Smart and Sustainable Nanotechnological Solutions in a Battle against COVID-19 and Beyond: A Critical Review

Agnieszka M. Jastrzębska* and Alexey S. Vasilchenko

ABSTRACT: The variety of available biocidal features make nanomaterials promising for fighting infections. To effectively battle COVID-19, categorized as a pandemic by the World Health Organization (WHO), materials scientists and biotechnologists need to combine their knowledge to develop efficient antiviral nanomaterials. By design, nanostructured materials (spherical, two-dimensional, hybrid) can express a diverse bioactivity and unique combination of specific, nonspecific, and mixed mechanisms of antiviral action. It can be related to the material’s specific features and their multiple functionalization strategies. This is a complex guiding approach in which an interaction target is constantly moving and quickly changing. On the other hand, in such a rush, sustainability may be put aside. Therefore, to elucidate the most promising nanotechnological solutions, we critically review available data within the frame of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other types of viruses. We highlight solutions that are, or could be, more sustainable and less toxic. In this regard, reduction of the number of synthetic routes, organic solvents, byproducts, and residues is highly recommended. Such efficient, green solutions may be further used for the prevention of virion—host interactions, treatment of the already developed infection, reducing inflammation, and finally, protecting healthcare professionals with masks, fabrics, equipment, and in other associated areas. Further translation into the market needs putting on the fast track with respect to principles of green chemistry, feasibility, safety, and the environment.

KEYWORDS: COVID-19, SARS-CoV-2, Smart nanomaterials, Nanotechnology, Antiviral, Protection, Prevention, Treatment, Mechanisms of action, Efficiency, Toxicity, Resistance, Safety, Sustainability

INTRODUCTION

A new type of disease was first reported in China close to the end of 2019 and was soon labeled by the World Health Organization (WHO) as pandemic coronavirus COVID-19.1 Novel SARS-CoV-2 virus was quickly transmissible, allowing it to spread to over 200 countries, infecting more than 40 million people and claiming over a million lives to date.2 The first infections with SARS-CoV-2 were noticed in the Hubei Province of China. Patients showed symptoms similar to pneumonia and were visualized to have abnormal features in their lungs. Difficulties in clinical recognition caused the necessity of sample screening with a polymerase chain reaction (PCR) within disclosed pathogen control panels. The first obtained results were negative, but further studies with next-generation sequencing, presented at the beginning of 2020, revealed the presence of an RNA virus.3 Meanwhile, the sequence of the novel virus genome showed similarities to SARS-CoV from the 2002–2003 outbreak. Therefore, it was named severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).4

The Coronaviridae family includes many species. When compared to the current pandemic, previous SARS-CoV and the Middle East respiratory syndrome (MERS-CoV) coronaviruses were characterized by lower transmission potential which allowed the effective prevention of spreading. It is noted that most of the hundreds of identified coronaviruses are transmissible only between animals, and this reservoir for SARS remains still unexplored.5 Cross-species transmission is also a specific “gene pool” allowing viruses to generate a new recombinant species.6 Some of these can adapt to new human hosts.5,6 To date, seven coronaviruses are proven to cause human diseases, and three times during recent years they caused a global health emergency. Nevertheless, most of them (for
instance, HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) develop a common cold in humans. Before SARS-CoV-2 appeared, SARS-CoV-1 caused severe disease with ~10% mortality and MERS-CoV caused ~35% mortality.

The most contagious so far is beta-SARS-CoV-2. Its sequence is 96% similar to beta-coronaviruses in comparison to the whole genome found in bats. It is, however, genetically different from other MERS coronaviruses. Pairwise protein sequence analysis revealed its belonging to the SARS-CoV family and various transformations during pandemic spreading. Similar genomes were also identified for beta-CoVs (Wuhan/IVDC-HB-01/2019, IVDC-HB-04/2020, IVDC-HB-05/2019, WIV04/2019) and the previous malignant IPBCAMS-WH-01/2019 virus. Therefore, it is likely that the expected consecutive genetical transformations will lead to lower malignancy of the SARS-CoV-2.

Because of the low fatality of previous HCoVs, the coronaviral drug discovery and nanotechnological-related studies on their prevention and treatment did not evolve into industrial application. While taking into consideration the significant infectivity of SARS-CoV-2, as well as long-range detrimental effects on human health, filling this gap of knowledge is undoubtedly an emergency.

Transmission of SARS-CoV-2 is high in comparison to other coronaviruses because of a long period of latency, high infectivity, and many asymptomatic carriers. It is estimated that in the case of Wuhan, the mean value of the rate of fatal development of symptoms (probability of dying) is 1.4%. The risk increases with age, and symptomatic adults between 30 and 60 years old are ~4% of the patients per year. This means that the majority of persons can be asymptomatic and unaware of spreading the virus. Their daily activities quickly cause person-to-person transmission for which the WHO highlights both hospital and family settings as most critical for rapid expansion of coronavirus.

This allows for further assumption that it also transmits through contaminated surfaces and self-inoculates within the nose, eyes, and mouth mucous membranes. A recent analysis on aerosol exposure concentrated on swab samples and surfaces of sickbed handrails, computer mice, floors, trash cans, and masks, as well as other personal protective equipment used by patients with severe disease. It also considered indoor air and the air outlets with a 300 L min⁻¹ flow rate for 30 min. The aerosol distribution characteristics showed a transmission distance of up to 4 m. This implies a potentially extraordinary infection risk for people contacting patients with COVID-19.

Available data on less contagious airborne endemic human coronavirus 229E (HCoV/229E) are helpful to better understand survival rates. These studies were carried out at temperatures of 6 and 20 °C and relative humidities (RH) of 30%, 50%, and 80%. It has been noted that at 20 °C and 50% RH aerosolized HCoV/229E virions survived for over 60 h. Afterward, 20% of virions remained contagious for over 6 days. This indicates more a complex role of the environmental features on virus survival than only a low temperature stabilization effect. Indeed, a recent study showed that a 1% decrease in relative humidity of indoor air causes 7%–8% increase in detected COVID-19 cases. In this context, low humidity of air can be critical in virus transmission and survival rates. Other studies on the persistence of coronaviruses showed that copper surfaces inactivate the virus in approximately 4 h.

Recent analysis also revealed that SARS-CoV-2 is new to human beings. Therefore, when facing less immunity during the winter season it is likely to transmit more readily. Lack of expected slowing of virus spreading concerning season changing showed that variables in outdoor temperatures are not enough to stop transmission on its own. In this regard, lowering the transmission of SARS-CoV-2 is assumed as the starting point for better control of the COVID-19 disease.

Transmission of the virus can also be affected by air conditions. A recent study demonstrated that even with moderate transmission of SARS-CoV-2, low humidity of air can be critical in virus transmission. These studies were carried out at temperatures of only 20 °C, which is not an unusual parameter for COVID-19-affected regions.

Transmission of SARS-CoV-2 is assumed as the starting point for exacerbating virus spreading. This implies a distance of up to 4 m. For instance, if the virus is transmitted from droplets on surfaces, it can lead to a higher risk of transmission within a shorter distance. This is particularly important in indoor settings where the virus can easily spread due to the closed environment.

Disinfectants are used to reduce the transmission of SARS-CoV-2. The effectiveness of these agents can vary depending on the type of disinfectant and its concentration. For example, sodium hypochlorite, glutardialdehyde, and isopropanol are effective against the virus. However, these agents can be toxic and should be used with caution.

Constantly postponing sustainability increases concern that better efficiency will result in a long-range undesirable impact on human health and the environment. It is accepted that designing sustainable nanotechnological solutions is challenging. Considering inherently nonhazardous materials and energy inputs/outputs takes time and must include integration and interconnectivity with available energy and materials’ flows. The proposed nanotechnological solutions are not carefully analyzed in terms of sustainability measures. As a consequence, natural, biodegradable, and biocompatible resources are still not widely used in development of nanomaterials.

In the context of fighting COVID-19, nanoparticle synthesis methods involving natural and renewable resources are the unquestionable benchmarks. Feasible, nontoxic, and scalable synthesis routes are beneficial to sustainability, as well as self-assembly techniques that are another good example of sustainable approaches. They are based on molecular interactions without chemical bonds breaking or forming. Techniques that allow for better controlling the properties by using building blocks, using reversibility, or providing external stimuli response are therefore a matter of interest for development of nanotechnological approaches against SARS-CoV-2 virus. The resulting amount of synthetic routes and
stages is favorably reduced together with the use of organic/toxic solvents and residues.\textsuperscript{42}

This perspective reports the current potential of smart antiviral nanotechnological solutions in fighting COVID-19. These are, or could be, less toxic and more sustainable. The advantage comes from broad coverage, more clear (specific and/or nonspecific) systematization, and critical discussion with knowledge on nanotechnology-based antiviral solutions. In the area of mixed modes of action, this work covers promising antiviral nanomaterials that act outside and/or inside the host concerning virus structural features, spreading pathways, and survival rates. In this regard, it describes development of complex multifunctional virucidals, possible variations in mechanisms of action, potential cytotoxicity, and resistance targets viz. the most actual SARS-CoV-2 infection cycle. We believe that this study will increase future awareness of a selection of nanotools for antiviral nanomaterials with rationally designed mechanisms of action that are useful for future fundamental and application studies.

In addition, this perspective goes beyond the COVID-19 pandemic, presenting the most promising and sustainable approaches that are already reported for other types of viruses in the hope that they will also find the possibility to confirm their applicability against SARS-CoV-2. In this regard, protection...
equipment with respect to safety, reliability, and sustainability are reviewed as well.

**NANOTECHNOLOGY FOR VIRUS PREVENTION AND TREATMENT**

Development of broad-spectrum antiviral drugs is a great challenge because of the many difficulties in using targeting approaches within virus-specific mechanisms of action. Broad-spectrum antivirals can act against many virus species that even exhibit significant differences in structural and phylogenetical natures. The problem of limited action can be solved with nanomaterials that offer properties allowing them to broadly interact with various types of viruses. Smart nanomaterials offering variety and diversity of available bioactive features can be promising for prevention and treatment of COVID-19.33 They can both prevent the formation of entry complexes at the host surface and provide therapeutic features inside the host after virus entry.

The urgent need for finding a universal solution against SARS-CoV-2 has resulted in the preparation of various review papers concentrating on listing already developed antiviral nanosystems,23−27 as well as emerging ones.38−32,23,33 These are highly valuable in searching for the most effective solutions in relation to known viruses. The knowledge is now developing so fast that it urgently needs to be revisited. For example, recent elucidation of viral NSP-family proteases such as Mpro main,43 or PLpro pappain-like cysteine protease44 allows developing new targeting approaches. Also, freshly discovered formation mechanisms of cytosolic double-membrane vesicles armed with crown-shaped molecular pore complexes45 significantly changes the previously assumed simplified conditions50 that are currently used for the analysis of nanomaterials’ antiviral potential.

In this section of the study, the available nanotechnological solutions are critically discussed concerning the newest reported life cycle and unique features of SARS-CoV-2. Many complex approaches developed for nanomaterials concern various antivirals that put at first place the material’s properties of finding its explicit influence on the whole viral life cycle. In the simplified scheme of viability observation, the antiviral activity against different types of viruses was demonstrated by inorganic metallic nanocompositions (silver,46 gold,47,48 copper45) and metal oxide nanoparticles (NPs) (tin oxide,50 zinc oxide,51 titanium dioxide52,53). Other nanotechnology-based approaches include carbon-based nanostructures (quantum dots,54,55 graphene56) and organic-based compositions57,58 as well as inorganic–organic hybrid systems.59 In most cases, there is no explicit information on the outcome, for instance, if the virus was irreversibly inactivated or still possessed the infectivity upon dilution. Also, can the observed antiviral effects be extended toward other types of viruses? In this context, defining the right mechanism for nanomaterial antiviral action is rather difficult. Moreover, analyzing nanomaterials in terms of biostatic or biocidal action is also not a fully adequate approach because the main criterion by which substances can be divided into biostatics and biocides is the reversibility or irreversibility of the inhibitory effect after the test object is no longer in contact with the drug.

Nevertheless, we have recognized that the available knowledge on nanomaterials bioactivity can be more clearly rearranged into specific and nonspecific groups of mechanisms of action. While using this approach, we can easily distinguish specific or nonspecific behaviors for the described nanomaterials. Moreover, we denote the right signposts and targets for subsequent development of innovative nanotechnological solutions based on a new generation of mixed mechanisms of action, such as those presented in Figure 1. Below, we give a more detailed explanation of criteria enabling nanomaterials to be classified into a specific or nonspecific group of action.

While choosing the right mechanism of action, it is important to answer only three questions. First, is the antiviral action equally effective against a minimum of two types of viruses, for example, enveloped and nonenveloped? Is the nanomaterial intentionally or nonintentionally guided by any nanotechnological or hybrid means to the site of its intensified action? This can be a reaction site localized in/on virus/cell or other places of choice. Finally, does the antiviral efficiency remain upon dilution and/or loss of nanomaterial—virus interaction?

In the context of the aforementioned questions, rethinking the mechanisms of antiviral action becomes a rather noncomplicated issue. Therefore, in the case of a specific mechanism of action, the nanomaterial mostly reversibly targets receptors or ligands on the surface of the virus or cell that leads to the prevention of virus−cell interaction. The second group is the nonspecific antivirals which have a destructive effect on various structures of the virion regardless of their taxonomic position and local place of stay. In other words, their action is not externally guided and leads to irreversible deactivation of the virus, also upon dilution. They can be thus safer for patients than those of only the nonspecific group. There is also the third group—mixed-type antivirals. They provide complex bioeffects that are challenging to understand and control. However, they can be also smartly tailored for the on-demand and/or stimuli—response manner of action.

Given the above, further discussion was arranged by the type of action (specific, nonspecific, and mixed) to facilitate recognition of mechanisms of action and possible challenges that need to be faced. This is especially important for development of antivirals with mixed mechanisms of action. Finally, we present data in Table 1 arranged by the type of virus to provide better recognition of the powerful nanomaterial-based solutions already verified against HCoV, SARS, MERS, and other viruses of current interest. Such an approach facilitates the need for standardization of nanomaterials that may be promising in development of broad-spectrum nanotechnological solutions.

**Nanomaterials with a Specific Mechanism of Antiviral Action.** Nanomaterials with a specific mechanism of action mostly act outside the host cell by inactivating virus particles before entering through the cell membrane. This contributes to the disruption of the first phase of the virus life cycle. The SARS-CoV-2 particle is not a very complicated structure in comparison to bacteria or mammalian cells. The virus features are schematically presented in Figure 1a. The ∼60−140 nm capsid is covered by a lipid-based viral envelope carrying a single-stranded RNA genome.60 The construction proteins can be divided into membrane (M), envelope (E), and spike (S), as well as the nucleocapsid (N) which hosts the RNA genome. The S proteins covers the virus surface and form ∼9−12 nm structures.61 The nucleocapsid additionally contains a wide range of different accessory and functional elements. These include viral NSP-family proteases together with recently discovered Mpro main,53 and PLpro pappain-like cysteines.61

Binding to viral structural elements is a simple solution that allows development of broad-spectrum, nontoxic antivirals. In such a case, the activity strictly depends on the reversible binding, which relates to the dilution effect mostly caused by the
| Virus type                        | Material               | Size (nm) | Surface modification/loading                                      | Mechanism of action                                                                 | Type of basic structure | ref  |
|----------------------------------|------------------------|-----------|------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------|------|
| Human coronavirus (HCoV-229E)    | Carbon QD              | 2−20      | Surface-modified with amine and boronic acid moieties             | Prevention of viral entry and replication                                             | Carbon nanostructures   | 54   |
|                                  | calix[4]arene          | no data   |                                                                  | Wide virucidal activity                                                               | Supramolecular structures| 57   |
| Human coronavirus (SARS-CoV)     | peptide-based plasmid NPs | 25        | Platform for vaccine development                                 | Immunity stimulation by formation of artificial entry complexes with viral spike protein | Inorganic α-helicals    | 162  |
| Human coronavirus (MERS-CoV)     | Au nanorods conjugated  | 20−50     | Surface-modified with peptide pregnancy-induced hypertension     | Membrane fusion inhibition                                                           | Metallic NPs            | 111  |
| Influenza virus (H1N1)           | Ag NPs                 | 2−3       | Loaded with virucidal drug oseltamivir                          | Prevention of viral entry and replication, influence ROS-signaling pathways, phosphorylation | Metallic/organic hybrid nanostructure | 59   |
|                                  | Au NPs                 | 12        | Surface-modified with antigens M2e and CpG                      | Reduction of viral activity                                                          | Metallic NPs            | 163  |
|                                  | CuI NPs                | ≈160      |                                                                  | Degradiation of viral proteins                                                       | Inorganic NPs           | 49   |
|                                  | TiO₂ NPs               | no data   | Surface-modified with DNA by ionic polylysine linkage            | Targeting the 3’-noncoding area of influenza                                          | Inorganic NPs           | 164  |
| Chitosan                         | 100−200                |           | Loaded with hemagglutinin                                        | Reduction of viral activity                                                          | Polymeric nanostructures| 165  |
| Chitosan                         | 140                    |           | Loaded with H1N1 antigen                                         | Reduction of viral activity                                                          | Polymeric nanostructures| 166  |
| Chitosan                         | 300−350                |           | Loaded with HA split                                             | Reduction of viral activity                                                          | Polymeric nanostructures| 167  |
| Chitosan                         | 200−250                |           | Loaded with M2e antigen                                          | Reduction of viral activity                                                          | Polymeric nanostructures| 168  |
| Liposomes                        | no data                |           | Loaded with influenza glycoproteins                             | Reduction of viral activity                                                          | Polymeric nanostructures| 58   |
| Ferritin                         | 13                     |           | Loaded with M2e antigen                                          | Reduction of viral activity                                                          | Self-assembled proteins and peptides | 169  |
| Q11 peptide                      | no data                |           | Loaded with acid polymerase                                      | Reduction of viral activity                                                          | Self-assembled proteins and peptides | 170  |
| N nucleocapside protein of RSV   | 15                     |           | Loaded with M2e antigen                                          | Reduction of viral activity                                                          | Self-assembled proteins and peptides | 171  |
| VLP                              | 80−120                 |           | Loaded with hemagglutinin                                        | Reduction of viral activity                                                          | Polymeric nanostructures| 172  |
| ISCOM                            | 80−120                 |           | Loaded with M2e antigen                                          | Reduction of viral activity                                                          | Polymeric nanostructures| 173  |
| STP702 (Fluquit)                 | 30−100                 |           | Loaded with M2, HA, NP, MLP, trehalose-6,6′-dimycolate          | Reduction of viral activity                                                          | Polymeric nanostructures| 174  |
| Swine influenza virus (H1N2)     | PLGA                   | 225       | Loaded with BPLS V proteins                                     | Reduction of viral activity                                                          | Polymeric nanostructures| 175  |
|                                  | γ-FGA                  | 200−300   | Loaded with inactivated virions                                 | Immunity stimulation by formation of artificial entry complexes with viral spike protein | Polymeric nanostructures| 176  |
| Chitosan                         | 572                    |           | Loaded with inactivated virions                                 | Immunity stimulation by formation of artificial entry complexes with viral spike protein | Polymeric nanostructures| 177  |
| Influenza virus (H3N2)           | ISCOM                  | 80−120    | Loaded with M2e antigen                                          | Reduction of viral activity                                                          | Polymeric nanostructures| 176  |
| Avian influenza virus (H5N1)     | ISCOM                  | 80−120    | Loaded with M2e antigen                                          | Reduction of viral activity                                                          | Polymeric nanostructures| 176  |
| Virus type                                      | Material        | Size (nm) | Surface-modification/loading | Type of basic structure/interactions | Mechanism of action                                                                 | Type of basic structure |
|------------------------------------------------|-----------------|-----------|-------------------------------|---------------------------------------|-------------------------------------------------------------------------------------|------------------------|
| Influenza virus (H7N9)                          | STP702 (Fluquit)| no data   |                               | Polymeric nanostructures (under preclinical trial)                                  | Reduction of viral activity, adsorption and inactivation                              | Carbon nanostructures  |
| *Endemic gastrointestinal avian influenza*      | GO              | 1–3 μm    |                               |                                       | Prevention of viral entry and replication                                              | Metallic NPs           |
| *Avian influenza*                               | GO              | 1–3 μm    |                               |                                       | Prevention of viral entry and replication                                              | Metallic NPs           |
| *Human parainfluenza 3 virus (HPIV-3)*         | Ag NPs          | 2–100 nm  |                               | Metallic NPs                          | Prevention of viral entry and replication                                              | Ag NPs                 |
| *Bovine parainfluenza 3 virus (BPI3V)*         | PLGA            | 225       |                               |                                       | Prevention of viral entry and replication                                              | Metallic NPs           |
| *Respiratory syncytial virus* (RSV)            | ISCOM           | 80–120    |                               |                                       | Prevention of viral entry and replication                                              | Metallic NPs           |
| *Porcine reproductive and respiratory syndrome* | Carbon QD       | ∼5        | Surface-modified with curcu-minine deliverables | Carbon nanostructures                 | Prevention of viral entry and replication                                              | Metallic NPs           |
| *Herpes simplex virus type 1 (HSV-1)*          | Carbon QD       | ∼5        | Surface-modified with curcu-minine deliverables | Carbon nanostructures                 | Prevention of viral entry and replication                                              | Metallic NPs           |
| *Porcine epidemic diarrhea virus* (PEDV)       | Carbon QD       | ∼5        | Surface-modified with curcu-minine deliverables | Carbon nanostructures                 | Prevention of viral entry and replication                                              | Metallic NPs           |
| Virus type                                  | Material            | Size (nm) | Surface-modification/loading | Mechanism of action                                                                 | Type of basic structure       | ref  |
|--------------------------------------------|---------------------|-----------|------------------------------|-------------------------------------------------------------------------------------|-------------------------------|------|
| Au NPs                                     | ∼10                 | Surface-modified with MES | Prevention of viral entry, interfere with viral attachment and entry, and cell-to-cell spread | Metallic NPs                     | 48   |
| Au NPs human papillomavirus type 16 (HPV-16) | 15                  | Surface-modified with MUS | Prevention of viral entry by strong reversible/irreversible binding and eventual virus deformation | Metallic NPs                     | 62   |
| SnO micro–nanowires                        | nanomicro           | Surface-modified with HS | Prevention of viral entry and cell-to-cell spread                                   | Inorganic nanostructures       | 50   |
| PEG-8-FMAAPTAC                             | no data             | –         | Blocking formation of the entry/fusion complex                                     | Hybrid polymeric nanostructures | 185  |
| Herpes simplex virus type 2 (HSV-2)        | Ag NPs              | 2–400 nm  | –                            | Prevention of viral entry and replication                                           | Metallic NPs                   | 46   |
| Au NPs                                     | 15                  | Surface-modified with MUS | Prevention of viral entry by strong irreversible binding and eventual virus deformation | Metallic NPs                     | 62   |
| ZnO micro–nanotetrapods                    | 300 nm–40 μm       | –         | Prevention of viral entry by direct binding                                        | Inorganic nanostructures       | 51   |
| Human immunodeficiency virus (HIV)         | Carbon QD           | ~2        | Edge-modified with boronic acid and amine moieties                                | Suppression of syncytium formation, interaction with gp120                       | Carbon nanostructures          | 55   |
| Graphene QDs                               | several μm         | –         | Inhibition of virus entry by direct binding                                       | Carbon nanostructures          | 114  |
| Human papilloma virus type 16 (HPV-16)     | Au NPs              | 15        | Surface-modified with MUS          | Prevention of viral entry by strong irreversible binding and eventual virus deformation | Metallic NPs                   | 62   |
| STP909 (Cervisil)                          | no data             | Loaded with siRNA       | Silencing of E7 gene                                                             | Polymeric nanostructures (under preclinical trial) | 186  |
| STP909 (Cervisil)                          | no data             | Loaded with siRNA       | Silencing of E7 gene                                                             | Polymeric nanostructures (under preclinical trial) | 186  |
| Peptide NPs                                | 180–210             | Loaded with E7 DNA nucleic acids | Immunization with induces stronger Th1 cellular immune response with a predominant interferon profile | Peptide-based gene delivery system for vaccination | 113  |
| Pseudorabies virus (PRV)                   | Carbon QD           | ~5        | –                            | Inducing interferon production and expression, inhibition of virus replication       | Carbon nanostructures          | 183  |
| GO                                         | nano–micro         | Surface-modified with PVP | Reduction of viral activity through single-layer structure, mechanical damage, electrostatic interactions | Carbon nanostructures          | 56   |
| rGO                                        | nano–micro         | Surface-modified with PVP | Reduction of viral activity through single-layer structure, mechanical damage, electrostatic interactions | Carbon nanostructures          | 56   |
| Feline calicivirus (FCV)                   | CuI NPs             | ~160      | –                            | ROS generation, capsid protein oxidation by CuI, amino acid oxidation in the viral capsid proteins | Inorganic NPs                   | 187  |
| Bacteriophages (MS2, PRD1, phiX174, ΦX177)| P25 TiO₂ NPs        | 25        | –                            | Direct binding and photocatalytic inactivation by UV light                          | Inorganic NPs                   | 52   |
| Orthopoxvirus                              | rGO                | 0.75 μm   | Surface-modified with heparin's synthetic analogue-dendritic polyglycerol         | Reduction of viral activity by direct binding                                      | Carbon nanostructures          | 188  |
| Pathogenic EV71 virus                      | GO                 | 1–3 μm    | Reduction of GO to rGO          | Virus capture, adsorption and reduction of activity                                | Carbon nanostructures          | 97   |
| Pseudotyped lentivirus (LV-VSV-G)          | Au NPs              | 15        | Surface-modified with MUS       | Prevention of viral entry by strong irreversible binding and eventual virus deformation | Metallic NPs                   | 62   |
extracellular environment. If the nanoagent does not immediately inactivate the virus, it is detached upon dilution allowing the virus to rebuild its infectivity. It is worth highlighting that this is also a key mode of action that determines the difference between virustatic and virucidal agents.62

Further targeting may involve the host cell membrane and associated cell-viral receptors which are targeted by many viruses during the first step of the replication cycle. These are angiotensin 2 converting enzyme (ACE2)63 and transmembrane serine protease 2 (TMPRSS2),64 as well as endosomal cysteine proteases (cathepsins).65 The affinity of SARS-CoV-2 proteases is higher toward ACE2 than TMPRSS2.

Preventing the binding to glycoproteins and their further inactivation is another good direction for designing smart nanotechnological solutions. Liposome nanostructures can be used here for this purpose. While being nontoxic and of natural origin, they can be substantially used for transportation of synthetic receptor glycan sialyl neolacto-N-tetraose c (LSTc)-sialoside that can bind and deactivate the influenza A virus.58 Influenza glycoprotein hemagglutinin (HA), as well as neuraminidase (NA), can be also used for liposome functionalization.66 Such prepared liposomes attach to binding sites and further release the antiviral drug Oseltamivir.67

The recent study using computational approaches revealed the specific binding features of the SARS-CoV-2 spike protein which is positively charged because of a majority of positively charged residues versus a minority of negatively charged ones. As a consequence, interactions between spike proteins and ACE2 receptors showed a 30% higher energy binding in the case of SARS-CoV-2 than previous SARS-CoV. These results are useful not only for understanding the mechanism of cell entry but also for designing the targeting nanoagents.68 Nevertheless, based on previous evidence and experience with SARS and MERS, the primary focus has been the S protein,69 considered as the ideal target for future COVID-19 nanotherapies.

While searching for new antiviral nanomaterials, it is noted that two-dimensional (2D) nanostructures also show a large potential in pathogen elimination. This large and diverse group includes graphene family materials (GFMs),70 2D oxides and hydroxides,71 transition metal dichalcogenides72 and nitrides,73 2D metal-organic covalent frameworks,74 ditransition metal phosphides, selenides, and sulﬁdes,75 as well as Xenes76 and MXenes.77 The family of MXenes is the most recent and also prospective member of this group of 2D materials. MXene phases, also known as the early transition metal carbides, nitrides, and carbonitrides were first reported by Naguib et al.77 While most MXenes were predicted theoretically and only a small portion was obtained experimentally,78 they have a large potential for further development. MXenes have already demonstrated large application potential in macromolecules adsorption,79 nanomedicine,80 and environmental remediation.81 Since 2016, biocidal features of MXenes continue to be widely developed.82−84 Recent results reveal their potential in antifouling materials,82,83 while their antiviral properties are yet to be explored.

Among other 2D nanomaterials, carbon-based nanostructures proved their efficiency in both bacteria and virus elimination.37 Several advanced nanotechnological solutions that involve GFMs were developed during the previous years that may be extended against COVID-19.89 A recent study considered the antiviral action of graphene oxide (GO) and reduced graphene oxide (rGO) toward the porcine epidemic diarrhea virus (PEDV) and pseudorabies virus (PRV).56 Results indicate a
reduction of the PEDV and PRV infections by GO conjugated with sustainable and nontoxic polyvinylpyrrolidone (PVP). The possible mechanism of action involved the antiviral influence of the negative surface charge of the developed 2D nanostructure, as well as its sharp edges.

It is worth mentioning that the zeta potential was previously indicated as a key for interactions of various nanostructures with microorganisms. For an antiviral nanomaterial, it should be larger to develop a local gradient of charge or the opposite to the positively charged viral envelope. The considered attachment can be thus much more effective. Sharp edges and zeta potential were also evaluated in the case of GO antiviral activity.

It should be stressed that the aforementioned effects may pose a safety risk because strong electrostatic interactions also occur between cell lipid headgroups and graphene oxide. Apart from potential problems with biocompatibility, GO-mediated multiplex interactions can be used for designing on-site disinfection of viruses such as virus of waterfowl (H7N9) and endemic gastrointestinal avian influenza (H9N2). Interestingly, the disinfection by virus entrapment occurs during temperature-dependent GO reduction to rGO and is most efficient at elevated temperatures such as ~56 °C.

**Nanomaterials with a Nonspecific Mechanism of Antiviral Action.** The most desirable property of the ideal antiviral nanomaterial is the nonspecific activity. The expected outcome is the irreversible deactivation of the virus no matter how large the subsequent dilution is. In this regard, detrimental virucidal effects cannot affect the treated cell. The needed selectivity is, therefore, a great challenge and a huge bottleneck in development of nonspecific antiviral nanomaterials. The potential toxicity of nanomaterials is a major concern in this case and needs careful and in-depth studies while designing antiviral nanotherapeutics for fighting respiratory diseases. If nontoxic, nanomaterials can be beneficial in specific targeting and treatment as they should not induce significant resistance. A more detailed discussion of the mentioned aspects is given in the further sections of this perspective.

When considering the nonspecific antiviral nanomaterials that act outside the cell, there is the need for development of the binding solution that will allow for obtaining broad-spectrum efficiency. This is of crucial importance for the prevention action against various types of viruses. As a consequence, targeting cell–virus interactions is being developed extensively and concentrates on achieving deactivation of virions through structural elements that are common to most types of viruses. This can be done by interacting positively charged NPs with negatively charged heparan sulfate (HS) groups. They are expressed by the host surface and are cofactors that directly bind with spike proteins to promote viral entry. Therefore, no matter if we consider specific or nonspecific mechanisms of antiviral action, the first gatekeeper for prevention still concerns interactions between the cell and the virus. In this regard, targeting cellular heparan sulfate is promising for development of future broad-spectrum antivirals.

While designing antiviral solutions that should work inside the treated host, the uptake is the second stage to consider. It must be effective, with again no harm to treated cells. The internalization mechanism may involve claritin or caveolae-mediated endocytosis, macropinocytosis, or phagocytosis. In this context, the size and shape of the uptaken nanomaterial have a crucial influence on the mechanism of entry. Differences in sizes, physicochemical properties, surface modifications, or the type of treated cells can significantly affect the penetration level and cellular entry. The size of ~50 nm is optimal for uptake by nonphagocytic cells. In this regard, the specific intracellular microenvironment of action is important to consider and is a matter of interest because it influences the aforementioned interactions.

For nonspecific treatment of infections, nanodrugs should first easily enter the host cell and work specifically in its interior to target various stages of viral action. Here, a wide range of different effects can be activated, depending on the type of entry (endocytosis) and further processing of new virions. In this regard, extensive research is needed to develop effective nanomaterial-based antiviral systems, as well as to understand their detailed mechanism of action. On the other hand, broad-spectrum therapy is challenging because *Coronaviridae* are diverse from a biological point of view, as well as rapidly mutate. Nevertheless, some interesting antiviral solutions are already available thus paving the way for more rapid development of nanodrugs against SARS-CoV-2 and other viruses.

Antiviral action toward HCoV-229E, a similar type of coronavirus, was already confirmed for carbon quantum dots (CQDs). The important thing here is the carbon precursor which was used for the synthesis of CQDs and their surface modification. In a recent study, CQDs with a concentration-dependent antiviral activity of EC50 of 52 μg mL−1 were obtained using hydrothermal carbonization of citric acid in a mixture with ethylenediamine. During synthesis, CQDs were subsequently modified with boronic acid ligands. This is important from the activity point of view because the surface modification of nanomaterials has a crucial impact on biological response. Indeed, the pristine CQDs obtained from 4-aminophenylboronic acid resulted in obtaining excellent EC50 values below 5.2 μg mL−1. The mechanism of action involved inhibition of virus entry by interaction with entry receptors and disturbing the viral replication step. Other studies confirmed that CQDs can be successfully used against various types of viruses as broad-spectrum antivirals (Table 1). Highly biocompatible CQDs synthesized from glycyrrhizic acid by a hydrothermal method were used for deactivation of porcine reproductive and respiratory syndrome virus (PRRSV). Other solutions considered the use of curcumin for the synthesis of cationic CQDs and their verification toward porcine epidemic diarrhea virus (PEDV). Obtained nanostructures inhibited entry and proliferation of viruses by binding with surface proteins and suppressing the synthesis of RNA.

Obtained results also indicate that CQDs, apart from halting virus invasion and replication steps, reduce accumulation of intracellular reactive oxygen species (ROS) accumulation, as well as stimulate an antiviral innate immune response. It is further noted that 2D materials can be also used as ROS scavengers. A recent study demonstrates the use of delaminated 2D Nb2C and Nb5C3 MXenes modified with poly-l-lysine (PLL) as effective ROS scavenging agents. Another study presents feasible ROS, reactive nitrogen species (RNS), and inflammatory cytokines scavengers based on 2D transition metal dichalcogenides (TMD). Delaminated 2D WS2, MoSe2, and WSe2 nanosheets surface modified with polyethylene glycol (PEG) effectively reduced mitochondrial and intracellular ROS and RNS in inflammatory cells. This effect can be highly beneficial for controlling nanomaterials toxicity and should be further investigated also in more complex antiviral systems.

While the suppression of viral replication additionally causes overproduction of proinflammatory cytokines and interferon-
stimulating genes (ISGs), it is important for smart therapeutic nanostructures to minimize the cytokine release (cytokine storm), which is one of the most detrimental effects of COVID-19. Novel nanoparticles were also reported to possess antiviral activity through a different mechanism of action, and gold nanoparticles (Au NPs) are the mostly studied antiviral nanostructure. MERS-CoV can be treated with Au NPs conjugated with the specific peptide called pregnancy-induced hypertension (PIH). It disturbs membrane fusion between virus and host cells mediated by the HR1/HR2 peptide pair. The obtained nanohybrids exhibited better biocompatibility and stability in vitro and in vivo. Respiratory syncytial virus (RSV) can be also successfully inhibited by Au NPs. The nontoxicity is maintained by coating with undecanulosonic acid (MUS) ligands. MUS ligands also proved their efficiency for designing broad-spectrum antiviral nanomaterials with a nonspecific mechanism of action against both enveloped (HSV, RSV, lentivirus, and dengue virus) and the so-called nonenveloped (“naked”) (HPV) types of viruses. Silver nanoparticles (Ag NPs) can be used as oseltamivir carriers toward H1N1 infection by condensation of chromatim, DNA fragmentation prevention, and targeting the caspase-3 function. Human parainfluenza 3 (HPIV-3) was also inactivated with Ag NPs by suppressing replication after blocking the function of cell—virus leveraging. Notably, the inhibitory effect was size dependent and zeta potential dependent. A subsequent study showed that the PLL linker can be also used to prepare titanium dioxide nanoparticles (TiO2 NPs) conjugated with DNA. This nanocarrier works by entering and targeting the 3′-noncoding area of the influenza A virus.

GFM can additionally advance development within the field of COVID-19 nanotherapies. Graphene quantum dots (GQD) can deliver drugs and inhibit a virus by target-specific interactions. A recent study involving GQD conjugated with non-nucleoside reverse transcriptase inhibitors (NNRTI) showed extraordinary anti-HIV activity with IC50 of 0.09 μg/mL. In another study, graphene oxide modified with nano-Ag (GO-Ag nanocomposite) was developed for the reduction of viability of porcine reproductive and respiratory syndrome virus (PRRSV) and epidemic diarrhea (PEDV). Obtained results showed that the GO-Ag nanocomposite was more beneficial compared to nano-Ag and GO alone. It prevented entering viruses into hosts and enhanced expression of interferon (IFN) and interferon-α (IFN-α)-stimulating genes. Other nanotechnological solutions include polymeric NPs as capping agents for the delivery of antiviral agents. Polymeric nanostructures offer feasible synthetic protocols, very low cytotoxicity, and good biocompatibility. Recent examples under preclinical trials include siRNA-loaded nanostructures based on “STP702” (Fluquix) for the delivery and targeting of avian flu (H5N1), swine flu (H1N1), and H7N9 viruses. Involvement of the “ALN-RSV01” targeting agent allowed direct binding with nucleocapsid “N” genes of respiratory syncytial virus (RSV). The RSV virus can be also inactivated using virus-like NPs, delivering the fusion proteins (F VLP) which induce killer T-cells naturally present in patients’ lungs. The polylactide nanostructures are also advantageous for delivery of antiviral agents. The biodegradable synthetic polylactic-co-glycolic acid (PLGA) is already approved by the United States Food and Drug Administration (FDA) for medicinal applications and can be further successfully used. Peptide-based NPs are also interesting candidates for antiviral nanomedicinal applications such as short-sequenced inhibitors that cause mutations within virus replication. Studies based on recent findings on formation of intracellular virus-induced cytosolic double-membrane vesicles may also provide a breakthrough in development of antiviral nanodrugs. Smart NPs after entering the host cells may target and subsequently block the function of crown-shaped pores. This will prevent transportation of the transcripted RNA outside the vesicles and further RNA translation.

**Virus Prevention and Treatment by Using Nanomaterials with Mixed Mechanisms of Action.** At the beginning, it is noted that dimensions of most types of nanomaterials are too large to be internalized into the viral capsid. Also, viruses do not express specific self-internalization mechanisms. Therefore, smart nanomaterials can mostly interact with external capsid machinery. A recent study thoroughly describes the structural elements of the SARS-CoV-2 virus. On the basis of this knowledge, we name the potential targets for smart antiviral hybrid-structured nanotechnological solutions with mixed specific and nonspecific mechanisms of action (Figure 1a). While considering nanomaterial dimensionality, it may first block the action of spike-family proteins such as S1 and S2 subunit functionals and other S glycoproteins. Subsequently, the nanomaterial can disturb the functioning of the membrane (M), envelope (E), and accessory (e.g., ORF7a) proteins. In the case of too large platform dimensionality or specific multifunctionality, the nanomaterial can additionally release ions or various therapeutic agents to travel through the envelope and target the internal protein machinery. Herein, it can disturb the group of various functional proteases such as pappain-like (NSP3) and main (NSP5) proteases, RNA replicase (NSP9), helicase (NSP13), as well as NSP 7, 8, 10, 12, and 15. Moreover, it may block the entry complex formation by releasing inhibitors of ACE2 and/or TMPRSS2 receptors.

If the first gatekeeper is broken and the virion enters the host, the nanomaterial can already be there as a result of safe internalization. After stimulus—response decomposition, it releases the second line of defense inside the host. The group of corresponding targets is presented in Figure 1b. The expected effect may cause the disturbance of virion endosomal acidification (in case of endocytosis), uncoating of RNA, formation of intracellular vesicles for RNA transcription, blocking of the corresponding crown-shape transportation pores and replication complexes formation (transcription and translation of RNA by host machinery), packaging of new virions (RNA coating and composing the proteins), and exocytosis of new virions (viral daughter particles).

The important step that can be targeted with smart antiviral nanomaterials with nonspecific action is the viral action inside the host. Preliminary investigations suggested that after SARS-CoV-2 entry, the viral capsid solubilize, and uncoated nucleocapsid proteins release the RNA directly into the host cytoplasm. However, more deep studies using cellular electron cryo-microscopy (cryo-EM) have shown that after entry SARS-CoV-2 induces formation of cytosolic double-membrane vesicles. Subsequently, they provide a unique microenvironment for RNA replication, while further replication stages involve helicase and RNA polymerases (RdRP). It was previously shown that many viruses induce complex membrane rearrangements to optimize and maximize RNA replication and transcription and thus protect the machinery against the host.
cell defense. These rearrangements are probably connected to the autophagic mechanism of action because they possess the morphotype of endoplasmic reticulum (ER) invagination or extrusion.\textsuperscript{122} It was also found that these small double-membrane vesicles are additionally armed with specific crown-shape molecular pore complexes.\textsuperscript{45} By using these pores, newly synthesized RNA can travel outside vesicles into the host cytoplasm. Therefore, it becomes clear that blocking the release of replicated RNA by a smart antiviral nanotherapeutic may be an efficient way for halting virus development inside infected cells.

Afterward, virion development stages can also be targeted using nanomaterials. These include viral proteins that are further translated inside the host and are proteolytically processed by the precise work of chymotrypsin-like and papain-like proteases. If this machinery exhibits any weak points connected with a unique expression of specific molecules, they may be also used for easy targeting with nanomaterials. After every construction element is ready, the new virion is assembled and released from the host into the exocytic system.\textsuperscript{123} Even if this journey appears unfinished, new virions may be already damaged by nanomaterials while showing less infectivity.

Also, there are many variations of possible combinations of components that can be used for development of smart antiviral nanomaterials. They are schematically envisioned in Figure 2.

Figure 2. High complexity of envisioned smart multicomponent multifunctional nanohybrid materials and possible arrangements that provide valuable features and corresponding specific and nonspecific mixed mechanisms of action for achieving most desirable nanotherapeutic effects.

Such multicomponent multifunctional hybrids can be designed by using both organic functionalities and inorganic nanocompartments. The base for the bottom-up construction is the so-called nanoplatform. It can be designed using spherical or 2D materials and further build up with other nano/bioagents to achieve each particular effect such as targeting, responsive delivery, therapy, imaging, toxicity diminishing, and stealthning nanoconstruction elements. If rationally planned and thoroughly verified, multicomponent multifunctional antiviral nanomaterials can offer the ideal combination of functionalities. As a result, the mixed specific and nonspecific mechanisms of action will allow achieving the most desirable nanotherapeutic effects, as presented in Figure 1.

RESISTANCE OF VIRUSES TOWARD ANTIVIRAL NANOMATERIALS

Viruses along with living organisms are subject to evolutionary selection processes. Their characteristic feature is the high frequency of spontaneous mutations, ensuring the development of resistance to almost any stress or impact.

SARS-CoV-2 is an RNA-containing virus. This type has an order of magnitude higher mutation rate compared to DNA-containing ones.\textsuperscript{124} However, the SARS-CoV-2 virus has an unsegmented genome, which excludes variability as a result of gene reassortment. To date, existing data on resistance of the SARS-CoV to various disinfectants revealed susceptibility to commonly used substances\textsuperscript{125} for which SARS-CoV-2 is sensitive as well.\textsuperscript{126}

The use of nanomaterials as antiviral agents is based on certain physicochemical properties that allow them to interact directly with viral particles (interference with receptor interaction or viral absorption) or to exert an effect through intermediate mechanisms (for instance, generation of ROS). Nanosized particles used as carriers for conventional antiviral drugs stays, however, outside of the framework of this paragraph.

In the framework of hypothesized considerations, inorganic nanomaterials can be arranged in order of probability of resistance development. Most likely, the resistance of the viral population could be developed to various absorbers. The idea underlying the concept of nanodisinfectants is the inactivation of viral particles due to absorption before they enter the cell. The driver of this process is the electrostatic interaction between positively charged viral proteins and nanomaterial, such as GO.\textsuperscript{56} Likely, a point substitution in the amino acid sequence of viral proteins will change the total net charge of the viral particle, leveling the factor of electrostatic or hydrophobic interaction. In the same way, bacterial cells become resistant to various cationic antimicrobial peptides.\textsuperscript{127}

Another way to prevent virus entry is to interfere with receptor interactions between the virus and the cell. It was found in experiments in vitro that metal NPs such as zinc oxide or surface-modified Au NPs have binding affinity to viral glycoproteins.\textsuperscript{128} Ag NPs can directly bind to HIV-1 gp120 glycoprotein knobs.\textsuperscript{129} A possible mechanism of resistance, in this case, may be associated with point changes in the composition of the glycoprotein due to mutation. In clinical practice, there is only one drug that interferes with receptor interactions—“Enfuvirtide”, which is 36 amino acid peptide that binds to the gp41 domain of the HIV-1 envelope inhibiting viral entry into cells.\textsuperscript{130} To date, resistant forms of HIV have already been registered, which have mutations altering co-receptor tropism, co-receptor affinity, or fusion kinetics.\textsuperscript{131}

Certain nanomaterials (fullerenes, graphene) can produce ROS under irradiation, which decompose the viral genetic material, lipids, and proteins.\textsuperscript{132} Similarly, ROS kills various microorganisms. However, unlike bacteria,\textsuperscript{133} viruses do not have genes encoding appropriated enzymes. Nevertheless, in 2012, a case of virus resistance to oxidative stress due to enzymatic inactivation was found.\textsuperscript{134} HSV-1 herpes simplex virus was observed to be somewhat resistant to inactivation by hydrogen peroxide, and it was found that catalase was located inside the HSV-1 envelope. The authors suggested that catalase was incorporated into the viral envelope during HSV-1 virion assembling. An important factor contributing to the emergence of resistant forms along with the mutation rate is the virion’s productivity. Maintaining a low level of production of new virions is a key point in the treatment of viral infections.\textsuperscript{135} However, it has been relatively recently discovered that viruses follow yet another survival strategy referred to by authors as “drug tolerance by synchronization”.\textsuperscript{136} It consists of synchronizing the life cycle of the viral population with a drug therapy model, which allows the virus to replicate only when the concentration of the therapeutic agent is low. Thus, antiviral
agents should be 100% nonspecific, eliminating the possibility of virus replication with the subsequent formation of a resistant population.

As a consequence, inorganic nanomaterials used as disinfectants and protection leave a little chance for viruses to survive and getting into the host. Nevertheless, the right way is to combine several nanomaterials with different mechanisms of action or targets in one formulation or nano-hybrid system, which significantly reduce the probability of resistance development. Today, as we know, no cases of the emergence of viral resistance to treatment with nanomaterials have been identified. Therefore, developed antivirals that involve nanomaterials can be assumed as presumably safe in terms of potential viral resistance.

**DEVELOPMENT OF ANTIVIRALS FOR PROTECTIVE EQUIPMENT**

It is accepted that COVID-19 patients suffer from a wide range of different symptoms or mostly are the silent carriers of SARS-CoV-2. So far, no fully effective antiviral treatment is available against COVID-19. Therefore, the person-to-person transmission of SARS-CoV-2 is a large problem that needs to be solved not only during this pandemic period but also beyond it. It is obvious that if the virus-carrying person while coughing or sneezing rapidly spread infected saliva droplets into the air. Droplets that dissolve and form aerosols are subsequently suspended in the air for a long period and can travel long distances through the air.\(^{15}\) At a first glance, keeping a minimum of 2 m of distance between infected people can be beneficial; however, droplets may still remain on surrounding surfaces. When virions persist on surfaces, they lead to surface-related person-to-person transmission.

Virions sizes, which range from 10 nm to 6 μm,\(^{137}\) allow them to be aspirated into lungs and settle on the surface of bronchia or even alveoli. It is accepted that wearing masks can reduce both the spreading and respiration of aerosol particles. However, bearing in mind virus particle sizes, it is questionable if masks composed of only fabric allow for an acceptable protection level. A recent study investigated the aerosol filtration efficiency of a variety of synthetic and natural fabrics including cotton, silk, polyester, flannel, and chiffon.\(^{137}\) As expected, the size and amount of particles that remained in the air after passing through the fabric varied significantly. A single layer of high thread count cotton cuts off around 80% for particles over 300 nm. A combination of layers of fabrics (for instance, one cotton layer plus two silk layers) gave better results (with over 90% cut off efficiency) probably because of differences in electrostatic properties of different fabrics and a large final thickness.

It was also noted that professional masks can block the virus but do not deactivate it which may still cause infective transmission. Therefore, a nanomaterial-based protective coating on fabric masks is needed to decrease the threat of infection.\(^{138}\) Also, other types of protective equipment can benefit from nanotechnology-based protective coatings. The first approach considered a biocidal nanosilver for coating surgical masks.\(^{139}\) The photocatalytic TiO\(_2\)–based nanostructures can be also used to adsorb SARS-CoV-2 virions from the air and further deactivate them by using UV light.\(^{140}\) Other approaches can also take advantage of low virus survival when placed on a copper surface.\(^{140}\)

Antiviral nanocoatings can be painted or sprayed on surfaces and may include silver, titanium dioxide, or copper NPs which will allow for strong blocking effects toward virus activity. The coatings may be dispersed over surfaces with aerosol or incorporated into paints that will enable the controlled release of metal ions from the surface.\(^{141}\) Recent advances also include nanoabsorbents that could deactivate the SARS-CoV-2 virus.\(^{142}\) Smart designs for surface protection (including masks) can also be based on a mixture of different NPs such as halloysite nanolamellae, nanosilver, nanoclay oxide, and nano-titanium dioxide. Therefore, a considered mechanism is based on the visible-light-driven photocatalytic function of the nanomaterials’ blend which requires the presence of light for activation of photocatalytic action.\(^{143}\) On the other hand, in very dark indoor or outdoor conditions, nanomaterials are set to a standby state.

Therefore, apart from composing the in-house simple mixtures of different NPs, the advanced nanotechnological solutions may include more hybrid types of nanostructures with unique and exciting biocidal action. The considered nanosolutions for the manufacturing of innovative personal protective equipment (including face masks) may further include 2D materials.\(^{144}\) Due to large recognizability, the first proposed solution involved graphene and its related materials. Graphene-based face masks offer features such as washability, reusability, and antistatic properties (repelling airborne particles), as well as bacteria and virus resistance.\(^{144}\)

Commercially available surgical masks can be functionalized with few-layer graphene by a dual-mode laser-induced forward transfer technique. These masks possessed outstanding super-hydrophobic, self-cleaning, and photothermal properties under sunlight illumination.\(^{145}\)

Other solutions include nanographene applied in the form of paints and varnishes to walls and surfaces of public settings that are high-risk areas for micro-organisms such as bacteria and viruses, including shopping malls, metro stations, airports, and event halls. These solutions feature the UV curability of the coating and a no-color formula.\(^{146}\) It should be noted that a large potential in pathogen elimination also comes from other interesting and diverse 2D structures.

There is no doubt that preventative actions in public and healthcare settings are of critical importance. Many researchers have recently turned their focus toward the problem of infection prevention, and a global effort is underway to minimize the spreading of SARS-CoV-2 and to protect healthcare professionals who are on the front lines of the pandemic, as well as people’s everyday activities. Rapid verification of the efficiency of these nanotechnological solutions toward the native SARS-CoV-2 virus is needed, as well as confirming their safety.

**NANOTECHNOLOGY IN A SPIRIT OF SUSTAINABLE DEVELOPMENT**

The COVID-19 pandemic has raised doubts that in the post-pandemic scenery sustainability will be pushed into the sidelines. The need for fast rebuilding the global economy may slow down implementation of more environmentally friendly solutions. The unprecedented health and economic crisis may, however, paradoxically force the world to revisit the green order. This can be done by using the 12 principles of green engineering, which were here adopted with minor changes from Anastas and Zimmerman et al.\(^{148}\) The principles decompose the general rule into functional pieces, in terms of products, processes, and systems, which allow maximizing sustainability in a globally understood fashion. These principles were herein adjusted for designing nanotechnological solutions and were schematically presented in Figure 3. They can be used as guidelines or a
checklist for development of more green nanomaterials. It is also noted that the principles correlate with the circle of sustainable development, presented in Figure 4. It divides the required features into three parts such as consumer demand, industry offer, and product end of use. In this context, the development of smart solutions against the COVID-19 pandemic is considered the unprecedented opportunity only if both the 12 principles and the cycle of sustainable development are preserved.

Nanotechnology can undoubtedly enable the rapid elimination of SARS-CoV-2 damage to public health. However, this investment needs to enable achieving global sustainability goals. In this context, it is important to search for solutions that significantly and positively support sustainability. Therefore, developed nanotechnological solutions must be even more intelligent, for instance, not only in terms of increasing the protective and treatment efficiency but also in minimizing potential hazards and postprocessing effects.

Developed nanotechnologies should be responsible. This means in regard to nanotechnological safety regulations mentioned, for instance, in "Nanosafety in Europe 2015–2025: Toward Safe and Sustainable Nanomaterials and Nanotechnology Innovations," as well as conclusions of the "2019 Global Summit on Regulatory Science" (GSRS19, 2019, Sept. 24–26), hosted by the European Commission’s Joint Research Center (JRC) and U.S. National Nanotechnology Initiative (NNI).

New nanotechnological solutions should care about a reduction of waste. The so-called E-Factor should be lowered as should toxic and potentially toxic reagents or intermediates that can harm humans and the environment. This applies to the entire production chain. In this aspect, it is suggested to replace toxic reagents with more environmentally friendly ones if they do not provide significant added value such as emerging multi-

Figure 3. Sustainable development of smart antiviral nanotechnological solutions by using the 12 principles of green engineering, adapted from Anastas and Zimmermann et al. (Reused with permission with minor changes).

Figure 4. Circle of sustainable development of smart antiviral nanotechnological solutions.
functional antiviral nanoplatorms, which can be designed by using nano-modifying agents of natural origin. Inorganic nanocomponents are already used to produce intelligent antiviral agents, but they mostly lack sustainability in general terms. Given graphene oxide as an example, it is highly recommended to produce it by electrochemical techniques. These, compared to the commonly used Hummers method, limit the use of harmful acids (potassium permanganate, concentrated sodium nitrate, and sulfuric acids) and waste in the form of water which is commonly used to rinse the final product. It is also important to reduce these nonsustainable stages to the necessary minimum. When considering the promising MXene materials, their synthesis techniques also have a lot of room for improvement in the aspect of sustainability. At the initial stage, hydrofluoric acid (HF) and delamination were commonly used in highly toxic mixtures of tetramethylammonium hydroxide (TMAOH) or tetrabutylammonium hydroxide (TBAOH). These solutions were recently replaced by a technique in which HF is formed in situ in a LiF/HCl mixture together with confirmation of the scalability. While the technology is based on strong acid reagents and the final product requires numerous washes, researchers put an effort to increase the sustainability added value by including natural reagents and antioxidants such as L-ascorbic acid, which is commonly known as vitamin C. This is a good direction for oxidation stability enhancement that can be truly considered as both effective and sustainable. Developed nanomaterials also require detailed instrumental characterization. Intensive data analysis helps in understanding the biological properties and mechanisms of action. The issues of cytotoxicity and ecotoxicity of the antiviral nanomaterials are crucially important in the aspect of sustainability. In other words, it is important to thoroughly characterize nanomaterials to enable assessment of their impact on end-user health and the environment. It is worth searching for more safe and sustainable approaches. Already known nanomaterials can be synthesized using green methods. The best example here is nanosilver. Silver ions can be reduced to metallic nanoparticles using natural antioxidants and biologically derived extracts. Developed synthesis techniques should, wherever possible, use green replacements for raw materials, greener processes, renewable energy, reused solvents, and other features with reduced impact on the planet and its resources. The development of modern therapeutic compounds and nanomaterials for use in medicine involves the selection of expensive ingredients and reagents of high purity that are produced with low yield and then repeatedly purified in processes generating large amounts of waste. The high prices of nanotechnologies and nanoproducts developed in this way limit their availability, which not only does not go with the spirit of sustainable development but is also simply not ecological. Sustainable development can be successfully implemented around smart solutions for nanomedicine in the aspect of combating the SARS-CoV-2 virus. Such solutions should be developed from the very beginning following the principles of green chemistry. In this regard, technological processes and stages should be simplified and/or optimized. For each antiviral nanoprotect, the life cycle analysis should be performed. Such analysis considers resources, processes, and product use/deposition/reuse. In this aspect, it is encouraged to use quantitative metrics to characterize improvements in sustainability.

When designing new effective nanotherapeutics, it is important to achieve maximum efficiency in delivering the active substance with a minimal concentration in the body. This is important for not only the choice of a therapeutic substance and method of therapy but also the carrier, which is specially designed to precisely release the substance on demand. Innovative systems of targeted drug delivery should be characterized by high selectivity. Materials used in drug delivery and so-called building blocks in the development of intelligent antiviral drug delivery platforms should work on demand and in place. In parallel, increasing emphasis is placed on fighting the SARS-CoV-2 virus using more safe and sustainable solutions. It is accepted that new therapies and used materials are cost generating regarding synthesis, biological research, and preclinical and clinical trials. Nevertheless, biobased materials can be also used such as chitosan and cellulose, as well as biodegradable polymers, and nanomaterials. In other words, antiviral NPs should pose no environmental problems when released in the process of recycling or biodegradation. Instead, they should be disintegrated efficiently in the natural environment.

For the case of protective equipment, if antiviral masks are produced, they should be based on natural raw materials and biodegradable polymers. In the situation of such widespread use of plastic masks, recycling poses a huge challenge. In the worst-case scenario, the materials used should be at least recyclable or reused. A good example is the recently reported possibility of reusing face masks and personal protective equipment from the healthcare professionals.

■ SUMMARY AND OUTLOOK

The scientific community can contribute greatly to battle the COVID-19 pandemic. Our best weapon here is research and development involving advanced nanotechnological solutions. By design, hybrid nanostructures can express a unique combination of mechanisms of antiviral action. However, these mechanisms need to be revisited to enable more rational development of the new generation of antiviral nanomaterials. As an exclusive outlook, we verify and categorize the potential antiviral effects into three modes of action that can be developed for nanomaterials and smartly managed against the SARS-CoV-2 virus.

The first type refers to the specific mechanism of nanomaterials action. This is the case when nanomaterial mostly reversibly targets receptors or ligands on the surface of the virus or cell that leads to the prevention of virus–cell interaction. The second type is the nonspecific action, which has a destructive effect on various structures of the virion regardless of their taxonomic position. Their action is not guided and leads to irreversible deactivation of the virus, also upon dilution. The third group concerns mixed-type antivirals. They provide complex bioeffects that are challenging to understand and control. On the other hand, they can be smartly tailored for the on-demand and/or stimuli–response manner of action.

To make the right choice on the needed mechanism, it is important to analyze the antiviral efficiency against a minimum of two types of viruses, for example, enveloped and non-enveloped. If the nanomaterial exhibits intensified action within the specific site of the chosen in vitro and/or in vivo model, it becomes clear that it is intentionally or nonintentionally guided. The locations of the reaction site and key nanomaterial functionalities need to be elucidated. Finally, it is equally
important to verify the antiviral efficiency upon dilution and/or upon losing nanomaterial—virus interaction.

Below, we envision target hot points, concerning the action of smart hybrid-structured antivirals with mixed mechanisms of antiviral action that may efficiently halt the SARS-CoV-2 virus morphology and life cycle inside the host cell.

For the case of infection (entry) prevention, the nanoparticulate antiviral system should work effectively outside the host cells, not allowing virions to introduce their genetic material inside them. Here, the relatively limited range of different effects can be used toward formation of the viral—host entry complex. The expected effects may include damage of the following:

1. viral envelope and membrane proteins
2. viral spike glycoproteins, disturbing their key infective action toward human host ACE2 and TMPRSS2
3. viral NSP-family proteases, disturbing their further action
4. nucleocapsid proteins, enclosing viral RNA
5. nucleic acids, forming sRNA fragments

As can be seen, the target is the disturbance of the starting point of the viral life cycle, i.e., the entry step. This can be done by blocking the viral—host membrane fusion or endocytosis by the host cell.

For the case of infection treatment, the nanodrug should first enter the host cell and work specifically in its interior to target the stages of viral action. Here, a wide range of different effects can be activated. The target effect may cause disturbance of the following:

1. acidification and solubilization of formed endosomes
2. uncoating of the sRNA
3. inhibition of intracellular cytosolic double-membrane vesicles formation (for RNA replication)
4. blocking crown-shape pores embedded in cytosolic vesicles (for transportation of RNA outside the vesicles)
5. inhibition of replication complexes formation (disturbing transcription and translation of RNA by host machinery)
6. packaging and assembly of new virions (RNA coating and forming the viral particles)
7. exocytosis and release of new virions (viral daughter particles)

The final expected outcome is a disturbance that causes blocking or significantly slowing the viral life cycle after host cell entry. This is important for replication and propagation steps. The inhibition of infection and/or secretion of viral daughter particles is needed. If they are released, however, their function should be highly damaged causing them to be out of order or possessing significantly lower infectivity.

When designing effective antiviral nanosystems, one can notice that many features of the material are verified and controlled. The reason is that the above-mentioned effects may correspond to direct physical and/or chemical interactions, as well as expressing the targeting agents, and the release of virucidal agents, ions, individual NPs, or reactive oxygen species. To the best of our knowledge, the material features to be assessed and controlled include the presence of metallic nanocomponents, ceramic—nanocomponents, and organic stabilizing agents and/or a solid envelope and also their size, shape, surface area, chemical composition, solubility, colloidal features (including hydrodynamic diameter and zeta potential), corresponding red—ox properties, and ROS scavenging features.

It should be additionally noted that the specific viral response to bioactive nanosystems (adaptation by mutations, resistance development) is not expected because virions are not considered as living organisms, and their changes are only associated with RNA replication cycles. It can be also assumed that if a complicated enough nanosystem is designed, it can generate some synergistic and/or additional biological effects not yet observed for enveloped viruses.

Also, the issue of the lack of stability of viral features is a major concern. Viruses are changing themselves (rapidly or slowly mutating), and they are constantly moving (around the cells and crossing their membranes). Developed nanomaterials need to be smart to face the corresponding pipelines. For this purpose, multiple functionalization strategies are needed. Developed nanodrugs need to provide effective, as requested, stepwise virucidal action. The positive effects need to be amplified, and virus particles should be targeted just before the creation of entry complexes to provide maximum protection of healthy cells. In this regard, minimization of disease symptoms (cytokine storm, among others) is highly requested. After performing their duty, developed nanomaterials should subsequently decompose and solubilize to nontoxic removable products.

The on-site toxicity, as well as acute and chronic off-target responses, must be carefully investigated to ensure maximum safety. Therefore, another aspect of the use of nanomaterials as virucidal agents is their biosafety. Nanomaterials can be used to inactivate the virus outside the cells (host) and as carriers for antiviral drugs into the cells. In the first case, this is a relatively more safe way to inactivate viruses, while the use of nanomaterials (especially inorganic NPs) for introduction into the body can have negative consequences, which, on the one hand, can be remote in time, and, on the other hand, can complicate the course of viral infection in the current moment.

In general, research works suggesting the use of inorganic nanomaterials as antiviral agents are based on the results of toxicity tests performed on various cell lines.128 It is worth noting that under in vitro conditions numerous NPs are recognized as low toxic. Often, the scope of such works is not related to a comprehensive study of the biosafety of NPs following relevant regulations. Moreover, only relatively recently the development of such regulations has become the subject of efforts of the scientific community.157

Significant coordinated efforts are underway to harmonize existing hazard and risk assessment methods in the framework of the NANoREG project.157 The main points that will have to be encountered in the certification of nanomaterials for nonmedical purposes can be identified when studying guidance developed by The Scientific Committee on Consumer Safety (SCCS).158 This guidance requires a thorough safety assessment of nanomaterials in the same way as other chemicals but with special attention to their extremely small size.

Due to the fact, that SARS-CoV-2 directly attacks lung cells, development of NPs-based inhalation-administered drugs against the virus was recently suggested with argumentation on systemic inactivation of the virus.159 The state-of-the-art studies, however, do not fully support the probability of success in this area because of possible detrimental health effects. This subject was comprehensively reviewed by Nho.159 The lungs are very sensitive organs that if constantly exposed to nanoparticle drugs with long-term repeated dose will inevitably cause accumulation of nanomaterials in lung tissues, resulting in inflammation, systemic circulation, and finally lung tissue injury. Also, a post-inhalation cough can appear after using therapeutic aerosols.160 This is a result of lung inflammation and increased hypersensitivity and/or changes in the epithelial lining fluid composition. In the frame of the recently assessed influence of
SARS-CoV-2 on the appearance of a cytokine storm, the additive inflammation by the presence of nanomaterials can cause catastrophically synergistic inflammation effects. As can be seen, the administration of nanomaterial-based drugs needs to be carefully investigated in long-term exposure aspects if administered into the lungs.

On the other hand, several solutions can be effective in cytotoxicity mitigation. This can be done by using stable nanocomposite structure (solid connection/interface) between nano-counterparts or by designing hybrids of 2D material and inorganic nanoparticles (including ceramic and/or metallic), as well as different organic moieties.

The certification process of nanomaterials for drug delivery and cosmetic products takes a long time and assumes that a nanomaterial meets several requirements. Toxicology research planning involves a thorough physical and chemical characterization of NPs. The main emphasis in assessing the hazard class should be placed on determining the parameters: absorption, distribution, metabolism, excretion. It is also important to determine the systemic availability of nanomaterial if it does not have systemic availability, then it is necessary to obtain information on local toxicity and genotoxicity.

Protective equipment modified with virucidal nanomaterials also needs to be studied for its potential toxicity. Only nontoxic nanomaterials or composite nanostructures with diminished toxicity are the best choices here because they minimize the risk of releasing nanomaterials and express specific types of ionic action instead of direct nanomaterial entry into the cells. Nevertheless, for the case of face masks, the potential inhalation of NPs should be considered, whereas in the case of other types of protective equipment, the lack of potential skin toxicity upon contact needs to be verified. In the next steps toward developing smart nanotechnologies, subsequent scaleup and distribution are needed together with a long-term strategy toward use, life cycle, reuse, deposition, and recycling.

Reflecting on a slightly more optimistic summary, it can be assumed that the impact of the COVID-19 pandemic on the economy, population, and planet can have both short- and long-term benefits. The health, social, and economic effects of the crisis require urgent and extraordinary action by businesses and governmental administrations. Many enterprises implemented contingency plans to survive the economic storm, which creates the need for integrated actions around sustainable development. Still, society, the environment, and the economy are the pillars of sustainable development. The need for rapid recovery after a pandemic period imposes the need for rapid development. It would not have been possible without modern technical solutions, among others, based on nanotechnology. This path will be followed by, for example, the European Union, which has the chance to include the Green Deal strategy in the plan of rebuilding the European economy after the coronavirus pandemic. The reconstruction of local and national economies should be based on a circular model. This is strictly linked to issues related to strategic raw materials, environmental protection, and energy independence. Therefore, sustainable development assumptions can be effectively implemented using smart nanotechnological solutions. In this regard, only a fast track to the market will enable maximization of the response toward COVID-19 and beyond.

Agnieszka M. Jastrzębska is a professor at the Warsaw University of Technology (WUT). She leads an interdisciplinary research team at the Faculty of Materials Science and Engineering, Department of Ceramic and Polymer Materials. Her original research works are concentrated in the area of nanotechnology for bioactive materials with multifunctional hybrid nanocomposite structures. Her current fields of interest comprise biomedical, environmental, and catalytic applications of novel 2D materials with emphasis given to their cyto- and ecotoxicological effects observed at relevant exposures.

Alexey S. Vasilchenko is currently the head of the Laboratory of Antimicrobial Resistance at the Tyumen State University. He obtained his Ph.D. in microbiology from the Institute of Ecology and Genetics of...
Microorganisms of the Russian Academy of Sciences. His research interests are focused on studies of the reaction of microorganisms to various nanomaterials at cellular and subcellular levels and the discovery of novel antimicrobials to overcome bacterial drug resistance.

**ACKNOWLEDGMENTS**

The study was accomplished thanks to the funds allotted by the National Science Centre based on Decisions No. DEC-2019/35/B/STS/02538 (“OPUS 18”) and No. UMO-2017/26/E/ST8/01073 (“SONATA BIS 7”). Additional financial support from the Warsaw University of Technology, Faculty of Materials Science and Engineering is also kindly acknowledged. Studies were funded by the BIOTECHMED-1 project granted by Warsaw University of Technology under the program Excellence Initiative: Research University (ID-UB).

**REFERENCES**

(1) WHO resources. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed May 07, 2020).

(2) Worldometers. https://www.worldometers.info/coronavirus/#countries (accessed Oct 17, 2020).

(3) Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K. S. M.; Lui, E. H. Y.; Wong, J. Y.; Xing, X.; Xiang, N.; Wu, Y.; Li, C.; Chen, Q.; Li, D.; Liu, T.; Zhao, J.; Liu, M.; Tu, W.; Chen, C.; Jin, L.; Yang, R.; Wang, Q.; Zhou, S.; Wang, R.; Liu, H.; Luo, Y.; Liu, Y.; Shao, G.; Li, H.; Tao, Z.; Yang, Y.; Deng, Z.; Liu, B.; Ma, Z.; Zhang, Y.; Shi, G.; Lam, T. T. Y.; Wu, J. T.; Gao, G. F.; Cowling, B. J.; Yang, B.; Leung, G. M.; Feng, Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N. Engl. J. Med.* 2020, 382 (13), 1199–1207.

(4) WHO Novel Coronavirus (2019-nCoV) situation reports. https://www.who.int/timetable/emergencies/novel-coronavirus-2019/novel-coronavirus-2019-ncov-situation-reports (accessed Oct 18, 2020).

(5) Saif, L. J. Animal Coronaviruses: Lessons for SARS. In Institute of Medicine (US) Forum on Microbial Threats. Learning from SARS: the transmission dynamics in 2019/novel-coronavirus-(2019-ncov)-situation-reports (accessed Oct 18, 2020).

(6) Zhang, J.; Jia, W.; Zhu, J.; Li, B.; Xing, J.; Liao, M.; Qi, W. Insights into the cross-species evolution of 2019 novel coronavirus. *N. Engl. J. Med.* 2020, 382 (6), 671–693.

(7) Hamid, S.; Mir, M. Y.; Rohela, G. K. Novel coronavirus disease (COVID-19): a pandemic (epidemiology, pathogenesis and potential therapeutics). *New Microbes New Infect.* 2020, 35, 100679.

(8) Nextstrain. Phylogeny of SARS-like betacoronaviruses including novel coronavirus from Wuhan using data generated by the Shanghai Public Health Clinical Center & School of Public Health, the National Institute for Viral Disease Control and Prevention, the Institute of Pathogen Biology, and the Wuhan Institute of Virology shared via GISAID. https://nextstrain.org/groups/blab/sars-like-cov (accessed Oct 18, 2020).

(9) Zhou, P.; Yang, X. L.; Wang, X. G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H. R.; Zhu, Y.; Li, B.; Huang, C. L.; Chen, H. D.; Chen, J.; Luo, Y.; Guo, H.; Jiang, R. D.; Liu, M. Q.; Chen, Y.; Shen, X. R.; Wang, X.; Zheng, X. S.; Zhao, K.; Chen, Q. J.; Deng, F.; Liu, L. Y.; Yan, B.; Zhan, F. X.; Wang, Y. Y.; Xiao, G. F.; Shi, Z. L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020, 579 (7798), 270–273.

(10) Guy, R. K.; DiPaola, R. S.; Romanelli, F.; Dutch, R. E. Rapid repurposing of drugs for COVID-19. *Science* 2020, 368 (6493), 829–830.

(11) Wu, J. T.; Leung, K.; Bushman, M.; Kishore, N.; Niehus, R.; de Salazar, P. M.; Cowling, B. J.; Lipsitch, M.; Leung, G. M. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nat. Med.* 2020, 26 (4), 506–510.
Respiratory Syndrome Virus. *ACS Appl. Nano Mater.* 2018, 1, 969–976.

(48) Baram-Pinto, D.; Shukla, S.; Gedanken, A.; Sarid, R. Inhibition of HSV-1 attachment, entry, and cell-to-cell spread by functionalized multivalent gold nanoparticles. *Small* 2010, 6 (9), 1044–1050.

(49) Fujimori, Y.; Sato, T.; Hayata, T.; Nagao, T.; Nakayama, M.; Nakayama, T.; Sugama, R.; Suzuki, K. Novel antiviral characteristics of nanosized copper (I) iodide particles showing inactivation activity against 2009 pandemic H1N1 influenza virus. *Appl. Environ. Microbiol.* 2012, 78 (4), 951–955.

(50) Trigilo, J.; Antoine, T. E.; Paulowicz, I.; Mishra, Y. K.; Adelung, R.; Shukla, D. Tin oxide nanowires suppress herpes simplex virus-1 entry and cell-to-cell membrane fusion. *PLOS One* 2012, 7 (10), e49174.

(51) Antoine, T. E.; Mishra, Y. K.; Trigilo, J.; Tiwari, V.; Adelung, R.; Shukla, D. Prophylactic, therapeutic and neutralizing effects of zinc oxide tetrapod structures against herpes simplex virus type-2 infection. *Antiviral Res.* 2012, 96 (3), 363–375.

(52) Gerrity, D.; Ryu, H.; Crittenden, J.; Abbassadejad, M. Photocatalytic inactivation of viruses using titanium dioxide nanoparticles and low-pressure UV light. *J. Environ. Sci. Health, Part A: Toxic/Hazard. Subst. Environ. Eng.* 2008, 43 (11), 1261–1270.

(53) News Northeastern. <https://news.northeastern.edu/2020/03/04/heres-how-nanoparticles-could-help-us-get-closer-to-a-treatment-for-covid-19/> (accessed Oct 24, 2020).

(54) Loczechin, A.; Seron, K.; Barras, A.; Giovanelli, E.; Belouard, S.; Chen, Y. T.; Metzler-Nolte, N.; Boukherroub, R.; Dubuisson, J.; Szunerits, S. Functional Carbon Quantum Dots as Medical Countermeasures to Human Coronavirus. *ACS Appl. Mater. Interfaces* 2019, 11 (46), 42964–42974.

(55) Fahmi, M. Z.; Sukmayani, W.; Khairunisa, S. Q.; Witaningrum, A. M.; Indriati, D. W.; Matondang, M. Q.; Y.; Chang, J.-Y.; Kotake, T.; Kameoka, M. Design of boronic acid-attributed carbon dots on inhibits H1N1 viral entry. *RSC Adv.* 2016, 6, 92996–93002.

(56) Ye, S.; Shao, K.; Li, Z.; Guo, N.; Zuo, Y.; Li, Q.; Lu, Z.; Chen, L.; He, Q.; Han, H. Antiviral Activity of Graphene Oxide: How Sharp Edged Structure and Charge Matter. *ACS Appl. Mater. Interfaces* 2015, 7 (38), 21571–21579.

(57) Geller, C.; Fontanay, S.; Moucher, M.; Bibiana, H. M.; Regnouf-de-Vains, J. B.; Finance, C.; Duval, R. E. Antisense properties of two calcif[4]arenes derivatives on the human coronavirus 229E. *Antiviral Res.* 2010, 88 (3), 343–346.

(58) Hendricks, G. L.; Weirich, K. L.; Viswanathan, K.; Li, J.; Shriver, Z. H.; Ashour, J.; Ploegh, H. L.; Kurt-Jones, E. A.; Fyguness, D. K.; Finberg, R. W.; Comollini, J. C.; Wang, J. P. Sialyneolacto-N-tetraose c calix[4]arenes derivatives on the human coronavirus 229E. *Antiviral Res.* 2012, 94 (3), 346.

(59) Li, Y.; Lin, Z.; Zhao, M.; Xu, T.; Wang, C.; Hua, L.; Wang, H.; Zhu, X.; B. Silver Nanoparticle-Based Codelivery of Osvatamivir to Inhibit the Activity of the H1N1 Influenza Virus through ROS-Mediated Signaling Pathways. *ACS Appl. Mater. Interfaces* 2016, 8 (37), 24385–24393.

(60) Kostarelos, K. Nanoscale nights of COVID-19. *Nat. Nanotechnol.* 2020, 15, 343–344.

(61) Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; Wang, X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 2020, 581 (7807), 215–220.

(62) Cagno, V.; Andreozzi, P.; D’Alicarnasso, M.; Jacob Silva, P.; Mueller, M.; Galloux, M.; Le Goiffic, R.; Jones, S. T.; Vallino, M.; Hodek, J.; Weber, J.; Sen, S.; Janecek, E. R.; Bekedam, A.; Sanavio, B.; Martinelli, C.; Donaliso, M.; Rameit, W.; Malti, M.; Eleouet, F. J.; Han, K.; Kral, P.; Kysar, G. Z. On Facing the Proliferation of Pseudorabies Virus and Porcine Reproductive and Respiratory Syndrome Virus. *ACS Appl. Nano Mater.* 2018, 1, 969–976.
angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* 2005, 11 (8), 875–879.

(64) Hofmann, M.; Kleine-Weber, H.; Schroeder, S.; Kruger, N.; Herrler, T.; Erichsen, S.; Schiergens, T. S.; Herrler, G.; Wu, N. H.; Nitsche, A.; Muller, M. A.; Drosten, C.; Pohlmann, S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020, 181 (2), 271–280.

(65) Simmons, G.; Bertram, S.; Głowacka, I.; Steffen, I.; Chajna, C.; Agudelo, J.; Lu, K.; Rennekamp, A. J.; Hofmann, H.; Bates, P.; Pohlmann, S. Different host cell proteases activate the SARS-coronavirus spike-protein for cell-cell and virus-cell fusion. *Virology* 2011, 413 (2), 265–274.

(66) Wagner, R.; Matrosovich, M.; Klenk, H. D. Functional between haemagglutinin and neuraminidase in influenza virus infections. *Rev. Med. Virol.* 2002, 12 (3), 159–166.

(67) Moscona, A. Global Transmission of Oseltamivir-Resistant Influenza. *N. Engl. J. Med.* 2009, 360, 953–956.

(68) Hassanzadeh, K.; Perez Pena, H.; Dragotto, J.; Buccarellu, L.; Iorio, F.; Pieraccini, S.; Sancini, G.; Feligioni, M. Considerations around the SARS-CoV-2 Spike Protein with Particular Attention to COVID-19 Brain Infection and Neurological Symptoms. *ACS Chem. Neurosci.* 2020, 11 (15), 2361–2369.

(69) Salvatori, G.; Liberto, L.; Maffei, M.; Aurisiachio, L.; Roscilli, G.; Palombo, F.; Marra, E. SARS-CoV-2 spike protein: an optimal immunological target for vaccines. *J. Transl. Med.* 2020, 18 (222), 1–3.

(70) Jastrzębska, A. M.; Kurtycz, P.; Olszyna, A. R. Recent advances in graphene family materials toxicity investigations. *J. Nanopart. Res.* 2012, 14 (1302), 1–21.

(71) Ma, R.; Sasaki, T. Nanosheets of oxides and hydroxides: Ultimate 2D charge-bearing functional crystallites. *Adv. Mater.* 2010, 22 (45), 5082–5104.

(72) Ahmadi, M.; Zabibi, O.; Jeon, S.; Yoonessi, M.; Dasari, A.; Ramakrishna, S.; Naebe, M. 2D transition metal dichalcogenide nanomaterials: advances, opportunities, and challenges in multifunctional polymer nanocomposites. *J. Mater. Chem. A* 2020, 8 (3), 845–883.

(73) Paciòł, D.; Meyer, J. C.; Girit, Ç. Ö.; Zettl, A. The two-dimensional phase of boron nitride: Few-atomic-layer sheets and suspended membranes. *Appl. Phys. Lett.* 2008, 92, 133107.

(74) Colson, J. W.; Dichtel, W. R. Rationally synthesized two-dimensional polymers. *Nat. Chem.* 2013, 5 (6), 453–465.

(75) Tang, Q.; Zhou, Z. Graphene-analogous low-dimensional materials. *Prog. Mater. Sci.* 2013, 58 (8), 1244–1315.

(76) Moller, A.; Goldberger, J.; Houssa, M.; Xu, Y.; Zhang, S. C.; Akinwande, D. Buckled two-dimensional Xene sheets. *Nat. Mater.* 2017, 16 (2), 163–169.

(77) Naguib, M.; Kurtoglu, M.; Presser, V.; Lu, J.; Niu, J.; Heon, M.; Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Kruger, N.; Nitsche, A.; Muller, M. A.; Drosten, C.; Pohlmann, S. A. Blockage of SARS-CoV-2 entry into human cells by a protease inhibitor. *Clin. Infect. Dis.* 2005, 41 (12), 1862–1869.

(78) Anasori, B.; Lu, J.; Niu, J.; Heon, M.; Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Kruger, N.; Nitsche, A.; Muller, M. A.; Drosten, C.; Pohlmann, S. Inhibition of SARS-CoV-2 entry into human cells by a protease inhibitor. *Clin. Infect. Dis.* 2005, 41 (12), 1862–1869.

(79) Shabani, A. A.; Gh, M. S.; Anasori, B.; Soroumeh, M. Antimicrobial Mode-Of-Action of Colloidal Ti3C2Tx MXene Nanosheets. *ACS Sustainable Chem. Eng.* 2018, 6 (12), 16586–16596.

(80) Jastrzębska, A.; Karwowska, E.; Wojciechowski, T.; Ziemkowska, W.; Rozmysłowska, A.; Chlubny, L.; Olszyna, A. The Atomic Structure of Ti2C and Ti3C2MXenes is Responsible for Their Antibacterial Activity Toward e. coli Bacteria. *J. Mater. Eng. Perform.* 2019, 28 (3), 1272–1277.

(81) Mei, L.; Zhu, S.; Yin, W.; Chen, C.; Nie, G.; Gu, Z.; Zhao, Y. Two-dimensional nanomaterials beyond graphene for antibacterial applications: current progress and future perspectives. *Theranostics* 2020, 10 (2), 757–781.

(82) Palmieri, V.; Papi, M. Can graphene take part in the fight against COVID-19? *Nano Today* 2020, 33, 100883.

(83) Jastrzębska, A. M.; Kurtycz, P.; Olszyna, A.; Karwowska, E.; Misakiewicz-Pęska, E.; Zaleńska-Radiwillo, M.; Doskocz, N.; Basiak, D. The Impact of Zeta Potential and Physicochemical Properties of TiO2-Based Nanocomposites on Their Biological Activity. *Int. J. Appl. Ceram. Technol.* 2015, 12 (6), 1157–1173.

(84) Jastrzębska, A. M.; Karwowska, E.; Olszyna, A. R.; Kunicki, A. Influence of bacteria adsorption on zeta potential of Al2O3 and Al2O3/Ag nanoparticles in electrolyte and drinking water environment studied by means of zeta potential. *Surf. Coat. Technol.* 2015, 271, 225–233.

(85) Jastrzębska, A. M.; Karwowska, E.; Kostecki, M.; Olszyna, A. R. Bacterial Adsorption with Graphene Family Materials Compared to NanoAlumina. *Main Group Chem.* 2017, 16 (3), 175–190.

(86) Jastrzębska, A. M.; Karcz, J.; Letmanowski, R.; Zabost, D.; Ciecierska, E.; Zdunek, J.; Karwowska, E.; Siekierska, M.; Olszyna, A.; Kunicki, A. Synthesis of the RGO/Al2O3 core–shell nanocomposite flakes and characterization of their unique electrostatic properties using zeta potential measurements. *Appl. Surf. Sci.* 2016, 362, 577–594.

(87) Jastrzębska, A. M.; Karcz, J.; Letmanowski, R.; Zabost, D.; Ciecierska, E.; Siekierska, M.; Olszyna, A. Synthesis of RGO/TiO2 nanocomposite flakes and characterization of their unique electrostatic properties using zeta potential measurements. *J. Alloys Compd.* 2016, 679, 470–484.

(88) Kettler, K.; Veltman, K.; van de Meent, D.; van Wezel, A.; Hendriks, A. J. Cellular uptake of nanoparticles as determined by particle properties, experimental conditions, and cell type. *Environ. Toxicol. Chem.* 2014, 33 (3), 481–492.

(89) Schoeman, D.; Fielding, B. C. Coronavirus envelope protein: current knowledge. *Virol. J.* 2019, 16 (69), 1–22.

(90) Frost, R.; Jonsson, G. E.; Chakarov, D.; Svedhem, B.; Kasemo, B. Graphene oxide and lipid membranes: interactions and nanocomposite structures. *Nano Lett.* 2012, 12 (7), 3356–3362.

(91) Song, Z.; Wang, X.; Zhu, G.; Nian, Q.; Zhou, H.; Yang, D.; Qin, C.; Tang, R. Virus capture and destruction by label-free graphene oxide for detection and disinfection applications. *Small* 2015, 11 (9–10), 1171–1176.

(92) Jung, J. H.; Park, B. H.; Oh, S. J.; Choi, G.; Seo, T. S. Integration of reverse transcriptase loop-mediated isothermal amplification with an immunochromatographic strip on a centrifugal microdevice for influenza A virus identification. *Lab Chip* 2015, 15 (3), 718–725.

(93) Singh, L.; Kruger, H. G.; Maguire, G. E. M.; Covender, T.; Parboosingh, R. The role of protease inhibitors in the treatment of viral infections. *Ther. Adv. Infect. Dis.* 2017, 4 (4), 105–131.

(94) Zhang, Q.; Chen, C. Z.; Swaroop, M.; Xu, M.; Wang, L.; Lee, J.; Wang, A. Q.; Pradhan, M.; Hagen, N.; Chen, L.; Shen, M.; Luo, Z.; Xu, X.; Yu, H.; Zheng, W.; Ye, Y. Heparan sulfate assists SARS-CoV-2 in cell entry and can be targeted by approved drugs in vitro. *Cell Discovery* 2020, 6 (1), 80.
and its Influence on Biological Properties. Chudy, M.; Wozniak, J.; Babcik, A.; Rusak, D. ACS Nano 2012, 7, 7942.

Scavenging Intracellular Reactive Oxygen and Nitrogen Species. S.; Kim, J.-H. Sustainable Nanosheet Antioxidants for Sepsis Therapy 2016, 1906206.

Nanosheets Based on Curcumin. L.; Xiao, S.; Liang, J. Glycyrrhizic-Acid-Based Carbon Dots with High Immunosuppression. ACS Sustainable Chemistry & Engineering 2018, 6, 3164.

Nanoparticle-Mediated Nonviral DNA Delivery for Effective Inhibition of Middle East Respiratory Syndrome Coronavirus. Ning, X. Novel Gold Nanorod-Based HR1 Peptide Inhibitor for Middle 2019, 395, 3084.

Preventing Viral Entry and Activation of the Antiviral Innate Immune System. Du, T.; Lu, J.; Liu, L.; Xiao, S.; Han. Antiviral Activity of Graphene Oxide—Silver Nanocomposites by Preventing Viral Entry and Activation of the Antiviral Innate Immune Response. ACS Appl. Bio Mater. 2018, 1 (5), 3164–3170.

Iannazzo, D.; Pistone, A.; Ferro, S.; De Luca, L.; Monforte, A. M.; Romeo, R.; Buemi, M. R.; Pannecoque, C. Graphene Quantum Dots Based Systems As HIV Inhibitors. Bioconjugate Chem. 2018, 29 (9), 3084–3093.

Dots Based Systems As HIV Inhibitors. ACS Appl. Bio Mater. 2018, 1 (5), 1286–1293.

Shafagati, N.; Patanarut, A.; Luchini, A.; Nowak, M. A.; Hill, A. L. Life cycle synchronization is a viral drug resistance. J. Virol. 2012, 86 (21), 11931–11934.

Vere Hodge, A.; Field, H. J. General Mechanisms of Antiviral Resistance. Gen. Ecol. Infect. Disease 2011, 13, 339–362.

Neagu, I. A.; Olejarz, J.; Freeman, M.; Rosenbloom, D. I.; Newcomb, W. W.; Brown, J. C. Internal catalase protects herpes simplex virus from inactivation by hydrogen peroxide. J. Virol. 2012, 86 (21), 11931–11934.

Spitz Steinberg, R.; Cruz, M.; Mahfouz, N. G. A.; Qiu, Y.; Hurt, R. H. Breathable Vapor Toxicant Barriers Based on Multilayer Graphene Oxide. ACS Nano 2017, 11 (6), 5670–5679.

Silver Nanocomposites by Modeling and chemical modification for finding peptide inhibitor against severe acute respiratory syndrome coronavirus main proteinase. Anal. Biochem. 2005, 337 (2), 262–270.

Parks, J. M.; Smith, J. C. How to Discover Antiviral Drugs Quickly. N. Engl. J. Med. 2020, 382, 2261–2264.

Blanchard, E.; Roingeard, P. Virus-induced double-membrane vesicles. Cell. Microbiol. 2015, 17 (1), 45–50.

Yabu, N.; Liu, D. X. Human Coronavirus: Host-Pathogen Interaction. Annu. Rev. Microbiol. 2019, 73, 529–557.

Irwin, K. J.; Renzette, N.; Kowalki, T. F.; Jensen, J. D. Antiviral drug resistance as an adaptive process. Virus Evolution 2016, 2 (1), 0014.

Babenau, H. F.; Kampf, G.; Cinatl, J.; Doerr, H. W. Efficacy of various disinfectants against SARS coronavirus. J. Hosp. Infect. 2005, 61 (2), 107–111.

WHO resources. https://www.who.int/publications-detail-red/redirect/cleaning-and-disinfection-of-environmental-surfaces-in-the-context-of-covid-19 (accessed Jun 22, 2020).

Joo, H.-S.; Fu, C.-I.; Otto, M. Bacterial strategies of resistance to antimicrobial peptides. Philos. Trans. R. Soc. B 2016, 371 (1695), 20150292.

Yadavalli, T.; Shukla, D. Role of Metal and Metal Oxide Nanoparticles as Diagnostic and Therapeutic Tools for Highly Prevalent Viral Infections. Nanomedicine 2017, 13, 219–230.

Echelguerra, J. L.; Burt, J. L.; Morones, J. R.; Camacho-Bragado, A.; Gao, X.; Lara, H. H.; Yacam, M. J. Interaction of silver nanoparticles with HIV-1. J. Nanobiotechnol. 2005, 3 (6), 6.

Dingens, A. S.; Arenz, D.; Overbaugh, J.; Bloom, J. D. Massively Parallel Profiling of HIV-1 Resistance to the Fusion Inhibitor Enfuvirtide. Viruses 2019, 11 (5), 439.

Miller, T. D.; Hazuda, D. J. HIV resistance to the fusion inhibitor enfuvirtide: Mechanisms and clinical implications. Drug Resist. Updates 2004, 7, 89–95.

Wiehe, A.; O’Brien, J.; Senge, M. O. Trends and targets in antiviral phototherapy. Photochem. Photobiol. Sci. 2019, 18, 2565–2612.

Henningham, A.; Döhrmann, S.; Nizet, V.; Cole, J. N. Mechanisms of group A Streptococcus resistance to reactive oxygen species. FEMS Microbiol. Rev. 2015, 39 (4), 488–508.

Newcomb, W. W.; Brown, J. C. Internal catalase protects herpes simplex virus from inactivation by hydrogen peroxide. J. Virol. 2012, 86 (21), 11931–11934.
Biodegradable nanoparticle delivery of inactivated swine influenza virus vaccine provides heterologous cell-mediated immune response in pigs. *J. Controlled Release* 2017, 247, 194–205.

(177) Dhakal, S.; Renu, S.; Ghimire, S.; Shaan Lakshmanappa, Y.; Hoghead, B. T.; Feliciano-Ruiz, N.; Lu, P.; HogenEsch, H.; Krakowka, S.; Lee, C. W.; Renukaradhya, G. J. Mucosal Immunity and Protective Efficacy of Intranasal Inactivated Influenza Vaccine Is Improved by Chitosan Nanoparticle Delivery in Pigs. *Front. Immunol.* 2018, 9, 934.

(178) Cai, M.; Wang, C.; Li, Y.; Gu, H.; Sun, S.; Duan, Y.; Lai, C.; Wang, K.; Yang, X.; Xing, L.; Zhang, P.; Wang, Z.; Zhang, S.; Guo, X.; Liu, S.; Tong, Y.; Wang, X.; Yang, P. Virus-like particle vaccine by intranasal vaccination elicits protective immunity against respiratory syncytial viral infection in mice. *Acta Biochim. Biophys. Sin.* 2017, 49 (1), 74–82.

(179) Ulery, B. D.; Phanse, Y.; Sinha, A.; Wannemuehler, M. J.; Narasimhan, B.; Bellaire, B. H. Polymer chemistry influences mononuclear uptake of polyanhydride nanospheres. *Pharm. Res.* 2009, 26 (3), 683–690.

(180) McGill, J. L.; Kelly, S. M.; Kumar, P.; Speckhart, S.; Haughney, S. L.; Henningson, J.; Narasimhan, B.; Sacco, R. E. Efficacy of mucosal polyanhydride nanovaccine against respiratory syncytial virus infection in the neonatal calf. *Sci. Rep.* 2018, 8 (1), 3021.

(181) Roux, X.; Dubuquoy, C.; Durand, G.; Tran-Tolla, T. L.; Castagne, N.; Bernard, J.; Petit-Camurcan, A.; Eleouet, J. F.; Riffault, S. Sub-nucleocapsid nanoparticles: a nasal vaccine against respiratory syncytial virus. *PLoS One* 2008, 3 (3), e1766.

(182) Hervé, P.-L.; Deloisy, C.; Descamps, D.; Rameix-Welti, M.-A.; Faccioli, J.; McLellan, J. S.; Eleouet, J. F.; Riffault, S. RSV N-nanorings fused to palivizumab-targeted neutralizing epitope as a nanoparticle RSV vaccine. *Nanomedicine* 2017, 13, 411–420.

(183) Du, T.; Liang, J.; Dong, N.; Liu, L.; Fang, L.; Xiao, S.; Han, H. Carbon Dots As Inhibitors Of Virus By Activation Of Type I Interferon Response. *Carbon* 2016, 110, 278–285.

(184) Barras, A.; Pagneux, Q.; Sane, F.; Wang, Q.; Boukherroub, R.; Hoher, D.; Szunerits, S. High Efficiency of Functional Carbon Nanodots as Entry Inhibitors of Herpes Simplex Virus Type 1. *ACS Appl. Mater. Interfaces* 2016, 8 (14), 9004–9013.

(185) Pachota, M.; Klysik-Trzcińska, K.; Synowiec, A.; Yukioka, S.; Yusa, S.-I.; Zając, M.; Zawilinska, B.; Szczubialka, K.; Pyrc, K.; Nowakowska, M. Highly Effective and Safe Polymeric Inhibitors of Herpes Simplex Virus in Vitro and in Vivo. *ACS Appl. Mater. Interfaces* 2019, 11 (30), 26745–26752.

(186) Villanueva, H. C.; Martinez-Carlin, I.; Lopez-Berestein, G.; Chavez-Reyes, A. Therapeutic silencing of HPV 16 E7 by systemic administration of siRNA-neutral DOPC nanoliposome in a murine cervical cancer model with obesity. *J. BUON* 2015, 20 (6), 1471–1479.

(187) Shionoiri, N.; Sato, T.; Fujimori, Y.; Nakayama, T.; Nemoto, M.; Matsunaga, T.; Tanaka, T. Investigation of the antiviral properties of copper iodide nanoparticles against feline calicivirus. *J. Biosci. Bioeng.* 2012, 113 (5), 580–586.

(188) Ziem, B.; Thien, H.; Achazi, K.; Yue, C.; Stern, D.; Silberreis, K.; Gholami, M. F.; Beckert, F.; Groger, D.; Mulhaupt, R.; Rabe, J. P.; Nitsche, A.; Haag, R. Highly Efficient Multivalent 2D Nanosystems for Inhibition of Orthopoxvirus Particles. *Adv. Healthcare Mater.* 2016, 5 (22), 2922–2930.