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Nanotechnology for Virus Treatment

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Highlights:

- Nanodelivery vehicles can improve the pharmacokinetic profile of antiviral drugs.
- Some nanomaterials have virucidal properties that can inhibit viral infections.
- Emerging nanodecoys can bind to viruses and neutralize their infectivity.
- Nanotherapeutics are being developed to address the SARS-CoV-2 virus outbreak.

Abstract:

The continued emergence of novel viruses poses a significant threat to global health. Uncontrolled outbreaks can result in pandemics that have the potential to overburden our healthcare and economic systems. While vaccination is a conventional modality that can be employed to promote herd immunity, antiviral vaccines can only be applied prophylactically and do little to help patients who have already contracted viral infections. During the early stages of a disease outbreak where vaccines are unavailable, therapeutic antiviral drugs can be used as a stopgap solution. However, these treatments do not always work against emerging viral strains and can be accompanied by adverse effects that sometimes outweigh the benefits. Nanotechnology has the potential to overcome many of the challenges facing current antiviral therapies. For example, nanodelivery vehicles can be employed to drastically improve the pharmacokinetic profile of antiviral drugs while reducing their systemic toxicity. Other unique nanomaterials can be leveraged for their virucidal or virus-neutralizing properties. In this review, we discuss recent developments in antiviral nanotherapeutics and provide a perspective on the application of nanotechnology to the SARS-CoV-2 outbreak and future virus pandemics.

Keywords: viral infection, nanomedicine, nanodelivery, virucidal nanomaterial, nanodecoy

Contents

1. Introduction

Technological advances and new therapeutic interventions have allowed us to overcome life-threatening viral diseases such as smallpox and poliomyelitis [1]. Yet, in the modern world, viral infections remain a significant burden on the global healthcare system [2-4]. There exists a constant struggle, where researchers and medical professional often must race to find viable strategies for managing newly mutated or emerging viral strains [5, 6].

Vaccination, where viral antigens are delivered to help confer immune protection, is the most widely used clinical modality to combat viruses. While vaccines against diseases such as hepatitis and measles have been successful, there are many challenges that prevent the widespread adoption of this strategy against other types of viruses [7]. For instance, the influenza virus has a high mutation rate, so new flu vaccines must be developed every year [8, 9]. Because vaccines are preventative in nature, pharmaceutical companies must make predictions about the specific strains of influenza that will circulate the following season, a process that is not always accurate. Furthermore, new vaccine development requires extensive time and resources, greatly impacting the ability of vaccines to be deployed against emerging disease outbreaks, which can have devastating economic and global health consequences [10]. Recent viral outbreaks in the last few decades, including those caused by the human immunodeficiency virus (HIV), influenza virus, Ebola virus, Zika virus, and coronaviruses, have been a major source of public concern and have highlighted the lack of infrastructure and strategies to expeditiously combat emerging pandemics [11]. Overall, the development of broadly applicable therapeutic strategies that can be rapidly deployed to combat viral diseases is of paramount importance [12].

Common therapeutic approaches against viruses employ drugs to inhibit different aspects of the viral life cycle [13-15]. Although antiviral drugs can be highly effective, they require strict patient compliance and can have harsh side effects [16, 17]. Recent advances in nanotechnology have the potential to help overcome these obstacles and offer exciting opportunities for developing novel broad-spectrum nanotherapeutic platforms to combat viral infections [18-20]. Antiviral drugs can be loaded into nanoparticles to enhance their bioavailability while reducing systemic toxicity. Targeted drug delivery can further reduce toxicity, increase efficacy, and sustain the therapeutic window for longer durations [21]. Some nanomaterials have innate toxicity that allows them to directly kill viruses [22]. More recently, nanoparticles have been functionalized and manipulated in a fashion that allows them to selectively bind to and neutralize

pathogens [23]. In this review, we will provide an overview of how nanotechnology can be used to help treat viral diseases (**Figure 1**). We begin with background in virology, elucidating how knowledge of the viral life cycle can be leveraged in the design of new therapeutics. Nanomedicine strategies to counter viral infections will then be discussed in detail, and a concluding perspective on the application of nanotherapeutics against the recent coronavirus outbreak will be provided.

2. Virology

Viruses have evolved to efficiently infect an immense variety of organisms. They are extremely infectious, such that a single virus particle, or virion, can replicate and begin the process of establishing its own ecosystem in a foreign host. The virion contains an outer protein coating, or capsid, to protect the genetic material of the virus and help mediate host cell invasion [24]. Viruses cannot survive on their own, so in order to proliferate they must infect other organisms. While structurally different, almost all viruses undergo a similar process of invasion, replication, and release as part of their life cycle (**Figure 2**).

2.1 Structural Composition

The morphology of viral capsids can be broadly classified into three categories: helical, icosahedral, and complex [25]. Helical viruses display protein subunits stacked around a central axis, forming a helix structure. Within this structure, the genome is bound to the helix through interactions between negatively charged nucleic acids and positively charged amino acids. Icosahedral capsids are hollow, quasi-spherical structures used by viruses such as HIV to contain their genome. Several viruses, particularly bacteriophages, have evolved capsids that are neither helical nor icosahedral, but rather a combination of both. These complex capsids often have additional surface moieties, such as protein tails, to assist with the introduction of viral nucleic acids into the interior of the host cell.

Numerous viruses have evolved with an envelope layer surrounding the capsid, which provides additional protection and functionality [26]. This envelope, which is comprised of a lipid bilayer, is commonly formed from the plasma membrane of host cells. The envelope produced in this process is generally modified with virally encoded proteins to assist with host cell binding and subsequent membrane fusion. To acquire this envelope, the viral capsid usually binds to the plasma membrane and coats itself through an outward budding process.

2.2 Viral Life Cycle

Invasion of the host cell is a critical step for the proliferation of viruses. Non-enveloped viruses can either disrupt the cell surface for direct entry or be endocytosed and then broken down in the endosome [27]. The disruption of the plasma membrane by a non-enveloped virus is generally executed by specific peptides on the surface of the viral capsid that are deployed in response to specific cues from the host cell. Once bound, the virion will integrate with the host cell by causing distortion and disruption at the plasma membrane [28]. Enveloped viruses enter the host cell through fusing directly with the plasma membrane or with the endosome after endocytosis. Similar to non-enveloped viruses, this process is receptor-mediated and activates in response to specific cellular signals. At this stage, the virus has successfully invaded the cell as part of the infection process [29].

Since viruses lack some essential components required for replication, they must take advantage of intrinsic machinery in the host cell to proliferate [30]. Depending on the composition of the virus' genetic material and the structure of its genome, additional components may also be needed beyond what is present in the host cell for proliferation. Ribonucleic acid (RNA)-based viruses are found as either single-stranded (ssRNA) or double-stranded (dsRNA) variants. The more common ssRNA viruses can be further classified as either positive-sense or negative-sense. Positive-sense ssRNA functions as messenger RNA (mRNA) and can be translated directly by the host cell. Negative-sense ssRNA is complementary to mRNA and must first be converted to positive-sense ssRNA by an RNA polymerase that is usually packaged within the virion. For dsRNA viruses, the viral genome is transcribed to generate mRNA by a viral polymerase. Viruses with a deoxyribonucleic acid (DNA)-encoded genome are typically comprised of double-stranded DNA, which can function as a template for transcription into mRNA. Since DNA viruses have genomes that are structurally similar to that of their targets, they can leverage the cellular machinery to express viral genes and replicate by incorporating their genetic material directly into the host's.

After the translation of viral proteins and their subsequent packaging to form new viral particles, the virions must be released from the host cells in order to propagate. Some viruses, predominantly naked viruses without an envelope, are released through cell lysis [31]. While a few viruses can directly induce cell lysis, many rely on natural cellular apoptosis. Enveloped viruses typically are released through outward budding [23]. During replication, viral proteins

with specific recognition markers are inserted into the plasma membrane and aggregate into patches after glycosylation by host enzymes. To create the viral envelope, the nascent viral capsids wrap themselves with this section of plasma membrane as they bud out of the cell. Once released, new virions can repeat the entire life cycle by hijacking uninfected cells.

Many viruses establish latent states where they become inactive and remain dormant inside the host cell. These cells act as viral reservoirs, which results in a long-term persistent infection. Viruses achieve latency in two ways, either through the use of episomes or through integration of the viral DNA into the host cell genome [32]. Episomal latency uses stabilized viral genetic material that can persist in the cytoplasm or nucleus of the host cell but can be susceptible to degradation by certain cellular processes. Direct genomic integration, or proviral latency, assists in the development of a large reservoir as the viral genome is duplicated alongside the host cell genome each time the cell divides [33]. Viral reservoirs remain dormant until a combination of external and internal stimuli induce reactivation.

2.3 Common Human Viruses

HIV, which is responsible for acquired immunodeficiency syndrome (AIDS), targets and progressively depletes $CD4^+$ helper T cells [34]. The HIV genome consists of ssRNA molecules within an enveloped capsid [35]. HIV infections begin with the interaction between the glycoproteins, mainly gp120, that are on the surface of the viral capsid and the C–C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) coreceptor on the target cells. The interaction results in the fusion of the viral envelope with the plasma membrane, which releases the viral capsid core into the cell. Once inside, the virus can begin replication to produce new virions or convert the ssRNA genome into dsDNA and establish latency within the cell. In the latter process, the reverse transcribed dsDNA utilizes the natural microtubule network within the cell to travel towards the nucleus. HIV can lie dormant for years, which is currently a major obstacle that prevents successful eradication of the disease [36]. As the virion travels frequently through the bloodstream, HIV is commonly spread with contaminated blood and the exchange of bodily fluids.

The human influenza A virus, which is responsible for 250,000 to 500,000 deaths per year, transmits mainly through contaminated aerosols and small airborne droplets [17]. This virus is structured with a negative-sense ssRNA genome encapsulated in a helical capsid within a viral envelope [37]. The envelope of the influenza virus is decorated with the viral proteins,

mainly hemagglutinin (HA) and neuraminidase (NA), that are responsible for host cell entry and subsequent release. To invade a potential target, HA helps bind the virus to surface glycoproteins with terminal sialic acid residues [38]. Following this binding, the virus is endocytosed and brought into the cell, where a pH drop in the endosome induces conformational changes to HA. The process exposes a fusion peptide that inserts into the endosomal membrane and facilitates viral entry into the cytosol. After entering the cell, viral ssRNA is transported to the host nucleus, where transcription and replication of the viral genome are carried out with RNA polymerase [37]. Once new virions are formed, NA catalyzes the hydrolysis of sialic acid residues to disrupt the HA–sialic acid binding. This process assists both in the movement of the virions within the cell and the eventual release of the virus outside of the cell.

The hepatitis viruses are a series of five unrelated viruses that cause liver inflammation [39]. Though all the viruses can target humans, hepatitis A, B, and C are the most medically relevant. The hepatitis B virus (HBV), a known oncovirus, is singularly responsible for the vast majority of hepatitis-related deaths due to its liver damaging properties [40]. The virus is an enveloped virus with DNA-based genetic information encapsulated within an icosahedral capsid [41]. Invasion by HBV is mediated by the interaction of preS1 protein with a common hepatocyte receptor called sodium taurocholate co-transporting polypeptide. From there, the capsid is released into the cell to continue the viral life cycle. HBV can also become latent, where antibodies against the hepatitis B core remain detectable while the hepatitis B surface antigen is undetectable [42]. This latency poses significant risk to patients, as it can result in chronic HBV infection, as well as several other complications.

The herpes simplex viruses (HSVs) are challenging to treat due to their ability to enter a latent state and lie dormant within cells [43]. These viruses, comprised of dsDNA encapsulated within an enveloped icosahedral capsid, enter the host cell through the binding of several glycoproteins on the surface of the viral capsid to transmembrane receptors. After transportation to the nucleus and subsequent replication, HSV buds from the inner nuclear membrane, merges with the outer nuclear membrane, and enters the cytoplasm without an envelope. The new virion can then exit the cell by enveloping through the plasma membrane. HSV type 1 (HSV-1) is also able to establish an episomal latent infection in sensory neurons [33]. During this latent phase, the virus expresses latency-associated transcript RNA, which regulates the host cell genome and inhibits natural cell death. The episomes remain in the cytoplasm until the virus is reactivated.

HSVs are easily transmitted through contaminated aerosols or droplets, as well as by direct contact [17].

The Zika virus consists of an enveloped icosahedral capsid containing a positive-sense ssRNA genome [44]. The viral genome encodes three structural proteins, each playing an important role in proliferation. The capsid protein (C protein) is suggested to be integral in the structure of the inner core, while the envelope protein (E protein) and membrane protein (M protein) are embedded in the viral envelope. The Zika virus establishes infection through the attachment of the E protein to host receptors, which mediates internalization of the virus via endocytosis. After entering into the cell, the virus uses the host's cellular machinery to replicate and assemble at the endoplasmic reticulum. The virion, which at this point has an M protein precursor, buds from the endoplasmic reticulum and gets transported to the Golgi apparatus. In the Golgi, the M protein is cleaved to form the mature virion for release via exocytosis.

The Ebola virus is commonly transmitted through direct contact with blood and bodily fluids and has caused deadly outbreaks mainly in sub-Saharan Africa [45]. The virus is comprised of a negative-sense ssRNA genome encapsulated by an enveloped viral capsid. Entry into host cells begins by attachment of surface glycoproteins to host receptors, including dendritic cell-specific ICAM-3-grabbing nonintegrin and asialoglycoprotein receptor. Phosphatidyl serine present on the viral envelope binds to a host cell receptor to trigger macropinocytosis, an endocytosis-like pathway that regulates the uptake of solute molecules, nutrients, and antigens [46]. The virus fuses with the macropinosome membrane in a process mediated through the interactions between surface glycoproteins and host Niemann-Pick C1 (NPC1), a protein that mainly acts as a cholesterol transporter. After replication of the viral genome, the new virions are assembled and transported to the plasma membrane, where the new virions bud from the host cell and are released to infect more cells [45].

With the recent global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), researchers are working to rapidly decode the method by which this virus operates [47]. In general, coronaviruses are enveloped positive-sense ssRNA viruses. Looking back at SARS-CoV, the binding and fusion mechanism is mediated by the spike glycoprotein (S protein) on the virion [48]. In the infection process, the S protein is cleaved into S1 and S2 subunits, both of which assist in the binding of the virus to the target cell. S1 contains the receptor binding domain (RBD), which binds to the peptidase domain of angiotensin-converting enzyme 2

(ACE2), while S2 is responsible for membrane fusion. The RBD region of the S protein is a variable part of the coronavirus genome. In the evolution of SARS-CoV-2, the mutations in the RBD resulted in a high affinity interaction with ACE2 [47]. With the binding of S1 to ACE2, S2 can be cleaved by host proteases, a critical step for viral infection, transmissibility, and pathogenesis [47, 48]. A polybasic cleavage site is present in SARS-CoV-2 at the junction of S1 and S2 for effective protease cleavage, but the consequence of this is currently unknown [48]. The cleavage of S protein in SARS-CoV-2 is mediated by cathepsin L, a lysosomal cysteine protease, which indicates entry into the host cell by receptor-mediated endocytosis [49].

3. Therapeutic Opportunities

A better understanding of viruses and their life cycle has helped to dramatically increase the number of antiviral therapeutics available. Over the last several decades, a number of antiviral therapies have been developed to target viral components or various aspects of the viral life cycle, including virus adsorption, fusion, and genomic replication [50]. Some approved drugs such as nucleoside analogues and acyclic nucleoside phosphonates can inhibit viral DNA polymerases. Other classes of antiviral drugs include reverse transcriptase and proteases inhibitors, which are commonly used against HIV. Structure-based therapeutics, such as zanamivir, have been developed against influenza NA. Along with these approved drugs, many other advances have emerged to inhibit viral infections while minimizing undesirable toxicity.

3.1 Disrupting Structure

There are many opportunities for incapacitating viruses based on their structural components. For enveloped viruses, a common target is the envelope itself due to its role in binding to host cells. A synthetic peptide derived from the amphipathic α-helix found on nonstructural protein 5A (NS5A) of hepatitis C virus (HCV) has been leveraged to cause the rupture and disintegration of viral envelopes [51]. The peptide, more commonly known as the AH or C5A peptide, can cause rupture by transforming the envelope membrane into a planar bilayer [52]. However, the rupturing ability is size-dependent, with complete rupture occurring in small viruses less than 70 nm in size, incomplete rupture in viruses up to 160 nm, and sometimes no rupture for significantly larger envelopes. To induce rupture, the AH peptide causes the formation of pores within vesicular structures after binding. For small vesicles with high membrane tension, the AH peptide binding interactions can cause destabilization. As the peptide

interacts with larger vesicles, the lower bending rigidity allows for the membrane to undergo rearrangement, rather than rupture [52]. Incomplete virus rupture allows room for recovery, so the peptide is only efficacious within a certain size range [53]. The effective range for the AH peptide encompasses a variety of medically relevant diseases caused by pathogens such as HCV and dengue virus, both of which have a diameter of 50 nm.

The AH peptide has also been shown to target HIV and measles, which have sizes ranging from 100 to 150 nm, indicating that the composition of the virus may also play a role in the antiviral capabilities of this peptide [54]. It has been found to target viral envelopes with a higher cholesterol content, so viruses such as West Nile virus and dengue virus are prime targets [53, 55]. Both viruses bud into the endoplasmic reticulum and have a naturally cholesterol-enriched envelope. Though HIV emerges from the plasma membrane, the virus is thought to bud from regions containing raft microdomains, which are also higher in cholesterol [53]. With the AH peptide, selective targeting and subsequent rupture of viruses based on their size and composition can be achieved, while cytotoxicity is minimized due to the large size of mammalian host cells.

3.2 Blocking Entry

Another strategy for treating viral diseases is to prevent virus invasion into host cells. At this stage, the viral cycle can be blocked by inhibiting the binding of the virus to host cell receptors, or by targeting the fusion of enveloped viruses with host cell membrane. Receptor blockage can be mediated through various strategies, the most common being through the use of antibodies [56]. Employing antibodies is a form of passive immunotherapy that neutralizes the pathogen directly by recognizing surface antigens responsible for receptor binding or entry into the host cell. This therapy has shown great promise against a variety of viruses in a highly specific manner. A monoclonal antibody developed against influenza H7N9 was shown to bind to HA on the surface of the virus and inhibit HA-mediated membrane fusion [57]. Similarly, monoclonal antibodies against Zika virus have been reported [58].

While monoclonal antibodies recognize a very specific binding site, bispecific and trispecific antibodies are multivalent drugs engineered to target more than one epitope [59-61]. A bispecific antibody against the Ebola virus and other filoviruses was developed to target the interaction with their entry receptor, NPC1 [62]. In the case of HIV, individual anti-HIV antibodies can neutralize specific isolates effectively [68]. However, resistant strains within the same patient are commonly found and can propagate without competition once others have been

depleted. Thus, targeting more than a single epitope is necessary to enhance efficacy. To address this issue, a trispecific antibody, where a single molecule was used to engage three separate targets, has been synthesized, and it exhibited higher potency and a broader spectrum than monoclonal and bispecific antibodies (**Figure 3**) [63]. The trispecific antibody was designed to target the CD4 binding site, the membrane proximal external region, and the V1V2 glycan site. Compared to its monovalent counterparts, the trispecific antibody significantly improved efficacy and provided complete protection in all rhesus macaques that were challenged with two different simian HIV strains.

Receptor binding interactions are generally unique to individual viruses. Rather than blocking these types of interactions, inhibiting the membrane fusion process can have broader implications. A novel antiviral inhibitor, known as LJ001, leverages the inability of a viral envelope to undergo restructuring and rebuilding in response to lesions or deformation [64]. The small molecule drug was shown to intercalate into viral membrane, causing damage to the lipid membrane environment and thus inhibiting the virus–cell fusion process. Host cells, on the other hand, constantly replenish their membrane components and are less susceptible to the toxic effects of this molecule. Through a different mechanism, another antiviral agent called glycyrrhizin was able to suppress infection from HIV, influenza A, and other viruses by lowering the membrane fluidity of the viral envelope, which inhibits the formation of fusion pores and thus blocks viral entry into the cell [65].

3.3 Inhibiting Replication

The replication of viruses is a critical step in their life cycle, allowing for proliferation and progression of the infection. A frequently utilized therapeutic agent against the replication process is RNA interference (RNAi) [66]. RNAi is easily programmable against different species of viruses and in general is minimally toxic to host cells. This therapy has proven to be a useful platform against various viruses, including respiratory syncytial virus (RSV), HBV, HCV, poliovirus, and HIV. RNAi centers around the use of either short interfering RNA (siRNA) or microRNA (miRNA), both of which have similar mechanisms of action. To prevent viral replication, siRNA molecules silence gene expression by facilitating degradation of the targeted mRNA transcript [66]. This strategy was proven effective against influenza, both as a therapeutic agent against infected cells as well as a prophylactic agent through a convenient inhalation

administration route [67, 68]. While effective, delivering siRNA into cells is a challenging process and unprotected siRNA can be easily degraded in the body [69].

There are multiple classes of small molecule therapeutics targeting the replication of viruses, including nucleoside, pyrophosphate, acyclic guanosine, and acyclic nucleoside phosphonate analogs [17]. These therapeutics mimic naturally occurring molecules and inhibit the activity of cellular or viral enzymes involved in the synthesis of new nucleic acids [70]. Remdesivir is a nucleoside analog that exhibits antiviral activity against a variety of pathogenic RNA viruses. After entering the cell, the drug is converted to an active triphosphate metabolite, which inhibits RNA-dependent RNA polymerase and thus suppresses viral replication. Remdesivir was first developed to treat the Ebola virus, and daily treatments provided complete protection against the disease as indicated by a reduction in clinical disease markers [71]. Through a similar mechanism of action, acyclic nucleoside phosphonate analogs have been utilized to treat a wide range of DNA viruses [72]. One widely used prodrug, cidofovir, undergoes two phosphorylation reactions to be converted into its active form. Once activated, it acts as a chain terminator of DNA synthesis that is catalyzed by viral DNA-dependent DNA polymerase.

Commonly used against RNA viruses, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs) thwart replication by binding to and blocking the function of reverse transcriptase, a viral enzyme that converts viral RNA into DNA [73]. Resistance against these classes of drugs can easily develop, so NNRTIs and NRTIs are commonly used with other therapeutics [17]. Lopinavir and ritonavir are examples of reverse transcriptase inhibitors that are frequently used together against HIV [74]. Integrase inhibitors prevent the integration of the viral genome into the host DNA to inhibit replication, and they can be effective against both RNA and DNA viruses [17].

3.4 Preventing Spread

In the viral life cycle, the assembly and release of new virions is essential to the propagation of the infection. Blocking either of these steps can greatly mitigate the spread of the virus in the body. Protease inhibitors are commonly used to prevent the assembly of new virions [17]. These molecules block the cleavage of protein precursors into functional products and thus prevent the synthesis of new viral components. In HIV and HCV treatment regimens, protease inhibitors are used alongside therapeutics that inhibit transcription or translation of the viral genome [75]. One such pairing against HIV is the protease inhibitor, indinavir, with nucleoside

analogues, zidovudine and lamivudine [76]. In a study, the combination treatment significantly hindered the progression of HIV to AIDS for 90% of patients. Ten protease inhibitors against HIV have been approved for clinical usage, however these compounds are limited by their poor bioavailability and high toxicity, an area that can be significantly improved using delivery systems [74]. Against HCV, protease inhibitors are commonly used in conjunction with HCV NS5A/NS5B polymerase inhibitors [77]. These therapies showed a sustained response for 12 weeks in over 90% of patients. While these combination therapies have shown remarkable results as a treatment, complete disease eradication has been challenging.

Using monoclonal antibodies, an inhibitor against the egress of influenza H7N9 has been developed [78]. The antibodies react to NA and can recognize the specific N9 antigenic sites on the surface of the influenza virus. Through direct contact with the active binding site of NA and by providing steric hinderance, the antibodies can block the budding of nascent virions from infected cells. Ebola virus has been also targeted through the inhibition of egress [79]. ISG15, an interferon-inducible, ubiquitin-like protein expressed during infection, was shown to inhibit the budding of Ebola virus-like particles by disrupting the function of Nedd4 and the ubiquitination of VP40.

3.5 Eradicating Reservoir

Reservoirs pose a veritable challenge in the treatment of viruses, as cells harboring viral genetic material can persist despite long-term treatment. Detecting reservoir cells can be extremely difficult since patients are generally asymptomatic and lack any signs of infection. Particularly in the case of HIV, latent reservoirs are one of the greatest obstacles in finding a cure. A critical step in eradicating reservoirs is through early identification. In a novel approach, an assay to measure inducible, replication-competent reservoirs within $CD4^+$ T cells was developed using reporter cells [80]. The simple assay required only a low volume of blood to quantify the viral RNA load from latent cells after reactivation, enabling it to be used for purposes such as screening latency-reversing agents and researching reservoir eradication strategies in the clinic.

The detection and subsequent elimination of reservoirs can be assisted by the reactivation of latent viruses (**Figure 4**). Reactivation of HIV type 1 (HIV-1) has been accomplished in a multitude of ways. Recently, AZD5582, a mimetic molecule of the second mitochondrial-derived activator of caspases, has been used to reverse latency in resting $CD4^+$ T cells by activating the non-canonical nuclear factor-κB (NF-κB) signaling pathway [81]. This was achieved by

inhibiting the cellular inhibitor of apoptosis proteins 1 (cIAP1) and cIAP2, which are responsible for degrading NF-κB-inducing kinase and thus suppress HIV-1 gene transcription. HIV-1 reservoirs have also been reactivated with the use of N-803, an interleukin-15 superagonist, along with the depletion of $CD8^+$ T cells [82]. In another approach, acitretin, a retinoic acid derivative, was used to enhance pro-apoptotic signaling and increase HIV transcription, thus facilitating the eradication of latent HIV reservoirs [83].

3.6 Reducing Inflammation

A severe complication of many viral infections is the hyperinduction of proinflammatory signaling, resulting in a cytokine storm. Attenuating the host inflammatory response has the potential to improve patient outcomes and increase the survival rates of many viral infections independent of antiviral therapeutics. Current strategies to treat cytokine storms caused by influenza virus center around reducing inflammation through immunomodulatory techniques [84]. One treatment approach uses a class of drugs called thiazolidinediones to target the peroxisome proliferator-activated receptors and downregulate inflammatory responses [85]. Targeting a similar outcome, antioxidants, which protect against reactive oxygen species (ROS), have been used to promote anti-inflammatory effects [84]. However, current evidence indicates that antioxidants, when used alone, may have little effect in treating cytokine storms, suggesting the need for co-administration with other antiviral drugs.

Another approach directly targets cytokines such as tumor necrosis factor (TNF) [86]. As a key cytokine for many viral diseases, TNF exerts a dramatic effect both on the local microenvironment and systemically. Studies have used neutralizing monoclonal antibodies and soluble TNF receptor fusion proteins to capture the cytokine and reduce its downstream inflammatory effects [84]. Results from clinical studies using this type of therapeutic approach have been largely inconsistent. Other approaches to lower inflammation include the use of statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and reduce the production of proinflammatory cytokines [87].

4. Nanotechnology Interventions

In recent years, nanotechnologies have been widely investigated and developed for antiviral treatment. Compared to traditional antiviral therapies, these nanoscale platforms offer many new opportunities in the field. Nanomaterials can not only help to improve current

therapeutics, but they can also be leveraged to create novel modalities that can kill or inhibit viruses through unique mechanisms of action.

4.1 Advantages of Nanotherapeutics

A classic application of nanomaterials for virus treatment is to improve the pharmacokinetic performance of existing antiviral drugs. By protecting the encapsulated therapeutics, nanoparticles can facilitate sustained drug release and extend the therapeutic window [88]. Nanoparticles can be designed to have long circulation and high drug loading properties, which are particularly important for hydrophobic drugs that cannot be administered systemically in their free form. Compared to free drugs, nanoparticle formulations can provide a significant advantage and better protect against viruses in circulation [89]. On the other hand, when applied topically, nanoparticles can reduce systemic exposure and provide protection through sustained local retention or transportation across certain biological barriers [90]. Nanoparticle systems may be further incorporated into a larger scale formulation, such as hydrogels, to provide additional layers of sustained drug release [91].

As nanomaterials are simple to functionalize and have comparable sizes to viruses, there are many biointerfacing opportunities between nanoparticle-based systems and viruses or virus-infected tissues. Nanoparticles can be composed of stimuli-responsive materials, or their surfaces can be conjugated with targeting ligands to guide their drug payloads into sites of high viral burden. Targeted delivery achieved in this fashion can not only increase the effective drug concentration at the disease site, but it can also improve the safety profile by decreasing off-target drug exposure [88]. Furthermore, nanoparticles are in an ideal size range to participate in multivalent interactions with various biological substrates. Multimodality can be conferred by surface modification with different types of ligands, which can help to diversify the functions of nanocarriers [92]. Another noteworthy point is that nanoparticles have a strong tendency for cellular uptake, especially by immune cells, which can promote intracellular accumulation in infected cells and access to intracellular pathogens [89].

Besides drug delivery, nanoparticles can be designed to directly interact with viruses and act as decoys to inhibit viral functions during different stages of an infection. By carefully selecting the nanomaterial or the type of surface modification, nanoparticle-based decoys capable of neutralizing a broad range of different viruses can be fabricated [23, 93, 94]. The comparable size scale of these nanodecoys relative to viruses is essential to their novel mechanism of action.

Compared to host cells that are generally greater than 10 μm in size, the diminutive nanoparticles can move more freely in the body while presenting a higher specific surface area. When applied in sufficient numbers, this gives the nanoparticles a much higher chance of encountering a virus target. Once contact occurs, nanoparticles are also large enough to restrict virus mobility and block fusion, which can be difficult to achieve with small molecule drugs.

4.2 Nanodelivery

Nanoparticles have several distinct advantages when employed as delivery vehicles. Acting as the cargo carrier, they can protect encapsulated drugs from both degradation in the body and undesired systemic toxicity to the host. Nanoparticles can be meticulously engineered to alter the biodistribution of payloads and increase accumulation in desired tissue sites while significantly reducing off-target effects [95]. Recently, a lipid nanoparticle formulation was demonstrated to selectively target either the liver, spleen, or lungs by simply changing the lipid composition [96]. In this fashion, nanodelivery systems can be used to drastically improve bioavailability and efficacy compared to direct administration of free drugs. At the target site, nanoparticles can control the release of the payload to allow for sustained release and a much longer therapeutic window, which may reduce the need for repeated dosing. The field of nanodelivery for antiviral drugs has matured significantly over the last two decades with some nanoformulations actively being explored in the clinic [90, 97, 98].

4.2.1 HIV

While curing HIV is challenging due to the existence of viral reservoirs, patients can live normally by taking a cocktail of antiretroviral drugs that effectively suppress the infection [99]. HIV patients must follow a strict highly active antiretroviral therapy regimen, which generally involves taking medication on a daily basis. Deviations from the schedule can significantly alter the infection status of patients [100]. Thus, many nanoparticle formulations have been introduced in this field to extend the therapeutic window, reducing the required dosing frequency and curbing the issue of patient compliance [101]. On this front, stavudine, a nucleoside analog has been loaded into gelatin nanoparticles and further covered with a layer of soya lecithin-liposome for dual-functionalized HIV-1 treatment [102]. While in circulation, the stavudine could be released slowly to help address plasma infections, but once engulfed by cells in the mononuclear phagocytic system, the gelatin core could be degraded to release the remaining stavudine for treating viral reservoirs. Other examples of nanodelivery platforms for HIV treatment include solid

lipid nanoparticles (SLNs) loaded with the protease inhibitor ritonavir [103] and hydrophobic core graft copolymer loaded with the NNRTI enzophenone-uracil [104]. Polymeric nanoparticles, particularly those composed of poly(lactic-*co*-glycolic acid) (PLGA), are an attractive platform for drug delivery largely due to their biodegradable and biocompatible properties [105-108]. Combination therapeutic approaches utilizing nanodelivery have also been widely reported [109-113]. As an example, a triple combination with elvitegravir, tenofovir alafenamide, and emtricitabine has been tested [114]. In mice intravaginally infected with HIV-1, subcutaneous treatment with the triple therapeutic nanoparticle reduced plasma viral loads to undetectable levels.

A nonconventional nanoparticle platform composed of endogenous ribonucleoprotein, or vaults, has been applied for HIV-1 treatment [115]. The barrel-shaped particles are found naturally in eukaryotic cells, and thus are thought to be highly biocompatible. It was shown that antiretroviral drugs such as zidovudine, tenofovir, and elvitegravir could be conjugated onto the surface of these vault nanoparticles, and the drug–nanoparticle conjugates were able to effectively inhibit HIV-1 infections in peripheral blood mononuclear cells (PBMCs) (**Figure 5**). Nanoformulations have also been functionalized with an additional targeted delivery moiety by genetically engineering natural extracellular vesicles with a single chain variable fragment antibody component that has a high affinity for gp140 expressed on the surface of infected cells [116]. The vesicles were loaded with the compound curcumin or apoptosis-inducing miRNA 143 (miR-143) to destroy the targeted viral reservoirs. The targeting effect led to impressive efficacy *in vitro* with HIV-infected cell lines, PBMCs isolated from HIV-1 infected patients, and in a solid tissue reservoir mouse model. Naturally derived platelet microparticles delivering tenofovir and lamivudine are another biomimetic membrane vesicle platform that has been leveraged for HIV-1 inhibition [117].

The unique properties of nanoparticles are particularly attractive for helping to overcome many barriers that prevent successful clinical translation of RNAi antiviral therapy [118]. Several nanoparticle platforms have been adopted to deliver siRNA into HIV-infected cells [119, 120]. In one example, siRNA that targets Beclin1 was incorporated into biodegradable cationic polyethylenimine (PEI) nanoplexes for intranasal delivery [121]. The nanoplexes inhibited HIV replication in microglial cells and human astrocytes as measured by secretion of viral p24 in the culture supernatant. When intranasally administered in healthy mice, the nanoplexes could cross the blood–brain barrier (BBB) and knockdown the overall Beclin1 expression in the brain by

65%. Beclin1-targeting siRNA has also been loaded into ferric–cobalt electromagnetic nanoparticles for treating HIV-1 infections of the central nervous system [122]. Another strategy for gene editing is with the clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) system [123]. By binding Cas9 guide RNA targeting viral genes onto the surface of magneto-electric nanoparticles, the resulting nanoformulation could reduce HIV latency in HC69.5 microglia cells by roughly 80% [124].

Various tissue-targeted nanoparticle formulations, such as those for vaginal delivery or topical application [125-129], as well as those for brain delivery to treat neuroAIDS [130-134], have been synthesized to better manage and prevent HIV infections at those tissue sites. For topical mucosal application in the vagina, maraviroc, an entry inhibitor that acts on the CCR5 receptor, and tenofovir disoproxil fumarate have been loaded into hydrogel nanoparticles with a lipid shell [135]. These nanolipogels were roughly 160 nm in size and could inhibit HIV-1 infections in TZM-bL cells as effectively as the free drugs. Vaginal application of the nanolipogels in mice resulted in drug retention up to 24 hours post-administration. Local delivery via the mucosal layer could reduce the systemic toxicity of the drugs. In terms of brain targeting, a magneto-plasmonic nanoparticle, which combined an iron oxide core with a thin gold nanoshell layer and was further loaded inside liposomes, has been used for image-guided delivery of tenofovir disoproxil fumarate [136]. The final formulation could be guided *in vivo* under an external magnetic field and enabled multimodal imaging with magnetic resonance imaging, magnetic particle imaging, and micro X-ray computed tomography capabilities.

Besides tissue targeting, nanoparticles have been utilized to selectively destroy HIV reservoirs [137, 138]. Lipid-coated PLGA nanoparticles loaded with autophagy-inducing peptides, Tat-Beclin1 or Tat-vFLIP-α2, have been shown to eradicate macrophage [139] and resting central memory $CD4^+$ T cell [140] viral reservoirs. The nanoparticles assisted in intracellular delivery, and while treatment of HIV-infected cells with the nanoparticles induced a dose-dependent killing, such cytotoxicity was not observed on healthy cells. The killing effect did not cause the reestablishment of HIV reservoirs and was confirmed in clinically isolated latently infected $CD4^+$ T cells. A single treatment with the Tat-Beclin1 or Tat-vFLIP-α2 nanopeptides reduced viral T cell reservoirs by 70.8% and 71.8% respectively. In addition, lipid-coated PLGA nanoparticles chemically conjugated with an anti-CD4 monoclonal antibody through maleimide–thiol click chemistry and loaded with various latency-reversing agents such as JQ1, disulfiram, or ingenol-3-

angelate, were optimized to selectively reactivate $CD4^+$ T cell reservoirs [141]. Once reactivated, the $CD4^+$ T cells became susceptible to elimination by other types of antiviral therapies. Compared to the nontargeted formulation, the anti-CD4-functionalized nanoparticles showed more than a 2-fold selective accumulation in the lymphatic tissues when administered subcutaneously into mice.

4.2.2 Influenza Virus

Metal-based nanoparticles are a popular platform used to deliver antiviral drugs for treating influenza infections [142-144]. NA inhibitors, including oseltamivir [145] and zanamivir [146], as well as amantadine [147], a nicotinic antagonist and noncompetitive NMDA antagonist that can inhibit influenza viral replication, have each been conjugated onto silver nanoparticles (AgNPs) for influenza treatment. The mechanisms of neutralization for all three formulations were similar in which the antiviral drug-conjugated nanoparticles were able to prevent influenza invasion and rescued cell populations by inhibiting caspase 3-mediated apoptosis and inhibiting intracellular ROS accumulation. Besides AgNPs, oseltamivir [148], zanamivir [149], and amantadine [150] have been functionalized onto selenium nanoparticles (SeNPs). In addition, ribavirin [151], a nucleoside analog, and umifenovir [152], an entry inhibitor, have similarly been conjugated onto SeNPs for treating influenza infections. Polymeric nanoparticles are another commonly utilized platform and have been used to deliver both miR-323a and favipiravir specifically to influenza viruses via a sialic acid targeting moiety [153]. Similarly, diphyllin and bafilomycin, two potent vacuolar ATPase inhibitors, were successfully loaded into polyethylene glycol (PEG)-functionalized PLGA nanoparticles and exhibited lower cytotoxicity but 2-fold and 5-fold higher antiviral activity, respectively [154].

Nanoparticulate delivery of siRNA for RNAi therapy has been frequently adopted for treating influenza infections. On this front, chitosan nanoparticles [155], calcium phosphate nanoparticles [156], and titanium oxide nanocomposites [157] have all been leveraged for gene silencing and inhibiting influenza viral replication. Titanium oxide nanocomposites in particular have been used to deliver deoxyribozymes, which are DNA enzymes that can be used to cleave viral RNA and have been shown to inhibit H5N1 viral titers by roughly 2650-fold *in vitro* [158]. Interestingly, silica-coated microcapsules have been used to deliver siRNAs after sol-gel synthesis [159]. The microcapsules could be endocytosed into cells and degraded, facilitating release of the siRNA cargo into the cytosol (**Figure 6**). Once in the cytosol, the siRNAs, which were designed against the viral nucleoprotein (NP) gene, could mediate the downregulation of

the target mRNA and prevent viral protein expression. The siRNA microcapsules were superior to transfection with the standard siRNA/PEI polyplexes and effectively inhibited H1N1 replication. Since siRNAs must enter the cytosol to have efficacy, cell-penetrating peptides have been leveraged to improve intracellular delivery [160].

4.2.3 HSV

The antiviral medication acyclovir, a nucleoside analog, is the most common and effective treatment for HSV infections, and thus nanodelivery platforms against HSV have focused primarily on this drug [161]. Several research groups have optimized the composition of SLNs for higher drug loading and better sustained release profiles [162-165]. In one example, the formulated SLNs were roughly 130 nm in size and had a drug loading of up to 90% for acyclovir [166]. The drugs inside the SLNs had an extended release profile of 7 days in simulated gastric fluid, simulated intestinal fluid, and phosphate buffered saline. The sustained release property allowed a single dose of acyclovir SLNs to achieve the same level of efficacy as fifteen equivalent doses of free acyclovir in a murine HSV-1 skin lesion model. Flexible lipid-based nanoparticles such as membrane vesicles [167] and liposomes [168] have also been used to deliver acyclovir. Both types of formulations have been incorporated into a higher order hydrogel matrix to further improve the drug release profile. Compared to commercial topical acyclovir cream, the flexible membrane vesicle-loaded hydrogels demonstrated superior efficacy in a subcutaneous HSV-1 mouse model. In addition, acyclovir can be encapsulated into nanoemulsions [169], chitosan nanoparticles [170], and carboxymethyl cellulose acetate butyrate nanoparticles [171].

HSVs can sometimes invade the eye and cause herpes keratitis. The eye is an immune-privileged site that contains multiple membrane layers to prevent penetration from foreign substances, thus making it difficult for drugs to enter. Various ocular nanoparticle delivery systems have been formulated with acyclovir to improve drug accumulation in the eye [172-175]. Another type of tissue-targeted delivery system is buccoadhesive films [176]. Acyclovir-loaded PLGA polymeric nanoparticles impregnated into buccal films have been shown to increase drug absorption by 3-fold and bioavailability by 8-fold in rabbit models [177]. Besides acyclovir, other types of antiviral drugs have been loaded into nanoformulations for HSV treatment. Alpha-gene trans-inducing factor siRNA-loaded PLGA-TPGS nanoparticles were found to inhibit HSV-1 replication *in vitro* and protected mice from HSV type 2 (HSV-2) vaginal infections [178]. C-glycosylflavonoid extracted from *Cecropia glaziovii* has been formulated

into PLGA nanoparticles [179], and chloroquine diphosphate has been incorporated into poly(lactic acid) nanoparticles [180] for HSV treatment. More recently, a Chinese herbal plant, *Rheum tanguticum*, was collected from the high mountains, ground down, and formulated into nanoparticles with a high-pressure homogenizer to suppress HSV-1 infections [181].

4.2.4 Other Viruses

The Ebola epidemic in 2013 and the Zika epidemic in 2015 garnered significant attention from the research community [182-186]. Several nanoformulations have been developed to combat the two viruses. For example, an oral drug, ivermectin, was loaded into biocompatible and biodegradable PLGA polymeric nanoparticles to treat Zika infections (**Figure 7**) [187]. PEG was conjugated onto the surface of the nanoparticles to protect against the harsh stomach acid. The exterior was further modified with the Fc portion of antibodies to help mediate nanoparticle transport across the epithelial barrier and into the bloodstream. When the formulation was administered orally to mice, roughly 65% of the nanoparticles were able to enter the bloodstream via Fc-mediated transcytosis. Under controlled experimental conditions, these nanoparticles were able to significantly inhibit expression of the Zika virus nonstructural protein 1. Furthermore, the formulation could be readily lyophilized for capsule packaging and had an extended drug release of 24 hours even at pH 3.

Nanoparticle formulations for Ebola virus treatment have been largely focused on RNAi therapy. To combat the Ebola virus, a cocktail of three siRNAs targeting the Zaire Ebola virus L protein, virion protein 24, and virion protein 35 genes were formulated into stable nucleic acid–lipid particles (SNALPs) by spontaneous vesiculation [188]. The SNALPs were designed to easily fuse with cell membrane and release the encapsulated cargo directly into the cytosol, allowing the siRNAs to exert their effect. In a non-human primate rhesus macaque model, seven doses of SNALPs were able to rescue all of the animals challenged with minimal toxicity. By adjusting the siRNA mismatches, modified SNALPs were able to cure all three macaques challenged with a mutated Makona Ebola variant [189]. Impressively, the therapy was given after the animals showed clinical signs of infection and were viremic. In another example, 48 siRNAs targeting the same Ebola essential proteins were screened against the Sudan Ebola virus strain [190]. The most efficacious siRNA targeting the virion protein 35 gene was incorporated into a lipid nanoparticle for *in vivo* delivery. In the rhesus macaque model, intravenous administration of the lipid nanoparticles conferred complete protection from the viral challenge

in all treated animals. Treatment delay optimizations showed that the efficacy of the formulation was not compromised unless it was administered more than 5 days post-infection, for which only a 50% survival was achieved.

Nanoformulations for RNAi have similarly been utilized to treat hepatitis infections [191]. In one instance, siRNA against the protein kinase C-related kinase 2 (PRK2) was encapsulated into a PEGylated lipid nanoparticle for HCV treatment [192]. Systemic administration of the siRNA nanoparticles in mice could reduce PRK2 expression in hepatocytes by 70%, which directly translated to a 100-fold reduction in serum viral titers. Against HBV, a redox-responsive polymeric nanoparticle loaded with the DrzBC or DrzBS DNAzyme has been used to block gene expression and prevent viral secretion [193]. Since hepatitis viruses mainly afflict hepatocytes, organotropic nanoparticle platforms can be designed to specifically deliver potent antiviral drugs to the liver [95, 96, 194]. In one instance, poly(amino acid)-based block copolymers were electrostatically coupled with the p41 antiviral peptide, a derivative of C5A, and functionalized with galactose for liver-specific delivery to treat HCV infections [195]. The ligand targets the asialoglycoprotein receptor that is primarily expressed on parenchymal liver cells, so when the nanoparticles were systemically administered into mice, there was a more than 2-fold increase in liver accumulation. Liver-targeted polymeric nanoparticles have been used to deliver ribavirin, a common antiviral ribonucleoside analog used to treat HCV and hepatitis E liver infections [196]. Vitamin E, or α-tocopherol, is an interesting liver-targeting ligand that has been utilized on cationic liposomes to deliver siRNA for HCV infections [197].

4.3 Virucidal Nanomaterials

Several nanomaterials such as metal nanoparticles and graphene-based nanosheets have natural virucidal effects due to their unique physicochemical properties [198]. They generally work by a common mechanism of action, which involves direct interaction with the envelope or capsid proteins of viruses, thus disrupting structural integrity and inhibiting infectivity. Additionally, some nanomaterials can interfere with viral gene replication inside of infected cells [23, 199, 200].

4.3.1 Metal Nanoparticles

Nanoparticles composed of silver are the most widely explored antiviral nanomaterial, and it has been shown that bare or coated AgNPs can inhibit a broad range of viruses [201]. It is difficult for viruses to develop resistance against this type of therapy, making it attractive,

especially against highly mutative viruses. AgNPs have been found to be effective both outside of cells to block virion entry as well as inside of infected cells to inhibit replication. For instance, commercially manufactured 30 to 50 nm AgNPs were found to have affinity to gp120 on HIV-1 and thus blocked fusion in a dose-dependent manner by disrupting the gp120–CD4 interaction in a cell-based assay [202]. AgNPs have been combined with broadly neutralizing antibodies for HIV treatment [203, 204]. Smaller 10 nm AgNPs were shown to effectively inhibit hemagglutination caused by H1N1 influenza A virus *in vitro* [205]. In another study, intranasal administration of AgNPs in mice challenged with H3N2 influenza virus showed efficacy comparable to oseltamivir [206]. AgNPs were also found to inhibit the intracellular replication of HBV and HIV-1, presumably due to the interaction between the nanoparticles and genetic material [207, 208]. A practical application of these nanoparticles for preventing the transmission of HIV was demonstrated by using them to coat condoms [209].

There are many other antiviral nanoparticles made of metals and their derivatives [210, 211]. For example, biogenic AgNPs and gold nanoparticles (AuNPs) synthesized with the seaweed *Sargassum wightii* [212] and monodispersed AuNPs synthesized with gallic acid [213] could inhibit HSV infection of Vero cells in a dose-dependent manner. A PEG-stabilized AuNP was found to inhibit the HIV-1 fusion process in a dose-dependent manner through blocking the gp120–CD4 interaction [214]. AuNPs have also been assembled onto a layered double hydroxide surface to inhibit HBV [215]. Interestingly, AuNPs have been co-loaded with efaverinz, a NNRTI, into niosomes and then furthered loaded into a thermosensitive gel to create a complex superstructure for sustained release against HIV-1 infections [216]. Copper iodide nanoparticles were found to generate ROS and oxidize capsid proteins, inhibiting swine H1N1 influenza virus [217] and feline calicivirus [218]. Lately, copper oxide nanoparticles have been used to prevent HSV-1 infections and were shown to reduce viral loads up to 83.3% [219]. Similar efficacy was seen using titanium dioxide nanoparticles against the H3N2 influenza virus [220] and iron oxide nanoparticles against the H1N1 influenza virus [221]. Gallium is a heavy metal that has been shown to inhibit HIV and *Mycobacterium tuberculosis* infections when formulated into nanoparticles [222, 223]. Gallium nanoparticles have been uniquely encapsulated into glucan microspheres derived from the cell walls of Baker's yeast to improve delivery in human macrophages [224].

Zinc-derived nanomaterials have been well studied for their antiviral applications. Mice prophylactically treated with 200 nm zirconia nanoparticles were able to protect 6 out of 7 mice challenged with a lethal dose of the H5N1 influenza virus [225]. In a recent study, bare and PEGylated zinc oxide nanoparticles were found to achieve 52.2% and 94.6% H1N1 virus inhibition rates, respectively, when used at the highest nontoxic nanoparticle concentrations [226]. PEGylated zinc oxide nanoparticles were also used to neutralize HSV-1 up to 92% in another study [227]. The effects of the surface chemistry on zinc oxide nanoparticles for neutralizing HSV-1 was explored in-depth in a different study [228]. The results indicated that surface modifications of toxic nanomaterials can significantly alter the mechanism of neutralization and their targeting profile. Zinc has been used to stabilize polyelectrolyte nanocomplexes for HIV-1 inhibition [229].

Silica nanoparticles (SiNPs) have been shown to block HIV and RSV infections *in vitro* at concentrations as low as 0.1 mg/mL and 0.01 mg/mL, respectively [230]. The neutralization effect was identified under transmission electron microscopy (TEM), where it was shown that the nanoparticles flooded the virions due to van der Waals binding to completely block off all protein interactions. In another study, the surface chemistry of mesoporous SiNPs was studied and optimized for the inhibition of HIV [231]. Using a green fluorescent protein viral transduction model, it was found that SiNPs modified with (3-aminopropyl)triethoxysilane (APTES) had the best efficacy when compared to the other alkoxysilane modifications, reducing infectivity by half (**Figure 8**). Here, the virucidal property of SiNPs was attributed largely to hydrophobic/hydrophilic properties, and computational simulation showed that the APTES group had the largest polar surface area. Furthermore, it has been shown that SiNPs can be functionalized onto planar surfaces [232], and silica can be wrapped around iron oxide magnetic nanoparticles [233] or titanium oxide nanoparticles [234] in a core–shell structure while still retaining virucidal properties.

4.3.2 Nanoemulsions

Nanoemulsions, a class of nanoparticles with simple and low-cost synthesis, were found effective in treating and preventing infections from certain viral strains. Nanoemulsions are manufactured by mixing a lipid phase with an aqueous phase in the presence of surfactants. Their mechanism of action against viruses largely relies on interaction with the viral envelope, with efficacy having been observed on enveloped viruses such as HSV-1, influenza A virus, and

vaccinia virus [235]. Common nanoemulsion formulations were established more than 20 years ago to disrupt bacteria membrane. For example, 8N8 is made by mixing 8 volumes of tributyl phosphate, 64 volumes of soybean oil, and 8 volumes of Triton X-100 [236]. In an *in vivo* study, two nanoemulsion formulations, 8N8 and 20N10, significantly improved the survival rate of mice exposed to influenza A virus when used as a prophylaxis [237]. In a study against the Ebola virus, a nanoemulsion ATB at a 10% concentration could inhibit 100% of viral reproduction in Vero cells after only 20 minutes of incubation [238]. The formulation has broad applicability as a virucide and was shown to be effective against both the Zaire Ebola strain and a strain isolated from the blood of infected monkeys.

4.3.3 Graphene-Based Nanosheets

Graphene and its derivatives have emerged as a novel class of antiviral material, especially for disinfecting viruses in a high-throughput manner. The antiviral activities of graphene and its derivatives come from their unique physicochemical properties. Graphene, as a two-dimensional nanomaterial, has an exceptionally high surface-to-volume ratio, enabling it to interact effectively with viruses. Graphene oxide (GO) is negatively charged and carries a significant number of reactive oxygenated groups on its surface, which can adsorb and destroy viruses through electrostatic forces and redox reactions. These interactions are made possible because some viruses are positively charged, or their capsid proteins have arginine-rich and positively charged domains [239]. Graphene also has excellent thermal and electrical conductivity, and researchers have utilized these physical properties to further improve the efficacy and efficiency of virus killing [240].

A GO nanomaterial was developed to disinfect EV71 and H9N2 viruses in aqueous solutions (**Figure 9**) [241]. For this platform, the initial virus adsorption and capture from aqueous suspension was due to electrostatic forces and hydrogen binding, and the subsequent disinfection was a consequence of the redox reaction between the virus and the abundant oxygenated groups on the GO surface. Researchers have leveraged the excellent thermal conductivity of graphene-based materials to expedite virus degradation. In an example, it was shown that modified GO could be effective against HSV-1 by acting as a photothermal agent to convert near infrared irradiation into localized heat [242]. Additional functionalization of the platform with magnetic nanoparticles enabled manipulation using an external magnet after viral capture in aqueous solutions. This process not only improved the photothermal efficiency by

concentrating the captured viruses at a single point, but it also made the collection and cleaning of destroyed viruses much easier. Inhibition of HSV-1 with GO can be further improved with the addition of a cell surface receptor mimic [243]. Interestingly, different types of virucidal nanomaterials, such as GO and AgNPs, have been combined to enhance antiviral efficacy and inhibit infections better than the use of either material alone [244].

Another GO platform was used to load curcumin, a natural polyphenol that has been reported to inhibit the replication and budding of RSV [245]. Curcumin has low solubility in water, and the use of GO increased the bioavailability of the drug, leading to stronger antiviral activity [246]. A similar strategy was employed by conjugating CHI499 and CDF119, both of which are NNRTIs, on graphene quantum dots for HIV treatment [247]. While the graphene nanodot itself had inhibition efficacy against the virus due to its innate toxicity, combining it with the NNRTIs significantly improved viral inhibition efficiency by targeting the reverse transcriptase aspect of HIV. In this case, the advantage of nanomaterials with high surface area was shown to be highly important. Another study demonstrated that graphite or graphite oxide showed a much weaker antiviral effect compared to its single-layered nanostructure counterparts [248]. Using graphene and its derivatives against viruses is still a field in its infancy, and the mechanisms of action are still a topic of investigation [248].

4.4 Nanodecoys

Some nanomaterials can be modified to specifically neutralize viruses via ligand–receptor interactions [94]. This class of nanotherapeutics, better known as nanodecoys, was initially developed to bind and neutralize bacterial toxins [249]. Given the broad applicability of this approach, nanodecoy formulations for antiviral therapy were recently reported. Nanodecoys can be classified into two main types. In the first, ligands that can selectively bind to viral receptors utilized for cellular invasion are conjugated onto nanoparticles. Virions encountering these ligands are captured and blocked by the nanodecoys, preventing them from binding to the surface of the intended target cells. Once inactivated, virions will eventually be cleared and degraded by the body's immune system. The other type of nanodecoys leverage cell membrane coating nanotechnology [18]. Here, purified cell membrane from a target cell is used to wrap around nanoparticles to form cell-mimicking nanosponges, and it has been shown that this approach can be broadly applied against a multitude of virus strains. The inclusion of a nanoparticulate core gives nanosponges the added advantage of being able to carry antiviral

drugs [250]. Nanosponges also have the potential to be used for vaccine development, as pathogens or pathogenic factors that have been neutralized by these nanoparticles can be safely delivered into the body without compromising immunogenicity [251-257].

4.4.1 Ligand-Functionalized Nanoparticles

A good understanding of the cellular invasion pathways employed by viruses can help researchers engineer new therapeutics. Using the virucidal AgNP as a base, various types of ligands have been functionalized onto the nanoparticle surface to enhance virus inhibition. AgNPs conjugated with mercaptoethane sulfonate were shown to inhibit HSV-1 entry by binding competitively with cellular heparan sulfate [258]. Similar concentrations of soluble mercaptoethane sulfonate did not achieve the same antiviral effect, potentially due to the lack of multivalency and steric hinderance, both of which are present in nanoparticle–virion interactions. Tannic acid is another molecule that has been attached to the surface of AgNPs to block viral entry due to its high affinity for proteins and sugars [259]. Interestingly, the ability of these AgNPs to neutralize viruses such as HSV-2 was size-dependent, where 33 nm particles significantly outperformed 13 nm and 46 nm nanoparticles. In another study with polysulfated AuNPs, it was found that larger nanoparticles inhibited viral entry better than their smaller counterparts, largely due to the formation of nanoparticle–virion clusters enabled by the larger contact area [260]. In addition to contact area, ligand density and steric shielding also play important roles in inhibition efficiency [261, 262].

AuNPs are also commonly used to generate nanodecoys [263]. Sialic acid, which is a common target for the influenza virus, was chemically conjugated onto AuNPs for multivalent inhibition [264]. In another example, AuNPs were functionalized with mercaptoethane sulfonate to inhibit HSV-1 [265]. Similar to the case with AgNPs, the modified AuNPs significantly outperformed free mercaptoethane sulfonate at the same concentration [258]. Similar results were achieved against HIV when AuNPs were functionalized with SDC-1721, which is a fragment of the potent TAK-779 inhibitor against CCR5 [266], and with sulfated ligands [267] or the peptide triazole [268], both of which bind directly to gp120. AuNPs that block the receptors on the target cell surface can similarly prevent viral entry [269]. More recently, sulfonate-capped AuNPs were engineered with improved virucidal effects by extending the length of the conjugated linkers [270]. The extended spacer arms exerted a force of roughly 189 pN on the bound virions and induced irreversible damage by effectively destroying the viral

capsids (**Figure 10**). In contrast to AuNPs functionalized with the shorter mercaptoethane sulfonate, the new formulation using mercapto-undecane sulfonate achieved similar efficacy even at lower concentrations. The nanoformulation was shown to have broad applicability and could neutralize HSV, human papilloma virus, RSV, dengue virus, and lentivirus.

Liposomal nanoparticle formulations functionalized with virus-targeting ligands, such as sialic acids, have been established for virus neutralization [271-273]. In contrast to the solid metal nanoparticles, liposomes are composed of phospholipid layers that better mimic cell membrane fluidity, a property that can enhance binding affinity with virions [274]. Broad-spectrum liposome decoys have been developed by extruding a mixture of phospholipids and heparin octasaccharide-conjugated phospholipids through a 200-nm polycarbonate membrane [93]. Using the liposomal formulation, the infectivity and replication of RSV, HSV-1, and human parainfluenza virus 3 were successfully inhibited. Heparin receptors assembled onto β-cyclodextrin nanoparticles have been shown to neutralize HSV-1, HSV-2, RSV, and human papilloma virus 16 [275]. Lactoferrin nanoparticles modified with sulfonate groups have been shown to target and neutralize HIV-1 through a similar mechanism [276]. Several viruses rely on cell surface heparan sulfate proteoglycans for invasion, and nanodecoys with the heparan receptor have been able to reduce the infectivity of a broad range of viruses [277, 278]. A chimeric peptide derived from the sequence of two entry inhibitors has been conjugated onto the surface of liposomes for antiviral therapy [279]. The peptide bound specifically to HIV-1 by interacting with gp41 and was shown to prevent viral replication in a dose-dependent manner. In addition, phospholipids can be rearranged into a planar nanostructure known as nanodiscs [280]. When conjugated with sialic acid, nanodiscs have been able to selectively bind to H1N1, H3N2, and H5N2 viruses and neutralize their infectivity in a plaque assay.

Molecularly imprinted polymers are a type of synthetic antibody analog [281]. Generally, a mixture of monomers and the target of interest, which serves as a template during polymerization, are allowed to react. After the template is removed, the resulting imprinted polymers can bind to the original target in a highly specific manner. Imprinted polymers templated using viruses have been anchored onto the surface of SiNPs coated with poly-dopamine [282]. Using various target templates, the resulting nanoparticles could neutralize and inhibit infection from f2, T4, and M13 phage viruses, which have distinctively different structures. SiNPs have also been used to neutralize HSV-1 and HSV-2 infections after

conjugation with sodium benzene sulfonate, a glycosaminoglycan-mimicking ligand [283]. More recently, sulfonate-functionalized SiNPs were further loaded with acyclovir for combination treatment against HSV infections [284]. Soluble CD4 peptide fragment-functionalized SiNPs have been shown to selectively capture and neutralize HIV [285].

Other types of unique nanoformulations have been developed to act as virus-inhibiting agents. One example employed icosahedral bacteriophage Qβ capsids, which could be structurally designed with sialic acid ligands to match the binding sites of the influenza spike protein [286]. The capsid nanoparticles were roughly 25 nm in size and could cover the entire influenza virus envelop to prevent infection both *in vitro* and *in vivo*. Sialic acid-conjugated polyamidoamine dendrimers have also been shown to selectively inhibit influenza infections [287-289]. Both the size of the dendrimer and the ligand density spacing have been determined to be important factors when designing an effective neutralizing agent [290]. Several other studies have employed dendrimers and the dendronization process on other nanoparticle cores for treating HIV infections [291-294]. Another strategy against the influenza virus employed multivalent peptide–polymer nanoparticles composed of a polyglycerol core functionalized with HA-targeting peptides [295]. The peptide-conjugated nanoparticles could prevent infection in more than 90% of cells in culture and was able to offer some protection in challenged mice. Other ligands such as boronic acid have been used to modify carbon nanodots, and the resulting formulation was shown to inhibit the cytopathic effects of HSV-1 in A549 and Vero cells by targeting the glycan receptors on the host cells [296]. Boronic acid-functionalized nanomaterials have been used to block HIV-1 [297], HCV [298, 299], pseudorabies virus [300], and porcine reproductive and respiratory syndrome virus (PRRSV) [300].

4.4.2 Cellular Nanosponges

Ligand-functionalized nanoparticles have been quite effective at blocking viral entry. However, development for these platforms requires a good understanding of the receptor–ligand interactions between the target cell and the virus. Furthermore, the ligands are quite selective in nature, so viral mutations can potentially negate binding efficiency. To improve upon the nanodecoy concept and broaden its applicability, researchers have explored the use of cell-like nanoplatforms [18, 94, 301]. By displaying the same surface receptors as the cells targeted by viruses, cell-mimicking nanodecoys are inherently resistant to viral mutations and have broad applicability. Cell membrane-coated nanoparticles were first pioneered in 2011 using red blood cell (RBC) membrane to extend the *in vivo* circulation time of nanoparticles [302]. It was

demonstrated that nanoscale cores camouflaged with RBC membrane could be identified as self and were able to better evade immune clearance [303]. Almost a decade later, cell membrane coating nanotechnology has expanded to the use of platelets [304, 305], cancer cells [306-308], white blood cells [309, 310], and bacteria [311], among others, to bestow new functionalities onto a wide range of nanosystems for payload delivery, immune modulation, and diagnostic applications [18, 274, 312]. This approach for nanoparticle functionalization enables nanoengineers to utilize the multifaceted biological interactions that are found in nature without the need for complex synthetic techniques. Different membrane modification strategies can also be employed to further enhance nanoparticle functionality [313-315].

An important application of cell membrane-derived nanoparticles is for biodetoxification [316]. With their ability to display the same surface receptors as host cells, cell membrane-camouflaged nanoparticles can act as nanodecoys to divert harmful toxins away from their intended targets. In the first demonstration of this concept, nanoparticles coated with RBC membrane were employed as cellular nanosponges to bind and neutralize α-toxin secreted by *Staphylococcus aureus* [249]. The nanosponges were found to efficiently complex with the toxin *in vitro* and completely abrogated its hemolytic activity. Due to their unique mechanism of action that leverages the natural affinity of toxins with cell membrane, RBC nanosponges have been employed to deactivate a broad range of toxins [317], including in animal models of live infection [318, 319]. They can also be used to concurrently bind multiple virulence factors from complex bacterial secretions [253, 320]. The profile of toxin binding to nanosponges is dependent on the source of the membrane coating [321]. Other applications of cellular nanosponges include the detoxification of organophosphates [322, 323], chemotherapeutics [324], and autoantibodies [325, 326].

Expanding upon the cellular nanosponge concept, the biointerfacing between cell membrane-coated nanoparticles and viruses was first utilized to enrich viral pathogens for diagnostics [327]. The rich sialic acid surface of RBCs was leveraged to capture influenza virions. After co-incubation, influenza-bound RBC nanoparticles significantly increased in hydrodynamic size. TEM images clearly showed influenza virions closely associated with the nanoparticles. By employing a magnetic nanoparticle core, the captured virions could be enriched to improve the sensitivity of diagnostic assays. It has been demonstrated that T cell membrane-coated nanoparticles (TNPs) can bind to HIV and neutralize its infectivity (**Figure 11**) [328, 329]. The

formulation took advantage of the CD4 receptor displayed on the T cell surface that HIV uses for docking. Compared to RBC membrane-coated nanoparticles, which did not show efficacy, TNPs could protect more than 80% of cells from two different HIV strains under controlled experimental conditions. Along the same lines, natural nanodecoys in the form of exosomes, which are small cellular vesicles derived from the inward budding of the endosomal compartment, have also been reported [330]. Owing to their origins, exosomes contain various proteins commonly found on the plasma membrane. Those isolated from human tracheobronchial epithelial cells were found to contain sialic acid residues on their surface and could bind to influenza A viruses in a highly specific manner to reduce viral infectivity [331]. Exosomes isolated from breast milk [332], semen [333, 334], and vaginal fluid [335] have also demonstrated the ability to neutralize and prevent HIV infections.

While nanosponges are generally derived from host cells, *Aedes albopictus* mosquito cell membrane-coated nanoparticles have been used to combat Zika viruses (**Figure 12**) [336]. Here, C6/36 cells were subjected to mechanical lysis under hypotonic conditions, sonicated, and then extruded to form membrane vesicles, which were then coated onto gelatin nanoparticles to form the nanodecoys. Co-incubation of the nanodecoys with Zika virus showed clear binding under TEM, and roughly 5×10^5 plaque-forming units of Zika virus could be adsorbed per microgram of the nanoparticles. The decoys were able to protect Vero cells against the virus and significantly reduced viral titers were found in the cell culture media by 10-fold. In the A129 mouse model, administration of the nanodecoys on day 0 and day 2 post-infection protected all mice from a lethal challenge of Zika virus. Additional dosing improved efficacy, inhibited infectivity in the blood and brain, and abrogated signs of the disease. Impressively, the nanodecoys were able to mitigate fetal microcephaly caused by the virus. Compared to untreated controls, fetuses from Zika-infected pregnant mice treated with the nanodecoys had greater body length and weight, as well as larger and heavier brains.

More recently, cellular nanosponges derived from NL20 lung epithelial cells and THP-1 macrophage cells have been shown to inhibit SARS-CoV-2 in a dose-dependent manner (**Figure 13**) [337]. The efficacy of the nanosponges originated from the presence of viral receptors such as ACE2 on the plasma membrane coating. The nanosponges could bind to SARS-CoV-2 in a highly specific manner via the virus' entry receptors and effectively reduced infectivity by up to 93%. In a preclinical safety evaluation, no noticeable hematological toxicity or immune cell infiltration into the

lungs was observed when the nanosponges were intratracheally administered to mice. It is believed that this approach to virus neutralization is agnostic to mutations and could have broad applicability against any virus strain that infects or interacts with the cells from which the nanosponge formulation is derived. While cellular nanosponges can display antiviral activity without the need to identify the exact invasion pathway, an in-depth understanding of viral entry may help to further improve the therapeutic effect. As an example, the human sodium taurocholate co-transporting polypeptide protein was genetically engineered onto HepG2 liver cells, and nanodecoys derived from the altered membrane were able to prevent HBV infections [338].

Besides binding to viruses, cellular nanosponges have been utilized for anti-inflammation therapy. Complications related to the host immune response can occur during a viral infection and cause issues such as a cytokine storm [84, 339, 340]. Significant and uncontrolled inflammation is oftentimes a major driver of patient mortality in the clinic. A plethora of interactions exist between immune signaling molecules and immune cells, and cell membrane-derived nanosponges of hematological origins have been shown to significantly reduce inflammatory effects by soaking up cytokines. For example, macrophage nanosponges were shown to display CD14 and Toll-like receptor 4 for lipopolysaccharide (LPS) binding, CD126 and CD130 for interleukin-6 (IL-6) binding, CD120a and CD120b for TNF-α binding, and CD119 for interferon γ (IFN-γ) binding [309]. When co-incubated with the various target molecules *in vitro*, macrophage nanosponges could neutralize each protein in a dose-dependent manner (**Figure 14**). When macrophage nanosponges were administered into mice immediately following LPS challenge, serum levels of TNF-α and IL-6 remained at basal levels. Treatment with the macrophage nanosponges was able to protect 60% of mice challenged with a lethal dose of LPS. In another instance, neutrophil nanosponges were used to treat rheumatoid arthritis, which is caused by chronic inflammation in the joints [310]. Similarly, the neutrophil nanosponges could neutralize a multitude of cytokines such as IL-1β and TNF-α due to the presence of their respective surface receptors. Biomimetic nanosponges can be manipulated using different techniques to bestow additional functionalities [313, 314, 341-343]. RBC nanosponges modified with melittin and oleyloxyethyl phosphorylcholine were able to selectively attract and neutralize phospholipase A2 (PLA2) [344], an enzyme implicated in autoimmune disorders such as acute pancreatitis [345].

5. Conclusions and Perspectives

The current outbreak caused by the novel SARS-CoV-2 has infected more than 21 million people and caused more than 750,000 deaths worldwide as of August 2020. This global pandemic serves as a grim reminder that, despite all of the technological breakthroughs of the past century, modern medicine remains ill-equipped to handle emerging viral outbreaks [346]. As the world races to develop a vaccine to control the spread of SARS-CoV-2, nanotherapeutics can act as one of the stopgap measures to halt the virus's advances [347-351]. A straightforward approach is to utilize nanoparticles to deliver antiviral drugs that may be effective against SARS-CoV-2 [352-354]. Drugs such as remdesivir [355-357], dexamethasone [358], lopinavir-ritonavir [359], and EIDD-2801 [360], among many others [361-365], can be incorporated into nanoparticles to improve their pharmacokinetic profiles and increase overall potency. Successful implementation of nanodelivery platforms to manage other types of coronaviruses has been demonstrated in the past. The vacuolar ATPase inhibitor, diphyllin, has been formulated into PEG-PLGA nanoparticles to achieve a 60-fold enhanced antiviral activity against the feline coronavirus (FCoV) in fcwf-4 cells while maintaining a 13-fold lower cytotoxicity as compared to the free drug [366].

Virucidal nanomaterials and nanodecoys can be employed to treat coronavirus-related infections [367-369]. Silver-based nanomaterials such as AgNPs, silver nanowires, and silver colloids have been shown to inhibit infections in swine testicle cells caused by the porcine-transmissible gastroenteritis coronavirus [370]. Other types of nanomaterials such as GO–AgNP conjugates [371] and polyanionic dendrimers [372] have been shown to inhibit FCoV and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively. Recently, the antiviral activity of graphene has been utilized in a practical approach, where it was coated directly onto surgical masks for self-sterilization purposes [373]. Boronic acid-functionalized carbon quantum dots (CQDs) have been demonstrated to inhibit human coronavirus 229E (HCoV-229E) infection of Huh-7 human liver cells at both the viral entry and the viral replication steps [374]. The efficacy was largely due to the boronic acid targeting the S protein on the coronavirus via a lectin–carbohydrate binding interaction. Peptide inhibitors targeting the S protein on MERS-CoV have been engineered and functionalized onto gold nanorods to block the interaction between the virus and the host cell [375]. In another example, CQDs loaded with therapeutics such as curcumin successfully prevented the proliferation of porcine epidemic diarrhea virus (PEDV) [376]. PEDV

infections in Vero cells have also been inhibited with silver sulfide nanoclusters by three orders of magnitude when compared to untreated controls [377]. Tellurium nanoparticles coated with bovine serum albumin were shown to form triangular nanostar-like structures capable of inhibiting PEDVs [378]. The nanostars were further functionalized with a heparan sulfate receptor and shown to also inhibit PRRSV in MARC-145 cells by blocking virus internalization and reducing ROS production. In this system, both the nanoparticle morphology and the type of functional ligand played major roles in the antiviral activity.

While metal-based nanomaterials have excellent virucidal properties, there are some concerns about their safety profile [379]. Nanoparticles fabricated using more biocompatible materials have similarly been shown to inhibit coronavirus-related infections. For example, a biopolymer platform was synthesized by crosslinking chitosan with genipin, a nontoxic molecule derived from plants, and subsequently reacting the product with glycidyltrimethyl-ammonium chloride [380-382]. The final nanospheres and microspheres could adsorb human coronavirus NL63 (HCoV-NL63) and mouse hepatitis virus to reduce their cytopathic effects in LLC-MK2 and LR7 cells, respectively. As mentioned previously, biomimetic cell membrane-based nanoparticles have been shown to reduce the infectivity of SARS-CoV-2 by serving as nanodecoys, and this approach may prove to be agnostic to future mutated strains of the virus [337]. While examples of nanotherapeutics designed specifically against SARS-CoV-2 are limited, this is a currently an area of active investigation. The promise that nanoscale platforms have displayed for combating other types of coronaviruses clearly indicates the potential of nanotechnology against the present outbreak.

In this review, we have summarized the major applications of nanotechnology for virus treatment. Advances in nanomedicine have the potential to alter the clinical landscape for antiviral therapies. Based on their unique properties, nanomaterials have several distinct advantages that can be leveraged to improve the activity of antiviral drugs. Payloads encapsulated within nanomaterials have less exposure to the external environment, which can help protect them from systemic degradation while reducing cytotoxicity. Nanoparticles can improve the pharmacokinetic profiles of current antiviral drugs by extending circulation time, targeting specific tissue sites, and increasing bioavailability. In particular, the utility of hydrophobic drugs that are normally difficult to formulate and deliver *in vivo* can be greatly enhanced with nanotechnology. Therapeutics that are incorporated into nanoparticles can also

benefit from a lengthened therapeutic window through sustained release, and these platforms can be further assimilated into hydrogel superstructures for additional capabilities [383].

Beyond the development of platforms for more traditional drug delivery applications, continued research in nanomedicine has yielded novel, broad-spectrum therapeutics for virus treatment. Various virucidal nanomaterials and nanodecoys have been designed to effectively neutralize and inhibit viral infections. Due to their ideal size characteristics and large surface area, nanoparticles can interact with viruses in a multivalent manner, allowing for much stronger binding interactions. Many nanoscale platforms can also be readily functionalized with targeting ligands to enhance their affinity towards specific viruses. Nanotherapeutics can be designed to combine multiple modalities to address different aspects of the viral life cycle. For instance, virucidal nanomaterials could potentially be loaded with an antiviral drug and further functionalized with a virus-inhibiting ligand. Recently, cellular nanosponges have emerged as an innovative approach for broad antiviral and anti-inflammation therapy. Fabricated by endowing nanoparticles with a layer of natural cell membrane coating, these nanodecoys can interface with viruses without the need to identify or understand the precise biological mechanisms underlying their infectivity. Overall, these emerging nanotherapies are inherently resistant to viral mutations and have the potential to be applied broadly against a variety of different viruses.

Looking toward clinical translation, there are several key challenges that need to be considered for antiviral nanotherapeutics. While there are numerous nanodrugs approved for use in human patients, the safety profile for each new nanoscale platform technology needs to be critically evaluated. Particularly for virucidal nanomaterials and nanodecoys, antiviral properties must be proven in the context of low toxicity. In addition, while current production techniques are sufficient for supplying the needs of preclinical studies, large-scale and cost-effective manufacturing is a major hurdle that must be overcome. The ability to mass produce novel nanoformulations following strict regulatory guidelines will be pivotal to their clinical success. Ultimately, continued research on nanotechnology for virus treatment will lead to the development new and innovative platforms that could markedly change how viral infections are managed in the clinic.

Declaration of Competing Interest

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

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Figures and Figure Captions

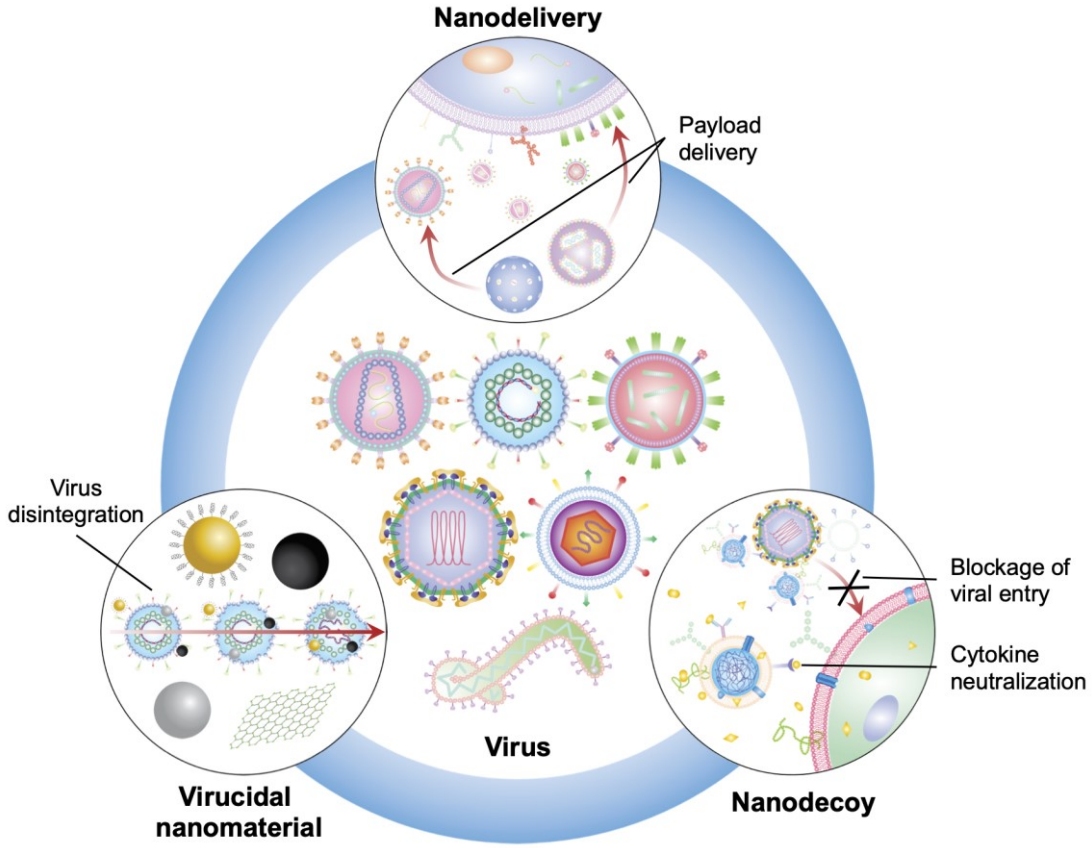


Figure 1. Nanotechnology approaches to treating viral diseases. Nanotechnology can improve antiviral therapy through various means: (1) nanoparticles can protect and deliver therapeutic cargoes specifically to viruses or infected cells and increase bioavailability; (2) some nanomaterials have virucidal properties that enable them to disrupt and alter viral structure; (3) nanodecoys can interact directly with viruses to neutralize their infectivity, or they can be used to soak up inflammatory cytokines and mitigate hyperinflammation.

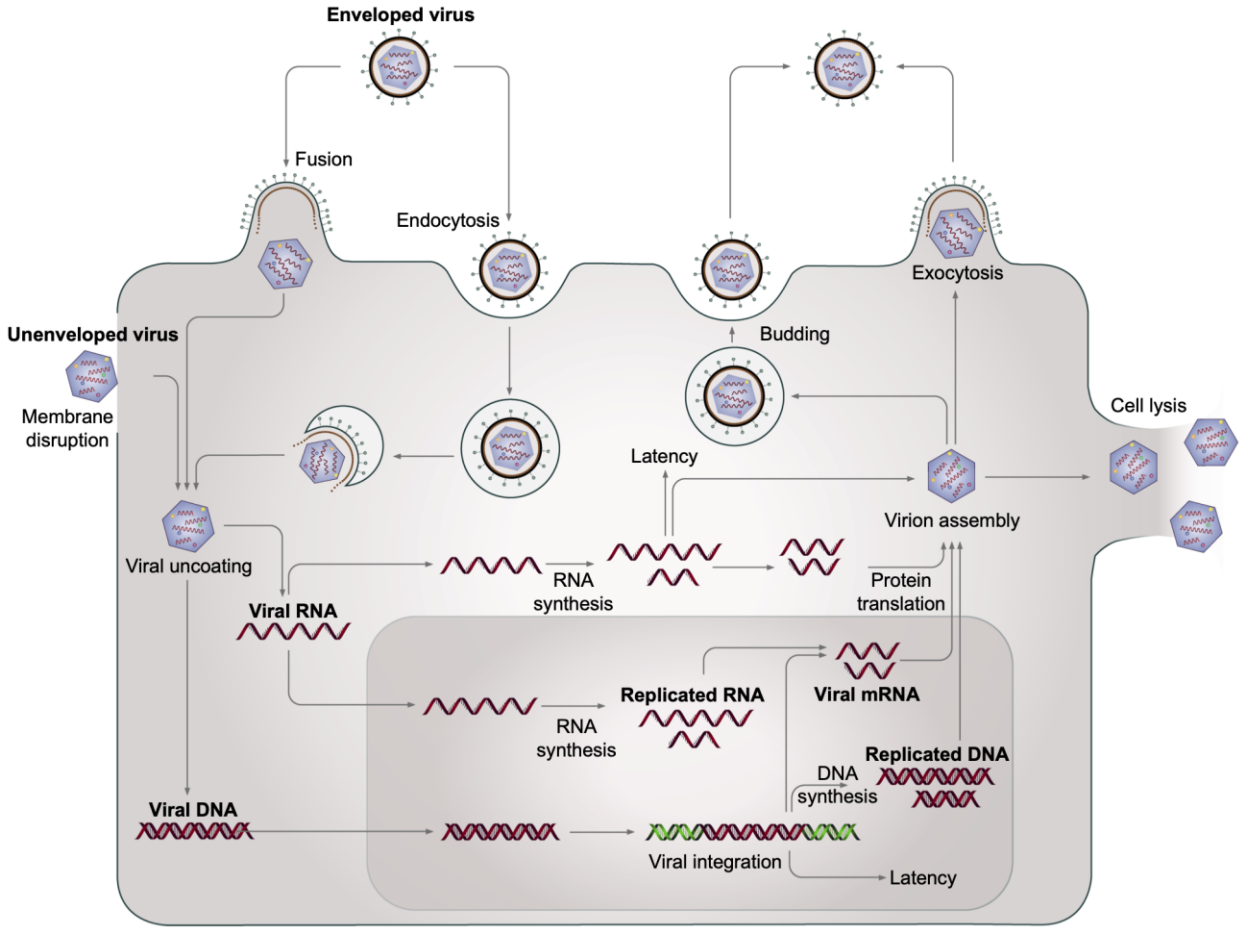


Figure 2. The life cycle of unenveloped and enveloped viruses. The viral life cycle can be broadly divided into entry, replication, and egress. Upon entry into a host cell, viruses release their contents for viral protein and genome replication. The copied genome is packaged into a new virion and released from the cell. Some viruses can establish latency in which the viral genome remains in the cell and reactivates in response to external factors.

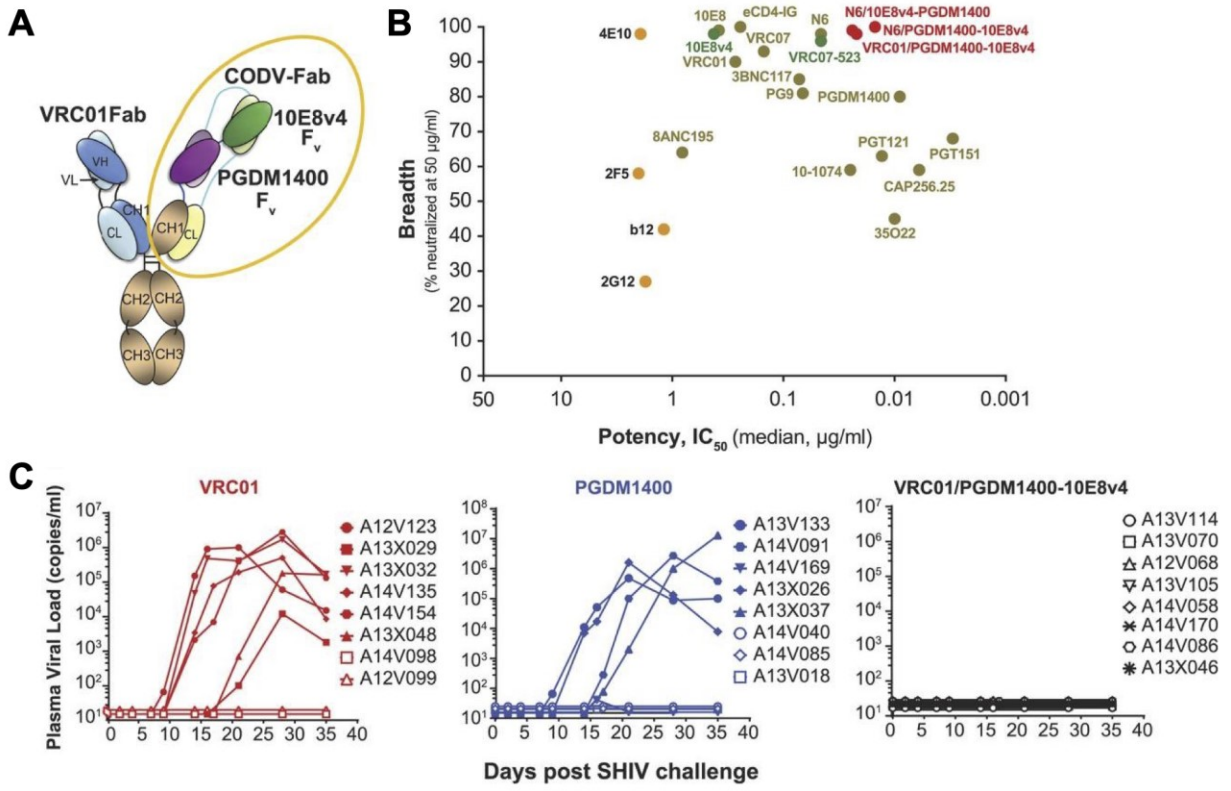


Figure 3. Trispecific antibody (Ab) against human immunodeficiency virus (HIV). A) Structure of a broadly neutralizing trispecific Ab with regions that target the CD4 binding site (VRC01Fab), the membrane proximal external region (10E8v4), and the V1V2 glycan site (PGDM1400). B) Breadth and potency of trispecific Abs (red) as compared to first generation Abs (orange), second generation or engineered Abs (brown), and structurally enhanced Abs (green). C) Plasma viral load in rhesus macaques challenged with a mixture of two simian HIV (SHIV) strains five days after treatment with trispecific Abs (VRC01/PGDM1400-10E8v4) or broadly neutralizing Abs (VRC01 or PGDM1400). Reproduced with permission [63]. Copyright 2017, American Association for the Advancement of Science.

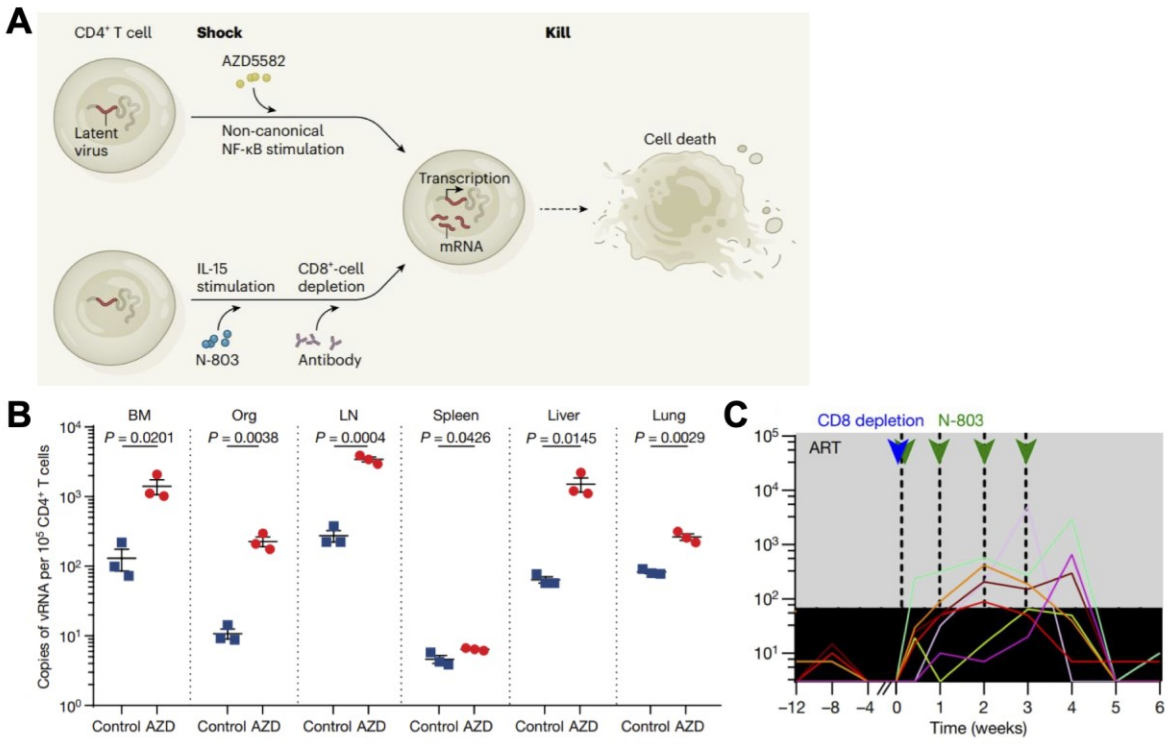


Figure 4. Shock and kill strategy to target human immunodeficiency virus (HIV) reservoirs. A) Latent HIV reservoirs can be 'shocked' into reactivation by either AZD5582 (top) or N-803 (bottom), after which the activated cells can be targeted and killed by standard antiviral therapies. B) Viral RNA in $CD4^+$ T cells from various organs after intraperitoneal administration of AZD5582 into BLT (bone marrow, liver, thymus) humanized mice. C) Plasma viral load in rhesus macaques with previously undetectable levels of simian immunodeficiency virus after $CD8^+$ T cell depletion and subcutaneous administration of N-803. Reproduced with permission [81, 82, 384]. Copyright 2020, Springer Nature.

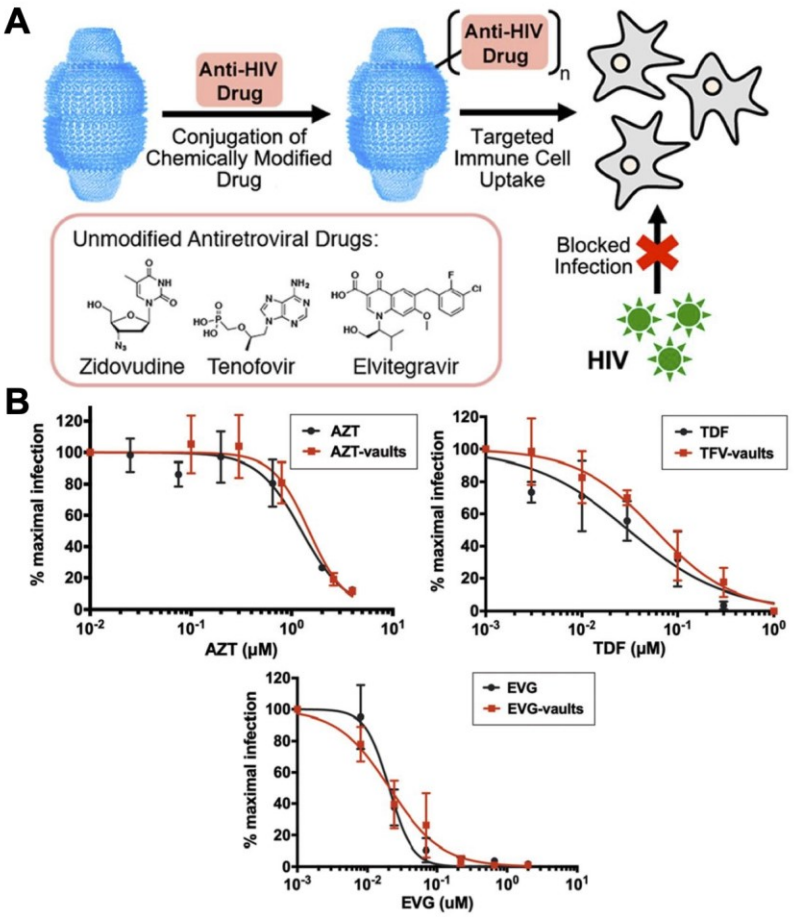


Figure 5. Antiretroviral drug-conjugated vault nanoparticles for inhibiting human immunodeficiency virus (HIV). A) Zidovudine (AZT), tenofovir (TDF), and elvitegravir (EVG) can be chemically conjugated onto natural ribonucleoprotein vault nanoparticles to protect immune cells from HIV infections. B) Infection rate of peripheral blood mononuclear cells (PBMCs) treated with drug-conjugated vault nanoparticles and free drug at different concentrations. Reproduced with permission [115]. Copyright 2019, American Chemistry Society.

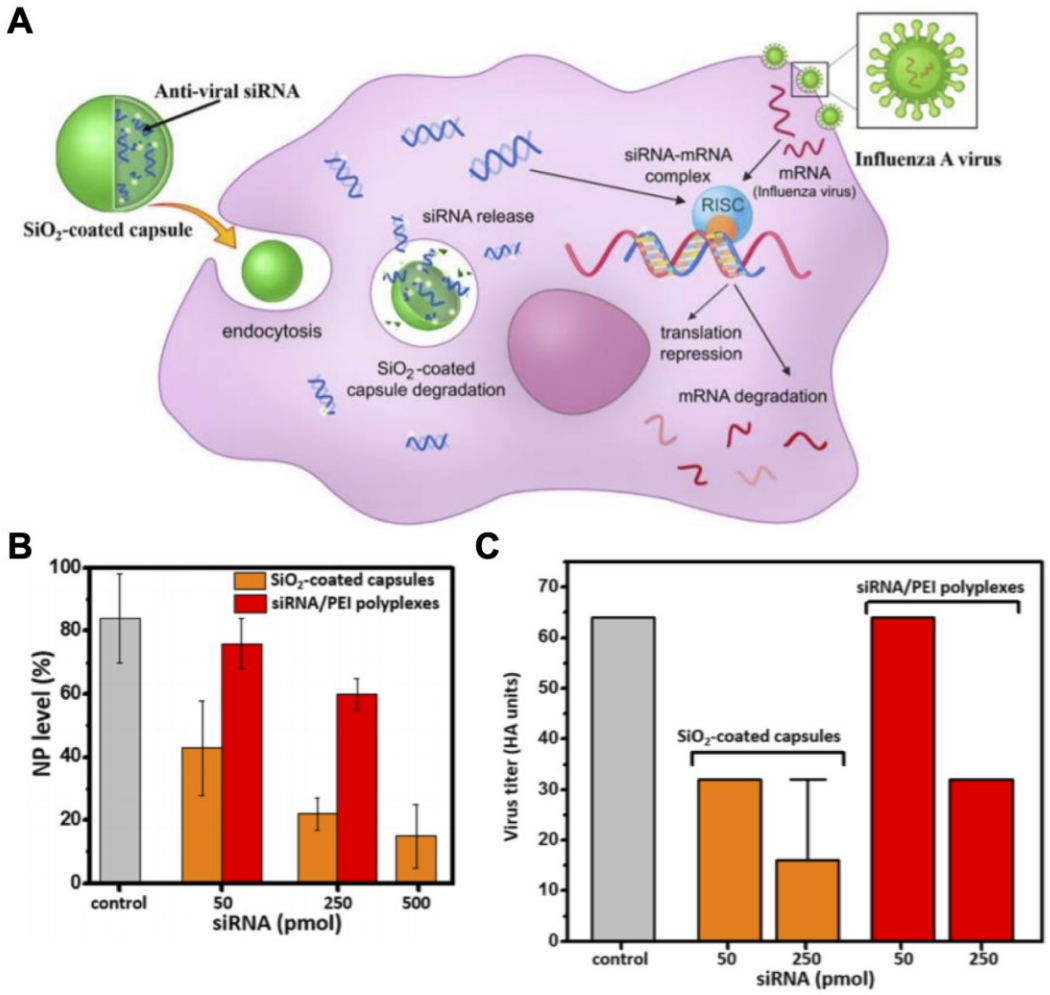


Figure 6. Silica (SiO_2)-coated microcapsules loaded with small interfering RNA (siRNA) for influenza treatment. A) SiO_2-coated microcapsules are endocytosed into the cell, where the siRNA is released into the cytosol and binds to the RNA-induced silencing complex (RISC) to facilitate gene knockdown. B) Nucleoprotein (NP) expression in A549 cells treated with siRNA delivered via SiO_2-microcapsules or polyethylenimine (PEI)-based polyplexes. C) H1N1 viral titers in the supernatant of A549 cells treated with siRNA delivered via SiO_2-microcapsules or PEI-based polyplexes. Reproduced with permission [159]. Copyright 2017, Springer Nature.

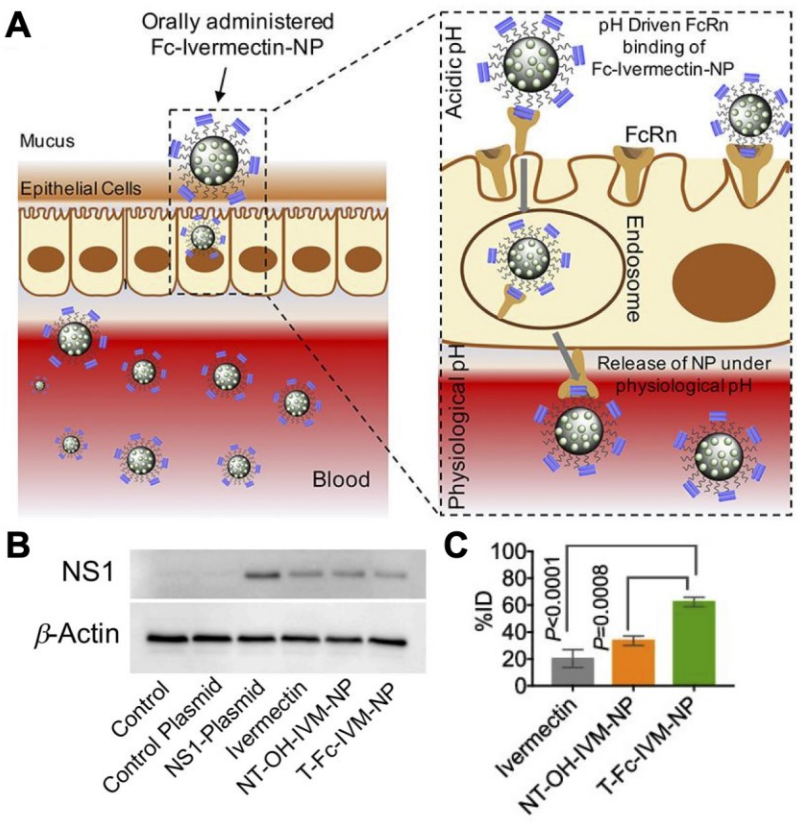


Figure 7. Orally delivered nanoparticles for the systemic treatment of Zika infections. A) Polymeric nanoparticles are loaded with ivermectin (IVM), an oral antiviral drug, and functionalized with polyethylene glycerol (PEG) and the Fc protein (T-Fc-IVM-NP). At acidic pH under 6.5, the Fc protein binds to the neonatal Fc receptor (FcRn) to facilitate transcytosis across the epithelium and into the bloodstream. Under physiological pH, the Fc binding interaction weakens, and the nanoparticles are released into circulation. B) Nonstructural protein 1 (NS1) expression in HEK293T cells treated with different nanoparticle formulations. C) Amount of nanoparticles in the bloodstream of mice after oral administration of T-Fc-IVM-NP, its nontargeted counterpart (NT-OH-IVM-NP), or free ivermectin. Reproduced with permission [187]. Copyright 2019, American Chemistry Society.

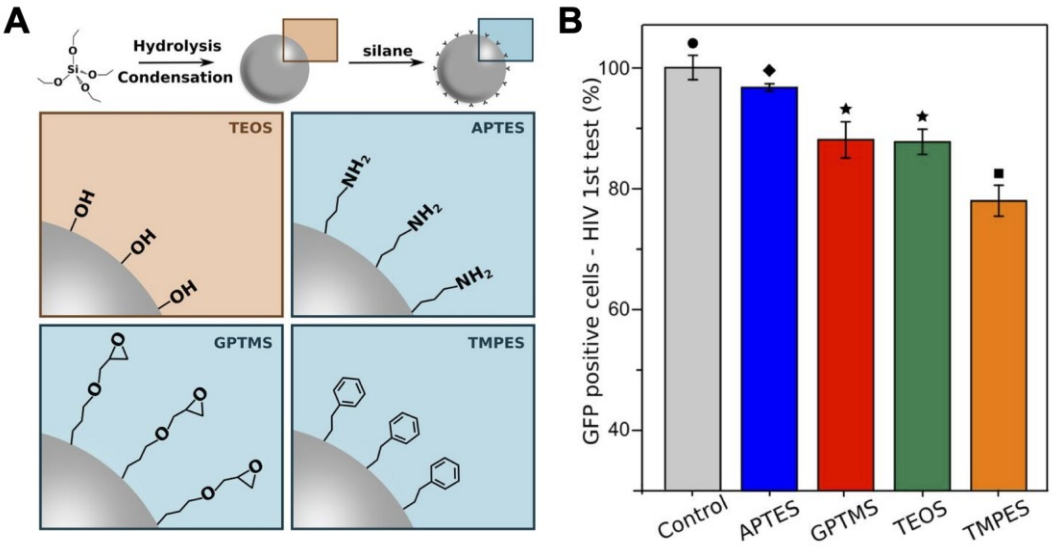


Figure 8. Surface-modified silica nanoparticles (SiNPs) for the inhibition of HIV. A) Through a co-condensation chemical reaction, the tetraethylorthosilicate (TEOS) functional group can be converted into (3-aminopropyl)triethoxysilane (APTES), (3-glycidyloxypropyl)trimethoxysilane (GPTMS), or trimethoxy(2-phenylethyl)silane (TMPES) surface groups. SiNPs with different surface chemistries are able to inhibit virus invasion to different degrees. B) Transduction efficiency of lentivirus harboring an HIV gp120 envelope when preincubated with various SiNPs. Reproduced with permission [231]. Copyright 2019, American Chemistry Society.

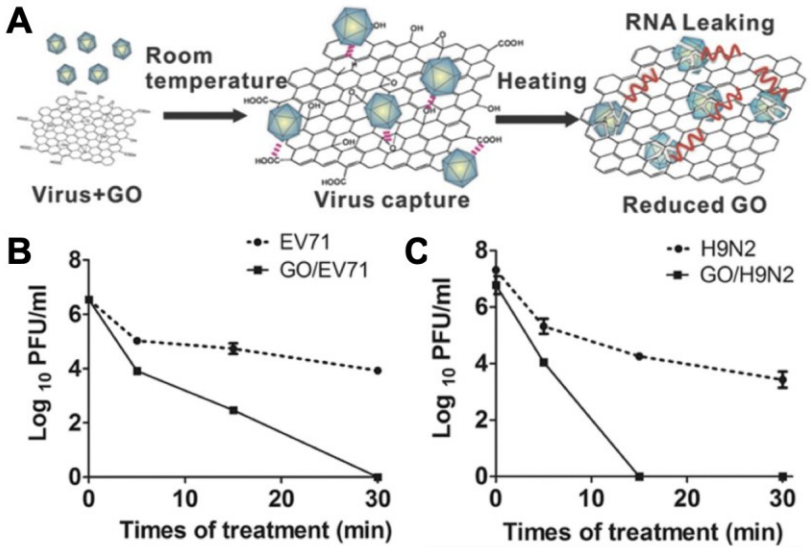


Figure 9. Graphene oxide (GO) nanosheets for destroying the structure of enterovirus 71 (EV71) and H9N2 influenza virus. A) GO nanosheets naturally adsorb viruses and can compromise viral integrity upon heating at a high temperature. B, C) Viral titers for EV71 (B) and H9N2 (C) upon heat treatment at 56 °C in the presence or absence of GO nanosheets. Reproduced with permission [241]. Copyright 2014, Wiley-VCH.

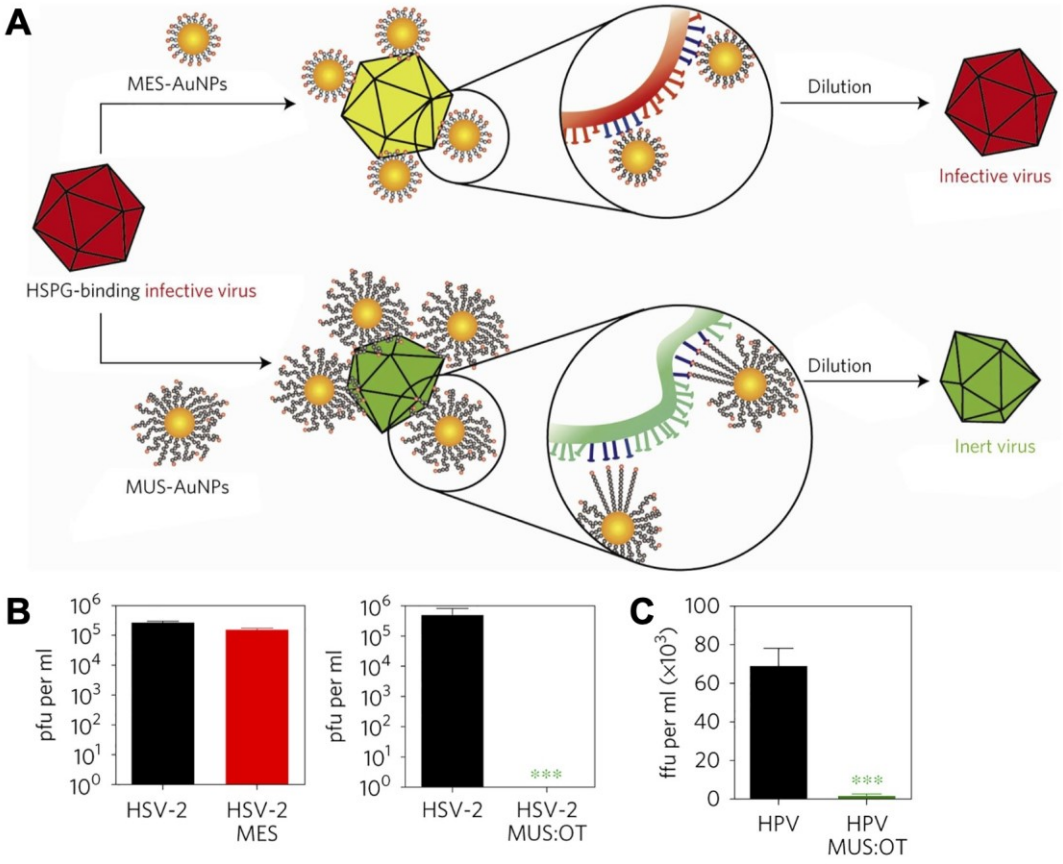


Figure 10. Undecanesulfonic acid-modified gold nanoparticles (MUS-AuNPs) as a broad-spectrum antiviral therapeutic. A) Viruses that target heparan sulfate proteoglycans (HSPG) will naturally bind to the HSPG-mimicking AuNPs. Compared to AuNPs with the shorter 3-mercaptoethylsulfonate (MES), MUS-AuNPs exert a destructive force on the viruses and permanently distort their structure upon binding. B) Infectivity of herpes simplex virus type 2 (HSV-2) preincubated with AuNPs modified with MES or MUS. C) Infectivity of human papilloma pseudovirus (HPV) when preincubated with AuNPs modified with MUS. Reproduced with permission [270]. Copyright 2018, Springer Nature.

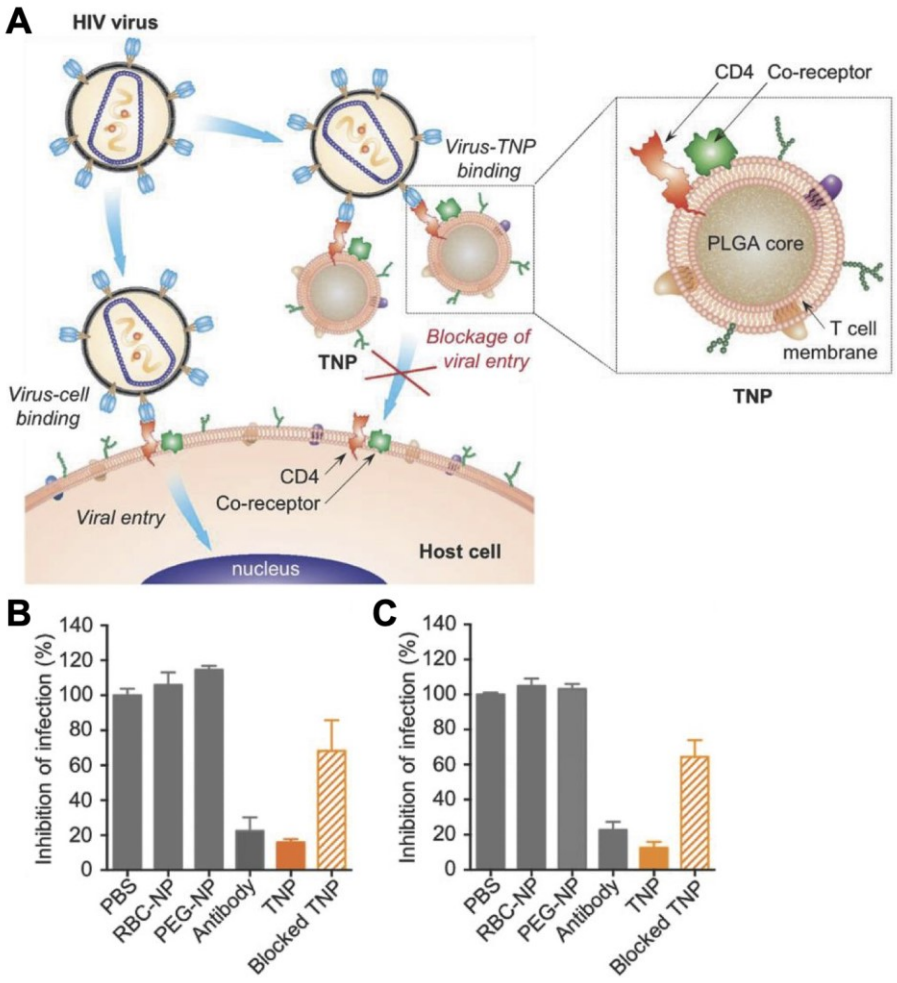


Figure 11. T cell membrane-coated polymeric nanoparticles (TNPs) for neutralizing human HIV. A) HIV invades helper T cells by binding to the CD4 receptor and a co-receptor. TNPs can act as decoys to bind HIV and prevent the virus from invading host cells. B) Inhibition of HIV infectivity on peripheral blood mononuclear cells by TNPs. C) Inhibition of HIV infectivity on human monocyte-derived macrophages by TNPs. Reproduced with permission [328]. Copyright 2018, Wiley-VCH**.**

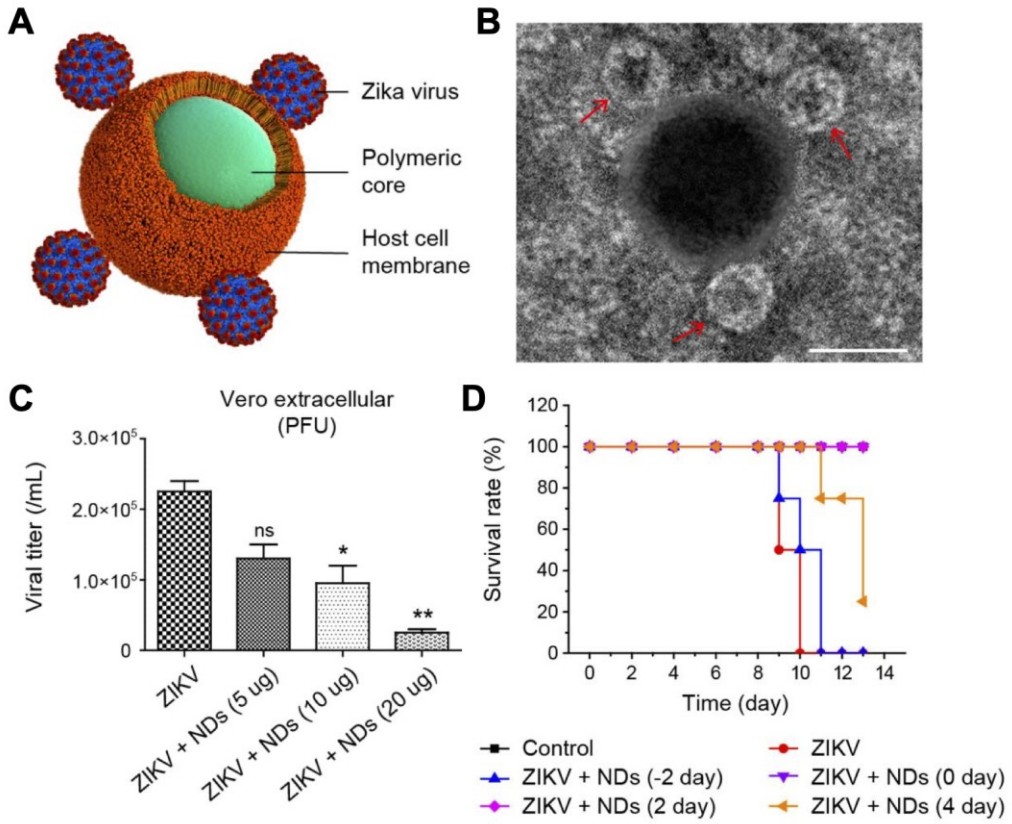


Figure 12. Mosquito cell membrane-coated gelatin nanoparticles as nanodecoys (NDs) for Zika virus (ZIKV). A) NDs functionalized with mosquito cell membrane have a natural affinity to ZIKV. B) TEM image showing ZIKVs bound to a ND. C) Viral titers in the supernatant of Vero cell cultures after incubation with ZIKV and various amounts of NDs. D) Survival of A129 mice intraperitoneally challenged with ZIKV and intravenously treated with NDs at different timepoints. Reproduced with permission [336]. Copyright 2019, American Chemistry Society.

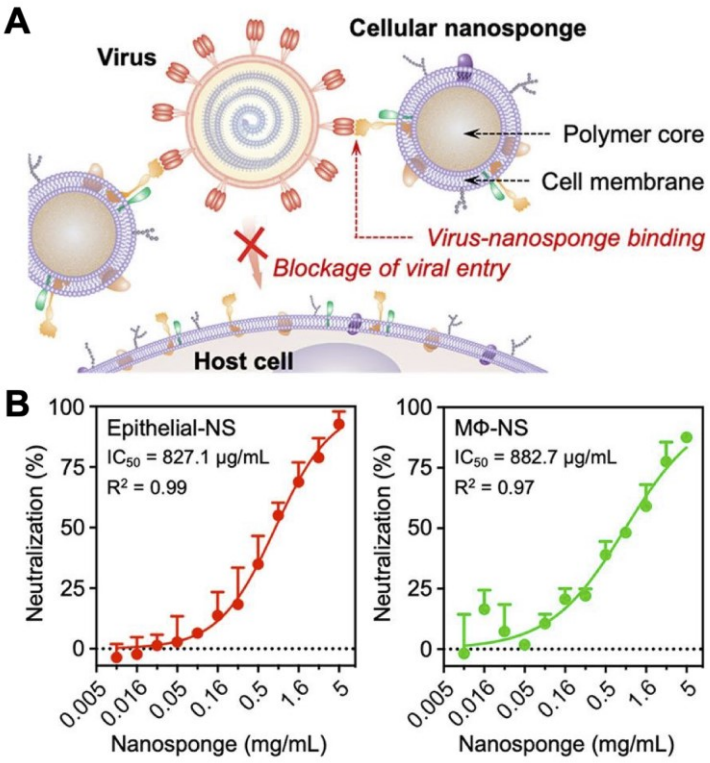


Figure 13. Cell membrane-coated nanosponges (NSs) for neutralizing SARS-CoV-2. A) Nanosponges are composed of a polymeric core coated by the membrane derived from the target cells of SARS-CoV-2. Upon binding to the nanosponges, the virus is neutralized and can no longer invade host cells. B) Dose-dependent neutralization of SARS-CoV-2 *in vitro* using cellular nanosponges fabricated from either epithelial cells (Epithelial-NS) or macrophages (MΦ-NS). Reproduced with permission [337]. Copyright 2020, American Chemistry Society.

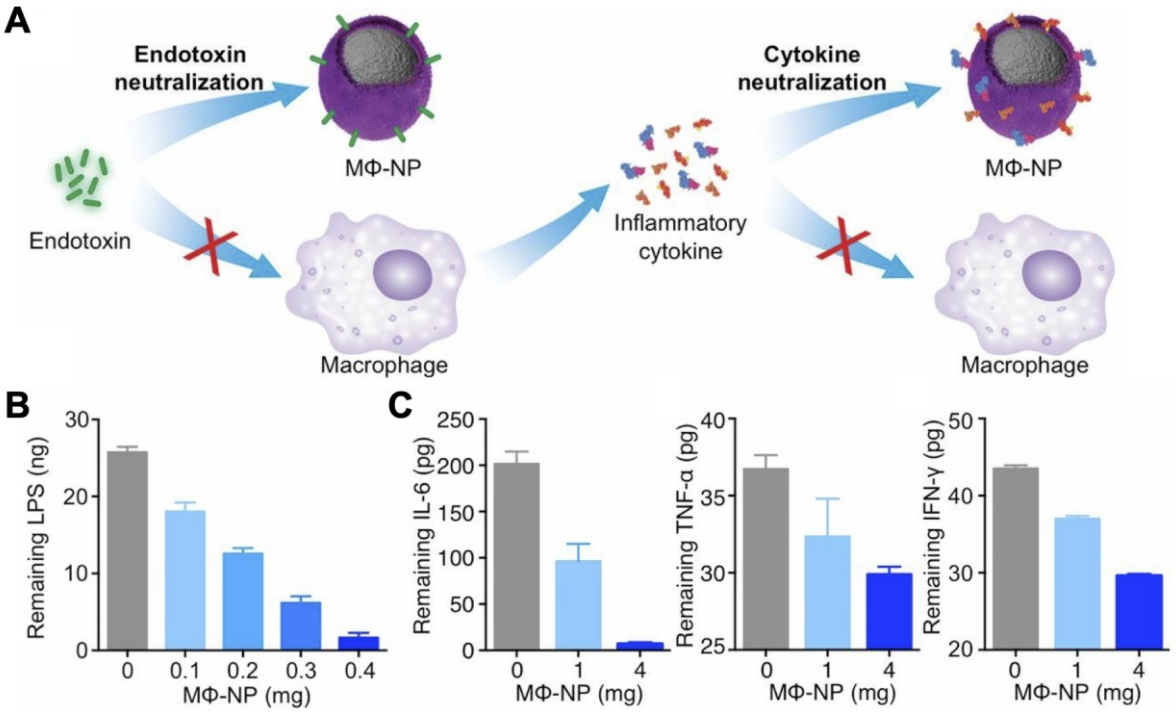
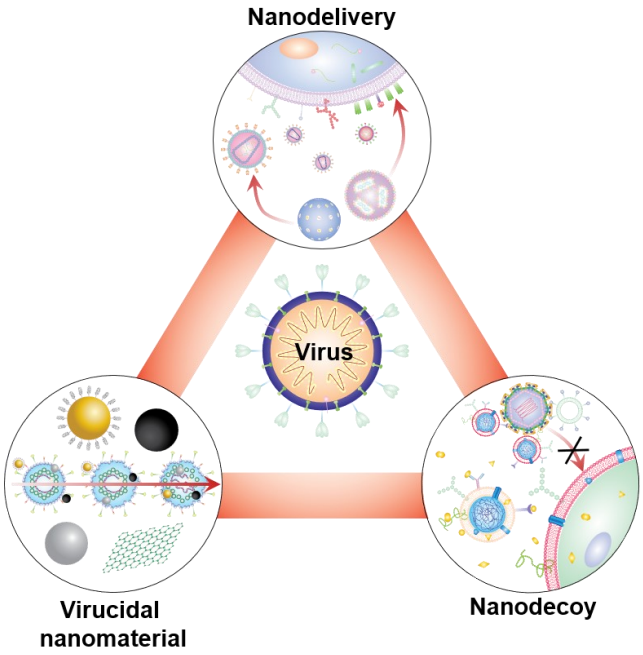


Figure 14. Macrophage membrane-coated nanoparticles (MΦ-NPs) as nanosponges for endotoxin and inflammatory cytokine neutralization. A) With a macrophage-like outer shell, MΦ-NPs can soak up bacterial endotoxins or inflammatory cytokines and prevent them from activating the immune system. B) Unbound lipopolysaccharide (LPS) remaining after incubation with different amounts of MΦ-NPs. C) Unbound interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ) remaining after incubation with different amounts of MΦ-NPs. Reproduced with permission [309]. Copyright 2017, National Academy of Sciences.

Graphical abstract



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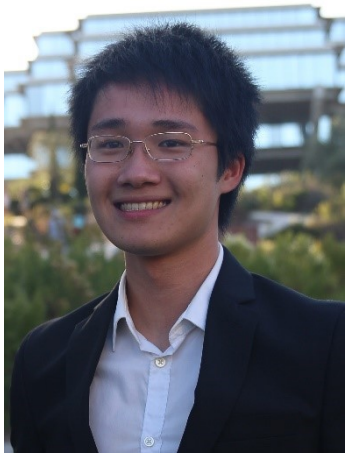

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