ROLE OF NANOTECHNOLOGY IN VIRAL INFECTED DISEASE

Shankar Lal Soni[1]*, Munesh Kumari[2], Raju[2], Anil[2], Ashish Sharma[2] and Akash Sharma[2]

[1]Professor, Arya College of Pharmacy, Jaipur, Rajasthan.
[2]Research Scholar, Arya College of Pharmacy, Jaipur, Rajasthan.

ABSTRACT

The ongoing creation of new viruses poses a serious threat to global health. Uncontrolled outbreaks can lead to pandemics, which can overwhelm our healthcare and economic systems. While vaccination is a traditional method for promoting herd immunity, antiviral vaccinations can only be used prophylactically and do little to treat patients who have already been infected. Virus infections were contracted. When vaccinations are unavailable in the early stages of a disease outbreak, therapeutic antiviral medicines can be employed as a stopgap measure. However, these medicines do not always work against new virus strains and sometimes have side effects that outweigh the advantages. Many of the obstacles that existing antiviral medicines face could be overcome by nanotechnology. Consider nano delivery Vehicles can be used to improve the pharmacokinetic profile of antiviral medicines while lowering systemic toxicity. Other unique nanomaterials with virucidal or virus-neutralizing characteristics can be used. In this review, we examine recent advances in antiviral nanotherapeutics and offer our thoughts on how nanotechnology can be used to combat the SARS-CoV-2 outbreak and future virus pandemics.

KEYWORDS:

INTRODUCTION

Technological advancements and innovative therapeutic methods have enabled us to defeat potentially fatal viral infections such as smallpox and poliomyelitis.[1] However, in today's environment, viral Infections continue to be a major burden on the worldwide healthcare system.[2-4] There is an ongoing conflict in which researchers and medical practitioners must frequently scramble to develop viable ways for controlling newly altered or emerging virus strains.[5-6]

The most extensively utilised clinical technique to combat viruses is vaccination, in which viral antigens are administered to assist bestow immune protection. While vaccines against diseases such as hepatitis and measles have been successful, there are other obstacles that hinder this technique from being widely adopted against other types of viruses.[7] Because the influenza virus, for example, has a high mutation rate, new flu vaccines must be generated every year.[8,9] Because vaccinations are preventative in nature, pharmaceutical companies must forecast which strains of influenza will spread the following season, a procedure that is not always accurate. Furthermore, new vaccine development takes a significant amount of time and resources, limiting vaccines' ability to be deployed against emerging disease outbreaks, which can be devastating.

Recent viral epidemics, such as those caused by the human immunodeficiency virus (HIV), influenza virus, Ebola virus, Zika virus, and coronaviruses, have occurred in the recent few decades have been a major cause of public worry, highlighting the absence of infrastructure and plans to tackle new pandemics quickly.[10] Overall, developing broadly applicable therapeutic techniques that may be promptly deployed to combat viral infections is critical.[11]

Drugs are commonly used in viral treatment techniques to block several components of the viral life cycle.[12-14] Although antiviral medications can be quite successful, they require rigorous patient compliance and sometimes have severe side effects.[15,18] Recent breakthroughs in nanotechnology have the potential to help overcome these barriers and provide new opportunities for developing novel technologies.

Targeted drug administration can further reduce toxicity, boost efficacy, and extend the therapeutic window.[19] Some nanomaterials have inherent toxicity, allowing them to kill viruses directly.[20] Nanoparticles have recently been discovered.

They have been functionalized and modified in such a way that they can selectively bind to and neutralise pathogens.[21] In this review, we will look at how nanotechnology can be used to treat viral infections (Fig. 1).
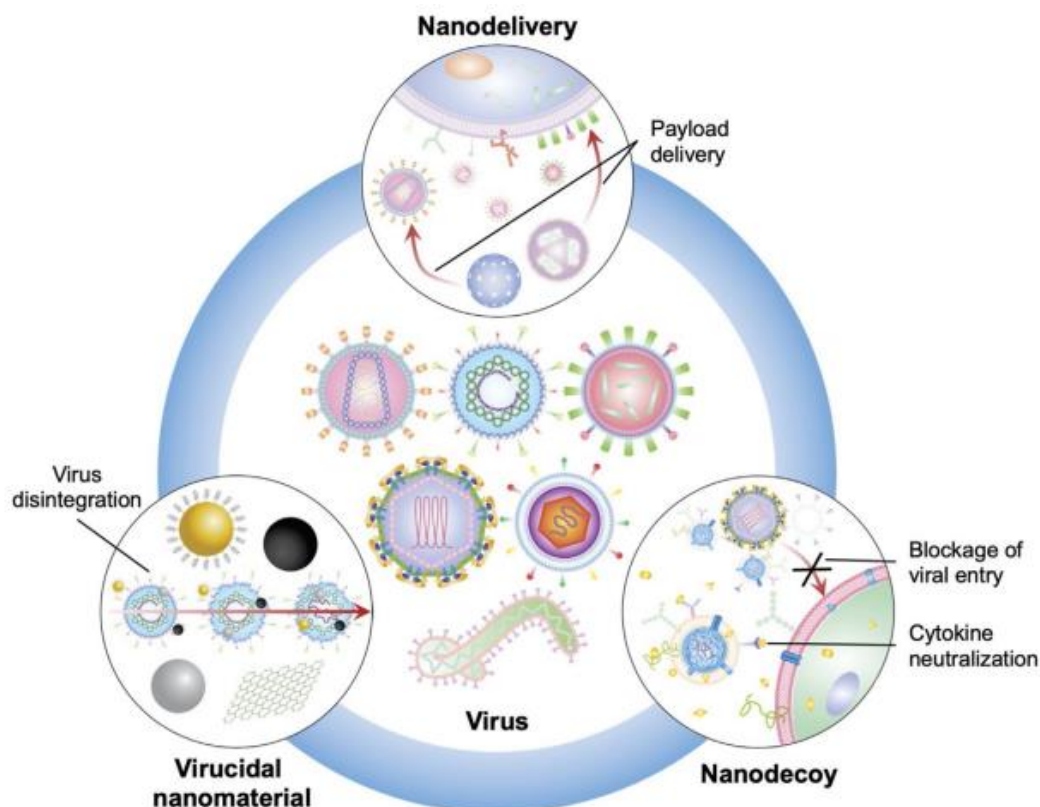
COMMON HUMAN VIRUSES
HUMAN IMMUNO VIRUS
HIV, which causes acquired immunodeficiency syndrome (AIDS), targets and gradually depletes CD4+ helper T cells.[22] The HIV genome is made up of ssRNA molecules encased in an encapsulated capsid.[23] HIV infections begin with a contact between glycoproteins on the surface of the viral capsid, primarily gp120, and the C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) coreceptor on target cells. plasma membrane, which releases the viral capsid core into the cell.

HUMAN INFLUENZAE VIRUS
The human influenza virus A virus that causes 250,000-500,000 deaths each year spreads primarily through contaminated aerosols and small airborne droplets.[17] A negative-sense ssRNA genome is wrapped in a helical capsid within a viral envelope in this virus.[24]

HEPATITIS VIRUS
The hepatitis viruses are a group of five unrelated viruses that cause inflammation of the liver.[39] Although all viruses can infect people, hepatitis A, B, and C are the most medically significant. Because of its liver-damaging features, the hepatitis B virus (HBV), a recognised oncovirus, is solely responsible for the great majority of hepatitis-related deaths.[25] The virus is an enclosed virus with genetic information encoded in DNA that is contained within an icosahedral capsid.[26] HBV invasion is mediated by the interaction of the preS1

protein with a hepatocyte receptor known as sodium taurocholate co-transporting polypeptide.

ZIKA VIRUS
The enclosed icosahedral capsid of the Zika virus contains a positive-sense ssRNA genome.[27] The viral genome encodes three structural proteins, each of which is essential for viral replication. The capsid protein (C protein) is thought to be essential for the inner core's structure, whereas the envelope protein is not.The viral envelope contains both the envelope protein (E protein) and the membrane protein (M protein).

EBOLA VIRUS
The Ebola virus is frequently spread by direct contact with blood and body fluids, and it has primarily caused lethal epidemics in Sub-Saharan Africa.[28] The virus is made up of a negative-sense ssRNA genome encased in an enclosed viral envelope capsid. Surface glycoproteins connect to host receptors, including dendritic cell-specific ICAM-3-grabbing nonintegrin and asialoglycoprotein receptor, to gain entry into host cells.Phosphatidyl serine on the viral envelope interacts to a host cell receptor, triggering macropinocytosis, an endocytosis-like pathway that regulates solute molecules, nutrients, and antigen uptake.[29]

Nanotechnology interventions
Nanotechnologies have been extensively researched and developed in recent years for antiviral treatment. When compared to standard antiviral medicines, these nanoscale platforms open up a plethora of new

possibilities in the sector. Nanomaterials can be used to not only improve present therapies, but also to develop innovative modalities that can kill or suppress viruses via novel modes of action.

Advantages of nanotherapeutics
One well-known use of nanomaterials in virus treatment is to improve the pharmacokinetic performance of existing antiviral medicines. Nanoparticles can enhance prolonged medication release and expand the therapeutic window by protecting the encapsulated medicines.[88] Nanoparticles with long circulation and strong drug loading qualities can be created, which is especially relevant for hydrophobic medicines that cannot be delivered systemically in their free form. Nanoparticle formulations can provide a major benefit over free medicines by providing improved protection against viruses in circulation.[30] When applied locally, nanoparticles, on the other hand, can limit systemic exposure and provide protection through sustained retention or movement across certain biological barriers.[31] Nanoparticle systems may be further incorporated into a larger scale formulation, such as hydrogels, to provide additional layers of sustained drug release.[32] Because nanoparticles are easy to functionalize and have similar sizes to viruses, there are several biointerfacing prospects between nanoparticle-based systems and viruses or virus-infected tissues. Nanoparticles can be made of stimuli-responsive materials, or their surfaces can be coupled with targeting ligands to direct medication payloads to virally infected areas.

This type of targeted administration not only increases the effective drug concentration at the illness site, but it also improves the safety profile by reducing off-target drug exposure.[88] Furthermore, nanoparticles have an optimal size range for multivalent interactions with a variety of biological substrates.Surface modification with different types of ligands can confer multimodality, which can aid to diversify the functionalities of nanocarriers.[33]

Nanodelivery
When used, nanoparticles have several different advantages as delivery vans. They can protect encapsulated pharmaceuticals from both degradation in the body and degradation in the environment by acting as a cargo carrier.
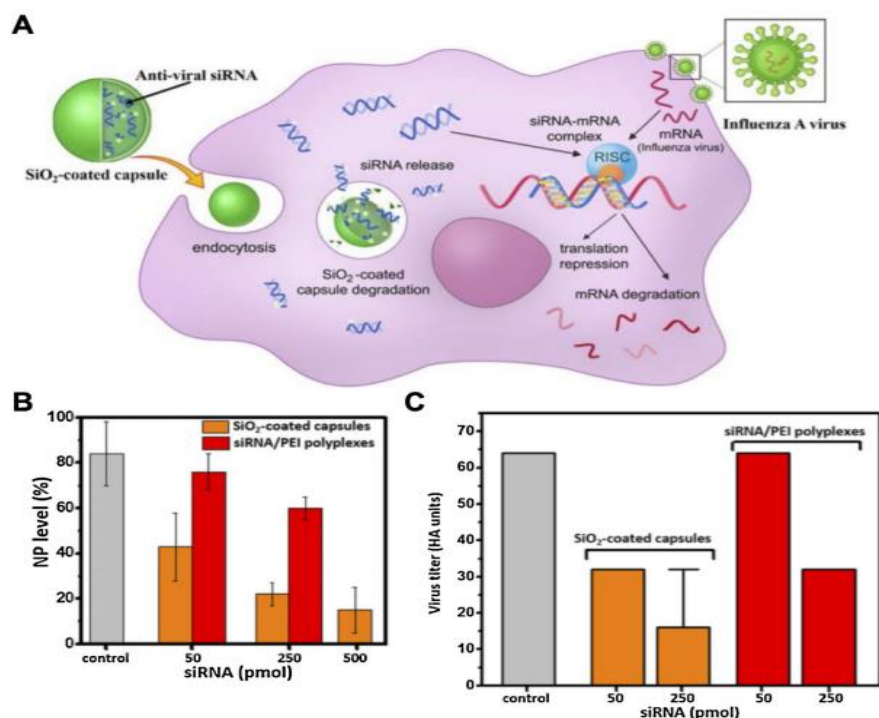

Fig. 6. Silica (SiO$_2$)-coated microcapsules loaded with small interfering RNA (siRNA) for influenza treatment. A) SiO$_2$-coated microcapsules are endocytosed into the cell, where the siRNA is released into the cytosol and binds to the RNA-induced silencing complex (RISC) to facilitate gene knockdown. 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.

Systemic toxicity to the host is undesirable. Nanoparticles can be meticulously tailored to modify payload biodistribution and improve accumulation in desirable tissue regions while remaining considerably small. limiting unintended consequences.[34] By simply modifying the lipid content, a lipid nanoparticle formulation was recently shown to selectively target the liver, spleen, or lungs.[35]

In this way, nanodelivery technologies can be employed to significantly improve bioavailability and efficacy when compared to free drug administration. Nanoparticles can control the release of the payload at

the target site, allowing for sustained release and a considerably longer therapeutic window. The field of nanodelivery for antiviral drugs has matured significantly over the last two decades with some nanoformulations actively being explored in the clinic.[36,37,38]

HIV

While curing HIV is difficult due to the presence of viral Patients can live normally in reservoirs by taking a mix of antiretroviral medications that successfully suppress the infection.[39] HIV Patients must adhere to a stringent highly active antiretroviral therapy regimen, which often entails daily medication administration. Deviations from the timetable can have a major impact on a patient's infection state.[40] As a result, numerous nanoparticle formulations have been introduced in this field to increase therapeutic window, lowering the required dose frequency and addressing patient compliance.[41] Stavudine, a nucleoside analogue, has been loaded into gelatin nanoparticles and then covered with a layer of soya lecithin-liposome for dual-functionalization Treatment for HIV-1.[42] The stavudine may be released slowly while in circulation to help address plasma infections, but once engulfed by cells in the mononuclear phagocytic system, the gelatin core might be dissolved to release the remaining stavudine for treating viral reservoirs. Solid lipid nanoparticles (SLNs) loaded with the protease inhibitor ritonavir.[43] and hydrophobic core graft copolymer loaded with the NNRTI enzophenone-uracil[44] are two further examples of HIV nanodelivery platforms. For HIV-1 treatment, a novel nanoparticle platform consisting of endogenous ribonucleoprotein, or vaults, has been used.[45]. Because the barrel-shaped particles occur naturally in eukaryotic cells, they are assumed to be extremely biocompatible. It has been demonstrated that antiretroviral medicines such as zidovudine, Tenofovir and elvitegravir could be coupled onto the surface of these vault nanoparticles, and the drug-nanoparticle conjugates inhibited HIV-1 infections in peripheral blood mononuclear cells (PBMCs) (Figure).
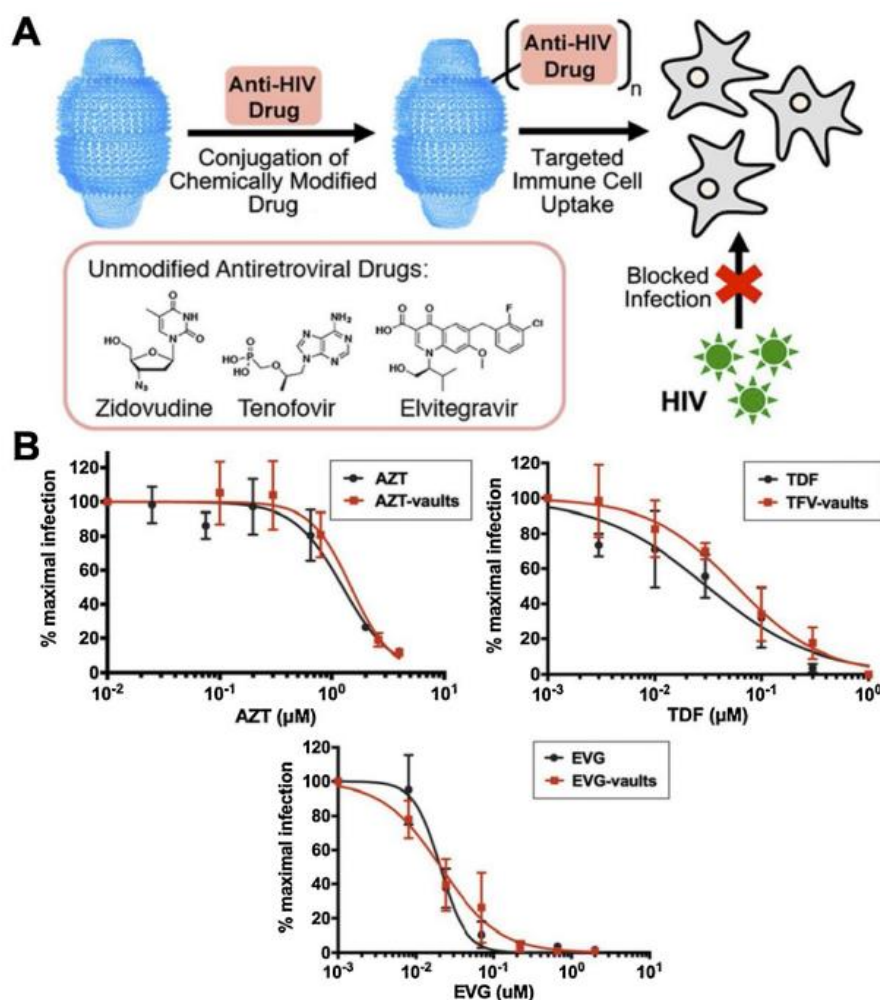

Fig:- drug-conjugated vault nanoparticles for inhibiting human immunodeficiency virus (HIV).A) Zidovudine (AZT),tenofovir (TDF), and elvitegravir (EVG) can be chemically conjugated onto natural ribonucleoprotein vault nanoparticles to protect immune cells from HIV infections. B) Infection rate of peripheral 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.

HIV

Metal-based nanoparticles are a prominent delivery platform for antiviral medicines used to treat influenza infections.[46-47]

NA inhibitors, such as zanamivir[146] and oseltamivir[48], As well as amantadine[49], a nicotinic antagonist and noncompetitive N-methyl-D-aspartate antagonist that can reduce influenza viral replication, silver nanoparticles (AgNPs) have been conjugated for influenza treatment. The processes of neutralisation were comparable for all three formulations, with antiviral drug-conjugated nanoparticles preventing influenza invasion and rescuing cell populations by blocking caspase 3-mediated death and intracellular ROS buildup. Aside from AgNPs, selenium nanoparticles (SeNPs) have been functionalized with oseltamivir[50], zanamivir[51], and amantadine[52]. Furthermore, ribavirin[53], a nucleoside analogue, and umifenovir[53], an entrance inhibitor, have been conjugated onto SeNPs for therapeutic purposes.

Polymeric nanoparticles are another extensively used platform that has been used to specifically deliver miR-323a and favipiravir to influenza viruses via a sialic acid targeting moiety.[54]

Similarly, diphyllin and bafilomycin, both powerful vacuolar ATPase inhibitors were successfully loaded into polyethylene glycol (PEG)-functionalized PLGA nanoparticles, resulting in decreased cytotoxicity but 2- to 5-fold increased antiviral efficacy.[55]

Nanoparticulate RNAi treatment administration has been widely used to treat influenza infections. On this front, chitosan nanoparticles[56], calcium phosphate nanoparticles[57], and chitosan nanoparticles[58] Titanium oxide nanocomposites[59] have all been used to silence genes and prevent influenza virus multiplication. Titanium oxide nanocomposites, in example, have been utilised to transport deoxyribozymes, which are DNA enzymes that can cleave viral RNA and have been demonstrated to reduce H5N1 viral titers in vitro by around 2650-fold.[60] Surprisingly, after sol-gel synthesis, silica-coated microcapsules have been employed to carry siRNAs.[61] The microcapsules could be endocytosed and destroyed by cells, allowing the siRNA cargo to be released into the cytosol (Fig. 6).

OTHER TYPES OF VIRUSES

The Ebola epidemic in 2013 and the Zika pandemic in 2015 drew a lot of attention from the scientific community.[62–66] To combat the two viruses, several nanoformulations have been devised. To treat Zika infections, for example, an oral medicine, ivermectin, was put into biocompatible and biodegradable PLGA polymeric nanoparticles (Fig. 7).[67] To protect the nanoparticles from stomach acid, PEG was conjugated onto their surface. The exterior was then modified with the Fc portion of antibodies to aid in the transport of nanoparticles past the epithelial barrier and into the bloodstream. When the formulation was given to mice orally, approximately 65% of the nanoparticles entered the bloodstream via Fcmediated transcytosis. These nanoparticles were able to significantly under controlled experimental circumstances. suppress the production of Zika virus nonstructural protein 1. Furthermore, the formulation was easily lyophilized for capsule packaging and showed a 24-hour drug release even at pH 3.
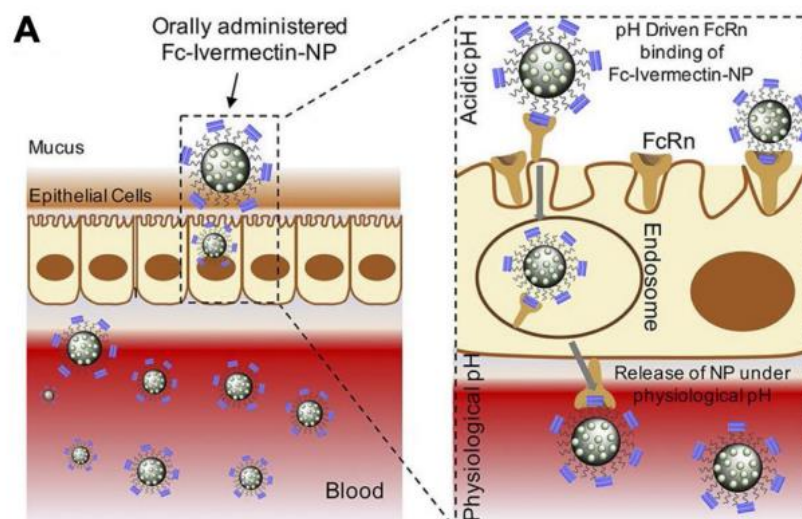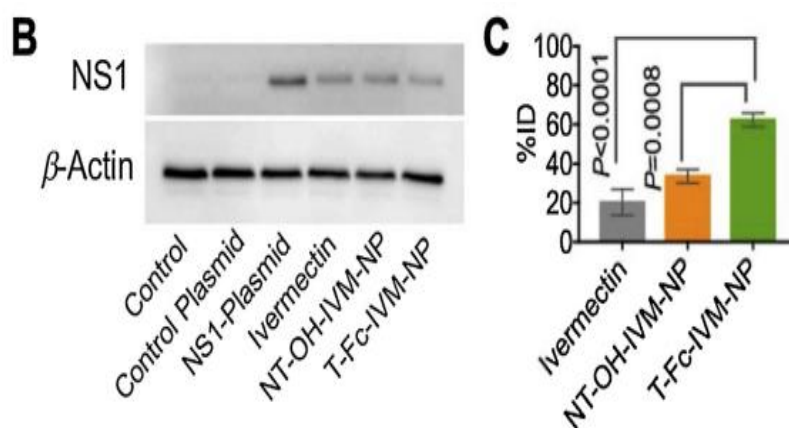
Fig. 7. Orally delivered nanoparticles for the systemic treatment of Zika infections. A) Polymeric nanoparticles are loaded with ivermectin (IVM), an oral antiviral drug, and functionalized with polyethylene glycerol (PEG) and the Fc protein (T-Fc-IVM-NP). At acidic pH under 6.5, the Fc protein binds 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 HEK293 T 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.

The majority of nanoparticle formulations for Ebola virus treatment have been focused on RNAi therapy. To battle the Ebola virus, a cocktail of three siRNAs targeting the Zaire Ebola virus L protein, virion protein 24, and virion protein 35 genes was spontaneously vesiculated into stable nucleic acid-lipid particles (SNALPs).[68]

VIRUCIDAL NANOPARTICLES
Because of their unique physicochemical features, certain nanomaterials, including metal nanoparticles and graphene-based nanosheets, have natural virucidal effects.[198] They all use the same mechanism of action, which involves direct interaction with virus envelope or capsid proteins, damaging structural integrity and decreasing infectivity. Furthermore, certain nanomaterials can disrupt viral gene replication within infected cells.[69,70]

METAL NANOPARTICLES
Silver nanoparticles are the most well studied antiviral nanomaterial, and it has been demonstrated that bare or coated AgNPs may suppress a wide spectrum of viruses.[71] Because it is difficult for viruses to develop resistance to this sort of therapy, it is appealing, particularly against highly mutative viruses. AgNPs have been shown to be effective both outside of cells to prevent virion entry and inside infected cells to prevent replication. In a cell-based test, commercially made 30-50 nm AgNPs were reported to have affinity for gp120 on HIV-1 and hence inhibited fusion in a dose-dependent manner by disrupting the gp120-CD4 interaction.[72] For HIV treatment, AgNPs have been coupled with broadly neutralising antibodies.[73,74] In vitro, smaller 10 nm AgNPs were demonstrated to effectively suppress H1N1 influenza A virus hemagglutination.[75] In a separate investigation, intranasal delivery of AgNPs to mice infected with the H3N2 influenza virus demonstrated effectiveness comparable to oseltamivir.[76] AgNPs were also reported to limit HBV and HIV-1 intracellular replication, likely due to interactions between the nanoparticles and genetic material.[77,78] The use of these nanoparticles to coat condoms proved a feasible application for reducing HIV transmission.[79]

NANO EMULSIONS
Nanoemulsions, a class of nanoparticles with simple and lowcost synthesis, were found effective in treating and preventing infections from certain viral strains. Nanoemulsions are manufactured bymixing 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.[80] 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.[81] In an in vivo study, two nanoemulsion formulations, 8N8 and 20N10, significantly improved the survival rate of Mice Infected With Influenza When utilised as a preventative measure, a virus.[82]

GRAPHENE NANO SHEETS
Graphene and its derivatives have emerged as a distinct class of antiviral material, particularly for high-throughput virus disinfection. Graphene and its derivatives have antiviral effects due to its unique physicochemical features. As a two-dimensional nanomaterial, graphene has an extremely high surface-to-volume ratio, allowing it to interact effectively with viruses. Graphene oxide (GO) is negatively charged and has a large number of reactive oxygenated groups on its surface that can adsorb and destroy viruses via

electrostatic forces and redox processes. Because some viruses are positively charged, or their capsid proteins contain arginine-rich and positively charged areas, these interactions are feasible.[83] Graphene also possesses great thermal and electrical conductivity, which

researchers have used to improve the efficacy and efficiency of virus killing.[84]

In aqueous solutions, a GO nanomaterial was produced to disinfect enterovirus 71 and H9N2 influenza virus viruses (Fig. 9).[85]
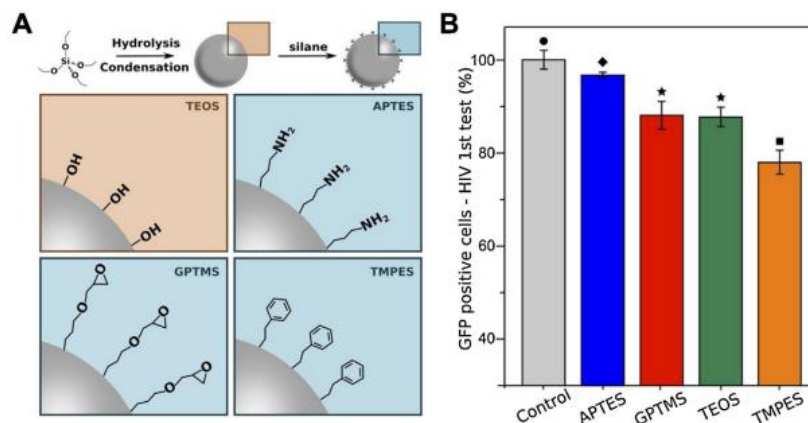

Fig. 8. Surface-modified silica nanoparticles (SiNPs) for the inhibition of HIV. A) Through a co-condensation chemical reaction, the tetraethylorthosilicate (TEOS) functional group can be converted into (3-aminopropyl)triethoxysilane (APTES), (3-glycidyloxypropyl)trimethoxysilane (GPTMS), or trimethoxy(2-phenylethyl)silane (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.
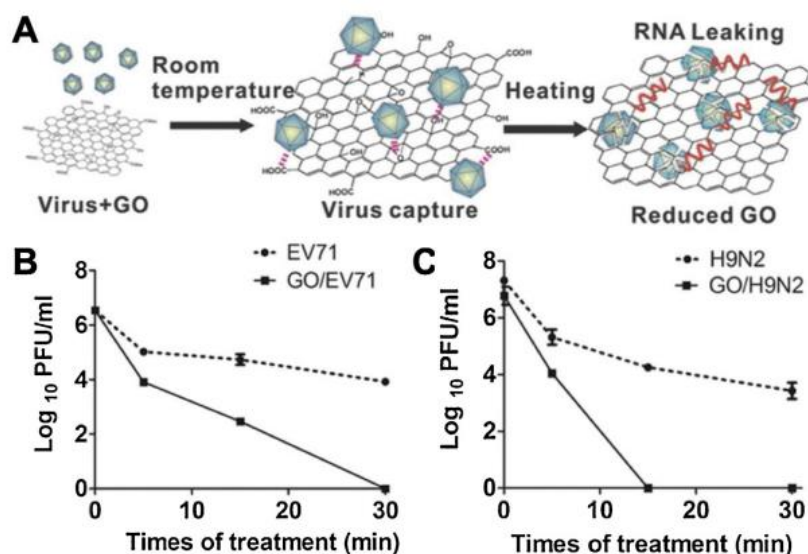

Fig. 9. Graphene oxide (GO) nanosheets for destroying the structure of enterovirus 71 (EV71) and H9N2 influenza virus. A) GO nanosheets naturally adsorb viruses and can compromise viral integrity upon heating at a high temperature. B, C) Viral titers for EV71 (B) and H9N2 (C) upon heat treatment at 56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

CONCLUSIONS AND PERSPECTIVES
As of August 2020, the current outbreak caused by the new SARS-CoV-2 virus had infected over 21 million individuals and killed over 750,000 people worldwide. This worldwide pandemic serves as a sobering reminder that, despite all of the technical advances of the last century, contemporary medicine is still unprepared to deal with developing viral outbreaks.[86] As the world strives to create a vaccine to combat SARS-CoV2, nanotherapeutics can serve as a stopgap approach to slow the virus's spread.[87-91] A straightforward approach is to use nanoparticles to deliver antiviral medicines that have the potential to be effective against SARS-CoV-2.[92-94]

Many drugs, including remdesivir[95-97], dexamethasone[98], lopinavir-ritonavir[99], and EIDD-2801[100], can be incorporated into nanoparticles to improve their pharmacokinetic characteristics and overall potency. In the past, nanodelivery systems have been used successfully to handle different types of coronaviruses. Diphyllin, a vacuolar ATPase inhibitor, was synthesised into PEG-PLGA nanoparticles to achieve 60-fold increased antiviral activity against the feline coronavirus (FCoV) in fcwf-4 cells while maintaining a 13-fold lower cytotoxicity compared to the free drug.[101] There is no virus treatment technology. Nanomedicine advancements have the potential to

change the clinical landscape for antiviral therapies. Nanomaterials have various specific benefits that can be used to boost the action of antiviral medications due to their unique features. Payloads encapsulated in nanoparticles are less exposed to the outside environment, which can protect them from systemic breakdown while lowering cytotoxicity By prolonging circulation time, targeting specific tissue areas, and boosting absorption, nanoparticles can improve the pharmacokinetic characteristics of current antiviral medicines. The value of hydrophobic medications, which are typically difficult to produce and distribute in vivo, can be considerably boosted by nanotechnology. Therapeutics integrated into nanoparticles can benefit from a longer therapeutic window via continuous release, and these platform scan be included into hydrogel superstructures for enhanced capabilities.[102]

REFERENCES

1. D.R. Hopkins, N. Engl. J. Med, 2013; 368: L 54–63.
2. P.N. Fonkwo, EMBO Rep, 2008; 9: S13–S17.
3. D.E. Bloom, D. Cadarette, Front. Immunol, 2019; 10: 549.
4. N.G. Reich, J. Lessler, J.K. Varma, N.M. Vora, Sci. Rep, 2018; 8: 1093.
5. K.K. Irwin, N. Renzette, T.F. Kowalik, J.D. Jensen, Virus Evol, 2016; 2: vew014.
6. R.K. Gupta, J. Gregson, N. Parkin, H. Haile-Selassie, A. Tanuri, L. Andrade Forero, P. Kaleebu, C. Watera, A. Aghokeng, N. Mutenda, J. Dzangare, S. Hone, Z.Z. Hang, J. Garcia, Z. Garcia, P. Marchorro, E. Beteta, A. Giron, R. Hamers, S. Inzaule, L.M. Frenkel, M.H. Chung, T. de Oliveira, D. Pillay, K. Naidoo, A. Kharsany, R. Kugathasan, T. Cutino, G. Hunt, S. Avila Rios, M. Doherty, M.R. Jordan, S. Bertagnolio, Lancet Infect. Dis, 2018; 18: 346–355.
7. J.B. Ulmer, U. Valley, R. Rappuoli, Nat. Biotechnol, 2006; 24: 1377–1383.
8. R.G. Pebody, M. Zambon, M. Ramsay, BMJ, 2018; 361: k2705.
9. A. Singanayagam, M. Zambon, A. Lalvani, W. Barclay, Lancet Infect. Dis, 2018; 18: E25–E32.
10. B. Allegranzi, C. Kilpatrick, J. Storr, E. Kelley, B.J. Park, L. Donaldson, Lancet Glob. Health, 2017; 5: E1178–E1180.
11. B. Gates, N. Engl. J. Med, 2018; 378: 2057–2060.
12. A. Tamori, M. Enomoto, N. Kawada, Mediat. Inflamm, 2016; 2016: 6841628.
13. M.S. Cohen, Y.Q. Chen, M. McCauley, T. Gamble, M.C. Hosseinipour, N. Kumarasamy, J.G. Hakim, J. Kumwenda, B. Grinsztejn, J.H. Pilotto, S.V. Godbole, S. Chariyalertsak, B.R. Santos, K.H. Mayer, I.F. Hoffman, S.H. Eshleman, E. Piwowar-Manning, L. Cottle, X.C. Zhang, J. Makhema, L.A. Mills, R. Panchia, S. Faesen, J. Eron, J. Gallant, D. Havlir, S. Swindells, V. Elharrar, D. Burns, T.E. Taha, K. Nielsen-Saines, D.D. Celentano, M. Essex, S.E. Hudelson, A.D. Redd, T.R. Fleming, N. Engl. J. Med, 2016; 375: 830–839.
14. J.A. Jackman, J. Lee, N.J. Cho, Small, 2016; 12: 1133–1139.
15. A.A. Okoye, L.J. Picker, Immunol. Rev, 2013; 254: 54–64.
16. E.M. Campbell, T.J. Hope, Nat. Rev. Microbiol, 2015; 13: 471–483.
17. D. Dou, R. Revol, H. Ostbye, H. Wang, R. Daniels, Front. Immunol, 2018; 9: 1581.
18. J.W. Mosley, A.G. Redeker, S.M. Feinstone, R.H. Purcell, N. Engl. J. Med, 1977; 296: 75–78.
19. C. Seeger, W.S. Mason, Virology, 2015; 479: 672–686.
20. K. Watashi, T. Wakita,Cold Spring Harb. Perspect. Med, 2015; 5: a021378.
21. D. Sirohi, R.J. Kuhn, J. Infect. Dis, 2017; 216: S935–S944.
22. D.-S. Yu, T.-H. Weng, X.-X. Wu, F.X.C. Wang, X.-Y. Lu, H.-B. Wu, N.-P. Wu, L.-J. Li, H.-P. Yao, Oncotarget, 2017; 8: 55750–55759.
23. S. Moller-Tank, W. Maury, Virology, 2014; 468-470: 565–580.
24. Hudelson, A.D. Redd, T.R. Fleming, N. Engl. J. Med, 2016; 375: 830–839.
25. M.S. Cohen, Y.Q. Chen, M. McCauley, T. Gamble, M.C. Hosseinipour, N. Kumarasamy, J.G. Hakim, J. Kumwenda, B. Grinsztejn, J.H. Pilotto, S.V. Godbole, S. Chariyalertsak, B.R. Santos, K.H. Mayer, I.F. Hoffman, S.H. Eshleman, E. Piwowar-Manning, L. Cottle, X.C. Zhang, J. Makhema, L.A. Mills, R. Panchia, S. Faesen, J. Eron, J. Gallant, D. Havlir, S. Swindells, V. Elharrar, D. Burns, T.E. Taha, K. Nielsen-Saines, D.D. Celentano, M. Essex, S.E. Hudelson, A.D. Redd, T.R. Fleming, N. Engl. J. Med, 2016; 375: 830–839.
26. A.C. Schmidt, Drugs 64 (2004) 2031–2046.
27. A. Calmy, B. Hirschel, D.A. Cooper, A. Carr, Lancet, 2007; 370: 12–14.
28. E. De Clercq, G. Li, Clin. Microbiol. Rev, 2016; 29: 695–747.
29. R.H. Fang, A.V. Kroll, W. Gao, L. Zhang,Adv. Mater, 2018; 30: 1706759.
30. J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, M.D.P. Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, H.S. Shin, Int. J. Nanobiotechnol. Pharm, 2018; 16: 71.
31. R. Vazquez-Munoz, B. Borrego, K. Juarez-Moreno, M. Garcia-Garcia, J.D. Mota Morales, N. Bogdanchikova, A. Huerta-Saquero, Toxicol. Lett, 2017; 276: 11–20.
32. R.M. Gulick, J.W. Mellors, D. Havlir, J.J. Eron, C. Gonzalez, D. McMahon, D.D. Richman, F.T. Valentine, L. Jonas, A. Meibohm, E.A. Emini, J.A. Chodakewitz, P. Deutsch, D. Holder, W.A. Schleif, J.H. Condra, N. Engl. J. Med, 1997; 337: 734–739.
33. E. Lawitz, M.S. Sulkowski, R. Ghalib, M. Rodriguez-Torres, Z.M. Younossi, A. Corregidor, E. DeJesus, B. Pearlman, M. Rabinovitz, N. Gitlin, J.K. Lim, P.J. Pockros, J.D. Scott, B. Fevery, T. Lambrecht, S. Ouwerkerk-Mahadevan, K.

Callewaert, W.T. Symonds, G. Picchio, K.L. Lindsay, M. Beumont, I.M. Jacobson, Lancet, 2014; 384: 1756–1765.

34. I.M. Gilchuk, S. Bangaru, P. Gilchuk, R.P. Irving, N. Kose, R.G. Bombardi, N.J. Thornburg, C.B. Creech, K.M. Edwards, S. Li, H.L. Turner, W. Yu, X. Zhu, I.A. Wilson, A.B. Ward, J.E. Crowe Jr., Cell Host Microbe, 2019; 26: 715–728.

35. A. Okumura, P.M. Pitha, R.N. Harty, Proc. Natl. Acad. Sci. U.S.A, 2008; 105: 3974–3979.

36. A. Sanyal, R.B. Mailliard, C.R. Rinaldo, D. Ratner, M. Ding, Y. Chen, J.M. Zerbato, N.S. Giacobbi, N.J. Venkatachari, B.K. Patterson, A. Chargin, N. Sluis-Cremer, P. Gupta, Nat. Med, 2017; 23: 885–889.

37. L. Wang, A.B. Sassi, D. Patton, C. Isaacs, B.J. Moncla, P. Gupta, L.C. Rohan, Drug Dev. Ind. Pharm, 2012; 38: 995–1007.

38. S. Pollock, R.A. Dwek, D.R. Burton, N. Zitzmann, AIDS, 2008; 22: 1961–1969.

39. D. Ramyadevi, P. Sandhya, Drug Deliv, 2014; 21: 276–292.

40. S.D. Mahajan, R. Aalinkeel, W.C. Law, J.L. Reynolds, B.B. Nair, D.E. Sykes, K.T. Yong, I. Roy, P.N. Prasad, S.A. Schwartz, Int. J. Nanomed, 2012; 7: 5301–5314.

41. Q. Cheng, T. Wei, L. Farbiak, L.T. Johnson, S.A. Dilliard, D.J. Siegwart, Nat. Nanotechnol, 2020; 15: 313–320.

42. L. Singh, H.G. Kruger, G.E.M. Maguire, T. Govender, R. Parboosing, Ther. Adv. Infect. Dis, 2017; 4: 105–131.

43. D. Lembo, M. Donalisio, A. Civra, M. Argenziano, R. Cavalli, Expert Opin. Drug Deliv, 2018; 15: 93–114.

44. D.D. Richman, D.M. Margolis, M. Delaney, W.C. Greene, D. Hazuda, R.J. Pomerantz, Science, 2009; 323: 1304–1307.

45. G.M. Lucas, R.E. Chaisson, R.D. Moore, Ann. Intern. Med, 1999; 131: 81–87.

46. J. das Neves, M.M. Amiji, M.F. Bahia, B. Sarmento, Adv. Drug Deliv. Rev, 2010; 62: 458–477.

47. D. Nayak, A. Boxi, S. Ashe, N.C. Thathapudi, B. Nayak, Mater. Sci. Eng. C, 2017; 73: 406–416.

48. F. Javan, A. Vatanara, K. Azadmanesh, M. Nabi-Meibodi, M. shakouri, J. Pharm. Pharmacol, 2017; 69: 1002–1009.

49. A. Leporati, M.S. Novikov, V.T. Valuev-Elliston, S.P. Korolev, A.L. Khandazhinskaya, S.N. Kochetkov, S. Gupta, J. Goding, E. Bolotin, M.B. Gottikh, A.A. Bogdanov, Nanomedicine, 2016; 12: 2405–2413.

50. J.A. Fulcher, K. Tamshen, A.L. Wollenberg, V.A. Kickhoefer, J. Mrazek, J. Elliott, F.J. Ibarrondo, P.A. Anton, L.H. Rome, H.D. Maynard, T. Deming, O.O. Yang, Bioconjug. Chem, 2019; 30: 2216–2227.

51. A.S. Levina, M.N. Repkova, B.P. Chelobanov, E.V. Bessudnova, N.A. Mazurkova, D.A. Stetsenko, V.F. Zarytova, Mol. Biol, 2017; 51: 633–638.

52. A.S. Levina, M.N. Repkova, N.A. Mazurkova, E.V. Makarevich, Z.R. Ismagilov, V.F. Zarytova, Int. J. Antimicrob. Agents, 2015; 46: 125–128.

53. A.S. Levina, M.N. Repkova, E.V. Bessudnova, E.I. Filippova, N.A. Mazurkova, V.F. Zarytova, Beilstein J. Nanotechnol, 2016; 7: 1166–1173.

54. Y. Li, Z. Lin, M. Zhao, T. Xu, C. Wang, L. Hua, H. Wang, H. Xia, B. Zhu, ACS Appl. Mater. Interfaces, 2016; 8: 24385–24393.

55. Z. Lin, Y. Li, M. Guo, T. Xu, C. Wang, M. Zhao, H. Wang, T. Chen, B. Zhu, RSC Adv, 2017; 7: 742–750.

56. Y. Li, Z. Lin, M. Zhao, M. Guo, T. Xu, C. Wang, H. Xia, B. Zhu, RSC Adv, 2016; 6: 89679–89686.

57. Y. Li, Z. Lin, M. Guo, Y. Xia, M. Zhao, C. Wang, T. Xu, T. Chen, B. Zhu, Int. J. Nanomed, 2017; 12: 5733–5743.

58. Z. Lin, Y. Li, M. Guo, M. Xiao, C. Wang, M. Zhao, T. Xu, Y. Xia, B. Zhu, RSC Adv, 2017; 7: 35290–35296.

59. Y. Li, Z. Lin, M. Guo, M. Zhao, Y. Xia, C. Wang, T. Xu, B. Zhu, Int. J. Nanomed, 2018; 13: 2005–2016.

60. Z. Lin, Y. Li, G. Gong, Y. Xia, C. Wang, Y. Chen, L. Hua, J. Zhong, Y. Tang, X. Liu, B. Zhu, Int. J. Nanomed, 2018; 13: 5787–5797.

61. Y. Li, Z. Lin, G. Gong, M. Guo, T. Xu, C. Wang, M. Zhao, Y. Xia, Y. Tang, J. Zhong, Y. Chen, L. Hua, Y. Hua H. Chun, M. Yeom, H.-O. Kim, J.-W. Lim, W. Na, G. Park, C. Park, A. Kang, D. Yun, J. Kim, D. Song, S. Haam, Polym. Chem, 2018; 9: 2116–2123.

62. C.-M.J. Hu, Y.-T. Chen, Z.-S. Fang, W.-S. Chang, H.-W. Chen, Int. J. Nanomed, 2018; 13: 8579–8593.

63. A. Jamali, F. Mottaghitalab, A. Abdoli, M. Dinarvand, A. Esmailie, M.T. Kheiri, F. Atyabi, Drug Deliv, Transl. Res, 2017; 8: 12–20.

64. A. Frede, B. Neuhaus, T. Knuschke, M. Wadwa, S. Kollenda, R. Klopfleisch, W. Hansen, J. Buer, D. Bruder, M. Epple, A.M. Westendorf, Nanomedicine, 2017; 13: 2395–2403.

65. A.S. Levina, M.N. Repkova, N.A. Mazurkova, V.F. Zarytova, IEEE Trans. Nanotechnol, 2016; 15: 248–254.

66. M. Repkova, A. Levina, B. Chelobanov, Z. Ismagilov, N. Shatskaya, S. Baiborodin, E. Filippova, N. Mazurkova, V. Zarytova, Int. J. Antimicrob. Agents, 2017; 49: 703–708.

67. A.S. Timin, A.R. Muslimov, A.V. Petrova, K.V. Lepik, M.V. Okilova, A.V. Vasin, B.V. Afanasyev, G.B. Sukhorukov, Sci. Rep, 2017; 7: 102.

68. C.E. Coltart, B. Lindsey, I. Ghinai, A.M. Johnson, D.L. Heymann, Philos. Trans. R. Soc. B, 2017; 372: 20160297.

69. K.A. Alexander, C.E. Sanderson, M. Marathe, B.L. Lewis, C.M. Rivers, J. Shaman, J.M. Drake, E. Lofgren, V.M. Dato, M.C. Eisenberg, S. Eubank, PLoS Negl. Trop. Dis, 2015; 9: e0003652.

70. C. Chang, K. Ortiz, A. Ansari, M.E. Gershwin, J. Autoimmun, 2016; 68: 1–13.

71. M.A. Johansson, L. Mier-y-Teran-Romero, J. Reefhuis, S.M. Gilboa, S.L. Hills, N. Engl. J. Med, 2016; 375: 1–4.

72. U. Samarasekera, M. Triunfol, Lancet, 2016; 387: 521–524.

73. B. Surnar, M.Z. Kamran, A.S. Shah, U. Basu, N. Kolishetti, S. Deo, D.T. Jayaweera, S. Daunert, S. Dhar, ACS Nano, 2019; 13: 11034–11048.

74. T.W. Geisbert, A.C. Lee, M. Robbins, J.B. Geisbert, A.N. Honko, V. Sood, J.C. Johnson, S. de Jong, I. Tavakoli, A. Judge, L.E. Hensley, I. Maclachlan, Lancet, 2010; 375: 1896–1905.

75. H. Liu, Y. Bai, Y. Zhou, C. Feng, L. Liu, L. Fang, J. Liang, S. Xiao, RSC Adv, 2017; 7: 28016–28023.

76. S. Huang, J. Gu, J. Ye, B. Fang, S. Wan, C. Wang, U. Ashraf, Q. Li, X. Wang, L. Shao, Y. Song, X. Zheng, F. Cao, S. Cao, J. Colloid Interface Sci, 2019; 542: 198–206.

77. M. Rai, K. Kon, A. Ingle, N. Duran, S. Galdiero, M. Galdiero, Appl. Microbiol. Biotechnol, 2014; 98: 1951–1961.

78. H.H. Lara, N.V. Ayala-Nunez, L. Ixtepan-Turrent, C. Rodriguez-Padilla, J. Nanobiotechnol, 2010; 8: 1.

79. H.H. Lara, L. Ixtepan-Turrent, E.N. Garza Trevino, D.K. Singh, J. Nanobiotechnol, 2011; 9: 38.

80. D.K. Singh, H.H. Lara, Retrovirology, 2012; 9: O1.

81. D.X. Xiang, Q. Chen, L. Pang, C.L. Zheng, J. Virol. Methods, 2011; 178: 137–142.

82. D. Xiang, Y. Zheng, W. Duan, X. Li, J. Yin, S. Shigdar, M.L. O'Connor, M. Marappan, X. Zhao, Y. Miao, B. Xiang, C. Zheng, Int. J. Nanomed, 2013; 8: 4103–4113.

83. L. Lu, R.W. Sun, R. Chen, C.K. Hui, C.M. Ho, J.M. Luk, G.K. Lau, C.M. Che, Antivir. Ther, 2008; 13: 253–262.

84. R.W. Sun, R. Chen, N.P. Chung, C.M. Ho, C.L. Lin, C.M. Che, Chem. Commun, 2005; 40: 5059–5061.

85. A. Mohammed Fayaz, Z. Ao, M. Girilal, L. Chen, X. Xiao, P. Kalaichelvan, X. Yao, Int. J. Nanomed, 2012; 7: 5007–5018.

86. L.A. Osminkina, V.Y. Timoshenko, I.P. Shilovsky, G.V. Kornilaeva, S.N. Shevchenko, M.B. Gongalsky, K.P. Tamarov, S.S. Abramchuk, V.N. Nikiforov, M.R. Khaitov, E.V. Karamov, J. Nanopart. Res, 2014; 16: 2430.

87. E.S.J.M. de Souza, T.D. Hanchuk, M.I. Santos, J. Kobarg, M.C. Bajgelman, M.B. Cardoso, ACS Appl. Mater. Interfaces, 2016; 8: 16564–16572.

88. D. Botequim, J. Maia, M.M. Lino, L.M. Lopes, P.N. Simoes, L.M. Ilharco, L. Ferreira, Langmuir, 2012; 28: 7646–7656.

89. L. Bromberg, D.J. Bromberg, T.A. Hatton, I. Bandin, A. Concheiro, C. Alvarez-Lorenzo, Langmuir, 2012; 28: 4548–4558.

90. H.R. Jafry, M.V. Liga, Q. Li, A.R. Barron, Environ. Sci. Technol, 2011; 45: 1563–1568.

91. T. Hamouda, A. Myc, B. Donovan, A.Y. Shih, J.D. Reuter, J.R. Baker, J.R. Microbiol. Res, 2001; 156: 1–7.

92. T. Hamouda, J.R. Baker Jr., J. Appl. Microbiol, 2000; 89: 3.

93. B.W. Donovan, J.D. Reuter, Z. Cao, A. Myc, K.J. Johnson, J.R. Baker Jr., Antivir. Chem. Chemother, 2000; 11: 41–49.

94. R.D. Requiao, R.L. Carneiro, M.H. Moreira, M. Ribeiro-Alves, S. Rossetto, F.L. Palhano, T. Domitrovic, Sci. Rep, 2020; 10: 5470.

95. A.K. Geim, K.S. Novoselov, Nat. Med, 2007; 6: 183–191.

96. Z. Song, X. Wang, G. Zhu, Q. Nian, H. Zhou, D. Yang, C. Qin, R. Tang, Small, 2015; 11: 1171–1176.

97. F.K. Ayittey, M.K. Ayittey, N.B. Chiwero, J.S. Kamasah, C. Dzuvor, J. Med. Virol, 2020; 92: 473–475.

98. W.C.W. Chan, ACS Nano, 2020; 14: 3719–3720.

99. G. Nikaeen, S. Abbaszadeh, S. Yousefinejad, Nanomedicine (Lond.), 2020; 15; 1501–1512.

100. M.C. Sportelli, M. Izzi, E.A. Kukushkina, S.I. Hossain, R.A. Picca, N. Ditaranto, N. Cioffi, Nanomaterials, 2020; 10: 802.

101. F. Alizadeh, A. Khodavandi, IEEE Trans. Nanobiosci, 2020; 19: 485–497.

102. V. Uskokovic, ´ Nanomedicine (Lond.), 2020; 15: 1719–1734.

103. T.Y. Hu, M. Frieman, J. Wolfram, Nat. Nanotechnol, 2020; 15: 247–249.

104. S. Ghosh, S.M. Firdous, A. Nath, EXCLI J, 2020; 19: 528–531.

105. S. Kumar, K. Zhi, A. Mukherji, K. Gerth, Viruses, 2020; 12: 486.

106. B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, H. Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, N. Engl. J. Med, 2020; 382: 1787–1799.

107. C.-M.J. Hu, W.-S. Chang, Z.-S. Fang, Y.-T. Chen, W.-L. Wang, H.-H. Tsai, L.-L. Chueh, T. Takano, T. Hohdatsu, H.-W. Chen, Sci. Rep, 2017; 7: 13043.

108. Y. Jiang, N. Krishnan, J. Heo, R.H. Fang, L. Zhang, J. Control. Release, 2020; 324: 505–521.