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Biomimetic Nanomaterial Strategies for Virus Targeting: Antiviral Therapies and Vaccines

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The ongoing coronavirus disease 2019 (COVID-19) pandemic highlights the importance of developing effective virus targeting strategies to treat and prevent viral infections. Since virus particles are nanoscale entities, nanomaterial design strategies are ideally suited to create advanced materials that can interact with and mimic virus particles. In this progress report, the latest advances in biomimetic nanomaterials are critically discussed for combating viral infections, including in the areas of nanomaterial-enhanced viral replication inhibitors, biomimetic virus particle capture schemes, and nanoparticle vaccines. Particular focus is placed on nanomaterial design concepts and material innovations that can be readily developed to thwart future viral threats. Pertinent nanomaterial examples from the COVID-19 situation are also covered along with discussion of human clinical trial efforts underway that might lead to next-generation antiviral therapies and vaccines.

1. Introduction

Over the past decade, there have been growing calls to recognize that emerging infectious diseases represent a major threat to global health and that we must be better prepared to deal with a future viral pandemic, which could arise from an unknown or understudied virus.[1] In 2018, the World Health Organization expanded on these viewpoints by preparing a list of viral and nonviral pathogens that could cause Disease X, a future human disease outbreak with epidemic or pandemic potential that would be triggered by a newly emerged pathogen.[2] In early 2020, the coronavirus disease 2019 (COVID-19) pandemic arose as the first Disease X and was caused by the global spreading of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has infected over 39 million people and caused over 1 100 000 deaths to date.[3] COVID-19 is considered by some experts to be a once-in-a-century pandemic[4] and has highlighted how viral pandemics can create a perfect storm of volatility, uncertainty, complexity, and ambiguity that is disrupting the institutions of daily life worldwide, including work, healthcare, education, and transportation.[5]

Our understanding of COVID-19 continues to grow since a local outbreak of pneumonia was reported in Wuhan, China in December 2019, and led to the discovery of the SARS-CoV-2 virus, which is related to other coronaviruses such as SARS and Middle East Respiratory Syndrome (MERS).[6] SARS-CoV-2 is believed to be a zoonotic virus that crossed over from bats[7] and acquired mutations via natural selection that caused the virus to more efficiently infect human cells and transmit among humans.[8] Early reports of human respiratory disease[9] have since been followed up by numerous, ongoing studies to gain further insight into COVID-19 disease pathogenesis, including how severe cases of COVID-19 can cause acute respiratory distress syndrome.[10] Various organs are affected by the disease, including lungs,[11] heart,[12] liver,[13] kidney,[14] and brain.[15] As such, there has been tremendous attention placed on the treatment and prevention of SARS-CoV-2 infections and growing attention to the role that materials science can play in stopping COVID-19 and, more broadly, the wide range of viral infections affecting global society along with future viral threats.[16]

The objective of this progress report is to cover the latest advances in biomimetic nanomaterials for combating viral infections, including in the areas of nanomaterial-enhanced viral replication inhibitors, biomimetic virus particle capture schemes, and nanoparticle vaccines. Major emphasis is placed on covering the most recent developments mainly within the past three years, while distilling key nanomaterial design principles that can lead to next-generation advanced materials for the treatment and prevention of viral infections. Where applicable, we also discuss how these nanomaterial strategies are being explored to stop SARS-CoV-2 along with coverage of relevant human clinical trial efforts.

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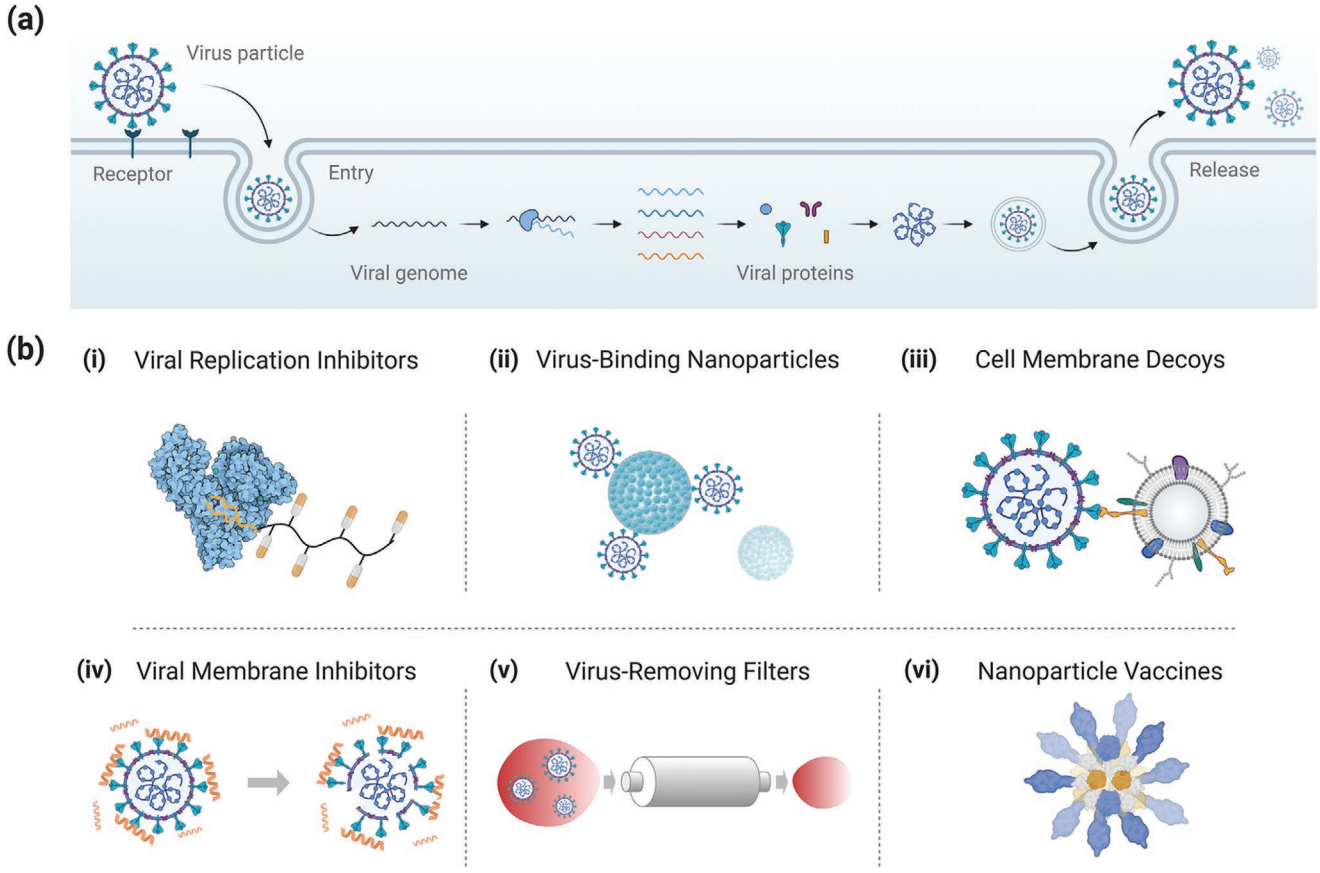
2. Advanced Materials for Virus Targeting

Virus particles ("virions") are biological nanoparticles that contain viral genetic material and are surrounded by a protein or lipid bilayer membrane coating. The particles are typically around 50–300 nm in diameter and are functionalized with glycoproteins that play an important role in binding to cells.[17] There are two main types: enveloped and nonenveloped viruses. Membrane-enveloped viruses are surrounded by a host-cell-derived lipid membrane that contains embedded glycoproteins while nonenveloped viruses have a protein-based capsid shell without lipid membrane.[18] In both cases, the glycoproteins on the virus particle surface are the major antigens, which are recognized by the host immune system and can elicit an antibody response.[19] Once the immune system is trained to recognize a viral antigen, the immune system can rapidly produce antibodies that bind to the virus particles and prevent them from causing infection.[20]

Fundamentally, virus particles are parasites that must infect susceptible cells and highjack cellular machinery in order to produce new virus particles.[21] The basic steps are presented in **Scheme 1**a. The first step involves virus particle binding to specific receptors on the cell membrane surface, which can result in cellular entry and start of the infection process. Each type of cell has a characteristic pattern of receptors found on the cellular surface and different viruses bind preferentially to particular ones. For example, many viruses bind specifically to glycan-functionalized receptors containing sulfonate or sialyl functional groups. Infected cells produce new copies of viral genetic material and viral proteins, which are then assembled in order to produce new virus particles that are released extracellularly and infect new cells. The process continues indefinitely until an organism succumbs to virus-induced cellular damage and related immune responses, and viruses can also spread between organisms via a wide range of transmission mechanisms.

Depending on the objective, various nanomaterial strategies can be useful to stop viruses, as presented in Scheme 1b. Conventionally, antiviral drugs have been developed to inhibit viral genome replication inside infected cells, thereby preventing the production of new virus particles.[22] Nanomaterial strategies have proven useful to enhance the pharmacological properties



Scheme 1. Biomimetic nanomaterial strategies for virus targeting. a) Overview of virus life cycle. Viruses cannot replicate independently and must infect cells. The replication machinery of infected cells is highjacked by viruses and used to create new copies of the viral genome and proteins, which are then assembled into new virus particles that are released from the cell and spread to infect other cells. b) Examples of different nanomaterial strategies for virus targeting. i) Nanomaterial-enhanced viral replication inhibitors can inhibit the production of new virus particles. ii) Virus-binding nanoparticles and iii) cell membrane decoys can bind to virus particles and prevent viral infection of cells. iv) Viral membrane inhibitors can disrupt membrane-enveloped virus particles, abrogating infectivity. v) Extracorporeal blood filters can remove circulating virus particles from the bloodstream to reduce disease burden. vi) Biomimetic nanoparticle vaccines that mimic the multivalent presentation of antigens on virus particle surfaces can elicit improved immune responses that lead to greater protection against future virus exposure.

of viral genome replication inhibitors, including circulation time. While it is advantageous to stop viral genome replication in order to help treat existing viral infections, there is also extensive interest in exploring how nanomaterials can be useful to prevent viral infections.[23] Virus-binding nanomaterials can attach to virus particles and prevent them from infecting cells. Pristine nanomaterials can be used along with receptor-functionalized ones and cell-membrane-decoy nanomaterials, which are coated with cell membrane extracts containing natural receptors.

Ongoing efforts have also devised nanomaterial-based strategies to effectively remove extracellular virus particles from infected organisms by either selectively disrupting virus particles or by removing them through extracorporeal filtration strategies. Moreover, some of the most recent and innovative advances have come from developing nanoparticle vaccines, especially self-assembling protein-based ones, which have demonstrated excellent potential to prevent multiple types of viral infections.[24] One of the most promising candidates has been rapidly advanced into human clinical trials as a potential universal flu vaccine[25] and similar strategies are now being applied to SARS-CoV-2. A key innovative aspect of these nanoparticle vaccines is that critical architectural properties of virus particles, particularly the specific organization of glycoprotein antigens, can now be mimicked with nanoscale precision and these advanced material capabilities have led to nanoparticle vaccine candidates with superior immunizing capabilities to currently used vaccine strategies in some cases. The latest progress in all of these areas is covered in the following sections.

3. Viral Replication Inhibitors

The most widely used class of direct-acting antiviral drugs encompasses small molecules that inhibit the genome replication of viruses inside infected cells.[26] These replication processes involve a multiprotein replication complex called the viral replicase[27] and antiviral therapy often targets one or more types of the viral proteins that form this complex. Key examples of antiviral drugs in this class include nucleoside and nucleotide analogues that inhibit the viral polymerase, which is the main enzyme involved in viral genome production.[28] Over the years, there have been extensive efforts to develop prodrugs[29]—inactive molecules that are metabolized into the active drug in vivo—and drug delivery systems that enable longer circulation time, targeted delivery, and/or improved safety of viral replication inhibitors, in line with broader innovation trends in the nanomedicine field as a whole. Promising examples include development of a once weekly, orally administered antiviral drug delivery platform that consists of several polymer matrices with different drug release profiles in order to consistently maintain pharmaceutically relevant concentrations of antiviral drugs in systemic circulation.[30]

One of the most recent examples of cutting-edge nanomaterial strategies to deliver viral replication inhibitors involves the class of macromolecular prodrugs, comprising polymer-functionalized antiviral drugs in complexation with serum proteins. Andersen et al. described the formation of polymer–protein–drug complexes that enable long-duration therapy with multiple antiviral drugs.[31] A polymer–protein complex comprised of a single, ≈7 kDa *N*-(2-hydroxypropyl) methacrylamide (PHPMA) chain per covalently attached albumin molecule was designed and exhibited much longer circulation half-time and higher concentrations in mice upon intravenous or subcutaneous administration, as compared to free PHPMA alone. Marked accumulation of the polymer–protein complex in mouse lymph nodes was also reported. Two antiviral drugs, azidothymidine (AZT) and lamivudine (3TC), were covalently incorporated into the monomer backbone via a labile disulfide linkage for eventual intracellular release of free drug molecules. These functionalized building blocks were assembled into a colloidal-like polymer–protein–drug complex consisting of one polymer chain with six AZT and four 3TC copies along with one albumin molecule and inhibited human immunodeficiency virus (HIV) infection of primary human T cells in vitro.

Frich et al. expanded on this macromolecular prodrug strategy by devising a "hitchhiking" scheme in which a polymer–drug conjugate was fabricated and exhibited noncovalent binding to serum albumin proteins, as indicated by biophysical experiments and increased circulation half-time in mice in vivo.[32] The key innovation was functionalizing the PHPMA component with 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE) lipid, which is a binding ligand for serum albumin proteins found in circulation (**Figure 1**a). A polymer–drug conjugate was synthesized consisting of DSPE–PHPMA and multiple copies of acyclovir (ACV), which is a nucleoside analogue that inhibits herpes simplex virus (HSV). It was verified that free ACV could be released from the DSPE–PHPMA–ACV complex upon incubation in physiologically relevant conditions containing glutathione (GSH). It was determined that $>100 \times 10^{-9}$ M ACV was released within 3 h from 1 g L^{-1} PHPMA–ACV in GSH-containing phosphate-buffered saline (PBS) while nearly negligible release was observed over an appreciably longer time period of 24 h in PBS without GSH. Importantly, DSPE–PHPMA–ACV also exhibited antiviral activity against HSV type 2 (HSV-2) infection of baby hamster kidney-derived ELVIS and human cervix-derived HeLa cells in vitro. Furthermore, subcutaneous administration of the polymer–drug complex helped to suppress vaginal HSV-2 infection in an in vivo mouse model based on viral infectivity measurements of vaginal wash and spinal cord specimens (Figure 1b).

In addition to forming polymer–drug complexes, recent efforts have focused on creating macromolecular prodrugs from chemical derivatives of nucleoside analogues that can form nucleic acid scaffolds. For example, Krüger et al. demonstrated that idoxuridine, a nucleoside analogue used to treat HSV infection, could be converted into a phosphoramidite derivative and then these building blocks were used to synthesize linear nucleic acid scaffolds with 7 or 14 attached drug molecules (Figure 1c).[33] In vitro release experiments revealed that the scaffolds are stable in serum-free cell culture medium while free idoxuridine was gradually released within 2–6 h in the presence of serum, indicating the potential utility of these scaffolds for in vivo applications (Figure 1d). Future work needs to continue exploring the prophylactic and therapeutic utility of macromolecular prodrugs of viral replication inhibitors in animal models, while there exist numerous potential advantages in terms of well-defined colloidal properties and targeted

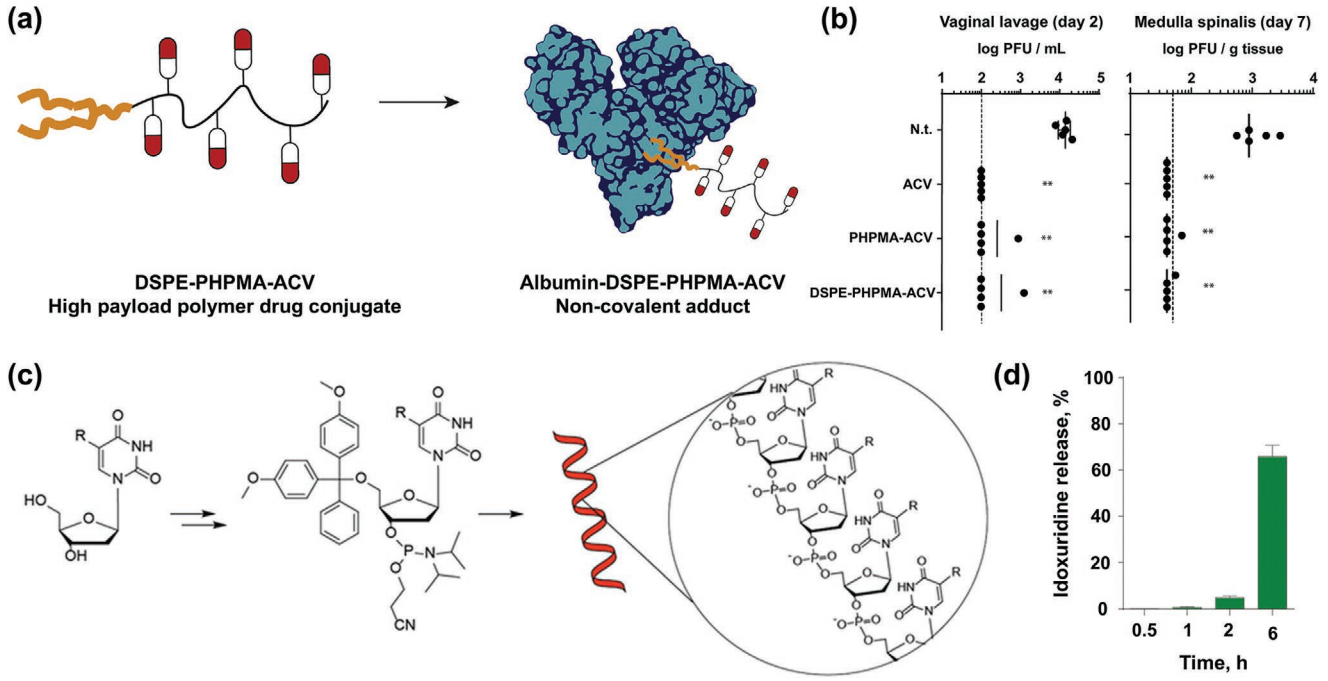


Figure 1. Biomaterial strategies to improve the pharmacological properties of viral replication inhibitors. a) Strategy to form long-circulating macromolecular prodrugs of nucleoside analogues based on noncovalent association with serum albumin proteins. Multiple copies of the nucleoside analogue, acyclovir (ACV), were covalently attached to a polymer consisting of 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine (DSPE) and poly(*N*-(2-hydroxypropyl)methacrylamide) (PHPMA) to form the DSPE-PHPMA-ACV complex. DSPE-PHPMA was found to bind noncovalently to serum albumin proteins, which was associated with a longer circulation half-time in mice. By contrast, PHPMA alone did not bind appreciably to albumins. b) Effect of subcutaneously (s.c.) administered DSPE-PHPMA-ACV, PHPMA-ACV, free ACV, and no treatment (N.t.) on vaginal herpes simplex virus type 2 (HSV-2) infection in an in vivo mouse model. The equivalent dose of ACV was fixed at 60 mg kg^{-1}. The data show the virus amount in vaginal wash collected on day 2 postinfection and in the spinal cord (medulla spinalis) on day 7 postinfection, respectively. The data are expressed in plaque-forming units (PFU) mL^{-1} wash sample or g^{-1} spinal cord tissue. Each data point corresponds to an individual mouse. The bars and dashed line in each panel represent geometric mean values and the detection limit for virus quantification, respectively. Statistical tests compared the treatment groups with the N.t. group and the marker ** denotes $p < 0.01$. Adapted with permission.[32] Copyright 2018, Elsevier. c) Strategy to convert small-molecule nucleoside analogues into polymerizable monomers that can form macromolecular prodrugs comprising nucleic acid polymer scaffolds. d) Percentage of free idoxuridine molecules, a nucleoside analogue, that were cleaved from a 14-mer polymer scaffold consisting of derivatized idoxuridine monomers, upon incubation in cell culture medium with 10% serum for 0.5, 1, 2, or 6 h time periods. Data are reported as mean ± standard deviation (s.d.). Reproduced under the terms of the CC-BY license.[33] Copyright 2019, The Authors, Wiley-VCH.

codelivery of two or more antiviral drugs to increase the barrier for drug-resistant virus strains to emerge.[34] There also remains an outstanding need to investigate the mechanisms of drug release in vivo and to also continue exploring how macromolecular prodrugs can be engineered to target specific organs.

4. Virus Particle Binding Inhibitors

4.1. Pristine Nanomaterials

Over the years, various classes of nanomaterials such as metal nanoparticles and carbon-based nanomaterials have been synthesized and there are well-developed methods to control atomic composition, size, and functional groups. Accordingly, systematic studies have long been conducted to test how different types of pristine nanomaterials—as-synthesized nanomaterials without additional surface functionalization—affect virus particles and have revealed a variety of antiviral mechanisms related to virus particle binding and steric blocking, chemical reactions involving nanomaterial-induced reactive species, and virus particle disruption, as extensively covered in numerous reviews.[35] To date, however, most of these antiviral activities have been characterized in vitro, while it is more challenging to use pristine nanomaterials in vivo where they can show diminished antiviral activity. Key challenges include nonspecific binding of nanomaterials to other biological components and the protein corona that can form spontaneously on nanomaterial surfaces upon immersion in physiological environments.[36] In addition to conventional nanomaterial options, there has also been extensive interest in designing nanomaterials from poorly soluble antimicrobial compounds, which can improve solubility and potential usability in some cases. For example, Huang et al. reported the fabrication of water-dispersible, benzoxazine monomer-derived carbon dots with ≈4 nm diameter, which inhibited a wide range of viruses, including Japanese encephalitis, Zika, and Dengue (**Figure 2**a).[37] Significant reductions in viral infectivity in vitro against baby hamster kidney-derived BHK-21 and monkey kidney-derived Vero cells were observed upon pretreatment of virus particles with the carbon dots (Figure 2b,c).

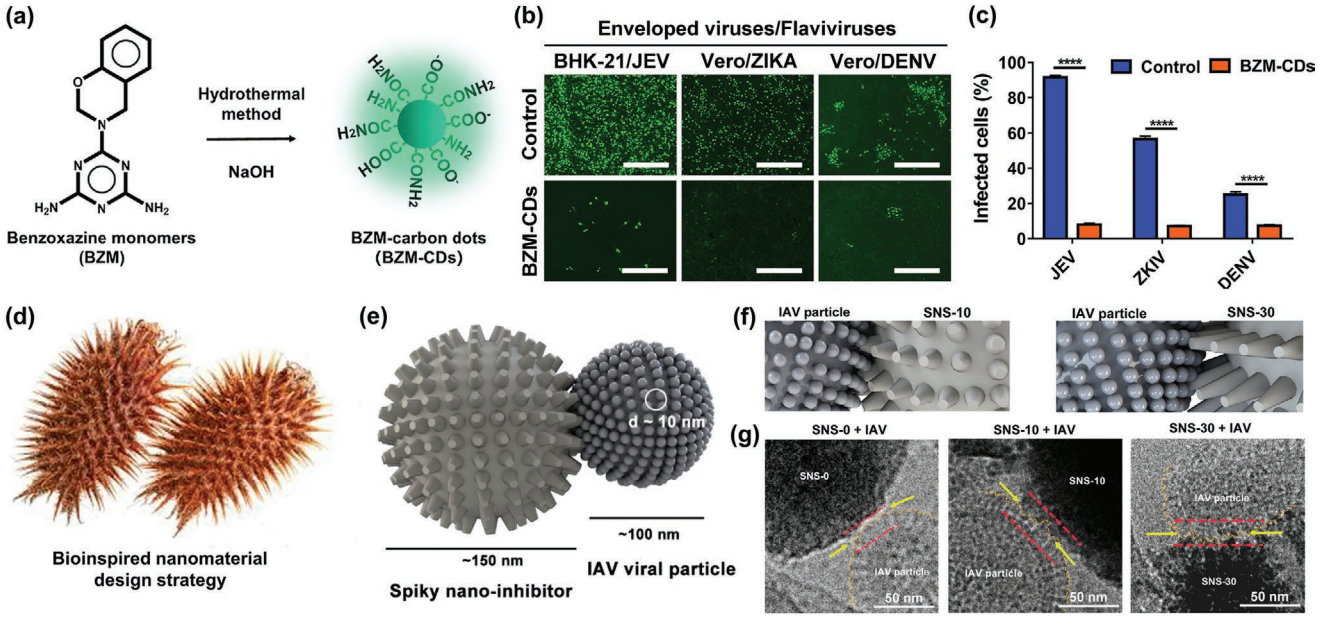


Figure 2. Nanomaterial design strategies for virus particle targeting. a) Schematic illustration to chemically functionalize ≈4 nm diameter carbon dots (CDs) with benzoxazine monomers (BZM), resulting in BZM-CDs with broad-spectrum antiviral activity. b) Immunofluorescence microscopy analysis of BZM-CD antiviral activity against multiple virus types. Japanese encephalitis virus (JEV), Zika virus (ZIKA), and Dengue virus (DENV) samples were treated with 75 μg mL^{-1} BZM-CDs. The BZM-CD-treated JEV sample was then used to infect BHK-21 cells while the BZM-CD treated ZIKA and DENV samples were then used to infect Vero cells. BZM-CDs and Control refer to the treatment and virus-only control groups, respectively. All scale bars are 400 μm. c) Percentage of virus-infected cells based on immunofluorescence microscopy data. Data are reported as mean ± standard error of the mean (s.e.m.). Statistical tests compared the treatment groups with the virus-only control groups and the marker **** denotes $p \leq 0.0001$. Reproduced with permission.[37] Copyright 2019, Elsevier. d) Image of *Xanthium strumariumuses* seeds with spiky appendages that support enhanced adhesion. e) Schematic illustration of ≈150 nm diameter spiky silica nanoparticles adhering to an ≈100 nm diameter influenza A virus (IAV) particle based on geometry-matching topology. f) Schematic illustrations of spiky nanostructures (SNS) with 10 or 30 nm average spike length (termed SNS-10 and SNS-30, respectively) binding to IAV virus particles. g) Cryogenic transmission electron microscopy (Cryo-TEM) images of IAV particle binding to topographically smooth SNS without spikes (termed SNS-0, left), SNS-10 (middle), and SNS-30 (right). Yellow arrows indicate virus-SNS contact region. All scale bars are 50 nm. Reproduced with permission.[39] Copyright 2020, American Chemical Society.

Another study involved the fabrication of water-dispersible, glycyrrhizic acid-derived carbon dots that inhibited porcine reproductive and respiratory syndrome virus (PRRSV) infection of nonhuman primate-derived MARC-145, Vero, and pig kidney-derived PK-15 cells by suppressing viral genome replication and stimulating innate immune responses.[38]

Taking inspiration from how a wide range of biological materials have spiky surfaces for increased adhesion, one of the most recent advances has been the development of spiky nanostructures that have improved contact with virus particles (Figure 2d). Based on the complex topology of spherical influenza virus particles, including the presence of protruding glycoproteins, Nie et al. fabricated spiky silica nanoparticles that exhibited improved adhesion to the virus particles, as compared to smooth silica nanoparticles (Figure 2e).[39] The spike dimensions were optimized so that the nanoparticle spikes could fit well in between the glycoprotein protrusions (Figure 2f,g). Notably, however, the spiky silica nanoparticles had low aqueous dispersibility, so they were initially coated with polyethylene glycol (PEG) but did not inhibit influenza virus infection of canine kidney-derived MDCK-II cells in vitro. Therefore, the spiky silica nanoparticles were coated with a red blood cell membrane extract, which facilitated antiviral activity in vitro, as indicated by reduced virus particle binding to cells and decreased viral infectivity. Cell membrane coatings are further discussed in Section 4.3 below and this example provides insight into how the biological functionality of nanomaterials can be modulated based on the surface coating. A combination of binding ligands and antiviral drugs was further conjugated on the spiky nanoparticle surface to enhance antiviral activity against influenza virus and inhibit infection of MDCK-II cells in vitro.[40] Porous gold nanoparticles with a high surface area have also been reported to inhibit infection of canine kidney-derived MDCK cells by a wide range of influenza virus strains in vitro.[41] Ultimately, such studies have provided insight into how nanoparticle composition and shape can influence antiviral activity and this research direction has been greatly enhanced in recent years by integrating nanomaterial design together with biomimetic surface functionalization with cell-mimicking receptors and cell membrane extracts.

4.2. Receptor-Functionalized Nanomaterials

4.2.1. Sulfonated Nanoparticles

Virus particle attachment to cell membrane receptors is a critical first step in the infection process and, for many types of viruses, involves viral protein binding to heparan sulfate proteoglycan receptors that are present on cell surfaces.[42] As

such, stopping these virus-cell binding interactions via competitive inhibitors can prevent infection and various classes of sulfonated polysaccharides have been explored, including heparin[43] and heparin-like molecules[44] along with metal complexes of sulfonated molecules, and exhibit antiviral activity in vitro.[45] Many of these antiviral molecules have been explored as topical microbicides to prevent vaginal transmission of viruses such as HIV, however, none have demonstrated efficacy in late-stage clinical trials and intracorporeal efficacy is more challenging to achieve.[46]

In light of these shortcomings and the potential utility of this biomimetic design concept in principle, there has been extensive interest in developing sulfonated nanoparticles with a well-controlled, multivalent presentation of sulfonate groups to inhibit susceptible viruses. Baram-Pinto et al. reported that sulfonate-functionalized gold nanoparticles can inhibit herpes simplex virus type 1 (HSV-1) infection of Vero cells in vitro by preventing cell entry of virus particles and hence reducing cell-to-cell spreading as well.[47] Notably, the sulfonate groups in that study were attached to gold nanoparticles via short-chain linkers with low conformational flexibility. Cagno et al. further investigated the design of sulfonate-functionalized gold nanoparticles with short-chain, low-flexibility and long-chain, high-flexibility linkers and discovered that the use of more flexible chains enabled improved antiviral activity in vitro with Vero cells, ex vivo with human epivaginal tissue cultures, and in vivo in mice (**Figure 3**a).[48] While both types of sulfonate-functionalized nanoparticles could bind to and inhibit viruses such as HSV-2, only the nanoparticles with flexible linkers could inhibit viruses upon dilution due to stronger binding interactions and heparin was also inactive (Figure 3b–d). Electron microscopy imaging further revealed that nanoparticle-virus particle interactions in the latter case resulted in virus particle disruption, indicating a virucidal ("virus-killing") type of mechanism (Figure 3e–g). Intranasal administration of the sulfonated nanoparticles also prophylactically inhibited respiratory syncytial virus (RSV) infection in mice in vivo.

Building on this work, Zacheo et al. recently explored how controlling the properties of the sulfonated ligands on the gold nanoparticle surface affects the degree of antiviral activity and identified glucose- and lactose-based ligands with virucidal activity against Dengue virus to inhibit infection of Vero and human liver-derived HepG2-hNTCP cells in vitro.[49] Dey et al. have also reported the fabrication of ≈100–200 nm diameter, hydrogel-like sulfonated nanogel particles and demonstrated that the nanogels can block HSV-1 infection of monkey kidney-derived Vero E6 cells in vitro.[50] Importantly, several types of nanogels were designed with different degrees of flexibility and more flexible nanogels showed greater antiviral activity. Cyclodextrin scaffolds functionalized with mercaptoundecane sulfonic acids have also exhibited broad-spectrum antiviral activity against numerous medically important viruses and further testing showed that HSV did not acquire resistance to the sulfonated cyclodextrin scaffolds.[51] The in vitro antiviral activity of sulfated polysaccharides to inhibit SARS-CoV-2 infection of money kidney-derived Vero-CCL81 and Vero E6 cells has been described in at least two recent works,[52] supporting that nanomaterial strategies involving sulfonate groups might be effective antiviral strategies to inhibit SARS-CoV-2 as well.

4.2.2. Sialylated Nanoparticles

Different viruses bind to specific types of cell surface receptors as part of the infection process and another key example involves the influenza virus, which is a leading cause of respiratory viral infections.[53] Hemagglutinin (HA) proteins on the influenza virus particle surface bind to sialic acid-containing glycan molecules that are prevalent on the surface of human lung cells as well as those of different animal species.[54] As with sulfonate-related binding interactions and protein–glycan interactions in general, individual events of viral protein binding to sialic acids are relatively weak and strong interactions depend on multivalency.[55] Accordingly, a wide range of nanomaterial scaffolds with multiple sialic acid residues have been designed to competitively bind to influenza virus particles and thus prevent viral infection. Recent efforts have focused on how precisely tuning the distance between sialic acid residues on the scaffold affects HA binding. For example, Bandlow et al. investigated how rigid scaffolds composed of self-assembled complexes of deoxyribonucleic acid (DNA) and peptide nucleic acid (PNA) enhanced binding interactions compared to more flexible, polyethylene glycol (PEG) scaffolds.[56] This finding agreed well with antiviral testing data on rigid and flexible core trivalent sialosides too.[57] Another important design variable has been considering linear versus branched scaffolds.[58] In one promising example, Kwon et al. reported the fabrication of a branched polyamidoamine scaffold that mirrored the inter-spacing distance between HA proteins on influenza virus particles and intranasal administration of this scaffold was able to protect mice from lethal influenza virus infection.[59] Other recent examples include more sophisticated nanomaterial designs involving three-way nucleic acid junctions[60] and star glycopolymers.[61]

In addition to polymer-like scaffolds, there has been ongoing exploration of sialic-functionalized nanoparticles and a key example involves bacteriophage capsid nanoparticles with well-controlled spacing of sialic acid-functionalized ligands (**Figure 4**a,b).[62] Capsid nanoparticles with the correct Sia1 sialic acid ligands could specifically bind to influenza virus particles while nanoparticles functionalized with other glycan ligands did not bind to virus particles (Figure 4c,d). Likewise, only Sia1-functionalized nanoparticles could inhibit influenza virus infection of MDCK-II and human lung-derived A549 cells in vitro in a dose-dependent fashion and influenza virus pretreatment with the nanoparticles also protected mice from infection-related weight loss in vivo (Figure 4e,f).

Richard et al. have also systematically investigated how sialic acid-functionalized gold nanoparticles can be designed in terms of core nanoparticle size and linker length and unraveled how these parameters influence multivalent binding interactions, which can give rise to highly specific binding to particular ligand geometries.[63] In terms of soft-matter nanoparticles, Bhatia et al. have also investigated the design of ≈250 nm diameter sialylated nanogel particles with varying degrees of flexibility and observed that highly flexible nanogel particles inhibited cell attachment of influenza virus by up to 400 times, as compared to more rigid nanogel particles.[64] The flexible nanogel particles also prevented influenza infection of MDCK-II cells in vitro down to picomolar concentrations. In

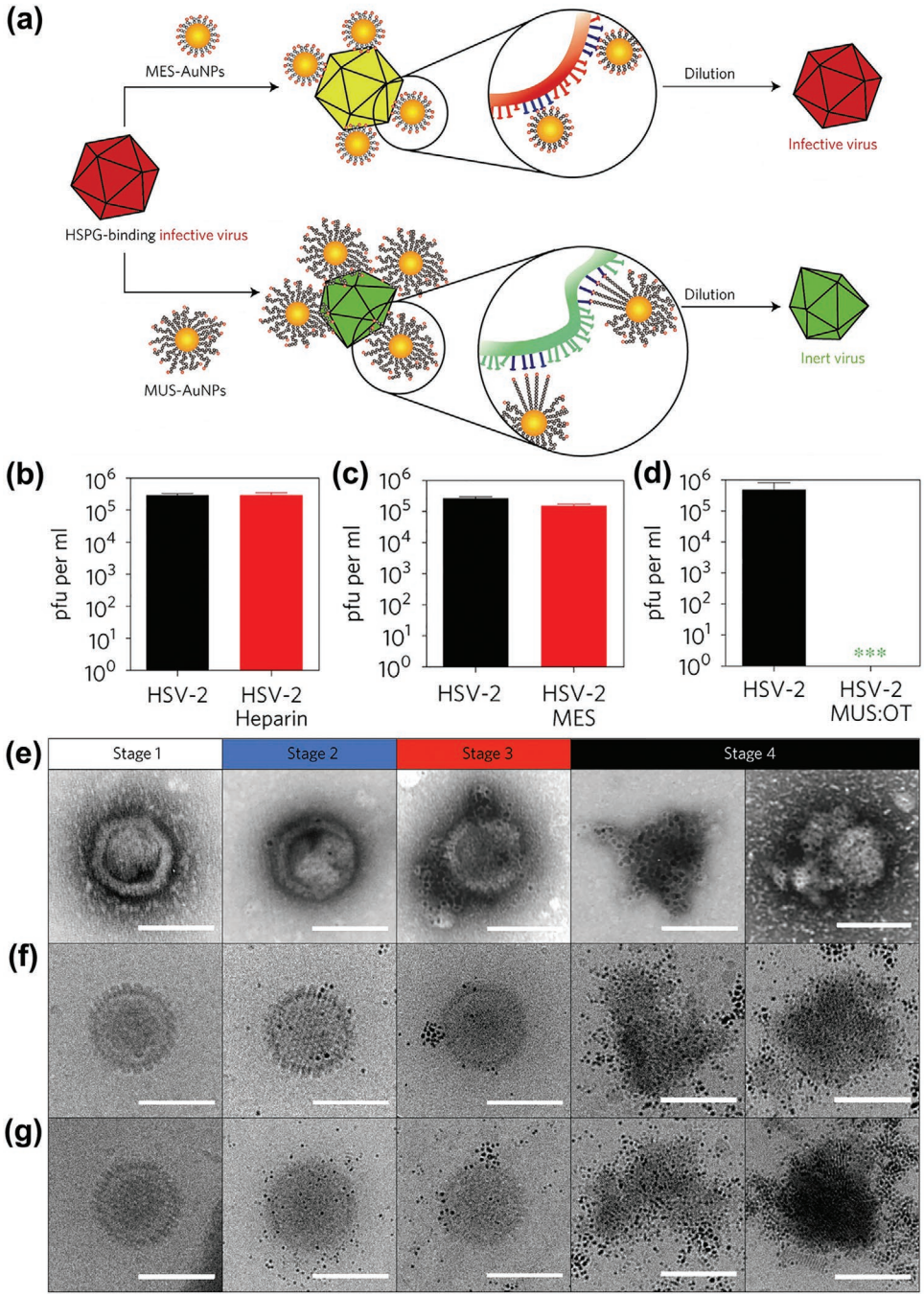


Figure 3. Sulfonate-functionalized inorganic nanoparticles as virucidal inhibitors to disrupt virus particles. a) Schematic illustration of nanoparticle strategies to inhibit virus particles that bind to heparan sulfate proteoglycan (HSPG) receptors on cellular surfaces during the infection process. The basic concept is to create biomimetic nanoparticles with sulfonate groups that can tightly bind to virus particles to prevent virus binding to HSPG cell receptors. Top row: Gold nanoparticles functionalized with low-flexibility 3-mercaptoethylsulfonate (MES), termed MES-AuNPs, can bind relatively weakly to virus particles to prevent infection. However, the inhibitory effect of MES-AuNPs is lost upon dilution and the virus particles remain infective. Bottom: Gold nanoparticles functionalized with high-flexibility undecanesulfonic acid (MUS), termed MUS-AuNPs, can bind relatively strongly to virus particles and prevent infection. The inhibitory effect of MUS-AuNPs is maintained upon dilution and nullifies viral infectivity due to irreversible virus particle disruption. Effects of b) heparin, c) MES-AuNPs, and d) MUS:OT-AuNPs on herpes simplex virus type 2 (HSV-2) infection in vitro. HSV-2 virus samples were incubated with 90% effective concentrations (EC_{90}) of the different antiviral materials, followed by dilution and viral infectivity quantification. Black and red columns in each panel correspond to virus-only control and treatment groups, respectively. Data are expressed in terms of plaque-forming units (PFU) mL^{-1} and reported as mean ± standard error of the mean (s.e.m.). Statistical tests compared the treatment groups with the virus-only control groups and the marker *** denotes $p < 0.001$. e–g) Transmission electron microscopy (TEM) images of HSV-2 virus particle interactions with MUS:OT-AuNPs during different interaction stages. The stages 1, 2, 3, 4 correspond to no nanoparticle binding, isolated nanoparticle-virus binding interactions, clustering of nanoparticle-virus binding interactions, and virus particle deformation with extensive nanoparticle binding, respectively. e) Image collection was conducted using standard TEM with dried samples and negative staining. f,g) Image collection was conducted using cryogenic TEM (cryo-TEM) with unstained samples. All scale bars are 100 nm. Adapted with permission.[48] Copyright 2017, Springer Nature.

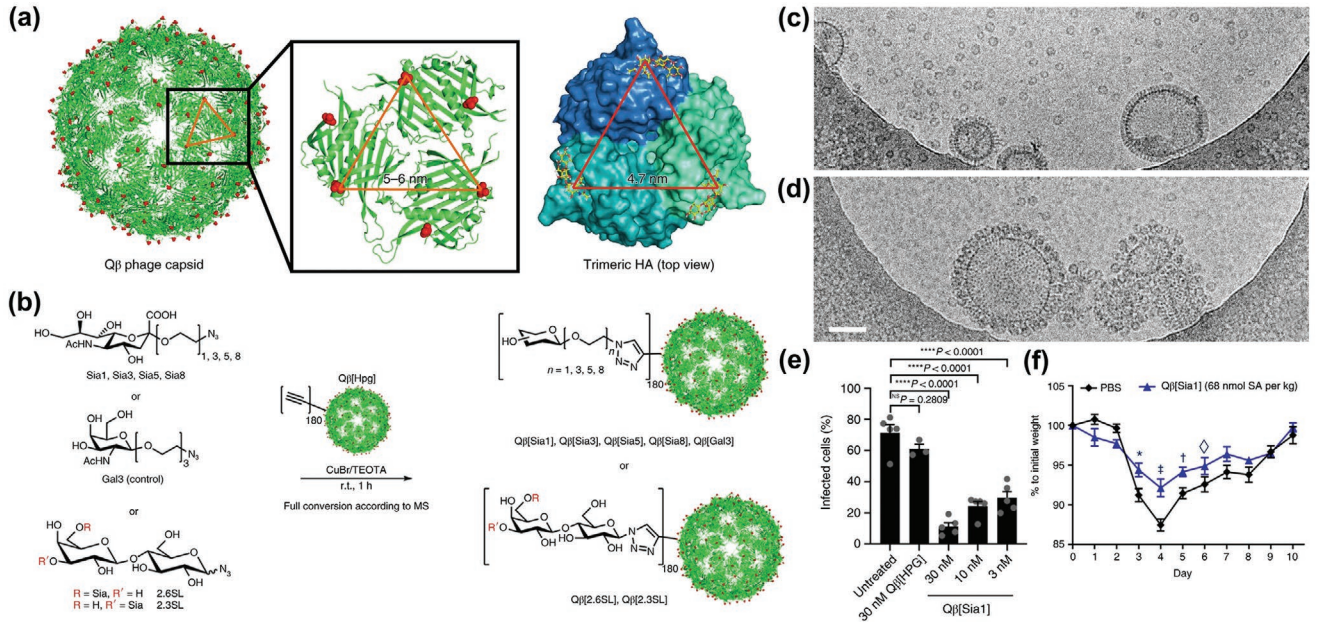


Figure 4. Bacteriophage capsid nanoparticles with multivalent ligand receptors to prevent virus infection. a) Molecular models of ≈25 nm diameter Qβ bacteriophage capsid nanoparticles and trimeric hemagglutinin (HA) glycoproteins on the influenza A virus (IAV) particle surface. Inset: magnified view of the Qβ bacteriophage capsid shows the periodic distance between sites (red dots) where sialic acid (Sia) ligands were covalently attached, which matches the distance between Sia-binding sites in HA trimers. b) Preparation of ligand-functionalized Qβ capsids. The capsid protein was recombinantly expressed with L-homopropargylglycine (Hpg) in order to present an alkyne functional group for ligand conjugation and formed Qβ[Hpg]. Sia ligands were attached to Qβ[Hpg] via mono-, tri-, penta-, or octaethylene glycol linkers to form Qβ[Sia1], Qβ[Sia3], Qβ[Sia5], and Qβ[Sia8], respectively. In addition, negative control Qβ capsids were prepared by conjugating *N*-acetylgalactosamine (Gal) with a triethylene glycol linker to form Qβ[Gal3]. Qβ capsids that only bind human- or avian-adapted IAV strains were also prepared by directly conjugating α-2,6-sialyllactose (2.6SL) and α-2,3-sialyllactose (2.3SL) without ethylene glycol linker. Ligand conjugation was achieved using copper-catalyzed azide-alkyne cycloaddition and verified by mass spectrometry (MS). TEOTA: tris[(1-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl]amine. c,d) Cryogenic transmission electron microscopy (Cryo-TEM) images of influenza virus particle interactions with Qβ capsids. Parts (c) and (d) show no binding to negative control Qβ[Gal3] capsids and extensive binding to Qβ[Sia1] capsids. The scale bar is 100 nm. e) Percentage of infected human lung A549 cells based on immunofluorescence microscopy for influenza virus samples pretreated with different concentrations of Qβ[Sia1] or Qβ[Hpg] capsids, along with virus-only control group (Untreated). Data are reported as mean ± standard error of the mean (s.e.m.). Each data point corresponds to an individual sample. Statistical tests compared the pretreatment groups with the virus-only control group and the markers **** and ^{NS} denote $p < 0.0001$ and $p > 0.05$, respectively. f) Effect of Qβ[Sia1] capsid nanoparticles on IAV infection in an in vivo mouse model. IAV was preincubated with Qβ[Sia1] or phosphate-buffered saline (PBS, mock pretreatment) before the pretreated virus samples were administered intranasally. The equivalent dose of Qβ[Sia1] was 68×10^{-9} M SA kg^{-1} mouse weight. The change in mouse body weight was reported for each day postinfection. Data are reported as mean ± s.e.m. Statistical tests compared the Qβ[Sia1]-pretreated group with the mock-pretreated group on each day and the markers *,‡,† and $^{\diamond}$ denote $p < 0.05$ and $p < 0.01$, respectively. Adapted with permission.[62] Copyright 2020, Springer Nature.

another interesting example, Kong et al. reported the development of sialic acid-functionalized lipid nanodisks that can bind to and cause perforation of influenza virus particles.[65] This example demonstrated that sialic acid-functionalized nanoparticles can exhibit additional mechanistic functions beyond inhibiting virus-cell interactions only and intravenous administration of the nanodisks also protected mice against lethal influenza virus infection in vivo.

In addition to new nanoparticle designs, there has been extensive recent progress in developing nanoscience measurement tools to quantify influenza viral protein-sialic acid binding interactions. For example, single-molecule force spectroscopy experiments have been conducted to comparatively measure the binding strength of influenza HA and neuraminidase proteins to sialic acid receptors[66] and the effects of multivalency on such interactions.[67] Di Iorio et al. have also fabricated sialic acid-functionalized lipid bilayers and measured the binding of ≈22 nm diameter clusters of recombinant influenza HA proteins to supported lipid bilayers by quartz crystal microbalance-dissipation (QCM-D) experiments.[68] Other techniques such as microcavity arrays can also measure the diffusional motion of HA proteins bound to sialic acid-functionalized supported lipid bilayers.[69] To date, most of these measurement strategies have been employed for understanding the fundamental role of multivalency in viral protein–glycan interactions while there remains tremendous potential to utilize these approaches for evaluating the functional performance of new nanomaterial inhibitors as well as to test drug inhibitor candidates that prevent such interactions.[70]

4.2.3. Additional Strategies

In addition to glycan-based decoy binding strategies for competitive inhibition, nucleic acid nanostructures have enabled creative design possibilities based on self-assembling, complex

topologies. For example, Kwon et al. reported the design of 3D DNA nanostructures with highly precise architectural features and incorporated Dengue viral protein-binding aptamers within the nanostructure, which could bind multivalently to Dengue virus particles.[71] Different nanostructures such as heptagons, hexagons, and stars were tested and it was discovered that the star nanostructure yielded the most potent inhibitory activity to prevent Dengue virus infection of Vero cells in vitro. The 50% effective concentration (EC_{50}) to inhibit Dengue virus was around 2×10^{-9} M for star nanostructures, as compared to 10×10^{-9} and 440×10^{-9} M for the hexagon and heptagon nanostructures, respectively. This example provides an important demonstration of how synthetic receptors can be engineered in the future to develop more potent nanomaterial options, especially from natural, biocompatible materials, and with self-assembling properties.

These synthetic capabilities have also inspired current efforts to develop nanomaterial inhibitors of SARS-CoV-2 based on understanding what receptor the virus binds and how to design receptor-mimicking decoys. Specifically, the latest scientific evidence supports that SARS-CoV-2 binds to the membrane-associated angiotensin-converting enzyme 2 (ACE2) receptor on cell surfaces as part of the infection process.[72] Han et al. have reported the computational design of peptides that correspond to structurally important regions of ACE2 and can bind to SARS-CoV-2 envelope proteins to prevent infection.[73] It was suggested that the inhibitory peptides could be attached to nanoparticles with multivalent presentation, while such design strategies would require a careful consideration of how to best optimize the peptide attachment in terms of attachment chemistry, flexibility, density, and peptide conformation. There is also interest in engineering the ACE2 protein to bind more strongly to SARS-CoV-2 envelope proteins[74] and experimental work to test antiviral peptide inhibitors in this direction is ongoing.

4.3. Cell Membrane Decoys

Over the past decade, there has been extensive and rapidly growing interest in coating synthetic nanoparticles with cell membrane extracts to confer advantageous biological properties. For example, Hu et al. demonstrated that coating polymeric nanoparticles with red blood cell membranes can increase circulation time in mice.[75] It has also been demonstrated that cloaking polymeric nanoparticles with the plasma membrane of human platelets can improve immunocompatibility in terms of lower macrophage uptake and reduced complement activation, along with additional platelet-like functionalities.[76] Ongoing progress in the field has also sparked interest in developing cell membrane-coated nanoparticles that contain virus-binding receptors and hence can bind to virus particles in order to prevent infection.[77]

Numerous viruses such as Dengue and Zika are transmitted by mosquito vectors[78] and Rao et al. demonstrated that gelatin nanoparticles coated with mosquito cell membrane extracts can bind to Zika virus particles, whereby each ≈130 nm diameter nanoparticle binds to multiple virus particles.[79] This approach led to dose-dependent reduction in viral infectivity of Vero cells in vitro and intravenous administration of the coated nanoparticles up to 2 days postinoculation also protected mice against virus-induced mortality and body weight loss and reduced the level of viral infection in the brain. Red blood cell membrane-coated magnetic nanoparticles with sialylated functional groups have also been employed to capture influenza virus particles.[80]

In addition to using natural cell membrane extracts that contain typical amounts of virus-binding receptors, there have been attempts to engineer cells to overexpress those receptors and to prepare cell-derived membrane vesicles accordingly. For example, Liu et al. devised a biosynthetic strategy to overexpress the membrane receptor of hepatitis B virus (HBV), which is called human sodium taurocholate cotransporting polypeptide (hNTCP), in HepG2 cells and prepared ≈200 nm diameter, cell membrane-derived vesicles that were used to inhibit HBV infection of HepG2-hNTCP cells in vitro and in mice with humanized livers in vivo (**Figure 5**a).[81] Compared to control membrane vesicles from the parent cell line with normal receptor quantities, the membrane vesicles from the engineered cell line with an overexpressed quantity of receptors exhibited appreciably greater antiviral activity levels and demonstrated improved treatment efficacy in the mouse model, as indicated by lower levels of HBV antibodies and nucleic acid copies (Figure 5b,c). Recently, Rao et al. reported the fabrication of cell membrane-derived vesicles from human monocyte cells that were genetically engineered to express the ACE2 receptor and the ACE2-functionalized vesicles could prevent SARS-CoV-2 infection of Vero E6 cells in vitro.[82]

Similar approaches have also been taken to treat and prevent infection by HIV, which is known to infect T cells.[83] Polymeric nanoparticles were coated with the plasma membranes of $CD4^+$ T cells, which contain the receptors needed for virus binding and cell entry, and the cell membrane-coated nanoparticles could inhibit HIV infection of peripheral blood mononuclear cells and human-monocyte-derived macrophages in vitro. Furthermore, it was suggested that this cell membrane decoy strategy could be potentially advantageous to work against multiple, genetically diverse HIV strains because all strains bind to the same cell receptors.[85] A follow-up study confirmed that the T cell membrane-coated nanoparticles could inhibit a wide range of HIV-1 strains and surprisingly induced autophagy of HIV-infected cells to suppress viral genome replication but had no effect on uninfected cells.[86] Recently, cell membrane-coated nanoparticles have also been developed to inhibit SARS-CoV-2 infection of Vero E6 cells in vitro (Figure 5d).[84] Nanoparticles coated with extracts from human lung epithelial type II or macrophage cells inhibited SARS-CoV-2 in a dose-dependent fashion while nanoparticles coated with extracts from red blood cells were inactive (Figure 5e). These findings emphasize the importance of rationally designing biomimetic nanomaterial strategies based on a precise understanding of how a certain virus affects cells, and further research is needed to clarify the potential utility of these inhibitory capabilities in vivo.

5. Viral Membrane Inhibitors

Most nanomaterial-based antiviral strategies focus on targeting viral protein components in order to prevent virus-cell

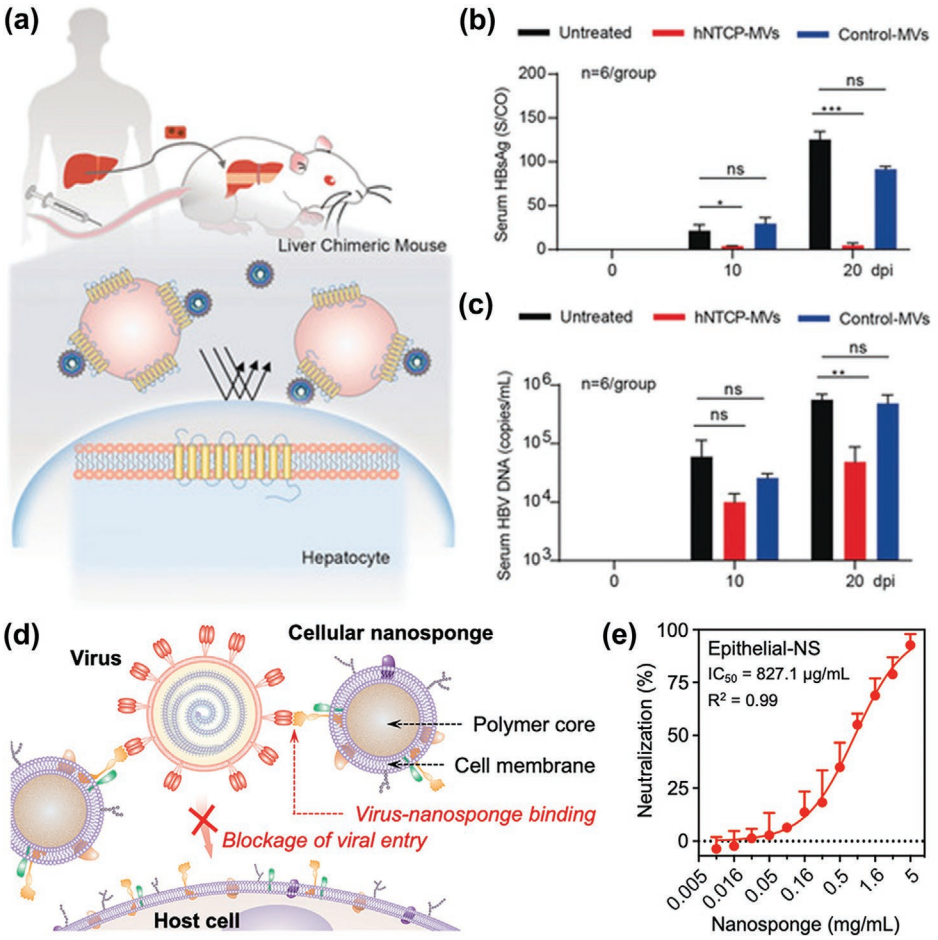


Figure 5. Cell membrane-mimicking nanoparticle decoy strategies to inhibit virus particles. a) Strategy to capture hepatitis B virus (HBV) virus particles by using cell-membrane-derived nanovesicles, thereby preventing hepatocyte cell infection. The vesicles were derived from human cells that overexpress the membrane-associated HBV receptor called human sodium taurocholate cotransporting polypeptide (hNTCP), and are called hNTCP-anchoring membrane vesicles (hNTCP-MVs). Control-MVs from normal cells without receptor overexpression were also fabricated and tested for comparison. b,c) Effect of intravenously administered hNTCP-MVs or Control-MVs on HBV infection in an in vivo humanized liver mouse model. Changes in amount of b) HBV antigen (HBsAg) and c) HBV DNA in serum were recorded on selected days postinfection for the treatment groups along with a negative control, untreated group. S/CO means signal-to-cutoff and a larger value means more viral antigen and vice versa. Data are reported as mean ± standard error of the mean (s.e.m.). Reproduced with permission.[81] Copyright 2018, Wiley-VCH. d) Strategy to capture severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus particles by using cell-membrane-coated polymeric nanoparticles termed nanosponges (NS). The membrane coatings are derived from target cells which SARS-CoV-2 infects and hence the coatings contain pertinent receptors to bind to SARS-CoV-2. e) Effect of epithelial-membrane-coated NS treatment on SARS-CoV-2 infectivity, as measured by plaque reduction neutralization experiments. The data are reported in terms of neutralization percentage (%) and expressed as mean ± standard deviation (s.d.). The 50% inhibitory concentration (IC_{50}) value is also reported and expressed in terms of membrane protein concentration units. Reproduced with permission.[84] Copyright 2020, American Chemical Society.

binding interactions as described in the preceding examples. However, various types of viruses use distinct binding receptors to enter cells and such strategies are therefore intrinsically limited to working against a relatively narrow subset of viruses. On the other hand, many viral epidemics are caused by membrane-enveloped viruses and a structurally intact viral membrane on enveloped viruses is necessary for viral infectivity, including virus-cell fusion.[87] As such, a wide range of broad-spectrum antiviral drug candidates have been explored to inhibit membrane-enveloped viruses based on targeting the viral membrane.[87]

One of the most exciting groups of drug candidates within this class are membrane-disruptive, antiviral peptides that inhibit membrane-enveloped viruses in order to abrogate viral infectivity.[88] Several antiviral peptides have been discovered that inhibit a wide range of membrane-enveloped viruses, such as hepatitis C virus (HCV)[89] and HIV,[90] and include a 27-mer amphipathic, α-helical (AH) peptide that exhibits membrane-curvature-selective disruptive activity to inhibit small, membrane-enveloped virus particles of ≈160 nm diameter or smaller.[91] In vitro antiviral testing experiments against various types of membrane-enveloped and nonenveloped viruses have been conducted using a wide range of permissive, model cell lines such as Vero cells and human liver-derived Huh 7.5 cells as well as primary cells such as mouse neuronal cells and human T cells. The results have demonstrated that some membrane-active peptides exhibit antiviral activity against enveloped viruses down to the nanomolar range along

with low cell cytotoxicity.[92] While viral envelopes are derived from host cell membranes, the AH peptide and possibly other peptides can exhibit selective rupture of highly curved viral membranes due to membrane-curvature-triggered membrane disruption.[93] Indeed, mammalian cells are much larger than virus particles and hence possess an appreciably lower degree of membrane curvature and this curvature difference provides a distinguishing factor between viral and mammalian cell membranes.[94] These promising mechanistic features have motivated researchers to explore how to utilize viral-membrane-targeting, antiviral peptides in vivo, while exploring design strategies to overcome traditional challenges of peptide therapeutics, such as high susceptibility to proteolytic enzymes and short circulation time.[95]

To overcome these challenges, Jackman et al. explored the development of an engineered version of the AH peptide, composed of all D-amino acids and termed AH-D, which was able to therapeutically treat lethal Zika virus infection in a mouse model in vivo.[92] The basic design concept was called lipid envelope antiviral disruption (LEAD) and posited that extracellular targeting of membrane-enveloped viruses can reduce the concentration of infectious virus particles in order to help curb viral infection (**Figure 6**a). Upon intravenous administration of the AH-D peptide starting 3 days post-virus inoculation, over 80% of mice survived Zika virus infection and exhibited markedly reduced clinical symptoms in general. Importantly, the AH-D peptide was able to significantly reduce the concentration of infectious virus particles in the blood as well as in multiple organs, including in the brain (Figure 6b). More extensive studies revealed that the AH-D peptide is able to cross the intact blood-brain barrier to treat Zika virus infection directly in the brain as well as to reduce infection-related brain inflammation (Figure 6c,d).

From a material science perspective, another noteworthy point is that a large portion of the mechanistic understanding about how AH and AH-D peptides work has been obtained from biosensing measurement strategies involving biomimetic, virus-particle-mimicking vesicles in combination with acoustic-, optical-, nanoplasmonic-, and fluorescence-microscopy-based techniques.[91,96] Examples include nanoparticle tracking analysis (NTA) and plasmonic nanohole sensors[97] (Figure 6e–i). Such insights have led to further exploration of the AH-D peptide as an antiviral drug candidate to prevent Zika virus infection of fetuses in pregnant mice[98] and forward-looking discussion about how the LEAD concept could be useful for broadly treating mosquito-borne virus infections, including not only Zika but also Dengue, Chikungunya, and Yellow Fever among various possibilities.[99] This capability could be especially beneficial when a mosquito-borne viral infection is clinically suspected but a differential diagnosis of the specific virus type is challenging.[100] The LEAD concept might be generally applicable to other types of membrane-enveloped viruses as well since the viral membrane represents an Achilles heel and there is a high barrier to the emergence of drug-resistant strains because the viral membrane is derived from host cell membranes and not encoded within the viral genome.[101] It has even been suggested that membrane-enveloped SARS-CoV-2 might be susceptible to viral membrane disruption[102] and these aspects are particularly important because SARS-CoV-2 infection in the brain has been linked to a wide range of COVID-19 disease conditions.[103]

While intravenously administered, antiviral peptides have demonstrated initial promise in some mouse models of viral infections, nanomaterial-based drug delivery strategies could improve pharmacological activities and lead to improved targeting possibilities. Zhang et al. have reported the development of a cationic, membrane-active antiviral peptide that was mixed together with anionic polymer chains to form ≈35 nm diameter nanoparticles.[104] These peptide-polymer nanoparticles exhibited in vitro antiviral activity against HCV infection of Huh 7.5 cells and HIV infection of TZM-bl cells, human lymphocytes, and monocyte-derived macrophages, respectively, and also showed lower levels of hemolytic activity against red blood cells than the free peptide alone. Intramuscular injection of the peptide-polymer nanoparticles showed improved treatment of HIV-1 infection in a mouse model in vivo, as compared to free peptide alone. In a follow-up study, a refined version of the peptide-polymer nanoparticles was developed that was functionalized with galactosyl sugar molecules in order to enable improved HepG2 cell internalization in vitro and preferential liver accumulation in mice in vivo.[105] Ongoing work can further expand the potential of targeting membrane-enveloped viruses by using antiviral peptides and other classes of small-molecule inhibitors[106] that impair viral membrane-associated proteins to prevent virus-cell fusion in combination with nanomaterial strategies to enhance targeted delivery prospects. In addition to directly targeting virus particles, it might be possible to also disrupt membrane-enveloped exosomes that carry viral components such as nucleic acids and proteins and can be involved in viral infection and transmission processes.[107]

6. Virus-Removing Blood Filters

Another approach to effectively remove circulating virus particles from the blood of infected hosts has relied on the use of extracorporeal blood-filtering devices and advances upon medical device technology that was originally used to treat sepsis infections.[108] Early work by Kang et al. demonstrated that a microfluidic device can effectively remove a wide range of bacterial and fungal pathogens from blood.[109] To achieve this objective, ≈130 nm diameter magnetic nanoparticles were functionalized with mannose-binding lectin (MBL) protein molecules, which can bind to sugar molecules found on the surface of various pathogens such as bacteria, fungi, protozoa, and viruses along with endotoxins.[110] The MBL-functionalized nanoparticles were mixed together with circulating blood, could bind to circulating pathogens, and then the nanoparticle-pathogen mixtures could be magnetically separated before the blood was returned to the host. In rat models of bacterial infection, more than 90% of bacteria were reduced along with decreased levels of inflammatory cytokines. Seiler et al. have further explored the use of an engineered version of MBL that demonstrated improved pathogen capture in blood and urine samples.[111]

Based on these findings, there has been ongoing progress to develop extracorporeal blood filters for virus particle removal applications as well. Tullis et al. demonstrated that

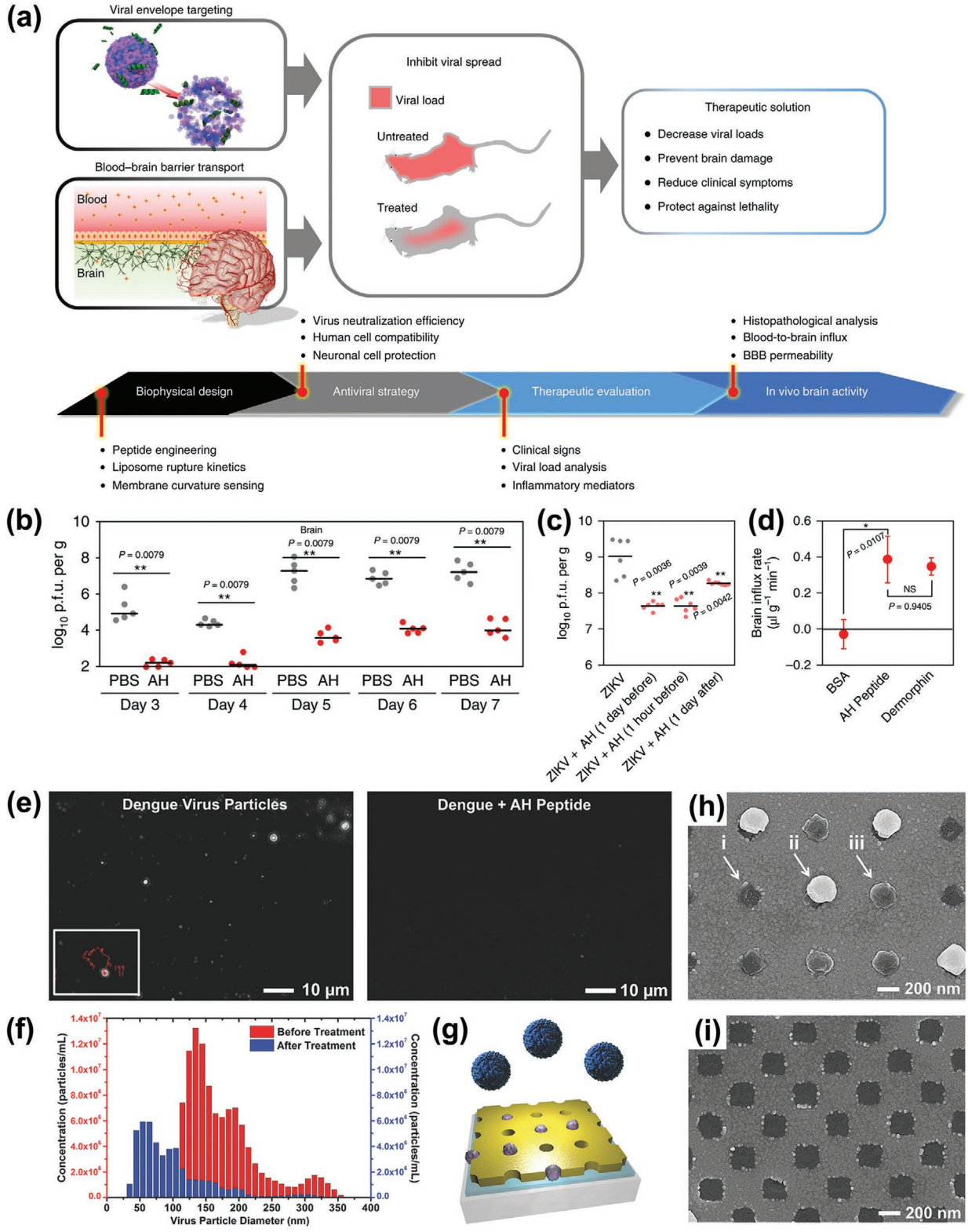


Figure 6. Viral membrane disruption strategies to inhibit membrane-enveloped viruses. a) Schematic illustration of lipid envelope antiviral disruption (LEAD) concept to inhibit membrane-enveloped viruses. The example is shown for a brain-penetrating, α-helical (AH-D) peptide that inhibited Zika virus infection in an in vivo mouse model, whereby peptide-induced virus particle disruption reduced disease severity and led to clinical improvements. b) Effect of intravenously administered AH-D peptide therapy on Zika virus infection in mouse brain in vivo on selected days post-inoculation, as compared to a negative control saline solution. The virus inoculation route was intravenous, resulting in systemic infection. c) Effect of intravenously administered AH-D peptide on Zika virus infection in mouse brain in vivo. AH-D peptide was intravenously administered either

hemodialysis treatment using a hollow-fiber cartridge that contained antibody-functionalized agarose beads could effectively remove HIV-1 virus particles and viral proteins from cell culture media and blood.[112] These capabilities have led to the exploration of clinical-stage medical device technology to broadly capture a wide range of circulating virus particles by replacing the antibody functionalization with MBL functionalization. Early reports indicated preliminary testing success to capture HIV and HCV virus particles along with binding to Dengue, influenza, Ebola, and Marburg viral proteins.[113] A pilot human clinical trial using a full-scale version of this medical device technology was used to remove HCV from the blood of 4 HCV-positive patients and resulted in an average drop in HCV viral loads of around 57%.[114] Follow-up studies showed HCV viral load reductions in additional patients and it was further suggested that continuous application of this treatment approach could potentially reduce HCV to clinically undetectable levels within a few days, especially if used in combination with conventional antiviral drug therapies.[115]

Büttner et al. have also reported that the medical device technology has been used to treat one patient with Ebola virus infection[116] and recent works have explored how these extracorporeal blood filters might be useful to remove coronaviruses and Marburg virus from infected blood.[117] With respect to the ongoing COVID-19 pandemic, it has also been noted that virus-removing blood filters could be a useful technology.[118] Given the small number of patients in the aforementioned clinical testing, it is difficult to draw definitive conclusions at the present stage, however, there are bright prospects to continue exploring virus-removing blood filter technology. The U.S. Food and Drug Administration recently approved the initiation of a feasibility study, with up to 40 human patients, to test the treatment efficacy of an extracorporeal blood filter based on this medical device technology for patients with a positive SARS-CoV-2 diagnosis and severe COVID-19 disease.[119]

In terms of future innovation in this direction, it is important to continue exploring how to develop improved filtration devices while also creating new biofunctionalization strategies to improve virus-binding capacity and perhaps apply peptide functionalization schemes to catalytically damage virus particles as opposed to intact virus particle binding alone. Looking forward, these medical device technologies can be particularly useful when used in conjunction with antiviral drug therapies to lower the amount of infectious virus particles in blood while also inhibiting the production of new virus particles among other possibilities.

7. Virus-Mimicking Nanoparticle Vaccines

7.1. Design Rationale

There has also been tremendous progress in developing nanoparticle-based vaccine strategies to prevent and treat viral infections. In general, viral infections provoke the immune system, which can recognize viral proteins on the virus particle surface ("antigens") and produce antibodies that bind to these antigens to neutralize virus particles.[120] In some cases, natural antibodies produced in response to a viral infection can have extremely high specificity and potency to inhibit virus particles.[121] For these reasons, the blood plasma from patients who recover from a certain type of virus infection is often given as a medical treatment to infected patients afflicted with the same type of virus infection.[122] In such cases, the plasma can contain high levels of neutralizing antibodies that bind to and inhibit virus particles.[123] However, the specific types and concentrations of antibodies present in blood plasma vary from person-to-person, potentially limiting reliable clinical use.[124] Hence, there has been extensive interest in recombinantly manufacturing specific, highly potent neutralizing antibodies as an alternative treatment option.[125] This latter approach allows more precise control over antibody composition and dosing. Recombinant antibody therapies also reduce the risk of antibody-dependent enhancement (ADE) side effects, which can arise in some cases from non-neutralizing antibodies that are also present in plasma.[125,126]

The same logic applies to vaccine development where the key objective is to administer a virus-mimicking immunogenic material so that a strong and focused immune response can be trained. The target objective is to generate high levels of potent neutralizing antibodies while minimizing production of non-neutralizing antibodies that can otherwise inadvertently promote virus infection in some cases. Over the past few years, virus-mimicking nanomaterial design strategies have been at the forefront of creating next-generation vaccine strategies now reaching human clinical trials. The combination of nanomaterials, biomimetics, and protein engineering has led to unprecedented capabilities to rationally finetune immune responses and elicit high levels of potent neutralizing antibodies in a safe and effective manner. These capabilities are currently being extended to develop a nanoparticle vaccine candidate to prevent SARS-CoV-2 infection.

Recent progress in the field highlights the merits of both natural and engineered protein scaffolds to create self-assembling, virus-mimicking nanoparticle vaccines with

1 day or 1 h before or 1 day after virus inoculation, which was given intracranially in this experiment. For panels (b) and (c), data are expressed in terms of plaque-forming units (PFU) g^{-1} brain tissue, each data point corresponds to an individual mouse, and the bar for each test group indicates the median value. d) One-way, blood-to-brain influx rate of intravenously administered AH-D peptide in mice in vivo, as compared to the negative control, bovine serum albumin (BSA) protein, and positive control, dermorphin peptide. Data are expressed as best-fit rate ± standard error (s.e.). NS means not significant. Reproduced with permission.[92] Copyright 2018, Springer Nature. e) Nanoparticle tracking analysis (NTA) micrographs of Dengue virus particles in solution before (left) and after (right) treatment with an antiviral, α-helical (AH) peptide. Inset corresponds to the Brownian motion of a representative, individual Dengue virus particle. f) Histogram plot of Dengue virus particle concentrations before and after treatment with AH peptide based on the measurement approach in panel (e). g) Strategy to immobilize individual virus-like particles composed of phospholipid-cholesterol membranes in metallic nanoholes for plasmonic biosensing experiments. Representative scanning electron microscopy (SEM) images of the virus-like particles in a nanohole array h) before and i) after treatment with AH peptide. Note that AH peptide caused rupture of virus-like particles, as indicated by the voids in panel (i). Reproduced with permission.[97] Copyright 2015, Wiley-VCH.

excellent biomechanical and immunological properties. The fast-moving progress on this subject is reviewed in this section along with coverage of other vaccine nanoparticle strategies.

7.2. Types of Nanoparticle Vaccines

There is broad interest in integrating material science and protein engineering strategies to develop safe, virus-mimicking nanoparticle vaccines that present viral protein antigens in a highly organized and symmetrical manner in order to induce strong immune responses.[127] Compared to free antigens, nanoparticle vaccines have several compelling advantages, including greater antigen stability, multivalent presentation of antigens, and targeted delivery.[128] As such, nanoparticle vaccines can bind multivalently to multiple receptors on B cells, which are immune cells involved in antibody production, resulting in more robust immune responses and high levels of immune protection.[24] A wide variety of nanoparticle types are being explored to prevent infectious diseases in general, including self-assembling protein nanoparticles, inorganic nanoparticles, liposomal nanoparticles, and polymer scaffolds.[129] Key design considerations include optimizing the antigen structure (more precisely, the immunogen structure) to elicit the desired immune response, tuning vaccine delivery, and inducing focused immune responses.[130] From a biomimetic perspective, one of the most promising recent design advances has involved self-assembled nanoparticle vaccines as discussed below along with introducing other nanoparticle vaccine design strategies.

7.2.1. Natural Protein Scaffolds

The earliest example of a natural protein scaffold to form a nanoparticle vaccine involved the use of ferritin, which self-assembles into nearly spherical, hollow nanoparticles that have ≈12 nm core diameter and are composed of 24 protein molecules with symmetrical organization.[131] By overcoming several challenges related to protein glycosylation and oligomerization, Kanekiyo et al. first reported the design of a ferritin-based, influenza nanoparticle vaccine in 2013 that presented eight trimers of influenza HA viral protein on the nanoparticle surface in a native-like configuration that enabled a superior immune response to conventionally used influenza vaccine strategies based on inactivated virus particles.[132] From a material science perspective, the key innovation was controlling the location at which ferritin and HA were genetically fused together in order to recombinantly express ferritin-HA fusion proteins that self-assembled into nanoparticles with repetitively spaced, trimeric HA spikes (**Figure 7**a,b). Ferritin-HA nanoparticle immunization induced a strong immune response, as indicated by high levels of neutralizing antibodies against multiple influenza H1N1 strains and protection against influenza virus infection in a ferret model (Figure 7c,d). Recently, Kelly et al. have elucidated how ferritin-HA nanoparticle vaccination in mice triggers principally germinal center expansion and maturation of memory B cells, which are involved in antibody production.[133] In another study, Yassine et al. further explored the development of ferritin nanoparticle vaccines that presented a truncated version of HA, which corresponded to the stem region that is conserved across different HA subtypes H1N1 and H3N2 and hence its trimeric presentation on the nanoparticle surface conferred protection against a wider range of influenza subtypes in mouse and ferret models.[134]

Ferritin nanoparticle vaccines have also been developed to prevent infections from viruses such as HIV-1 and Sliepen et al. first reported the design of ferritin nanoparticles presenting HIV-1 envelope (Env) protein trimers, which demonstrated high levels of immunogenicity in mice and rabbits.[136] Neutralizing antibodies were generated to inhibit some but not all HIV-1 strains, and it was particularly challenging to inhibit certain strains classified as "difficult-to-neutralize".[137] It was discussed how the nanoparticle design might be improved by reducing steric hindrance between adjacent Env trimers. He et al. refined the structure-based design of the trimeric Env antigens presented on the ferritin nanoparticle surface along with optimizing spacing between the trimers in order to yield more robust B cell responses.[138] More detailed engineering of the Env antigen structure increased Env trimer recognition on the ferritin nanoparticles by a broader range of naïve B cells, resulting in elicitation of broadly neutralizing antibodies.[139] Due to the high sequence variation among Env proteins across different HIV-1 strains, Sliepen et al. have designed a new Env antigen structure based on a consequence sequence incorporating the epitopes of many broadly neutralizing antibodies, and presented the Env antigen trimers on ferritin nanoparticles to yield strong neutralizing antibody responses in rabbits and macaques.[140] In addition, He et al. have reported additional protein engineering efforts to improve the stability of wild-type Env antigens by switching out the ectodomain with a more stable version from an engineered Env antigen, which enabled improved generation of neutralizing antibodies that can inhibit difficult-to-neutralize HIV-1 strains, in mice and rabbits.[141] Together, the ongoing work with ferritin-Env nanoparticle vaccines to prevent HIV-1 infection demonstrates the superior immune responses generated by antigen trimers on the nanoparticle surface, while highlighting the potential to combine these nanomaterial efforts with antigen-based protein engineering efforts.

Such possibilities have also been explored for a wide range of other viruses and support the broad versatility of ferritin nanoparticle technology for developing next-generation vaccines. Kanekiyo et al. have designed a ferritin nanoparticle vaccine to prevent Epstein-Barr virus (EBV) infection by conjugating ferritin molecules to a truncated domain from the EBV gp350 protein that contains the receptor-binding site needed for B cell infection.[142] On the ferritin nanoparticle surface, the antigen formed dimers, which is a distinct conformation to the trimeric presentation cases discussed above. Importantly, compared to the soluble gp350 antigen, the nanoparticle vaccine still elicited markedly increased levels of neutralizing antibodies by 10- to 100-fold in mice and nonhuman primates and also conferred protective immunity on mice in a lethal virus challenge model. Bu et al. have also developed another form of a ferritin nanoparticle vaccine to prevent EBV infection based on a different antigen (gH), which alone and in complexation with gL and gp42 proteins helps to generate neutralizing antibodies that inhibit virus-cell fusion and works against multiple cell types instead of only preventing B cell infection.[143]

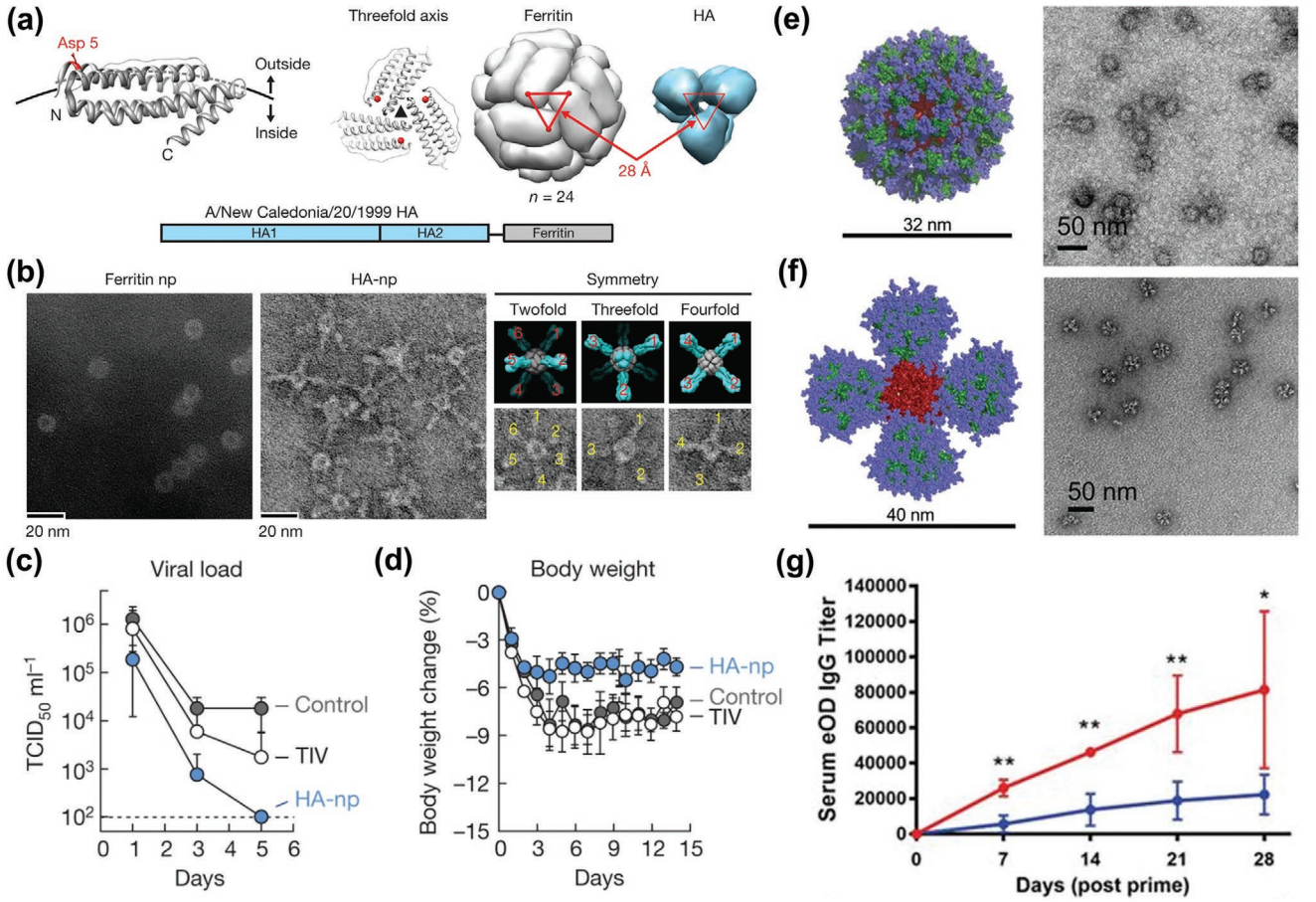


Figure 7. Self-assembling natural protein scaffolds for nanoparticle vaccines. a) Schematic illustration of ferritin-based nanoparticle vaccine design for influenza A virus (IAV). From left to right: Molecular model of a single ferritin subunit; Three subunits form a symmetrical arrangement; 24 subunits combine to form a spherical nanoparticle with octahedral symmetry; IAV hemagglutinin (HA) antigen trimers were displayed on the ferritin nanoparticle. Bottom: Sequence design of a ferritin-HA fusion protein that can self-assemble into a ferritin-HA nanoparticle vaccine. b) Transmission electron microscopy (TEM) images of negatively stained ferritin nanoparticles (Ferritin np; left) and ferritin-HA nanoparticles (HA-np; middle). Computational models and magnified TEM images of HA-nps on different axes of symmetry. In each image, the number of HA spikes are counted for an individual HA-np. c,d) Effect of HA-np vaccine or trivalent inactivated vaccine (TIV) immunization on protection against influenza virus intranasal challenge in an in vivo ferret model. Changes in viral titer of c) nasal washes and d) body weight were recorded on selected days postchallenge for the HA-np- and TIV-immunized groups along with a mock-immunized control group. Viral titers were quantified in terms of 50% tissue culture infectious dose ($TCID_{50}$). Data are reported as mean ± standard deviation (s.d.) and mean ± standard error of the mean (s.e.m.) for viral titer and body weight changes, respectively. Reproduced with permission.[132] Copyright 2013, Springer Nature. e,f) Nanoparticle vaccine strategies for HIV envelope antigens. Molecular models and corresponding TEM images of negatively stained nanoparticle vaccine samples. Scale bars are 50 nm. e) An HIV envelope antigen termed eOD was fused with lumazine synthase and 60 subunits of the fusion protein self-assembled into ≈32 nm diameter nanoparticle vaccines (eOD-60mer). f) An HIV envelope antigen trimer termed MD39 was fused with ferritin and 24 subunits of the fusion protein self-assembled into ≈40 nm diameter nanoparticle vaccines (MD39-8mer). g) eOD-specific antibody titers in serum of mice immunized with eOD-60mer (red) or deglycosylated eOD-60mer (blue). Data are reported as mean ± 95% confidence interval. Reproduced with permission.[135] Copyright 2019, The American Association for the Advancement of Science.

In another important example, Wang et al. have reported a dual-targeting, ferritin nanoparticle vaccine strategy to prevent and treat chronic HBV infection in mice based on activating two types of immune cells to induce high and persistent levels of neutralizing antibodies.[144] Recent work has further demonstrated that ferritin nanoparticles are an excellent platform to present viral antigens for developing HCV vaccines that might work against a wide range of HCV genotypes[145] and also to develop vaccines for treating RSV infection.[146] Notably, in the latter case, a glycosylated version of the RSV antigen was designed that induced a higher ratio of neutralizing antibodies to non-neutralizing antibodies in mice and nonhuman primates, which could be significant because higher levels of non-neutralizing antibodies are thought to be associated with antibody-mediated disease enhancement.[146]

In addition to fabricating ferritin nanoparticles composed of one type of building block component, there has been interest in developing two-component ferritin nanoparticles in order to present oligomers of multiple antigens on the nanoparticle surface. For example, Georgiev et al. reported the development of ferritin nanoparticles composed of two types of ferritin constructs, one of which was fused to an influenza virus antigen

and the other one of which was fused to an HIV-1 antigen, and nanoparticle self-assembly resulted in trimeric presentation of both antigens.[147] Importantly, vaccination with this nanoparticle strategy in guinea pigs could induce neutralizing antibodies that inhibited both viruses. Since there are many different subtypes of influenza virus, Kanekiyo et al. expanded on this nanoparticle design strategy to design and coassemble ferritin-HA constructs encoding HA with one of two receptor-binding domains (RBDs) and the resulting nanoparticles had mosaic HA trimers that presented a mixture of RBDs to yield a broader antibody response than nanoparticles with either RBD alone.[148] Vaccination in mice led to the discovery of a neutralizing antibody that works against a wide range of influenza virus strains. Accordingly, nanoparticle-based strategies presenting multiple antigens have been suggested as one possible route to create a universal influenza vaccine.[25]

While ferritin nanoparticles have proven useful for creating vaccine nanoparticle technology, there has been extensive interest in identifying other natural protein scaffolds that can self-assemble into nanoparticles with different sizes. Also in 2013, Jardine et al. reported the development of ≈32 nm diameter, self-assembling nanoparticles composed of 60 recombinantly expressed lumazine synthase (LS) protein molecules from *Aquifex aeolicus*, which exhibit symmetrical organization, and designed an LS fusion protein together with HIV-1 Env antigen that could form nanoparticles with enhanced B cell activation and lymph node trafficking properties.[149] In follow-up work, an improved version of the LS nanoparticle vaccine platform was designed and induced promising immune responses in different mouse models in vivo, toward the goal of eliciting broadly neutralizing antibodies against HIV-1 infection.[150] Havenar-Daughton et al. further investigated single-dose immunization of rhesus monkeys with this HIV-1 nanoparticle vaccine and noted that subcutaneous immunization yielded markedly larger B cell responses and lymph node drainage than intramuscular drainage.[151] Tokatlian et al. have also explored how antigen glycosylation of LS- and ferritin-based HIV-1 nanoparticle vaccines is an important factor in modulating antibody responses (Figure 7e,f).[135] The results demonstrated that antigen glycosylation is an important factor in eliciting high levels of antigen-specific antibody levels and appreciably lower levels were observed with deglycosylated antigen (Figure 7g). Additionally, Krebs et al. have investigated ≈23 nm diameter nanoparticle self-assembly from the E2 protein of *Geobacillus stearothermophilus* in order to create nanoparticle vaccines presenting an HIV-1 Env antigen fragment, which yielded an antigen-specific antibody in immunized rabbits although multiple rounds of immunization were needed to elicit moderately protective, neutralizing antibody levels in a large fraction of rabbits.[152]

As seen in these examples, it is important to point out that self-assembled nanoparticles from different natural protein scaffolds have distinct functionalities, as noted by how protein scaffolds fused together with full-length viral protein antigens can only self-assemble into nanoparticles for some, but not all, of the scaffold options and antigen spacing is another important factor affecting both nanoparticle self-assembly and immunogenicity.[138] In part, such design issues have motivated the use of full-length viral proteins or truncated versions thereof and the type of nanoparticle structure can also affect antigen oligomerization in some cases.[142]

Another important point concerns the nanoparticle vaccine fabrication strategy. To date, the structural components of virus-mimicking nanoparticle vaccines have been recombinantly expressed in host cells in vitro and, upon expression, spontaneously self-assemble into antigen-presenting nanoparticles. In such cases, the nanoparticle vaccine suspension is then injected into animals as part of the immunization process. As an alternative strategy, recent work has also investigated nucleic-acid-based vaccination strategies that could enable the in vivo expression of nanoparticle structural components and, in some cases, in vivo self-assembly of protein-based nanoparticle vaccines. Melo et al. reported the development of a lipid-nanoparticle-encapsulated alphavirus ribonucleic acid (RNA) replicon encoding the HIV Env antigen fused with LS.[153] A single injection of this lipid nanoparticle suspension encoding the HIV Env antigen yielded high levels of Env-specific antibodies and also led to improved B cell responses compared to recombinant protein immunization. In another demonstration, Xu et al. reported the use of a DNA vaccine plasmid to induce the in vivo expression of a nanoparticle structural component comprising an HIV Env antigen fused with LS, and demonstrated its in vivo structural assembly in mice based on functional studies along with improved immune responses in mice and guinea pigs compared to immunization with a similar delivery strategy encoding antigen monomers only.[154] The design concept was further generalized to other natural protein scaffolds, such as ferritin nanoparticles, which also induced high immune responses and the delivery strategy could also be adapted to influenza HA antigen in order to endow mice with protective immunity against a lethal influenza virus challenge.

From a translational perspective, there has been tremendous progress in developing ferritin-HA nanoparticle vaccines for preventing influenza infections based on ongoing human clinical trials being conducted in the United States. Preliminary data from the first-in-human trial (NCT03186781) of a ferritin-HA nanoparticle vaccine provided initial evidence that the vaccine is safe and well-tolerated in humans while another human clinical trial (NCT03814720) is ongoing to evaluate the dosing, safety, tolerability, and immunogenicity of ferritin-HA-stem nanoparticles as a potential universal flu vaccine candidate.

7.2.2. Engineered Protein Scaffolds

The insights gained from nanoparticle vaccines based on self-assembling natural protein scaffolds have highlighted the importance of tuning antigen structure, conformation, density, and spacing on the nanoparticle surface. While several types of self-assembling proteins exist in nature, the number of options is intrinsically limited, which has prompted researchers to further explore the design of nanoparticle vaccines from self-assembling, engineered protein scaffolds that enable greater control over nanomaterial properties. Toward this goal, King et al. reported computational strategies to design 24-subunit protein nanomaterials composed of two types of self-assembling protein subunit components, and experimentally demonstrated that it was possible to rationally tune the

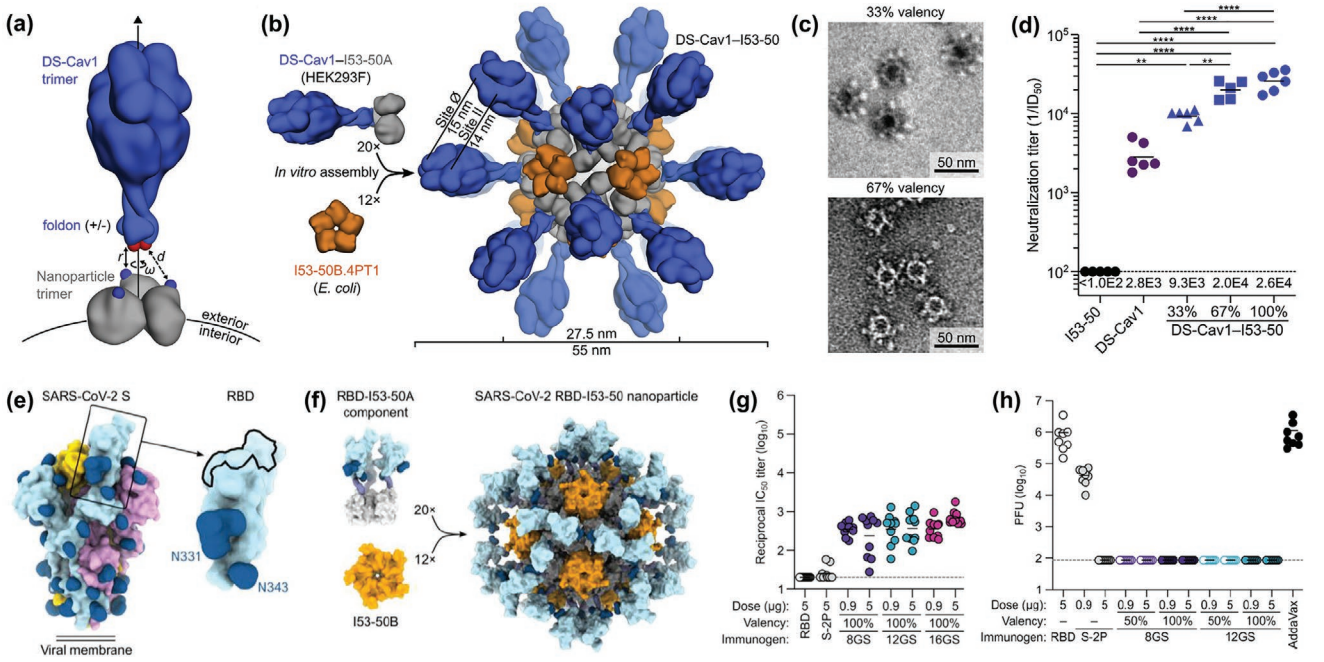


Figure 8. Engineered protein scaffolds for nanoparticle vaccines and coronavirus disease 2019 (COVID-19) application. a) Schematic illustration of respiratory syncytial virus (RSV) antigen trimer design. A fusion of the engineered protein I53-50A and RSV antigen DS-Cav1 (termed DS-Cav1-I53-50A) was constructed and self-assembles to form trimers. b) Schematic illustration of two-component RSV nanoparticle vaccine design. Two oligomeric components, DS-Cav1-I53-50A trimer and I53-50B.4PT1 pentamer, self-assemble in a 20:12 molar ratio to form DS-Cav1-I53-50 nanoparticles in vitro. The protruding spikes are antigen trimers. c) Transmission electron microscopy images of negatively stained DS-Cav1-I53-50 nanoparticle vaccines with 33% (top) and 67% (bottom) valency, which is defined by the percentage of DS-Cav1-I53-50A trimers versus bare I53-50A trimers that were used in the nanoparticle preparation. The scale bars are 50 nm. d) Serum neutralizing antibody titers from mice immunized with DS-Cav1-I53-50 with 33%, 67%, or 100% valency, I53-50 nanoparticles without antigen, or trimeric DS-Cav1 soluble antigen. Note that 100% valency means that only DS-Cav1-I53-50A trimers were used. Data are expressed in terms of the 50% inhibitory dose reciprocal ($1/ID_{50}$) and the bar indicates the geometric mean, which is listed for each test group. Each data point corresponds to an individual mouse. The dashed line is the assay limit of detection. Statistical tests were conducted between groups and the markers *,**,***,**** denote $p < 0.05$, $p < 0.01$, $p < 0.0001$, and $p < 0.0001$, respectively. Reproduced with permission under CC-BY license.[157] Copyright 2019, Elsevier. e) Schematic illustration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S envelope protein and its receptor-binding domain (RBD). f) Schematic illustration of two-component SARS-CoV-2 nanoparticle vaccine design. Two oligomeric components, RBD-I53-50A trimer and I53-50B pentamer, self-assemble in a 20:12 molar ratio to form RBD-I53-50 nanoparticles in vitro. Note the RBD antigen and I53-50A protein are connected via an 8, 12, or 16 glycine and serine residues, which are termed 8GS, 12GS, and 16GS, respectively. g) SARS-CoV-2 neutralizing titer of serum from mice immunized with a single dose of RBD-I53-50 nanoparticles, soluble S protein trimer (S-2P), or human convalescent sera (HCS) from recovered COVID-19 patients. Data are expressed in terms of the 50% inhibitory concentration reciprocal ($1/IC_{50}$). h) Effect of RBD-I53-50 nanoparticle immunization on SARS-CoV-2 virus intranasal challenge in mice in vivo, as compared to immunization with soluble RBD monomers, S-2P, and AddaVax adjuvant only. The viral titers in lung tissue were measured two days postchallenge and quantified in terms of plaque-forming units (PFU). For panels (g) and (h), each data point corresponds to an individual mouse, the horizontal bar for each test group indicates the geometric mean, and the dashed lines show the assay limits of detection. Reproduced under the terms of the CC-BY-ND 4.0 license.[161] Copyright 2020, The Authors, bioRxiv.

nanomaterial structure, shape, and symmetry in alignment with the computational designs.[155] In another study, Bale et al. applied similar approaches to design larger, two-component protein nanomaterials composed of 120 subunits with icosahedral symmetry and had 24–40 nm diameters that are similar to the size of small viral capsids.[156] Another advantage of using two-component engineered proteins is greater control over the fabrication process. Natural protein scaffolds self-assemble upon recombinant expression while engineered protein components can be expressed independently and then mixed as desired to self-assemble into nanoparticles in vitro.

Marcandalli et al. reported the first example of an engineered-protein-based nanoparticle vaccine that was built from two self-assembling components and presented multiple copies of a trimeric RSV envelope antigen termed DS-Cav1 (**Figure** 8a,b).[157] One protein component was designed to present DS-Cav1 and spontaneously formed trimers by itself, while the other protein component formed pentamers by itself. The two protein components were expressed independently and, when mixed together in vitro, 20 trimers of the first protein component and 12 pentamers of the second protein component self-assembled to form two-component nanoparticles with ≈55 nm diameter inclusive of the antigen trimer spikes. Unlike previous nanoparticle vaccine designs, it was possible to control the density of DS-Cav1 antigen trimer on the nanoparticle surface based on mixing different amounts of the first protein component with a genetically fused version of the first protein component that presents DS-Cav1 (Figure 8c). Importantly, the nanoparticle presentation of DS-Cav1 trimers not only improved antigen physical stability but also nanoparticle vaccine immunization in mice and nonhuman primates led to nearly 10-fold higher neutralizing antibody titers along with a

greater proportion of neutralizing antibodies in the antibody response than immunization with soluble DS-Cav1 trimers (Figure 8d). Brouwer et al. have also used a similar two-component nanoparticle strategy to present HIV-1 envelope antigen trimers.[158] In this case, the two-component nanoparticle induced particularly high antibody responses after a single round of immunization, as compared to the same antigen trimers in soluble form and displayed on single-component ferritin nanoparticles. There is ongoing exploration of different nanoparticle shape designs[159] and how nanoparticle formulations can improve lymph node targeting in nonhuman primate models.[160]

In terms of COVID-19 vaccine development, Walls et al. recently reported the development of a two-component nanoparticle vaccine candidate that displays the RBD of a SARS-CoV-2 envelope protein antigen (Figure 8e).[161] From a nanomaterial design perspective, a key innovation was introducing a genetically encoded flexible linker to connect the smaller RBD domain with the main nanoparticle structure. It is also noteworthy that the basic self-assembling nanoparticle design involved the same two protein components as in the RSV and HIV-1 nanoparticle vaccines described above, demonstrating the modular nature of nanoparticle vaccines and the ability to rationally swap antigens to support rapid vaccine development (Figure 8f). Importantly, the COVID-19 nanoparticle vaccine induced nearly ten-fold greater neutralizing antibody titers in mice than a soluble antigen trimer even when the nanoparticles were administered at a five-time lower dose (Figure 8g). The nanoparticle vaccine also induced a greater proportion of neutralizing antibodies in the antibody response, as compared to human convalescent sera. This immune response resulted in complete protection against SARS-CoV-2 infection in an in vivo virus challenge mouse model (Figure 8h). The combination of these features has further spurred ongoing manufacturing efforts to create a COVID-19 nanoparticle vaccine in abundant quantities for potential human clinical trials. Looking forward, Ueda et al. have also continued designing new nanoparticle vaccine designs that are tailored for different types of viral protein domains[157] and there is excellent potential to continue exploring protein-based nanoparticle vaccines. As control over the molecular-level biomimetic features of protein-based nanoparticle vaccines continues to improve, there will be growing emphasis on production scalability and how these nanoparticle vaccines can compete with other vaccine candidates in terms of practical factors such as cost, storage, and scalability.

7.2.3. Additional Scaffold Options

While there has been tremendous progress in developing protein-based nanoparticle vaccines to prevent viral infections, liposome- and inorganic nanoparticle-based strategies have also proven advantageous and demonstrate important nanomaterial design features. In one promising example, Moon et al. reported the development of interbilayer-crosslinked multilamellar vesicles (ICMV) in which protein antigens were loaded in the liposomal interior while immunomodulatory lipid-like molecules could be incorporated into the bilayer membranes.[162] In early proof-of-concept work, this platform design led to nearly 1000 times greater antibody responses than conventional liposome-based vaccines and elicited multiple arms of the immune response. Bazzill et al. utilized the ICMV strategy to incorporate HCV envelope antigens and immunization in this case led to 6- to 20-fold higher IgG antibody titers in mouse serum compared to immunization with the soluble antigen alone.[163] Fan et al. have also expanded on the ICMV strategy and developed lipid–polymer hybrid multilamellar vaccine particles (MVP) to incorporate Ebola virus antigen as well.[164] In this case, MVP immunization generated strong and durable antigen-specific antibody and immune cell responses in mice, and single-dose immunization protected 80% of mice from lethal Ebola virus infection. By contrast, an ICMV-based vaccine only protected 40% of mice and the difference in vaccine-mediated immune protection was suggested to arise from the greater antigen-specific T cell response elicited by the MVP vaccine. Despite promising scientific results, more attention needs to be placed on scaling up manufacturing capabilities and quality control practices in order to move toward potential clinical translation of these complex, liposome-based nanoparticle vaccines incorporating viral protein antigens.

In addition to self-assembling protein- and liposome-based nanoparticle vaccines, there have also been extensive efforts to utilize inorganic nanoparticles to present viral protein antigens.[165] One reason is the ability to control the size of inorganic nanoparticles and there is an optimal size range for lymph node targeting.[166] For example, Zhang et al. comprehensively investigated how nanoparticle size affects the immune response elicited by antigen-functionalized, spherical gold nanoparticles. Nanoparticles with 50–100 nm diameters had longer retention in lymph nodes, leading to markedly improved antigen-specific antibody production compared to smaller nanoparticles with 5–15 nm diameters.[167] Additional recent efforts include the development of chemical functionalization strategies to covalently attach HIV-1 envelope antigens on iron oxide nanoparticles[168] and on silica nanoparticles.[169] These ongoing efforts have provided critical insights into how the nanoscale properties of vaccine scaffolds are a critical determinant of immunization performance, while further underscoring how far nanomaterial research progress has come in the past few years to develop cutting-edge biomimetic nanoparticle vaccines that outperform other leading vaccine options in some cases.

7.2.4. Comparison with COVID-19 Vaccine Candidates

The nanoparticle vaccines described above are focused on nanomaterial-based strategies to present viral protein antigens in virus particle-mimicking configurations. Among the different scaffold options, recent progress to develop self-assembling protein nanoparticle vaccines has stood out and demonstrated the merits of precisely engineered, multivalent antigen presentations for eliciting strong and robust immune responses, as compared to free antigens without scaffold. While at least one self-assembling, protein-based nanoparticle vaccine candidate based on ferritin nanoparticle technology is in clinical trials for protection against influenza infection, to our knowledge,

no such protein-based nanoparticle vaccine candidate has yet reached human clinical trials for COVID-19. Nevertheless, there is continued progress in this direction, including an additional recent report describing several types of self-assembling, protein-based nanoparticle vaccine candidates that can induce strong immune responses against SARS-CoV-2.[170] At least one company has also reported plans to start human clinical trials of a self-assembling, protein-based nanoparticle vaccine for COVID-19 by early 2021.[171]

Meanwhile, there has been tremendous progress in developing other classes of COVID-19 vaccines, including ones that utilize nanomaterial delivery platforms and are now in late-stage human clinical trials.[172] Several promising COVID-19 vaccine candidates are based on messenger RNA (mRNA) technology, whereby an mRNA strand can be designed to encode a viral protein antigen and then delivered to cells.[173] Once the mRNA strand crosses the cellular plasma membrane and reaches the cytosol, it is possible for the cellular machinery to begin expressing the encoded viral protein antigen. When this concept is applied in vivo, the expressed antigens can elicit an immune response that confers protection against future virus exposure.[174] The basic vaccination concept is similar to recombinant protein vaccines, while mRNA-based vaccines have several compelling features such as more rapid development, simpler manufacturing, and greater scalability—features that have proven especially critical and advantageous during the COVID-19 pandemic.[175]

To practically use mRNA-based vaccines, it has been imperative to develop nanomaterial delivery platforms as carriers to encapsulate and efficiently deliver mRNA to cells, which would otherwise be degraded and ineffective in physiological environments. Among the different carrier options, lipid nanoparticles have emerged as one of the most promising options and several of the leading COVID-19 vaccines consist of mRNA-based vaccines with lipid nanoparticle carriers.[176] In these vaccine candidates, the mRNA encodes a SARS-CoV-2 antigen such as an envelope protein or domain thereof, which can be programmed to form trimers once expressed.[177] The lipid nanoparticle carrier itself serves to protect and deliver the mRNA and can also incorporate adjuvants to boost the immune response.[178] Compared to self-assembling, protein-based nanoparticle vaccines, a noteworthy point is that current mRNA-based vaccine candidates in human clinical trials for COVID-19 can generate up to antigen trimers, while the development of mRNA-based vaccines to create self-assembling, protein-based nanoparticle vaccines remains to be further explored.

As discussed above, several studies have reported that protein-based nanoparticle vaccines with multivalent antigen presentation can induce stronger immune responses than free antigen trimers. Importantly, proof-of-concept studies have also provided initial evidence that nucleic-acid-based vaccination strategies can be used to produce protein-based nanoparticle vaccines in vivo. Future research on this topic will likely benefit from the progress achieved with mRNA-based vaccines for COVID-19 and next-generation vaccine development efforts should likely be aimed at integrating the functional benefits of self-assembling, protein-based nanoparticle vaccines with the practical advantages of mRNA-based vaccines.

8. Conclusions and Outlook

Nanomaterials have long been explored for treating and preventing viral infections while the recent convergence of biomimetics and nanomaterial design has heralded exciting developments in the areas of antiviral therapies and vaccines. The incorporation of biomimetic features has proven particularly critical to enable biologically relevant functions of nanomaterials, such as virus-specific binding and targeted immune responses, and progress in the field of biomimetic nanomaterials has greatly accelerated over the past few years. Many of the classes of biomimetic nanomaterials described herein are being actively explored to thwart COVID-19 and an overview of the latest progress in developing these different classes of virus-targeting biomimetic nanomaterials is provided in **Table 1**.

For example, pioneering work on nanoparticle vaccines composed of rationally designed, self-assembled protein molecules was first reported in 2013 and protein-based nanoparticle vaccines are already in human clinical trials as a universal flu vaccine candidate. These developments are an important, practical demonstration of the nanoarchitectonics concept[179] and highlight how the precise design and intermolecular self-assembly of protein molecules can result in virus-mimicking nanoparticles that are safe and noninfective yet elicit similar immune responses to native virus particles. Ongoing advances in nanoparticle vaccine manufacturing and delivery will continue to broaden clinical prospects and are further aided by the recent achievement to rapidly create a virus-mimicking, protein-based nanoparticle vaccine that protects against SARS-CoV-2 infection in a mouse model. Importantly, modular protein-based nanoparticle vaccines are being developed whereby the basic nanoparticle structure is conserved and the choice of immune-stimulating antigen(s) can be tuned rationally—design features which are advantageous for rapid response countermeasures to blunt future viral outbreaks, including epidemics and pandemics.

In addition to nanomaterial-based vaccines, there are numerous other directions where biomimetic nanomaterials are poised to improve virus targeting capabilities. One important area that remains underexplored in terms of in vivo applications, is the class of virus-binding nanoparticles that mimic cell membranes or receptors and can bind to virus particles in order to prevent virus–cell interactions. To date, most relevant studies have involved pretreatment of virus particles with the nanomaterial ex vivo before the inoculation step or nanomaterial administration in vivo either shortly before or after virus inoculation. However, it can take several days after virus inoculation for clinically relevant symptoms of viral infections to manifest themselves in animal models—the time point at which an antiviral therapy would typically be administered—and hence further exploration of therapeutic treatment strategies is warranted. It would be enlightening to determine if intravenous administration of virus-binding nanoparticles might help to reduce systemic levels of virus particles during clinical stages of infection and alleviate disease burden. More attention also needs to be placed on understanding the pharmacological properties of virus-binding nanoparticles, and biomimetic nanoparticles in general, and whether they can be devised to target specific organs that may be afflicted with high viral burden. Potential safety issues related to intravenous infusion of biomimetic nanomaterials such as complement

Table 1. Status of biomimetic nanomaterials under development as next-generation antiviral therapy and vaccine options. COVID-19 applications, including SARS-CoV-2 test results, are described where applicable.

Nanomaterial class	Current status of technology development
Nanomaterial-enhanced viral replication inhibitors	– Demonstrated in vitro antiviral activity against selected viruses.
	– Exhibited prophylactic activity to protect against vaginal transmission of viral infection in a mouse model in vivo.
	– Not yet tested for COVID-19 applications.
Virus particle binding inhibitors	– Demonstrated in vitro antiviral activity against a wide range of membrane-enveloped and nonenveloped viruses.
	– Virus pretreatment and postexposure prophylactic treatment can protect against viral infections in mouse models in vivo.
	– Not yet tested for COVID-19 applications.
Cell membrane decoys	– Demonstrated in vitro antiviral activity against a wide range of receptor-binding viruses.
	– Postexposure prophylactic and therapeutic treatment can inhibit viral infections in mouse models in vivo.
	– Can prevent SARS-CoV-2 infection in vitro.
Viral membrane inhibitors	– Demonstrated in vitro antiviral activity against a wide range of membrane-enveloped viruses.
	– Therapeutic and prophylactic administration can inhibit viral infections in mouse models in vivo.
	– Can potentially inhibit membrane-enveloped SARS-CoV-2 virus particles.
Virus-removing blood filters	– Captured viral proteins and virus particles from cell culture media and blood in vitro.
	– Limited human clinical testing has been conducted to treat patients infected with certain viruses, including HCV and Ebola.
	– Human clinical feasibility study approved to start enrolling COVID-19 patients with severe disease.
Virus-mimicking nanoparticle vaccines	– Elicited strong immune responses in vivo and protected against virus challenges in animal models, including SARS-CoV-2.
	– At least one protein-based nanoparticle vaccine for influenza virus is currently in human clinical trials.
	– Human clinical trials for at least one protein-based nanoparticle vaccine for COVID-19 are planned to start in early 2021.

activation-related pseudoallergy (CARPA) should also be evaluated.[180] In addition to enabling a wide range of possible biological functions, biomimetic coatings such as the ones described herein might also increase the biological safety of nanomaterials and consequently improve clinical prospects as well.[181]

Although biomimetic nanomaterials were already receiving extensive attention over the past few years, the ongoing COVID-19 pandemic has brought heightened awareness of the urgent need to develop cutting-edge advanced materials to deal with the challenges of viral threats now and in the future. Looking forward, biomimetic nanomaterials that interact with and mimic virus particles have excellent potential to help solve the biggest challenges related to viral infections and continued innovation in these directions can lead to next-generation antiviral therapies and vaccines.

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Conflict of Interest

J.A.J. and N.-J.C. are listed as coinventors on patents and patent applications that are related to peptide molecules for antiviral therapy. The other authors declare no conflict of interest.

Keywords

antiviral, biomimetic, COVID-19, nanomaterials, therapy, vaccine, virus

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