginate combinations are alternative, efficient, and safe natural adjuvant systems for hepatitis B vaccine in mouse model. Evid Based Complement Alternat Med. 2016;2016:7659684.

Abdisa T, Tagesu T. Review on Newcastle disease of poultry and its public health importance. J Veter Sci Technol. 2017;8:441.

Abinaya M, Vaseeharan B, Divya M, Sharmili A, Govindarajan M, Alharbi NS, Kadaikunnan S, Khaled JM, Benelli G. Bacterial exopolysaccharide (EPS)-coated ZnO nanoparticles showed high antibiofilm activity and larvicidal toxicity against malaria and Zika virus vectors. J Trace Elem Med Biol. 2018;45:93–103.

Akbarzadeh A, Kafshdooz L, Razban Z, Tbrizi AD, Rasoulpour S, Khalilov R, Kavetskyy T, Saghfi S, Nasibova AN, Kaamyabi S, Kafshdooz T. An overview application of silver nanoparticles in inhibition of herpes simplex virus. Artif Cells Nanomed Biotechnol. 2018;46:263–7.

Al-Ghananeem AM, Smith M, Coronel ML, Tran H. Advances in brain targeting and drug delivery of anti-HIV therapeutic agents. Expert Opin Drug Deliv. 2013;10:973–85.

Alkhatib MH, Aly MM, Rahbeni RA, Balamash KS. Antimicrobial activity of biocompatible microemulsions against *Aspergillus niger* and herpes simplex virus type 2. Jundishapur J Microbiol. 2016;9:e37437.

Almeida KB, Araujo JL, Cavalcanti JF, Romanos MTV, Mourao SC, Amaral ACF, Falcao DQ. In vitro release and anti-herpetic activity of *Cymbopogon citratus* volatile oil-loaded nanogel. Rev Bras. 2018;28:495–502.

Amirkhanov RN, Mazurkova NA, Amirkhanov NV, Zarytova VF. Composites of peptide nucleic acids with titanium dioxide nanoparticles IV. Antiviral activity of nanocomposites containing DNA/PNA duplexes. Russ J Bioorg Chem. 2015;41:140–6.

Antoine TE, Hadigal SR, Yakoub AM, Mishra YK, Bhattacharya P, Haddad C, Valyi-Nagy T, Adelung R, Prabhakar BS, Shukla D. Intravaginal zinc oxide tetrapod nanoparticles as novel immunoprotective agents against genital herpes. J Immunol. 2016;196:4566–75.

Antoine TE, Mishra YK, Trigilio J, Tiwari V, Adelung R, Shukla D. Prophylactic, therapeutic and neutralizing effects of zinc oxide tetrapod structures against herpes simplex virus type-2 infection. Antivir Res. 2012;96:363–75.

Ardestani MS, Fordoei AS, Abdoli A, Cohan RA, Bahramali G, Sadat SM, Siadat SD, Moloudian H, Koopaei NN, Bolhasani A, Rahimi P, Hekmat S, Davari N, Aghasadeghi MR. Nanosilver based anionic linear globular dendrimer with a special significant antiretroviral activity. J Mater Sci Mater Med. 2015;26:179.

Argenta DF, Bidone J, Misturini FD, Koester LS, Bassani VL, Simoes CMO, Teixeira HF. In vitro evaluation of mucosa permeation/retention and antiherpes activity of genistein from cationic nanoemulsions. J Nanosci Nanotechnol. 2016;16:1282–90.

Ariza-Saenz M, Espina M, Bolanos N, Calpena AC, Gomara MJ, Haro I, Garcia ML. Penetration of polymeric nanoparticles loaded with an HIV-1 inhibitor peptide derived from GB virus C in a vaginal mucosa model. Eur J Pharm Biopharm. 2017;120:98–106.

Ariza-Saenz M, Espina M, Calpena A, Gomara MJ, Perez-Pomeda I, Haro I, Garcia ML. Design, characterization, and biopharmaceutical behavior of nanoparticles loaded with an HIV-1 fusion inhibitor peptide. Mol Pharm. 2018;15:5005–18.

Asgary V, Shoari A, Moayad MA, Ardestani MS, Bigdeli R, Ghazizadeh L, Khosravy MS, Panahnejad E, Janani A, Bashar R, Abedi M, Ahangri Cohan R. Evaluation of G2 citric acid-based dendrimer as an adjuvant in veterinary rabies vaccine. Viral Immunol. 2018;31:47–54.

Augustine R, Ashkenazi DL, Arzi RS, Zlobin V, Shofti R, Sosnik A. Nanoparticle-in-microparticle oral drug delivery system of a clinically relevant darunavir/ritonavir antiretroviral combination. Acta Biomater. 2018;74:344–59.

Ayoub MM, Elantouny NG, El-Nahas HM, Ghazy FED. Injectable PLGA Adefovir microspheres; the way for long term therapy of chronic hepatitis-B. Eur J Pharm Sci. 2018;118:24–31.

Bahl K, Senn JJ, Yuzhakov O, Bulychev A, Brito LA, Hassett KJ, Laska ME, Smith M, Almarsson O, Thompson J, Ribeiro AM, Watson M, Zaks T, Ciaramella G. Preclinical and clinical demonstration of immunogenicity by mRNA vaccines against H10N8 and H7N9 influenza viruses. Mol Ther. 2017;25:1316–27.

Baram-Pinto D, Shukla S, Gedanken A, Sarid R. Inhibition of HSV-1 attachment, entry, and cell-to-cell spread by functionalized multivalent gold nanoparticles. Small. 2010;6:1044–50.

Baram-Pinto D, Shukla S, Perkas N, Gedanken A, Sarid R. Inhibition of herpes simplex virus type 1 infection by silver nanoparticles capped with mercaptoethane sulfonate. Bioconjug Chem. 2009;20:1497–502.

Barras A, Pagneux Q, Sane F, Wang Q, Boukherroub R, Hober D, Szunerits S. High efficiency of functional carbon nanodots as entry inhibitors of herpes simplex virus type 1. ACS Appl Mater Interfaces. 2016;8:9004–13.

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. Nanomedicine. 2016;12:2299–310.

Bayon E, Morlieras J, Dereuddre-Bosquet N, Gonon A, Gosse L, Courant T, Le Grand R, Marche PN, Navarro FP. Overcoming immunogenicity issues of HIV p 24 antigen by the use of innovative nanostructured lipid carriers as delivery systems: evidences in mice and non-human primates. NPJ Vaccines. 2018;3:46.

Belgamwar A, Khan S, Yeole P. Intranasal chitosan-g-HPβCD nanoparticles of efavirenz for the CNS targeting. Artif Cells Nanomed Biotechnol. 2018;46:374–86.

Bernasconi V, Bernocchi B, Ye L, Le MQ, Omokanye A, Carpentier R, Schon K, Saelens X, Staeheli P, Betbeder D, Lycke N. Porous nanoparticles with self-adjuvanting M2e-fusion protein and recombinant hemagglutinin provide strong and broadly protective immunity against influenza virus infections. Front Immunol. 2018;9:2060.

Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus—a comprehensive review. Clin Rev Allergy Immunol. 2013;45:331–79.

Broglie JJ, Alston B, Yang C, Ma L, Adcock AF, Chen W, Yang LJ. Antiviral activity of gold/copper sulfide core/shell nanoparticles against human norovirus virus-like particles. PLoS One. 2015;10:e0141050.

Brown IH. History and epidemiology of Swine influenza in Europe. Curr Top Microbiol Immunol. 2013;370:133–46.

Brown VR, Bevins SN. A review of virulent Newcastle disease viruses in the United States and the role of wild birds in viral persistence and spread. Vet Res. 2017;48:68.

Cagno V, Andreozzi P, D'Alicarnasso M, Silva PJ, Mueller M, Galloux M, Le Goffic R, Jones ST, Vallino M, Hodek J, Weber J, Sen S, Janeček ER, Bekdemir A, Sanavio B, Martinelli C, Donalisio M, Rameix Welti MA, Eleouet JF, Han YX, Kaiser L, Vukovic L, Tapparel C, Král P, Krol S, Lembo D, Stellacci F. Broad-spectrum non-toxic antiviral nanoparticles with a virucidal inhibition mechanism. Nat Mater. 2018;17:195–203.

Capek I. Viral nanoparticles, noble metal decorated viruses and their nanoconjugates. Adv Colloid Interf Sci. 2015;222:119–34.

Carja G, Grosu EF, Petrarean C, Nichita N. Self-assemblies of plasmonic gold/layered double hydroxides with highly efficient antiviral effect against the hepatitis B virus. Nano Res. 2015;8:3512–23.

Chahal JS, Khan OF, Cooper CL, McPartlan JS, Tsosie JK, Tilley LD, Sidik SM, Lourido S, Langer R, Bavari S, Ploegh H, 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.

Chaowanachan T, Krogstad E, Ball C, Woodrow KA. Drug synergy of tenofovir and nanoparticle-based antiretrovirals for HIV prophylaxis. PLoS One. 2013;8:e61416.

Chatziprodromidou IP, Arvanitidou M, Guitian J, Apostolou T, Vantarakis G, Apostolos Vantarakis A. Global avian influenza outbreaks 2010–2016: a systematic review of their distribution, avian species and virus subtype. Syst Rev. 2018;7:17.

Chiou CJ, Tseng LP, Deng MC, Jiang PR, Tasi SL, Chung TW, Huang YY, Liu DZ. Mucoadhesive liposomes for intranasal immunization with an avian influenza virus vaccine in chickens. Biomaterials. 2009;30:5862–8.

Choi B, Jo DH, Anower AKMM, Islam SMS, Sohn S. Chitosan as an immunomodulating adjuvant on T-cells and antigen-presenting cells in herpes simplex virus type 1 infection. Mediat Inflamm. 2016;2016:4374375.

Chowdhury MYE, Kim TH, Uddin MB, Kim JH, Hewawaduge CY, Ferdowshi Z, Sung MH, Kim CJ, Lee JS. Mucosal vaccination of conserved sM2, HA2 and cholera toxin subunit Al (CTAI) fusion protein with poly γ-glutamate/chitosan nanoparticles (PC NPs) induces protection against divergent influenza subtypes. Vet Microbiol. 2017;201:240–51.

Clark CM, Guerrero-Plata A. Respiratory syncytial virus vaccine approaches: a current overview. Curr Clin Microbiol Rep. 2017;4:202–7.

Climent N, Garcia I, Marradi M, Chiodo F, Miralles L, Maleno MJ, Gatell JM, Garcia F, Penades S, Plana M. Loading dendritic cells with gold nanoparticles (GNPs) bearing HIV-peptides and mannosides enhance HIV-specific T cell responses. Nanomedicine. 2018;14:339–51.

Coulibaly FS, Ezoulin MJM, Purohit SS, Ayon NJ, Oyler NA, Youan BBC. Layer-by-layer engineered microbicide drug delivery system targeting HIV-1 gp120: physicochemical and biological properties. Mol Pharm. 2017;14:3512–27.

Cunha-Reis C, Machado A, Barreiros L, Araújo F, Nunes R, Seabra V, Ferreira D, Segundo MA, Sarmento B, Neves JD. Nanoparticles-in-film for the combined vaginal delivery of anti-HIVmicrobicide drugs. J Control Release. 2016;243:43–53.

Dai X, Zhou ZH. Structure of the herpes simplex virus 1 capsid with associated tegument protein complexes. Science. 2018;360:eaao7298.

De Clercq E, Li G. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev. 2016;29:695–747.

Deng L, Chang TZ, Wang Y, Li S, Wang S, Matsuyama S, Yu GY, Compans RW, Li JD, Prausnitz MR, Champion JA, Wang BZ. Heterosubtypic influenza protection elicited by double-layered polypeptide nanoparticles in mice. Proc Natl Acad Sci U S A. 2018b;115:E7758–67.

Deng L, Mohan T, Chang TZ, Gonzalez GX, Wang Y, Kwon YM, Kang SM, Compans RW, Champion JA, Wang BZ. Double-layered protein nanoparticles induce broad protection against divergent influenza A viruses. Nat Commun. 2018a;9:359.

Deng L, Wang BZ. A perspective on nanoparticle universal influenza vaccines. ACS Infect Dis. 2018;4:1656–65.

Deokar AR, Nagvenkar AP, Kalt I, Shani L, Yeshurun Y, Gedanken A, Sarid R. Graphene-based "hot plate" for the capture and destruction of the herpes simplex virus type 1. Bioconjug Chem. 2017;28:1115–22.

Desai J, Thakkar H. Enhanced oral bioavailability and brain uptake of darunavir using lipid nanoemulsion formulation. Colloids Surf B: Biointerfaces. 2019;175:143–9.

Dey P, Bergmann T, Cuellar-Camacho JL, Ehrmann S, Chowdhury MS, Zhang MZ, Dahmani I, Haag R, Azad W. Multivalent flexible nanogels exhibit broad-spectrum antiviral activity by blocking virus entry. ACS Nano. 2018;12:6429–42.

Dhakal S, Goodman J, Bondra K, Lakshmanappa YS, Hiremath J, Shyu DL, Ouyang K, Kang KI, Krakowka S, Wannemuehler M, Won Lee C, Narasimhan B, Renukaradhya GJ. Polyanhydride nanovaccine against swine influenza virus in pigs. Vaccine. 2017a;35:1124–31.

Dhakal S, Hiremath J, Bondra K, Lakshmanappa YS, Shyu DL, Ouyang K, Kanga KI, Binjawadagi B, Goodman J, Tabynov K, Krakowka S, Narasimhan B, Won Lee C, Gourapura J, Renukaradhya GJ. Biodegradable nanoparticle delivery of inactivated swine influenza virus vaccine provides heterologous cell-mediated immune response in pigs. J Control Release. 2017b;247:194–205.

Dhakal S, Renu S, Ghimire S, Lakshmanappa YS, Hogshead BT, Feliciano-Ruiz N, Lu FJ, HogenEsch H, Krakowka S, Lee CW, Renukaradhya GJ. Mucosal immunity and protective efficacy of intranasal inactivated influenza vaccine is improved by chitosan nanoparticle delivery in pigs. Front Immunol. 2018;9:934.

Di Gianvincenzo P, Marradi M, Martinez-Avila OM, Bedoya LM, Alcami J, Penades S. Gold nanoparticles capped with sulfate-ended ligands as anti-HIV agents. Bioorg Med Chem Lett. 2010;20:2718–21.

Dolez PI. Nanoengineering: global approaches to health and safety issues. Amsterdam: Elsevier; 2015.

Donalisio M, Leone F, Civra A, Spagnolo R, Ozer O, Lembo D, Cavalli R. Acyclovir-loaded chitosan nanospheres from nano-emulsion templating for the topical treatment of herpesviruses infections. Pharmaceutics. 2018;10:46.

dos Santos TC, Rescignano N, Boff L, Reginatto FH, Simoes CMO, de Campos AM, Mijangos C. In vitro antiherpes effect of C-glycosyl flavonoid enriched fraction of *Cecropia glaziovii* encapsulated in PLGA nanoparticles. Mater Sci Eng C Mater Biol Appl. 2017;75:1214–20.

Du T, Liang JG, Dong N, Lu J, Fu YY, Fang LR, Xiao S, Han HY. Glutathione-capped Ag_2S nanoclusters inhibit coronavirus proliferation through blockage of viral RNA synthesis and budding. ACS Appl Mater Interfaces. 2018;10:4369–78.

El Naggar HM, Madkour MS, Hussein AH. Preparation of mucosal nanoparticles and polymer-based inactivated vaccine for Newcastle disease and H9N2 AI viruses. Vet World. 2017;10:187–93.

Endsley AN, Ho RJY. Enhanced anti-HIV efficacy of indinavir after inclusion in CD4-targeted lipid nanoparticles. J Acquir Immune Defic Syndr. 2012;61:417–24.

Fang XY, Wu XL, Li CE, Zhou BW, Chen XY, Chen TF, Yang F. Targeting selenium nanoparticles combined with baicalin to treat HBV-infected liver cancer. RSC Adv. 2017;7:8178–85.

Farhadian A, Dounighi NM, Avadi M. Enteric trimethyl chitosan nanoparticles containing hepatitis B surface antigen for oral delivery. Hum Vaccin Immunother. 2015;11:2811–8.

Fatima M, Zaidi NUSS, Amraiz D, Afzal F. In vitro antiviral activity of *Cinnamomum cassia* and its nanoparticles against H7N3 influenza A virus. J Microbiol Biotechnol. 2016;26:151–9.

Fayaz AM, Ao ZJ, Girilal M, Chen LY, Xiao XZ, Kalaichelvan PT, Yao XJ. Inactivation of microbial infectiousness by silver nanoparticles-coated condom: a new approach to inhibit HIV- and HSV-transmitted infection. Int J Nanomedicine. 2012;7:5007–18.

Feng CC, Fang PX, Zhou YR, Liu LZ, Fang LR, Xiao SB, Liang JG. Different effects of His-Au NCs and MES-Au NCs on the propagation of pseudorabies virus. Global Chall. 2018;2:1800030.

Feng F, Sakoda Y, Ohyanagi T, Nagahori N, Shibuya H, Okamastu M, Miura N, Kida H, Nishimura S. Novel thiosialosides tethered to metal nanoparticles as potent influenza A virus haemagglutinin blockers. Antivir Chem Chemother. 2013;23:59–65.

Figueira TN, Augusto MT, Rybkina K, Stelitano D, Noval MG, Harder OE, Veiga AS, Huey D, Alabi CA, Biswas S, Niewiesk S, Moscona A, Santos NC, Castanho MARB, Porotto M. Effective in vivo targeting of influenza virus through a cell-penetrating/fusion inhibitor tandem peptide anchored to the plasma membrane. Bioconjug Chem. 2018;29:3362–76.

Fries L, Shinde V, Stoddard JJ, Thomas DN, Kpamegan E, Lu HX, Smith G, Hickman SP, Piedra P, Glenn GM. Immunogenicity and safety of a respiratory syncytial virus fusion protein (RSV F) nanoparticle vaccine in older adults. Immun Ageing. 2017;14:8.

Fujimori Y, Sato T, Hayata T, Nagao T, Nakayama M, Nakayama T, Sugamata R, Suzuki K. Novel antiviral characteristics of nanosized copper(I) iodide particles showing inactivation activity against 2009 pandemic H1N1 influenza virus. Appl Environ Microbiol. 2012;78:951–5.

Gaikwad S, Ingle A, Gade A, Rai M, Falanga A, Incoronato N, Russo L, Galdiero S, Galdiero M. Antiviral activity of mycosynthesized silver nanoparticles against herpes simplex virus and human parainfluenza virus type 3. Int J Nanomedicine. 2013;8:4303–14.

Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules. 2011;16:8894–918.

Galus A, Mallet JM, Lembo D, Cagno V, Djabourov M, Lortat-Jacob H, Bouchemal K. Hexagonal-shaped chondroitin sulfate self-assemblies have exalted anti-HSV-2 activity. Carbohydr Polym. 2016;136:113–20.

Gao Y, Kraft JC, Yu D, Ho RJY. Recent developments of nanotherapeutics for targeted and long-acting, combination HIV chemotherapy. Eur J Pharm Biopharm. 2018;138:75–91.

Gc JB, Pokhrel R, Bhattarai N, Johnson KA, Gerstman BS, Stahelin RV, Chapagain PP. Graphene-VP40 interactions and potential disruption of the Ebola virus matrix filaments. Biochem Biophys Res Commun. 2017;493:176–81.

Gebretadik FA, Seifu MF, Gelaw BK. Review on Ebola virus disease: its outbreak and current status. Epidemiology (Sunnyvale). 2015;5:204.

German Advisory Committee Blood (Arbeitskreis Blut), Subgroup 'Assessment of Pathogens Transmissible by Blood'. Human immunodeficiency virus (HIV). Transf Med Chemother. 2016;43:203–22.

Gerson T, Makarov E, Senanayake TH, Gorantla S, Poluektova LY, Vinogradov SV. Nano-NRTIs demonstrate low neurotoxicity and high antiviral activity against HIV infection in the brain. Nanomedicine. 2014;10:177–85.

Gong Y, Chowdhury P, Midde NM, Rahman MA, Yallapu MM, Kumar S. Novel elvitegravir nanoformulation approach to suppress the viral load in HIV-infected macrophages. Biochem Biophys Rep. 2017;12:214–9.

Govindarajan M, Benelli G. Ovicidal and larvicidal potential on malaria, dengue and filariasis mosquito vectors. J Clust Sci. 2017;28:15–36.

Gupta S, Kesarla R, Chotai N, Misra A, Omri A. Systematic approach for the formulation and optimization of solid lipid nanoparticles of efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. Biomed Res Int. 2017;2017:5984014.

Haider A, Das S, Ojha D, Chattopadhyay D, Mukherjee A. Highly monodispersed gold nanoparticles synthesis and inhibition of herpes simplex virus infections. Mater Sci Eng C Mater Biol Appl. 2018;89:413–21.

Hajializadeh F, Ghahri H, Talebi A. Effects of supplemental chromium picolinate and chromium nanoparticles on performance and antibody titers of infectious bronchitis and avian influenza of broiler chickens under heat stress condition. Vet Res Forum. 2017;8:259–64.

Hang XF, Peng HR, Song HY, Qi ZT, Miao XH, Xu WS. Antiviral activity of cuprous oxide nanoparticles against Hepatitis C virus in vitro. J Virol Methods. 2015;222:150–7.

Haque A, Akcesme FB, Pant AB. A review of Zika virus: hurdles toward vaccine development and the way forward. Antivir Ther. 2018;23:285–93.

Hasan S, Jamdar SF, Alalowi M, Al Ageel Al Beaiji SM. Dengue virus: a global human threat: review of literature. J Int Soc Prevent Communit Dent. 2016;6:1–6.

Hashiguchi S, Yoshida H, Akashi T, Komemoto K, Ueda T, Ikarashi Y, Miyauchi A, Konno K, Yamanaka S, Hirose A, Kurokawa M, Watanabe W. Titanium dioxide nanoparticles exacerbate pneumonia in respiratory syncytial virus (RSV)-infected mice. Environ Toxicol Pharmacol. 2015;39:879–86.

Hillaireau H, Dereuddre-Bosquet N, Skanji R, Bekkara-Aounallah F, Caron J, Lepetre S, Argote S, Bauduin L, Yousfi R, Rogez-Kreuz C, Desmaële D, Rousseau B, Gref R, Andrieux K, Clayette P, Couvreur P. Anti-HIV efficacy and biodistribution of nucleoside reverse transcriptase inhibitors delivered as squalenoylated prodrug nanoassemblies. Biomaterials. 2013;34:4831–8.

Hu RL, Li SR, Kong FJ, Hou RJ, Guan XL, Guo F. Inhibition effect of silver nanoparticles on herpes simplex virus 2. Genet Mol Res. 2014;13:7022–8.

Iannazzo D, Pistone A, Galvagno S, Ferro S, De Luca L, Monforte AM, Da Ros T, Hadad C, Prato M, Pannecouque C. Synthesis and anti-HIV activity of carboxylated and drug-conjugated multi-walled carbon nanotubes. Carbon. 2015;82:548–61.

Inoue T, Tanaka Y. Hepatitis B virus and its sexually transmitted infection—an update. Microbial Cell. 2016;3:420–37.

Ishihara T, Kaneko K, Ishihara T, Mizushima T. Development of biodegradable nanoparticles for liver-specific ribavirin delivery. J Pharm Sci. 2014;103:4005–11.

Ishwarya R, Vaseeharan B, Anuradha R, Rekha R, Govindarajan M, Alharbi NS, Kadaikunnan S, Khaled JM, Benelli G. Eco-friendly fabrication of Ag nanostructures using the seed extract of *Pedalium murex*, an ancient Indian medicinal plant: histopathological effects on the *Zika virus* vector *Aedes aegypti* and inhibition of biofilm-forming pathogenic bacteria. J Photochem Photobiol B. 2017;174:133–43.

Jackman JA, Lee J, Cho NJ. Nanomedicine for infectious disease applications: innovation towards broad-spectrum treatment of viral infections. Small. 2016;12:1133–9.

Jamali A, Mottaghitalab F, Abdoli A, Dinarvand M, Esmailie A, Kheiri MT, Atyabi F. Inhibiting influenza virus replication and inducing protection against lethal influenza virus challenge through chitosan nanoparticles loaded by siRNA. Drug Deliv Transl Res. 2018;8:12–20.

Jampílek J. Potential of agricultural fungicides for antifungal drug discovery. Expert Opin Drug Discovery. 2016a;11:1–9.

Jampílek J. How can we bolster the antifungal drug discovery pipeline? Fut Med Chem. 2016b;8:1393–7.

Jampílek J. Design and discovery of new antibacterial agents: advances, perspectives, challenges. Curr Med Chem. 2018;25:4972–5006.

Jampílek J, Kráľová K. Nano-antimicrobials: activity, benefits and weaknesses. In: Ficai A, Grumezescu AM, editors. Nanostructures for antimicrobial therapy. Amsterdam: Elsevier; 2017. p. 23–54.

Jampílek J, Kráľová K. Application of nanobioformulations for controlled release and targeted biodistribution of drugs. In: Sharma AK, Keservani RK, Kesharwani RK, editors. Nanobiomaterials: applications in drug delivery. Warentown: CRC Press; 2018. p. 131–208.

Jampílek J, Kráľová K. Recent advances in lipid nanocarriers applicable in the fight against cancer. In: Grumezescu AM, editor. Nanoarchitectonics in biomedicine—recent progress of nanoarchitectonics in biomedical science. Amsterdam: Elsevier; 2019a. p. 219–94.

Jampílek J, Kráľová K. Nanotechnology based formulations for drug targeting to central nervous system. In: Keservani RK, Sharma AK, editors. Nanoparticulate drug delivery systems. Warentown: Apple Academic Press & CRC Press; 2019b. p. 151–220.

Jampílek J, Kráľová K. Natural biopolymeric nanoformulations for brain drug delivery. In: Keservani RK, Sharma AK, Kesharwani RK, editors. Nanocariers for brain targetting: principles and applications. Warentown: CRC Press; 2019c. p. 131–204.

Jampílek J, Kráľová K. Nano-biopesticides in agriculture: state of art and future opportunities. In: Koul O, editor. Nano-biopesticides today and future perspectives. Amsterdam: Academic Press & Elsevier; 2019d. p. 397–447.

Jampílek J, Záruba K, Oravec M, Kuneš M, Babula P, Ulbrich P, Brezaniová I, Tříska J, Suchý P. Preparation of silica nanoparticles loaded with nootropics and their in vivo permeation through blood–brain barrier. Biomed Res Int. 2015;2015:812673.

Jazayeri SD, Ideris A, Zakaria Z, Shameli K, Moeini H, Omar AR. Cytotoxicity and immunological responses following oral vaccination of nanoencapsulated avian influenza virus H5 DNA vaccine with green synthesis silver nanoparticles. J Control Release. 2012;161:116–23.

Jiang Y, Cao S, Bright DK, Bever AM, Blakney AK, Suydam IT, Woodrow KA. Nanoparticle-based ARV drug combinations for synergistic inhibition of cell-free and cell-cell HIV transmission. Mol Pharm. 2015;12:4363–74.

Jinu U, Rajakumaran S, Senthil-Nathan S, Geetha N, Venkatachalam P. Potential larvicidal activity of silver nanohybrids synthesized using leaf extracts of *Cleistanthus collinus* (Roxb.) Benth. ex Hook. f. and *Strychnos nux-vomica* L. *nux-vomica* against dengue, Chikungunya and Zika vectors. Physiol Mol Plant Pathol. 2018;101:163–71.

Jorquera PA, Tripp RA. Synthetic biodegradable microparticle and nanoparticle vaccines against the respiratory syncytial virus. Vaccine. 2016;4:45.

Joshy KS, Alex SM, Snigdha S, Kalarikkal N, Pothen LA, Thomas S. Encapsulation of zidovudine in PF-68 coated alginate conjugate nanoparticles for anti-HIV drug delivery. Int J Biol Macromol. 2018a;107:929–37.

Joshy KS, Snigdha S, George A, Kalarikkal N, Pothen LA, Thomas S. Poly(vinylpyrrolidone)-lipid based hybrid nanoparticles for anti viral drug delivery. Chem Phys Lipids. 2018b;210:82–9.

Joshy KS, George A, Snigdha S, Joseph B, Kalarikkal N, Pothen LA, Thomas S. Novel core-shell dextran hybrid nanosystem for anti-viral drug delivery. Mater Sci Eng C Mater Biol Appl. 2018c;93:864–72.

Joshy KS, Snigdha S, George A, Kalarikkal N, Pothen LA, Thomas S. Core-shell nanoparticles of carboxy methyl cellulose and compritol-PEG for antiretroviral drug delivery. Cellulose. 2017;24:4759–71.

Jyothi KR, Beloor J, Jo A, Minh NN, Choi TG, Kim JH, Akter S, Lee SK, Maeng CH, Baik HH, Kang I, Ha J, Kim SS. Liver-targeted cyclosporine A-encapsulated poly (lactic-co-glycolic) acid nanoparticles inhibit hepatitis C virus replication. Int J Nanomedicine. 2015;10:903–21.

Kelmann RG, Colombo M, Lopes SCD, Nunes RJ, Pistore M, Agnol DD, Rigotto C, Silva IT, Roman SS, Teixeira HF, Oliveira Simões CM, Koester LS. Pentyl gallate nanoemulsions as potential topical treatment of herpes labialis. J Pharm Sci. 2016;105:2194–203.

Khanal M, Barras A, Vausselin T, Feneant L, Boukherroub R, Siriwardena A, Dubuisson J, Szunerits S. Boronic acid-modified lipid nanocapsules: a novel platform for the highly efficient inhibition of hepatitis C viral entry. Nanoscale. 2015;7:1392–402.

Khanal M, Vausselin T, Barras A, Bande O, Turcheniuk K, Benazza M, Zaitsev V, Teodorescu CM, Boukherroub R, Siriwardena A, Dubuisson J, Szunerits S. Phenylboronic-acid-modified nanoparticles: potential antiviral therapeutics. ACS Appl Mater Interfaces. 2013;5:12488–98.

Khandelwal N, Kaur G, Chaubey KK, Singh P, Sharma S, Tiwari A, Singh SV, Kumar N. Silver nanoparticles impair Peste des petits ruminants virus replication. Virus Res. 2014;190:1–7.

Kos J, Ku CF, Kapustíková I, Oravec M, Zhang HJ, Jampílek J. 8-Hydroxyquinoline-2-carboxanilides as antiviral agents against avian influenza virus. ChemistrySelect. 2019;4:4582–7.

Krishnaraj RN, Chandran S, Pal P, Berchmans S. Investigations on the antiretroviral activity of carbon manotubes using computational molecular approach. Comb Chem High Throughput Screen. 2014;17:531–5.

Kuchipudi SV, Niessly RH. Novel flu viruses in bats and cattle: "pushing the envelope" of influenza infection. Vet Sci. 2018;5:71.

Kumar P, Lakshmi YS, Bhaskar C, Golla K, Kondapi AK. Improved safety, bioavailability and pharmacokinetics of zidovudine through lactoferrin nanoparticles during oral administration in rats. PLoS One. 2015;10:e0140399.

Kumar SD, Singaravelu G, Ajithkumar S, Murugan K, Nicoletti M, Benelli G. Mangrove-mediated green synthesis of silver nanoparticles with high HIV-1 reverse transcriptase inhibitory potential. J Clust Sci. 2017a;28:359–67.

Kumar P, Lakshmi YS, Kondapi AK. Triple drug combination of zidovudine, efavirenz and lamivudine loaded lactoferrin nanoparticles: an effective nano first-line regimen for HIV therapy. Pharm Res. 2017b;34:257–68.

Lallawmawma H, Sathishkumar G, Sarathbabu S, Ghatak S, Sivaramakrishnan S, Gurusubramanian G, Kumar NS. Synthesis of silver and gold nanoparticles using *Jasminum nervosum* leaf extract and its larvicidal activity against filarial and arboviral vector *Culex quinquefasciatus* say (Diptera: *Culicidae*). Environ Sci Pollut Res. 2015;22:17753–68.

Lara HH, Ixtepan-Turrent L, Garza-Trevino EN, Rodriguez-Padilla C. PVP-coated silver nanoparticles block the transmission of cell-free and cell-associated HIV-1 in human cervical culture. J Nanobiotechnol. 2010;8:15.

Lauster D, Glanz M, Bardua M, Ludwig K, Hellmund M, Hoffmann U, Hamann A, Boettcher C, Haag R, Hackenberger CPR, Herrmann A. Multivalent peptide-nanoparticle conjugates for influenza-virus inhibition. Angew Chem Int Ed. 2017;56:5931–6.

Lee EC, Nguyen CTH, Strounina E, Davis-Poynter N, Ross BP. Structure-activity relationships of GAG mimetic-functionalized mesoporous silica nanoparticles and evaluation of acyclovir-loaded antiviral nanoparticles with dual mechanisms of action. ACS Omega. 2018;3:1689–99.

Lee IH, Palombo MS, Zhang XP, Szekely Z, Sinko PJ. Design and evaluation of a CXCR4 targeting peptide 4DV3 as an HIV entry inhibitor and a ligand for targeted drug delivery. Eur J Pharm Biopharm. 2019;138:11–22.

Lee KL, Twyman RM, Fiering S, Steinmetz NF. Virus-based nanoparticles as platform technologies for modern vaccines. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2016;8:554–78.

Lee MY, Yang JA, Jung HS, Beack S, Choi JE, Hur W, Koo H, Kim K, Yoon SK, Hahn SK. Hyaluronic acid-gold nanoparticle/interferon α complex for targeted treatment of hepatitis C virus infection. ACS Nano. 2012;6:9522–31.

Lembo D, Swaminathan S, Donalisio M, Civra A, Pastero L, Aquilano D, Vavia P, Trotta F, Cavalli R. Encapsulation of Acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. Int J Pharm. 2013;443:262–72.

Levina AS, Repkova MN, Ismagilov ZR, Shikina NV, Mazurkova NA, Zarytova VF. Efficient inhibition of human influenza a virus by oligonucleotides electrostatically fixed on polylysine-containing TiO_2 nanoparticles. Russ J Bioorg Chem. 2014;40:179–84.

Li CM, Zheng LL, Yang XX, Wan XY, Wu WB, Zhen SJ, Li YF, Luo LF, Huang CZ. DNA-AuNP networks on cell membranes as a protective barrier to inhibit viral attachment, entry and budding. Biomaterials. 2016;77:216–26.

Liang F, Lindgren G, Lin A, Thompson EA, Ols S, Rohss J, John S, Hassett K, Yuzhakov O, Bahl K, Brito LA, Salter H, Ciaramella G, Loré K. Efficient targeting and activation of antigen presenting cells in vivo after modified mRNA vaccine administration in rhesus macaques. Mol Ther. 2017;25:2635–47.

Liang JJ, Wei JC, Lee YL, Hsu SH, Lin JJ, Lin YL. Surfactant-modified nanoclay exhibits an antiviral activity with high potency and broad spectrum. J Virol. 2014;88:4218–28.

Liang TJ. Hepatitis B: the virus and disease. Hepatology. 2009;49:13–21.

Lin GM, Li L, Panwar N, Wang J, Tjin SC, Wang XM, Yong KT. Non-viral gene therapy using multifunctional nanoparticles: status, challenges, and opportunities. Coord Chem Rev. 2018a;374:133–52.

Lin JK, Wang K, Xia XY, Shen L. Quantification of multivalency in protein-oligomer-coated nanoparticles targeting dynamic membrane glycan receptors. Langmuir. 2018c;34:8415–21.

Lin ZF, Li YH, Gong GF, Xia Y, Wang CB, Chen Y, Hua L, Zhong JY, Tang Y, Liu XM, Zhu B. Restriction of H1N1 influenza virus infection by selenium nanoparticles loaded with ribavirin via resisting caspase-3 apoptotic pathway. Int J Nanomedicine. 2018b;13:5787–97.

Lu L, Sun RWY, Chen R, Hui CK, Ho CM, Luk JM, Lau GKK, Che CM. Silver nanoparticles inhibit hepatitis B virus replication. Antivir Ther. 2008;13:253–62.

Mandal S, Belshan M, Holec A, Zhou Y, Destache C. An enhanced emtricitabine-loaded long-acting nanoformulation for prevention or treatment of HIV infection. Antimicrob Agents Chemother. 2017b;61:e01475–16.

Mandal S, Prathipati PK, Kang GB, Zhou Y, Yuan Z, Fan WJ, Li QS, Destache CJ. Tenofovir alafenamide and and elvitegravir loaded nanoparticles for long-acting prevention of HIV-1 vaginal transmission. AIDS. 2017a;31:469–76.

Marcos-Almaraz MT, Gref R, Agostoni V, Kreuz C, Clayette P, Serre C, Couvreur P, Horcajada P. Towards improved HIV-microbicide activity through the co-encapsulation of NRTI drugs in biocompatible metal organic framework nanocarriers. J Mater Chem B. 2017;5:8563–9.

Martins C, Araujo F, Gomes MJ, Fernandes C, Nunes R, Li W, Santos HA, Borges F, Sarmento B. Using microfluidic platforms to develop CNS-targeted polymeric nanoparticles for HIV therapy. Eur J Pharm Biopharm. 2019;138:111–24.

McConnachie LA, Kinman LM, Koehn J, Kraft JC, Lane S, Lee W, Collier AC, Ho RJY. Long-acting profile of 4 drugs in 1 anti-HIV nanosuspension in nonhuman primates for 5 weeks after a single subcutaneous injection. J Pharm Sci. 2018;107:1787–90.

McGill JL, Kelly SM, Kumar P, Speckhart S, Haughney SL, Henningson J, Narasimhan B, Sacco RE. Efficacy of mucosal polyanhydride nanovaccine against respiratory syncytial virus infection in the neonatal calf. Sci Rep. 2018;8:3021.

McKenzie Z, Kendall M, Mackay RM, Tetley TD, Morgan C, Griffiths M, Clark HW, Madsen J. Nanoparticles modulate surfactant protein A and D mediated protection against influenza A infection in vitro. Philos Trans R Soc Lond B Biol Sci. 2015;370:20140049.

Metz SW, Thomas A, Bracjbill A, Xianwen Y, Stone M, Horvath K, Miley M, Luft C, DeSimone JM, Tian S, de Silva AM. Nanoparticle delivery of a tetravalent E protein subunit vaccine induces balanced, type-specific neutralizing antibodies to each dengue virus serotype. PLoS Negl Trop Dis. 2018;12:e0006793.

Meyer M, Huang E, Yuzhakov O, Ramanathan P, Ciaramella G, Bukreyev A. Modified mRNA-based vaccines elicit robust immune responses and protect guinea pigs from Ebola virus disease. J Infect Dis. 2018;217:451–5.

Milovanovic M, Arsenijevic A, Milovanovic J, Kanjevac T, Arsenijevic N. Nanoparticles in antiviral therapy. In: Grumezescu AM, editor. Antimicrobial nanoarchitectonics: from synthesis to applications. Amsterdam: Elsevier; 2017. p. 383–410.

Mishra YK, Adelung R, Roehl C, Shukla D, Spors F, Tiwari V. Virostatic potential of micro-nano filopodia-like ZnO structures against herpes simplex virus-1. Antivir Res. 2011;92:305–12.

Mohideen M, Quijano E, Song E, Deng Y, Panse G, Zhang W, Clark MR, Saltzman WM. Degradable bioadhesive nanoparticles for prolonged intravaginal delivery and retention of elvitegravir. Biomaterials. 2017;144:144–54.

Moon HJ, Lee JS, Talactac MR, Chowdhury MYE, Kim JH, Park ME, Choi YK, Sung MH, Kim CJ. Mucosal immunization with recombinant influenza hemagglutinin protein and poly γ-glutamate/chitosan nanoparticles induces protection against highly pathogenic influenza A virus. Vet Microbiol. 2012;160:277–89.

Morcol T, Hurst BL, Tarbet EB. Calcium phosphate nanoparticle (CaPNP) for dose-sparing of inactivated whole virus pandemic influenza A (H1N1) 2009 vaccine in mice. Vaccine. 2017;35:4569–77.

Mori Y, Ono T, Miyahira Y, Nguyen VQ, Matsui T, Ishihara M. Antiviral activity of silver nanoparticle/chitosan composites against H1N1 influenza A virus. Nanoscale Res Lett. 2013;8:93.

Murray M. Ebola virus disease: a review of its past and present. Anesth Analg. 2015;121:798–809.

Murugan K, Dinesh D, Paulpandi M, Althbyani ADM, Subramaniam J, Madhiyazhagan P, Wang L, Suresh U, Kumar PM, Mohan J, Rajaganesh R, Wei H, Kalimuthu K, Parajulee MN, Mehlhorn H, Benelli G. Nanoparticles in the fight against mosquito-borne diseases: bioactivity of *Bruguiera cylindrica*-synthesized nanoparticles against dengue virus DEN-2 (*in vitro*) and its mosquito vector *Aedes aegypti* (Diptera: Culicidae). Parasitol Res. 2015;114:4349–61.

Murugan K, Jaganathan A, Rajaganesh R, Suresh U, Madhavan J, Senthil-Nathan S, Rajasekar A, Higuchi A, Kumar SS, Alarfaj AA, Nicoletti M, Petrelli R, Cappellacci L, Maggi F, Benelli G. Poly(styrene sulfonate)/poly(allylamine hydrochloride) encapsulation of TiO_2 nanoparticles boosts their toxic and repellent activity against Zika virus mosquito vectors. J Clust Sci. 2018;29:27–39.

National Nanotechnology Initiative. Big things from a tiny world. Arlington, VA: National Nanotechnology Initiative; 2008.

Ndeboko B, Lemamy GJ, Nielsen PE, Cova L. Therapeutic potential of cell penetrating peptides (CPPs) and cationic polymers for chronic hepatitis B. Int J Mol Sci. 2015;16:28230–41.

Nowacek AS, Balkundi S, McMillan J, Roy U, Martinez-Skinner A, Mosley RL, Kanmogne G, Kabanov AV, Bronich T, Gendelman HE. Analyses of nanoformulated antiretroviral drug charge, size, shape and content for uptake, drug release and antiviral activities in human monocyte-derived macrophages. J Control Release. 2011;150:204–11.

Nunes R, Araujo F, Barreiros L, Bartolo I, Segundo MA, Taveira N, Sarmento B, das Neves J. Noncovalent PEG coating of nanoparticle drug carriers improves the local pharmacokinetics of rectal anti-HIV microbicides. ACS Appl Mater Interfaces. 2018;10:34942–53.

Orlowski P, Kowalczyk A, Tomaszewska E, Ranoszek-Soliwoda K, Wegrzyn A, Grzesiak J, Celichowski G, Grobelny J, Eriksson K, Krzyzowska M. Antiviral activity of tannic acid modified silver nanoparticles: potential to activate immune response in herpes genitalis. Viruses. 2018a;10:524.

Orlowski P, Tomaszewska E, Gniadek M, Baska P, Nowakowska J, Sokolowska J, Nowak Z, Donten M, Celichowski G, Grobelny J, Krzyzowska M. Tannic acid modified silver nanoparticles show antiviral activity in herpes simplex virus type 2 infection. PLoS One. 2014;9:e104113.

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. 2018b;9:1115.

Osminkina LA, Timoshenko VY, Shilovsky IP, Kornilaeva GV, Shevchenko SN, Gongalsky MB, Tamarov KP, Abramchuk SS, Nikiforov VN, Khaitov MR, Karamov EV. Porous silicon nanoparticles as scavengers of hazardous viruses. J Nanopart Res. 2014;16:2430.

Papp I, Sieben C, Ludwig K, Roskamp M, Boettcher C, Schlecht S, Herrmann A, Haag R. Inhibition of influenza virus infection by multivalent sialic-acid-functionalized gold nanoparticles. Small. 2010;6:2900–6.

Parboosing R, Maguire GEM, Govender P, Kruger HG. Nanotechnology and the treatment of HIV infection. Viruses. 2012;4:488–520.

Park SJ, Ko YS, Lee SJ, Lee C, Woo K, Ko G. Inactivation of influenza A virus via exposure to silver nanoparticle-decorated silica hybrid composites. Environ Sci Pollut Res. 2018;25:27021–30.

Patel BK, Parikh RH, Patel N. Targeted delivery of mannosylated-PLGA nanoparticles of antiretroviral drug to brain. Int J Nanomedicine. 2018;13:97–100.

Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S, Shin HS. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnol. 2018;16:71.

Pavunraj M, Baskar K, Duraipandiyan V, Al-Dhabi NA, Rajendran V, Benelli G. Toxicity of Ag nanoparticles synthesized using stearic acid from *Catharanthus roseus* leaf extract against *Earias vittella* and mosquito vectors (*Culex quinquefasciatus* and *Aedes aegypti*). J Clust Sci. 2017;28:2477–92.

Pentak D, Kozik V, Bąk A, Dybał P, Sochanik A, Jampílek J. Methotrexate and cytarabine-loaded nanocarriers for multidrug cancer therapy. Spectroscopic study. Molecules. 2016;21:1689.

Pieler MM, Frentzel S, Bruder D, Wolff MW, Reichl U. A cell culture-derived whole virus influenza A vaccine based on magnetic sulfated cellulose particles confers protection in mice against lethal influenza A virus infection. Vaccine. 2016;34:6367–74.

Pisárčik M, Jampílek J, Lukáč M, Horáková R, Devínsky F, Bukovský M, Kalina M, Tkacz J, Opravil T. Silver nanoparticles stabilised by cationic gemini surfactants with variable spacer length. Molecules. 2017;22:1794.

Pisárčik M, Lukáč M, Jampílek J, Bilka F, Bilková A, Pašková Ľ, Devínsky F, Horáková R, Opravil T. Silver nanoparticles stabilised with cationic single-chain surfactants. Structure-physical properties-biological activity relationship study. J Mol Liq. 2018;272:60–72.

Plourde AR, Bloch EN. A literature review of Zika virus. Emerg Infect Dis. 2016;22:1185–92.

Pomeranz LE, Reynolds AE, Hengartner CJ. Molecular biology of pseudorabies virus: impact on neurovirology and veterinary medicine. Microbiol Mol Biol Rev. 2005;69:462–500.

Prathipati PK, Mandal S, Pon G, Vivekanandan R, Destache CJ. Pharmacokinetic and tissue distribution profile of long acting tenofovir alafenamide and elvitegravir loaded nanoparticles in humanized mice model. Pharm Res. 2017;34:2749–55.

Qi M, Zhang XE, Sun XX, Zhang XW, Yao YF, Liu SL, Chen Z, Li W, Zhang ZP, Chen JJ, Cui Z. Intranasal nanovaccine confers homo- and hetero-subtypic influenza protection. Small. 2018;14:1703207.

Quach QH, Ang SK, Chu JHJ, Kah JCY. Size-dependent neutralizing activity of gold nanoparticle-based subunit vaccine against dengue virus. Acta Biomater. 2018;78:224–35.

Rafiei S, Rezatofighi SE, Ardakani MR, Madadgar O. In vitro anti-foot-and-mouth disease virus activity of magnesium oxide nanoparticles. IET Nanobiotechnol. 2015;9:247–51.

Rai M, Deshmukh SD, Ingle AP, Gupta IR, Galdiero M, Galdiero S. Metal nanoparticles: the protective nanoshield against virus infection. Crit Rev Microbiol. 2016;42:46–56.

Ramya S, Shanmugasundaram T, Balagurunathan R. Biomedical potential of actinobacterially synthesized selenium nanoparticles with special reference to anti-biofilm, anti-oxidant, wound healing, cytotoxic and anti-viral activities. J Trace Elem Med Biol. 2015;32:30–9.

Rao L, Wang WB, Meng QF, Tian MF, Cai B, Wang YC, Li AX, Zan MH, Xiao F, Bu LL, Li G, Li A, Liu Y, Guo SS, Zhao XZ, Wang TH, Liu W, Wu J. A biomimetic nanodecoy traps Zika virus to prevent viral infection and fetal microcephaly development. Nano Lett. 2019;19:2215–22.

Renganathan S, Aroulmoji V, Shanmugam G, Devarajad G, Rao KV, Rajendar V, Park SH. Silver nanoparticle synthesis from carica papaya and virtual screening for anti-dengue activity using molecular docking. Mater Res Express. 2019;6:035028.

Ribeiro-Viana R, Sanchez-Navarro M, Luczkowiak J, Koeppe JR, Delgado R, Rojo J, Davis BG. Virus-like glycodendrinanoparticles displaying quasi-equivalent nested polyvalency upon glycoprotein platforms potently block viral infection. Nat Commun. 2012;3:1303.

Rodriguez-Perez L, Ramos-Soriano J, Perez-Sanchez A, Illescas BM, Munoz A, Luczkowiak J, Lasala F, Rojo J, Delgado R, Martin N. Nanocarbon-based glycoconjugates as multivalent inhibitors of Ebola virus infection. J Am Chem Soc. 2018;140:9891–8.

Ross KA, Loyd H, Wu WW, Huntimer L, Ahmed S, Sambol A, Broderick S, Flickinger Z, Rajan K, Bronich T, Mallapragada S, Wannemuehler MJ, Carpenter S, Narasimhan B. Hemagglutinin-based polyanhydride nanovaccines against H5NI influenza elicit protective virus neutralizing titers and cell-mediated immunity. Int J Nanomedicine. 2015;10:229–43.

Sametband M, Shukla S, Meningher T, Hirsh S, Mendelson E, Sarid R, Gedanken A, Mandelboim M. Effective multi-strain inhibition of influenza virus by anionic gold nanoparticles. Med Chem Commun. 2011;2:421–3.

Sato Y, Matsui H, Yamamoto N, Sato R, Munakata T, Kohara M, Harashima H. Highly specific delivery of siRNA to hepatocytes circumvents endothelial cell-mediated lipid nanoparticle-

associated toxicity leading to the safe and efficacious decrease in the hepatitis B virus. J Control Release. 2017;266:216–25.
Sboui S, Tabbabi A. Marburg virus disease: a review literature. J Genes Proteins. 2017;1:1.
Scherliess R. Future of nanomedicines for treating respiratory diseases. Expert Opin Drug Deliv. 2019;16:59–68.
Senanayake TH, Gorantla S, Makarov E, Lu Y, Warren G, Vinogradov SV. Nanogel-conjugated reverse transcriptase inhibitors and their combinations as novel antiviral agents with increased efficacy against HIV-1 infection. Mol Pharm. 2015;12:4226–36.
Seok H, Noh JY, Lee DY, Kim SJ, Song CS, Kim YC. Effective humoral immune response from a H1N1 DNA vaccine delivered to the skin by microneedles coated with PLGA-based cationic nanoparticles. J Control Release. 2017;265:66–74.
Seyfoddin A, Sherwin T, Patel DV, McGhee CN, Rupenthal ID, Taylor JA, Al-Kassas R. Ex vivo and in vivo evaluation of chitosan coated nanostructured lipid carriers for ocular delivery of Acyclovir. Curr Drug Deliv. 2016;13:923–34.
Sharma G, Thakur K, Setia A, Amarji B, Singh MP, Raza K, Katare OP. Fabrication of acyclovir-loaded flexible membrane vesicles (FMVs): evidence of preclinical efficacy of antiviral activity in murine model of cutaneous HSV-1 infection. Drug Deliv Transl Res. 2017b;7:683–94.
Sharma RK, Cwiklinski K, Aalinkeel R, Reynolds JL, Sykes DE, Quaye E, Oh J, Mahajan SD, Schwartz SA. Immunomodulatory activities of curcumin-stabilized silver nanoparticles: efficacy as an antiretroviral therapeutic. Immunol Investig. 2017a;46:833–46.
Shionoiri N, Sato T, Fujimori Y, Nakayama T, Nemoto M, Matsunaga T, Tanaka T. Investigation of the antiviral properties of copper iodide nanoparticles against feline calicivirus. J Biosci Bioeng. 2012;113:580–6.
Shohani S, Mondanizadeh M, Abdoli A, Khansarinejad B, Salimi-Asl M, Ardestani M, Ghanbari M, Haj MS, Zabihollahi R. Trimethyl chitosan improves anti-HIV effects of atripla as a new nano-formulated drug. Curr HIV Res. 2017;15:56–65.
Siddiq A, Younus I, Shamim A, Badar S. Nanostructures for antiviral therapy: in the last two decades. Curr Nanosci. 2017;13:229–46.
Sillman B, Bade AN, Dash PK, Bhargavan B, Kocher T, Mathews S, Su H, Kanmogne GD, Poluektova LY, Gorantla S, McMillan JE, Gautam N, Alnouti Z, Edawa H, Gendelman HE. Creation of a long-acting nanoformulated dolutegravir. Nat Commun. 2018;9:443.
Singh L, Kruger HG, Maguire GEM, Govender T, Parboosing R. The role of nanotechnology in the treatment of viral infections. Ther Adv Infect Dis. 2017;4:105–31.
Singh SM, Alkie TN, Abdelaziz KT, Hodgins DC, Novy A, Nagy E, Sharif S. Characterization of immune responses to an inactivated avian influenza virus vaccine adjuvanted with nanoparticles containing CpG ODN. Viral Immunol. 2016b;29:269–75.
Singh SM, Alkie TN, Nagy E, Kulkarni RR, Hodgins DC, Sharif S. Delivery of an inactivated avian influenza virus vaccine adjuvanted with poly(D,L-lactic-co-glycolic acid) encapsulated CpG ODN induces protective immune responses in chickens. Vaccine. 2016a;34:4807–13.
Smith G, Liu Y, Flyer D, Massare MJ, Zhou B, Patel N, Ellingsworth L, Lewis M, Cummings JF, Glenn G. Novel hemagglutinin nanoparticle influenza vaccine with Matrix-M™ adjuvant induces hemagglutination inhibition, neutralizing, and protective responses in ferrets against homologous and drifted A(H3N2) subtypes. Vaccine. 2017;35:5366–72.
Stanaway JD, Flaxman AD, Naghavi M, Fitymaurice C, Vos T, Abubakar I, Abu-Raddad LJ, Assadi R, Bhala N, Cowie B, Forouzanfour MH, Groeger J, Hanafiah KM, Jacobsen KH, James SL, MacLachlan J, Malekzadeh R, Martin NK, Mokdad AA, Mokdad AH, Murray CJL, Plass D, Rana S, Rein DB, Richardus JH, Sanabria J, Saylan M, Shahraz S, So S, Vlassov VV, Weiderpass E, Wiersma ST, Younis M, Yu C, El Sayed ZM, Cooke GS. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease study. Lancet. 2016;388:1081–8.
Stone J, Thornburg NJ, Blum DL, Kuhn SJ, Wright DW, Crowe JE. Gold nanorod vaccine for respiratory syncytial virus. Nanotechnology. 2013;24:295102.
Suganya P, Vaseeharan B, Vijayakumar S, Balan B, Govindarajan M, Alharbi NS, Kadaikunnan S, Khaled JM, Benelli G. Biopolymer zein-coated gold nanoparticles: synthesis, antibacterial

potential, toxicity and histopathological effects against the *Zika virus* vector *Aedes aegypti*. J Photochem Photobiol B. 2017;173:404–11.

Sujitha V, Murugan K, Paulpandi M, Panneerselvam C, Suresh U, Roni M, Nicoletti M, Higuchi A, Madhiyazhagan P, Subramaniam J, Dinesh D, Vadivalagan C, Chandramohan B, Alarfaj AA, Munusamy MA, Barnard DR, Benelli G. Green-synthesized silver nanoparticles as a novel control tool against dengue virus (DEN-2) and its primary vector *Aedes aegypti*. Parasitol Res. 2015;114:3315–25.

Suresh U, Murugan K, Panneerselvam C, Rajaganesh R, Roni M, Aziz A, Al-Aoh HAN, Trivedi S, Rehman H, Kumar S, Higuchi A, Canale A, Benelli G. *Suaeda maritima*-based herbal coils and green nanoparticles as potential biopesticides against the dengue vector *Aedes aegypti* and the tobacco cutworm *Spodoptera litura*. Physiol Mol Plant Pathol. 2018;101:225–35.

Suwannoi P, Chomnawang M, Sarisuta N, Reichl S, Mueller-Goymann CC. Development of Acyclovir-loaded albumin nanoparticles and improvement of Acyclovir permeation across human corneal epithelial T cells. J Ocul Pharmacol Ther. 2017;33:743–52.

Szunerits S, Barras A, Khanal M, Pagneux Q, Boukherroub R. Nanostructures for the inhibition of viral infections. Molecules. 2015;20:14051–1408.

Szymanska E, Orlowski P, Winnicka K, Tomaszewska E, Baska P, Celichowski G, Grobelny J, Basa A, Krzyzowska M. Multifunctional tannic acid/silver nanoparticle-based mucoadhesive hydrogel for improved local treatment of HSV infection: in vitro and in vivo studies. Int J Mol Sci. 2018;19:387.

Takizawa N, Yamasaki M. Current landscape and future prospects of antiviral drugs derived from microbial products. J Antibiot. 2018;71:45–52.

Tang R, Zhai YJ, Dong LL, Malla T, Hu K. Immunization with dendritic cell-based DNA vaccine pRSC-NLDC145.gD-IL21 protects mice against herpes simplex virus keratitis. Immunotherapy. 2018;10:189–200.

Tao W, Hurst BL, Shakya AK, Uddin MJ, Ingrole RS, Hernandez-Sanabria M, Arya RP, Bimler L, Paust S, Tarbet EB, Gill HS. Consensus M2e peptide conjugated to gold nanoparticles confers protection against H1N1, H3N2 and H5N1 influenza A viruses. Antivir Res. 2017;141:62–72.

Taubenberger JK, Morens DM. Influenza: the once and future pandemic. Public Health Rep. 2010;125:16–26.

Thammakarn C, Satoh K, Suguro A, Hakim H, Ruenphet S, Takehara K. Inactivation of avian influenza virus, Newcastle disease virus and goose parvovirus using solution of nano-sized scallop shell powder. J Vet Med Sci. 2014;76:1277–80.

Thi EP, Lee ACH, Geisbert JB, Ursic-Bedoya R, Agans KN, Robbins M, Deer DJ, Fenton KA, Kondratowicz AS, MacLachlan I, Geisbert TW, Mire CE. Rescue of non-human primates from advanced Sudan ebolavirus infection with lipid encapsulated siRNA. Nat Microbiol. 2016;1:16142.

Thi EP, Mire CE, Lee ACH, Geisbert JB, Zhou JZ, Agans KN, Snead NM, Deer DJ, Barnard TR, Fenton KA, MacLachlan I, Geisbert TW. Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected nonhuman primates. Nature. 2015;521:362–5.

Thi EP, Mire CE, Ursic-Bedoya R, Geisbert JB, Lee ACH, Agans KN, Robbins M, Deer DJ, Fenton KA, MacLachlan I, Geisbert TW. Marburg virus infection in nonhuman primates: therapeutic treatment by lipid-encapsulated siRNA. Sci Transl Med. 2014;6:250ra116.

Timin AS, Muslimov AR, Petrova AV, Lepik KV, Okilova MV, Vasin AV, Afanasyev BV, Sukhorukov GB. Hybrid inorganic-organic capsules for efficient intracellular delivery of novel siRNAs against influenza A (H1N1) virus infection. Sci Rep. 2017;7:102.

Tomitaka A, Arami H, Huang ZH, Raymond A, Rodriguez E, Cai Y, Febo M, Takemura Y, Nair M. Hybrid magneto-plasmonic liposomes for multimodal image-guided and brain-targeted HIV treatment. Nanoscale. 2018;10:184–94.

Trefry JC, Wooley DP. Silver nanoparticles inhibit vaccinia virus infection by preventing viral entry through a macropinocytosis-dependent mechanism. J Biomed Nanotechnol. 2013;9:1624–35.

Trigilio J, Antoine TE, Paulowicz I, Mishra YK, Adelung R, Shukla D. Tin oxide nanowires suppress herpes simplex virus-1 entry and cell-to-cell membrane fusion. PLoS One. 2012;7:e48147.

Ursic-Bedoya R, Mire CE, Robbins M, Geisbert JB, Judge A, MacLachlan I, Geisbert TW. Protection against lethal Marburg virus infection mediated by lipid encapsulated small interfering RNA. J Infect Dis. 2014;209:562–70.

Vijayakumar S, Ganesan S. Gold nanoparticles as an HIV entry inhibitor. Curr HIV Res. 2012;10:643–6.

Wang C, Zhu WD, Luo Y, Wang BZ. Gold nanoparticles conjugating recombinant influenza hemagglutinin trimers and flagellin enhanced mucosal cellular imunity. Nanomedicine. 2018b;14: 1349–60.

Wang L, Chang TZ, He Y, Kim JR, Wang S, Mohan T, Berman Z, Tompkins SM, Tripp RA, Compans RW, Champion JA, Wang BZ. Coated protein nanoclusters from influenza H7N9 HA are highly immunogenic and induce robust protective imunity. Nanomedicine. 2017;13:253–62.

Wang W, Zhao YL, Zhao XH, Zu YG, Fu YJ. Anti-HSV-1 activity of glycyrrhizic acid nanoparticles prepared by supercritical antisolvent process. Curr Nanosci. 2015;11:366–70.

Wang Y, Deng L, Kang SM, Wang BZ. Universal influenza vaccines: from viruses to nanoparticles. Expert Rev Vaccines. 2018a;17:967–76.

Warren G, Makarov E, Lu Y, Senanayake T, Rivera K, Gorantla S, Poluektova LY, Vinogradov SV. Amphiphilic cationic nanogels as brain-targeted carriers for activated nucleoside reverse transcriptase inhibitors. J Neuroimmune Pharmacol. 2015;10:88–101.

World Health Organization. Global hepatitis report. 2017. http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1.

Xiang DX, Chen Q, Pang L, Zheng CL. Inhibitory effects of silver nanoparticles on H1N1 influenza A virus in vitro. J Virol Methods. 2011;178:137–42.

Xiang DX, Zheng Y, Duan W, Li XJ, Yin JJ, Shigdar S, O'Connor ML, Marappan M, Zhao XJ, Miao YQ, Xiang B, Zheng CLL. Inhibition of A/Human/Hubei/3/2005 (H3N2) influenza virus infection by silver nanoparticles in vitro and in vivo. Int J Nanomedicine. 2013;8:4103–13.

Yadavalli T, Shukla D. Role of metal and metal oxide nanoparticles as diagnostic and therapeutic tools for highly prevalent viral infections. Nanomedicine. 2017;13:219–30.

Yang HW, Ye L, Guo XD, Yang CL, Compans RW, Prausnitz MR. Ebola vaccination using a DNA vaccine coated on PLGA-PLL/γPGA nanoparticles administered using a microneedle patch. Adv Healthc Mater. 2017b;6:1600750.

Yang L, Li W, Kirberger M, Liao WZ, Ren JY. Design of nanomaterial based systems for novel vaccine development. Biomater Sci. 2016b;4:785–802.

Yang XX, Li CM, Huang CZ. Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. Nanoscale. 2016a;8:3040–8.

Yang XX, Li CM, Li YF, Wang J, Huang CZ. Synergistic antiviral effect of curcumin functionalized graphene oxide against respiratory syncytial virus infection. Nanoscale. 2017a;9:16086–92.

Yang Y, He HJ, Chang H, Yu Y, Yang MB, He Y, Fan ZC, Iyer SS, Yu P. Multivalent oleanolic acid human serum albumin conjugate as nonglycosylated neomucin for influenza virus capture and entry inhibition. Eur J Med Chem. 2018;143:1723–31.

Ye SY, Shao K, Li ZH, Guo N, Zuo YP, Li Q, Lu ZC, Chen L, He QG, Han HY. Antiviral activity of graphene oxide: how sharp edged structure and charge matter. ACS Appl Mater Interfaces. 2015;7:21571–9.

Zacharias ZR, Ross KA, Hornick EE, Goodman JT, Narasimhan B, Waldschmidt TJ, Legge KL. Polyanhydride nanovaccine induces robust pulmonary B and T cell immunity and confers protection against homologous and heterologous influenza A virus infections. Front Immunol. 2018;9:1953.

Zazo H, Millan CG, Colino CI, Lanao JM. Applications of metallic nanoparticles in antimicrobial therapy. In: Grumezescu AM, editor. Antimicrobial nanoarchitectonics: from synthesis to applications. Amsterdam: Elsevier; 2017. p. 411–44.

Zhao K, Li SS, Li W, Yu L, Duan XT, Han JY, Wang XH, Jin Z. Quaternized chitosan nanoparticles loaded with the combined attenuated live vaccine against Newcastle disease and infectious bronchitis elicit immune response in chicken after intranasal administration. Drug Deliv. 2017;24:1574–86.

Zhao K, Rong GY, Hao Y, Yu L, Kang H, Wang X, Wang XH, Jin Z, Ren ZY, Li ZJ. IgA response and protection following nasal vaccination of chickens with Newcastle disease virus DNA vaccine nanoencapsulated with $Ag@SiO_2$ hollow nanoparticles. Sci Rep. 2016;6:25720.

Zhou T, Su H, Dash P, Lin Z, Shetty BLD, Kocher T, Szlachetka A, Lamberty B, Fox HS, Poluektova L, Gorantia S, McMillan J, Gautam N, Mosley RL, Alnouti Y, Edgawa B, Gendelman HE. Creation of a nanoformulated cabotegravir prodrug with improved antiretroviral profiles. Biomaterials. 2018;151:53–65.

Ziem B, Azab W, Gholami MF, Rabe JP, Osterrieder N, Haag R. Size-dependent inhibition of herpesvirus cellular entry by polyvalent nanoarchitectures. Nanoscale. 2017;9:3774–83.

Ziem B, Thien H, Achazi K, Yue C, Stern D, Silberreis K, Gholami MF, Beckert F, Groeger D, Muelhaupt R, Rabe JP, Nitsche A, Haag R. Highly efficient multivalent 2D nanosystems for inhibition of orthopoxvirus particles. Adv Healthc Mater. 2016;5:2922–30.

Zoppe JO, Ruottinen V, Ruotsalainen J, Ronkko S, Johansson LS, Hinkkanen A, Jarvinen K, Seppala J. Synthesis of cellulose nanocrystals carrying tyrosine sulfate mimetic ligands and inhibition of alphavirus infection. Biomacromolecules. 2014;15:1534–42.

Zuckerman AJ. Hepatitis viruses. In: Baron S, editor. Medical microbiology. 4th ed. Galveston: University of Texas Medical Branch at Galveston; 1996. p. 1–169.