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PERSPECTIVE

Toward Nanotechnology-Enabled Approaches against the COVID-19 Pandemic

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ABSTRACT: **The COVID-19 outbreak has fueled a global demand for effective diagnosis and treatment as well as mitigation of the spread of infection, all through large-scale approaches such as specific alternative antiviral methods and classical disinfection protocols. Based on an abundance of engineered materials identifiable by their useful physicochemical properties through versatile chemical functionalization, nanotechnology offers a number of approaches to cope with this emergency. Here, through a multidisciplinary Perspective encompassing diverse fields such as virology, biology, medicine, engineering, chemistry, materials science, and computational science, we outline how nanotechnology-based strategies can support the fight against COVID-19, as well as infectious diseases in general, including future pandemics. Considering what we know so far about the life cycle of the virus, we envision key steps where nanotechnology could counter the disease. First, nanoparticles (NPs) can offer alternative methods to classical disinfection protocols used in healthcare settings, thanks to their intrinsic antipathogenic properties and/or their ability to inactivate viruses, bacteria, fungi, or yeasts either photothermally or *via* photocatalysis-induced reactive oxygen species (ROS) generation. Nanotechnology tools to inactivate SARS-CoV-2 in patients could also be explored. In this case, nanomaterials could be used to deliver drugs to the pulmonary system to inhibit interaction between angiotensin-converting enzyme 2 (ACE2) receptors and viral S protein. Moreover, the concept of "nanoimmunity by design" can help us to design materials for immune modulation, either stimulating or suppressing the immune response, which would find applications in the context of vaccine development for SARS-CoV-2 or in counteracting the cytokine storm, respectively. In addition to disease prevention and therapeutic potential, nanotechnology has important roles in diagnostics, with potential to support the development of simple, fast, and cost-effective nanotechnology-based assays to monitor the presence of SARS-CoV-2 and related biomarkers. In summary, nanotechnology is critical in counteracting COVID-19 and will be vital when preparing for future pandemics.**



COVID-19: SETTING THE SCENE FOR NANOTECHNOLOGY

Through millions of years of evolution, viruses have gained a variety of molecular mechanisms for entry into cells; long-term survival within cells; and activation, inhibition, or modification of the host defense mechanisms at all levels.[1] Their ability to transfer genes with high efficiency inspired the development of noninfectious recombinant viral vectors for gene-therapy applications, beginning in 1990.[2−4] Efforts were then underway to improve the safety of viral vectors, including developing nonviral drug-delivery systems inspired by the natural capabilities of viruses. Researchers in the field of nanomedicine have designed a variety of nanosystems that can mimic the gene-transfer capacity and high infectivity of viral vectors. By learning the molecular mechanisms behind these vectors, nanomedicine and biomedical researchers have developed delivery systems used in different fields, including cancer therapy and regenerative medicine.[5,6] However, nanotechnology is not only inspired by virology to develop novel delivery tools but also at the forefront in combatting dangerous viruses.

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Viral infections are one of the leading causes of morbidity and mortality worldwide and one of the main reasons for significant economic losses.[7−9] Standard treatment approaches mainly rely on vaccination and therapeutics derived through targeting key processes in the virus life cycle. However, many viruses evolve subject to selective pressures, often becoming drug resistant, which necessitates additional resources for the development of new drugs.

A novel coronavirus causing pneumonia was identified in China in December 2019. On February 11, the Coronavirus Study Group (CGS) of the International Committee on Virus Taxonomy (ICTV) designated the virus as SARS-CoV-2 based on phylogeny and taxonomy.[10] The same day, the Director General of the World Health Organization (WHO) designated the disease caused by SARS-CoV-2 "coronavirus disease 2019" (COVID-19). On March 11, 2020, the WHO declared the COVID-19 outbreak a pandemic. As of May 2020, SARS-CoV-2 has spread across the world in over 185 countries, with millions of infections and hundreds of thousands of deaths.[11]

The main symptoms of COVID-19 are fever (85.6%), cough (68.7%), and fatigue (39.4%). Other less common symptoms include dyspnea, headache, loss of appetite, panting, sore throat, vomiting, diarrhea, rhinorrhea, and abdominal pain. The severity of disease in patients depends mainly on the presence of comorbidities such as hypertension, diabetes, and coronary heart disease.[12,13] The incubation period is reported to be between 5 and 14 days before disease onset.[14] Recent reports indicate that some COVID-19 patients exhibit damage in other organs such as the heart, kidney, eye (conjunctivitis), and brain (encephalitis).[15−18] The race is on to develop drugs and treatment options to combat COVID-19, harnessing all of the tools and technologies modern molecular medicine can offer.

The genome of SARS-CoV-2 has been fully sequenced[19] and shows a high degree of similarity in key genes with other coronaviruses causing respiratory diseases such as SARS-CoV.[20] Based on knowledge gathered during the SARS-CoV epidemic, a key target of the virus includes the surface receptor in human cells, angiotensin-converting enzyme II (ACE2), which is required for efficient uptake in host cells.[19,21−23]

The C-terminal domain (*i.e.*, receptor-binding domain of the envelope-embedded spike (S) 1 protein) of SARS-CoV-2 binds ACE2. The molecular details of this interaction have been provided by solving the crystal structure of the complex.[24] Because binding of the S protein to ACE2 is critical for the first steps of infection, the most common treatment approaches focus on disrupting this key event. At present, there are three main strategies to block ACE2 binding: (i) administration of soluble, recombinant ACE2 protein, which acts as a decoy receptor to scavenge the virus and, thus, to prevent uptake into host cells;[21] (ii) vaccination with antibodies that specifically bind to the S protein and interfere with ACE2 interaction; and (iii) inhibition of host proteases that process the S protein and are essential for ACE2 binding and subsequent membrane fusion to enable intracellular delivery of the virus.[23]

As shown in Figure 1, the first events of the infection (*i.e.*, the interactions of the virus with the target cells expressing ACE2) are in the process of being elucidated at the molecular level. However, as patients suffering from severe symptoms—which usually develop only after several days or a week—already bear a high viral load in the lungs, there is a pressing need for strategies not only to prevent infection of the host cells but also to attack pre-existing persistent viruses and to prevent life-threatening processes, such as hyperinflammation in the lung and multiple-

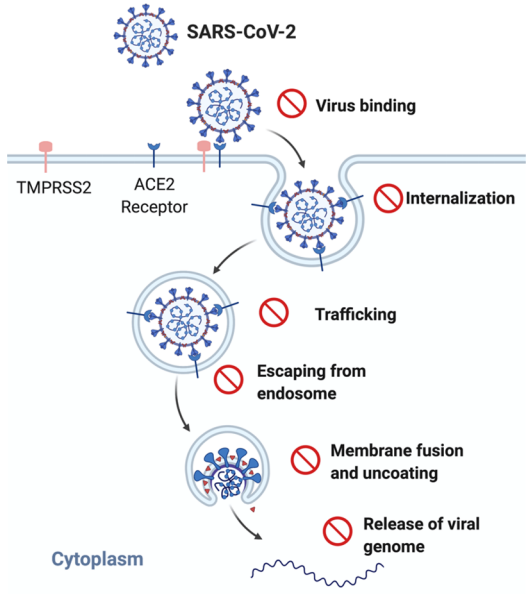

Figure 1. SARS-CoV-2 viral life cycle and potential targets for nanomaterials. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on the host cell surface. Transmembrane serine protease 2 (TMPRSS2) facilitates cellular entry through protease activity. Later, viral particles are internalized and enter into endosomes. Due to the low pH of endosomes, viral particles are uncoated and the viral genome is released for protein synthesis. Following viral RNA and protein synthesis, new infectious particles are assembled and released.

organ failure.[25] Notably, a comprehensive protein−protein interaction (PPI) map of most viral proteins with the human proteome has been established to provide potentially novel targets for treatment employing already U.S. Food and Drug Administration (FDA)-approved drugs *via* a process known as drug repurposing.[26]

The development process of antiviral therapies typically requires years before the therapies can be made widely available[27] because there are a number of regulatory steps required to establish the safety and efficacy of vaccines and drugs.[28] Moreover, the highly specific viral targets might change as SARS-CoV-2 continues to mutate, resulting in resistance to medication, such as has been observed when attempting to treat other viral infections. Overviews of the identification of candidate drugs for SARS-CoV-2 are detailed in refs 29−31.

In the past decade, there has been growing interest in novel, broad-spectrum antiviral compounds, which might be less prone to resistance and could be employed against a wide class of different viruses, including new variants.[32−34] Importantly, such therapies could be prescribed until more sophisticated, targeted drugs and vaccines are available for each new emerging virus.

Nanotechnology offers a number of solutions to fight viruses, both outside and inside the host, and several nanotechnology-based platforms have already been successful in preclinical studies to counter several human viral pathogens such as HIV, human papilloma virus, herpes simplex, and respiratory viruses.[32−35] Nanotechnology-based approaches should be leveraged to help the fight against COVID-19 as well as any future pandemics, in a number of ways, including (i) novel vaccines and drugs, where nanomaterials can be leveraged for direct delivery of broad-spectrum antivirals and to support

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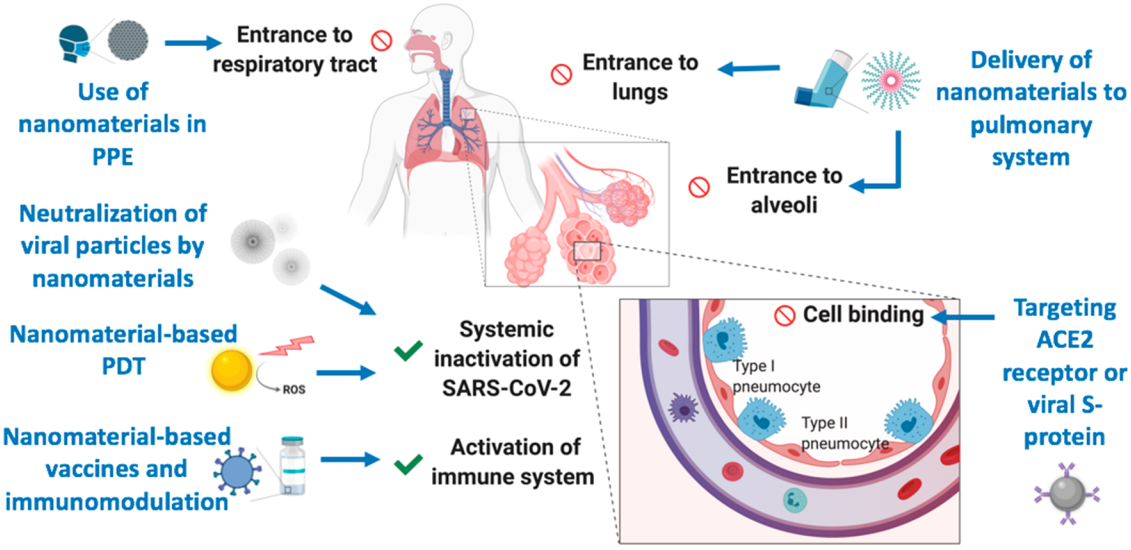

Figure 2. Nanomaterials for prevention and therapy of COVID-19. Integrating nanomaterials into personal protective equipment (PPE) can prevent the entrance of SARS-CoV-2 in the respiratory system. Nanomaterials could also be used to deliver drugs to the pulmonary system *via* inhalators. Cellular binding of viral particles at the alveoli can be inhibited using targeted nanoparticles (NPs) against angiotensin-converting enzyme 2 (ACE2) receptors or viral S protein. Various mechanisms can be used to inactivate viral particles systemically such as using neutralizing NPs or photocatalytic nanomaterials. Nanomaterial-based vaccines or immunomodulation can be used to prevent SARS-CoV-2 infection or even to boost the immune response during infection. PDT, photodynamic therapy.

targeted therapies to the lungs; (ii) highly specific, rapid, and sensitive tests to detect infection or to detect immunity (serological tests); (iii) superfine filters for face masks or blood filtering; (iv) novel surfaces or surface coatings that are resistant to viral adhesion and can inactivate the virus; and (v) the improvement of tools for contact tracing (Figure 2).

This crisis has also highlighted the importance of rapid prototyping/manufacturing for addressing unforeseen needs, such as in case of a pandemic, where large-scale production of equipment including ventilators and personal protective equipment (PPE) is urgently needed and nanotechnology may aid (*e.g.*, in providing readily synthesizable materials for equipment manufacturing as well as for the improvement of their efficiency and durability). In the next sections, we expand and elaborate on the specific contributions that nanotechnology can offer to counter COVID-19 and similar pandemics.

NANOTECHNOLOGY TOOLS TO INACTIVATE SARS-CoV-2 IN PATIENTS

The main target of SARS-CoV-2 is the respiratory tract (upper airways, lung),[36] although other organs might also be infected (*e.g.*, gut, kidney) and vasculature[21] also appears to be a prime target. The expression of ACE2 probably determines uptake by different tissues.[37]

In addition to discussing immune-based approaches, because the lung is the most critically affected organ, we will center our discussion on the various options to inactivate the virus in the deep lung and to target the essential host cells for drug delivery. The virus reaches the alveoli and enters alveolar epithelial type II cells (AECII), due to the relatively high abundance of ACE2 and a permissive cellular milieu. These cells serve as a reservoir of the virus, which finally spreads throughout the lung, leading to the lung function impairment seen in severe cases. Airborne nanomaterials are optimally suited to penetrate into the deep lung due to the physicochemical properties of such aerosols, existing on the same size scale particles that penetrate most readily to the deep airways. Hence, nanomedicine is already actively pursuing ideas to deliver drugs, therapeutic proteins, and mRNAs by exploiting nanodevices for pulmonary delivery.[38,39]

Moreover, the rapid emergence of SARS-CoV-2 has exposed one of the main weaknesses in the current medical landscape: the lack of broad-spectrum antiviral drugs. At present, there are only a handful of approved antivirals, and they are mostly virus-specific. Hence, when a new virus emerges, little can be done pharmacologically to slow down its spread. Some research efforts have been focused on the development of broad-spectrum drugs, which could potentially offer some efficacy against future emerging viruses (and maybe SARS-CoV-2). The various approaches developed over the years are mainly based on the creation of entry inhibitors.[40,41] A highly conserved part in viruses is the attachment ligand (VAL). In most known respiratory viruses,[42] the VAL targets either heparan sulfate proteoglycans (HSPG)[43] or sialic acids (SA).[44] Both HSPG and SA mimics have shown *in vitro* ability to bind to viruses, blocking their interaction with cell membranes, and often in a broad-spectrum way.[45−47]

In the context of nanomedicine, many nanomaterials have been developed, ranging from polymers[48] to dendrimers,[49] oligomers, NPs,[50] liposomes,[51] and small molecules.[52] However, successful clinical translation has been hindered by the fact that, upon dilution, these compounds lose efficacy as the virus-compound complex dissociates leaving viruses free to restart their replication cycle. Recently, it has been shown that this limitation can be overcome by synthesizing NPs that, after binding, are able to inhibit viral infectivity irreversibly by permanently damaging the virion, refueling the hope for a true, broad-spectrum antiviral drug.[53] Because the focus is also on the development of a drug specific to SARS-CoV-2, a good entry inhibitor could be based on blocking the S spike protein interaction with the cellular ACE2 receptor.[19,21−23] Regardless of the specific approach, it is imperative that novel, effective antivirals be based on compounds that exhibit very low or negligible toxicity profiles, as patients will most likely need to

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receive those drugs for extended periods of time and will already be weakened. For these reasons, when designing antiviral drugs, clearance mechanisms have to be kept in mind. An example of this process is the recent redesign of broad-spectrum antiviral NPs into equally effective modified cyclodextrins.[54] Moreover, nanotechnology may offer nanotheranostic approaches to fill the existing gap between diagnostics and therapy.[55−57] The simultaneous management of both diagnostics and therapy for those suffering from COVID-19 or in future pandemics, as for many other diseases, is an additional potential strategy to take into consideration in which nanomaterials have proven to be effective tools. The advantages of the capabilities of nanotechnology and nanomaterials for combined therapeutics and diagnostics has been widely explored in cancer research; however, there have been considerable efforts in the past few years to extend the scope of this approach to other areas including infectious diseases.[58]

Nanomaterial-Based Vaccine Development and Immunomodulation. Following the publication of the genetic sequence of SARS-CoV-2 on January 11, 2020, intense research efforts have been devoted to developing a vaccine against COVID-19. With unprecedented speed, this extraordinary scientific mobilization led the first vaccine candidate to enter the Phase I human clinical trial on March 16, 2020, and other novel candidates are rapidly following.[59] Up to May 22, 2020, there are 10 COVID-19 candidate vaccines in clinical evaluations and 114 in preclinical development.[60]

Concerning vaccine and immunization research, nanomaterials can assist in multiple ways to boost the upregulation required by the immune system and to direct the immune response specifically against antigens. Immune-targeted nanotherapeutics can be developed through their rational manufacture at the nanoscale level by designing nanomaterials that are able to amplify host's immune response, for instance as adjuvants in the context of vaccination.

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The development of a vaccine will rely either on the direct administration of viral antigens (*e.g.*, in the form of recombinant proteins, vectored vaccines, or whole inactivated or attenuated virus) or RNA- or DNA-encoding viral antigens.[27] Candidate antigens for immunization are surface proteins such as the immunogenic spike protein (S1), which is already targeted by antibodies of convalescent patients.[27] Because the S1 protein is also essential for cellular uptake, many researchers are using this protein as the primary target for a vaccine.

There are many issues related to the delivery of a drug, protein, or RNA into the patient as the cargo is often degraded, not bioavailable, or is swiftly cleared. Nanotechnology provides multiple solutions to these challenges though, as nanocarriers can overcome some of these limitations.

Biocompatible polymeric-, lipid-based, or inorganic NPs can be tuned with respect to their physicochemical properties to encapsulate cargo proteins with high loading efficiency, improving protein delivery and pharmacokinetics over conventional approaches.[38] Intranasal delivery of polymer-encapsulated antigen triggers a strong immune response, and the success of vaccination depends on the appropriate type of polymer in combination with the antigen.[61,62] Similarly, researchers have developed lipid and lipid-based NPs as delivery platforms for mRNAs or siRNAs to enable the synthesis of key viral proteins for vaccination or to inactivate critical viral target genes, respectively.[39] The field of therapeutic mRNAs to support vaccination has gained momentum, as well,[63] at least in part due to nanotechnology-enabled strategies for cargo delivery. Moreover, the versatility of nanoplatforms as antigen-presenting systems offers great opportunities. Considering the possibility of random viral mutations that may alter the antigen shape, functionalizing nanomaterials with a wide number of molecules at the same time to target the virus, or motifs that are specific for pathogens, will increase the efficiency of vaccines and their ability to prevent viral infection.

Several companies are working on mRNA vaccines encoding SARS-CoV-2 proteins such as the spike protein, encapsulated in nanoliposomes with specific physicochemical properties that are potentially akin to those documented for immunization against certain tumor antigens.[64] The design of such nanocarriers, which will need to escape recognition by scavenger cells and to be nontoxic and nonimmunogenic, is a challenge that will require substantial time prior to clinical availability.

On March 16, 2020, Moderna, through a partnership with the Vaccine Research Center at the U.S. National Institutes of Health, enrolled the first participants into a Phase I clinical trial testing an mRNA vaccine (mRNA-1273) encapsulated in lipid NPs—a record time of just 63 days following sequence selection (NCT04283461).[65] The enrollment of the first cohort of participants (18 to 55-year-old healthy subjects) concluded on April 16, 2020.[66] CureVac and BioNTech (in partnership with Pfizer) are currently working on similar vaccines; Pfizer/BioNTech, in particular, have recently started the recruitment in Phase I/II trials (NCT04368728, NCT04380701). A DNA plasmid vaccine by Inovio Pharmaceuticals (INO-4800) has showed promising results in mice and guinea pigs according to a recent article published in *Nature Communications*[67] and has entered Phase I testing in humans (NCT04336410).

Another candidate COVID-19 vaccine for Phase I clinical trial is from the University of Oxford and AstraZeneca (NCT04324606).[68] Around 1110 people will take part in the trial, which started recruitment at the end of April 2020. The vaccine is based on a chimpanzee adenovirus vaccine vector (ChAdOx1) and the SARS-CoV-2 spike protein. Chimpanzee adenoviral vectors against different pathogens have been already tested in thousands of subjects with demonstrated safety. To date, ChAdOx1 has been administered to six rhesus macaques exposed to high doses of SARS-CoV-2. The vaccine was unable to prevent infections, although it reduced the severity of the disease: no signs of virus replication were observed in the lungs, with significantly lower levels of respiratory disease and no lung damage compared to control animals, according to a recent article deposited in *bioRxiv*.[69] Another adenoviral vector vaccine developed by CanSino Biological Inc. and Beijing Institute of Biotechnology using a genetically engineered replication-defective adenovirus type 5 vector to express the SARS-CoV-2 spike protein (Ad5-nCoV) is currently being tested in Phase I/II trials (NCT04398147, NCT04341389, NCT0431312).

Although vaccines based on novel DNA and mRNA technologies might be promising, there are no such kinds of

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vaccines on the market, and it is unknown whether they can be effective in humans. Moderna, for instance, has generated preliminary safety data on different mRNA-based vaccines targeting other respiratory viruses, but their more advanced program (on a cytomegalovirus vaccine) is still in Phase II clinical testing. However, on May 18, Moderna announced that mRNA-1273 elicited antibody titers above the levels observed in convalescent individuals (and therefore considered potentially protective) in all eight initial participants across the 25 and 100 μg dose cohorts of the Phase I trial (NCT04283461).[70] The company, after having received a fast-track approval from the FDA, is now moving on Phase II trials.

Conversely, strong evidence exists regarding the efficacy of protein-based vaccines such as recombinant-protein, viral-vector, attenuated, or inactivated vaccines across different infectious diseases, with licensed vaccines already existing for all of these platforms.[27] All of the aforementioned approaches are currently being explored in the context of SARS-CoV-2.[27] An inactivated vaccine developed by the China National Pharmaceutical Group (Sinopharm), in collaboration with the Wuhan Institute of Biological Products, is currently tested in a Phase I/II trial (ChiCTR2000031809), and a second inactivated vaccine (in collaboration with the Beijing Institute of Biological Products) has been currently approved for clinical testing (ChiCTR2000032459). A third aluminum salt (alum) adjuvanted inactivated vaccine, developed by Beijing-based Sinovac Biotech's, was able to provide partial or complete protection in rhesus macaques, according to a recent article published in *Science*,[71] and is currently being tested in Phase I/II trials (NCT04383574, NCT04352608).

Live-attenuated vaccines are intrinsically immunogenic (*e.g.*, due to the presence of viral DNA), but extensive safety tests are required due to the rare possibility of reversion to a pathogenic form able to cause infection. Vaccine candidates based in this application have previously been designed for SARS-CoV with high stability.[72,73] Recombinant-protein vaccines and inactivated vaccines are safer but might require adjuvants to increase their immunogenicity. In the context of SARS-CoV-2, adjuvants are important for two reasons. First, adjuvants might increase the efficacy of the vaccine, especially in subjects with impaired immunological function, such as the elderly, or in subjects with comorbidities resulting in immune dysfunctions; in these patient cohorts, SARS-CoV-2 has a high lethality rate. Second, adjuvants can reduce the amount of vaccine protein(s) required per dose, which could facilitate scaling-up vaccine production in a reduced time frame.

Beyond alum, which is in fact a nanoscale material[74] that was developed in the 1920s for the tetanus and diphtheria toxoids,[75] approval for a new adjuvant did not occur until 1997, with the introduction of the oil-in-water emulsion of squalene oil and polysorbate 80 and sorbitan trioleate surfactants (MF59) in the seasonal influenza vaccine for the elderly.[76] The use of MF59 was further expanded to pandemic and avian influenza vaccines.[77] Other adjuvants in licensed vaccines have been approved since 2000, as well: (a) AS03 (used for pandemic and avian influenza vaccines), similar to MF59, but including α-tocopherol as an additional immune stimulant; (b) AF 03 (used for pandemic influenza vaccines), an alternative squalene emulsion containing polyoxyethylene, cetostearyl ether, mannitol, and orbitan oleate;[78] (c) AS 01 (used for herpes zoster vaccine), a liposome-based vaccine adjuvant system containing two immunostimulants, 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL, a Toll-like receptor 4 agonist) and saponin QS-21, which activates the ACT-NLRP3 inflammasome pathway;[79] and (d) AS04 (used for hepatitis B and human papilloma virus vaccines), which is a combination of MPL and aluminum hydroxide.[76,80]

In this context, the concept of "nanoimmunity by design" relies on the rational design of distinct physicochemical properties and specific functionalization of nanomaterials intended for fine-tuning their potential effects on the immune system.[81] Nanomaterials have emerged as promising tools for immune modulation, either stimulating or suppressing the immune response. In fighting SARS-CoV-2, these properties may find applications for both prevention and therapy and in the context of vaccine development.

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Mounting evidence indicates that nanomaterials such as graphene,[82] nanodiamonds,[83] carbon nanotubes,[84] and polystyrene particles[85] bear an intrinsic capacity to activate the immune system, depending on their functionalization.[86] For instance, graphene oxide functionalized with amino groups ($GO\text{-}NH_2$) induces activation of STAT1/IRF1 interferon signaling in monocytes and T cells, resulting in the production of T cell chemoattractants, and macrophage 1 (M1) 1/T-helper 1 (Th1) polarization of the immune response, with negligible toxicity.[82] Remarkably, the ability of licensed adjuvants such as AS01 and AS03 to enhance adaptive immunity has been linked to their capacity to boost STAT1/IRF1 interferon signaling.[87] In addition, recent SARS-CoV and MERS-CoV studies suggest that the development of a Th1-type response is central for controlling infection, which also may be true for SARS-CoV-2.[88]

Several groups and consortia have been screening and characterizing nanomaterials according to their immunomodulatory properties and absence of cytotoxicity.[56,57,82−84,86] The development of an adjuvant for clinical use is a lengthy process that requires extensive Phase III randomized trials in large and diverse cohorts of subjects, and the process generally requires several years.[76] Pharmaceutical giants such as GlaxoSmithKline (GSK), which owns the ASs mentioned above and other adjuvant platforms, are engaged in several partnerships to embed their adjuvant systems with SARS-CoV-2-protein-based vaccines. A full-length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with the saponin-based Matrix M developed by Novavax is in Phase I clinical testing (NCT04368988).[89]

Although it is unlikely that novel adjuvants would be used in the context of the current pandemic, the SARS-CoV-2 pandemic offers an opportunity to reflect on the potential of nanotechnology for vaccine adjuvant development. In this context, it is critical to stream coherent pipelines covering *in vitro* and *in vivo* experiments specifically to select candidate materials that might be tested for clinical implementation as vaccine adjuvants.[90]

In this view, the status of nanomaterial-based vaccine adjuvants has been reviewed.[91,92] In particular, immunomodulatory effects induced on the innate immune signaling have been demonstrated.[91] For example, nanomaterials such as GO can elicit an inflammasome sensor (NLRP3)-dependent expression of IL-1β in macrophages.[93] Notably, alum, the most commonly

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used adjuvant in human vaccines, induces the release of this cytokine in macrophages through the same NRLP-induced mechanism. These results suggest that nanomaterials such as GO and alum may be useful for medical applications.[94]

Considering that new vaccine development typically requires years to be approved and applied to the general population, there is also an urgent need to study how to improve treatment approaches. According to the first Phase III clinical studies, the antiviral drug Remdesivir, which was recently approved by the FDA for COVID-19 treatment in the United States, seems to be a promising treatment for adults diagnosed with COVID-19. Nano-based strategies have already been applied to enhance the effectiveness of Remdesivir in the context of other emerging viral infections (Nipah virus),[95] suggesting the suitability of nanotechnology to assist with similar strategies for the treatment of COVID-19 as well as other possible pandemics in the future.[96]

Can Nanotechnology Help to Control the Cytokine Storm? One of the main features of COVID-19 is the triggering of a cytokine storm in the body, also known as cytokine release syndrome (CRS), which results from an excessive immune response and leads to the severe deterioration of patient health.[25,97,98] This inflammatory storm is one of the major causes of the acute respiratory distress syndrome (ARDS) that is often associated with multiple-organ failure, representing the leading causes of death in critical patients.[98] In particular, the role of interleukin (IL)-6 has been highlighted in patients requiring assisted ventilation. Ongoing clinical trials are testing drugs that block the receptor of IL-6 (Tocilizumab, an anti-IL-6 receptor antibody, and Sarilumab) or IL-6 itself (Siltuximab).

Whereas a well-regulated cytokine response that is rapidly triggered by the host's innate immunity can serve to prevent and to counteract an infection, an excessive, unbalanced, prolonged immune response can seriously harm the body. Therefore, therapeutic strategies aimed at effectively suppressing the cytokine storm are under investigation. Nanomaterials have been exploited to adjust the immune response to an optimized level, and such proprieties might be explored to inhibit cytokine releases.[99] Nanosystems can enhance the specificity/efficiency of immunosuppressant delivery to target immune cells, with consequent reductions in drug dose, drug distribution to nontarget tissues and organs, and possible side effects. In addition, specific nanotools can be designed to evade the immune system and to enhance the solubility of poorly soluble immunosuppressant agents; the potential of finely tuning their surface charge opens possibilities for encapsulation strategies and offers accommodation for a high drug load. All of these mechanisms may also occur simultaneously, enhancing the activity of immunosuppressive agents.

Concerning the role of macrophages in COVID-19, the presence of ACE2-expressing CD68+CD169+ macrophages containing SARS-CoV-2 nucleoprotein antigen and showing an increased release of IL-6 was observed in infected spleen and lymph nodes.[100] Notably, immunohistochemical and immunofluorescence analyses of lymph nodes and spleen tissue from autopsy samples of patients who died from COVID-19 revealed lymphocytic apoptosis. The tissues infected by SARS-CoV-2 also showed an upregulated expression of Fas, suggesting a role for $CD169^{+}$ macrophages in viral spreading, aberrant inflammation, and activation-induced lymphocyte apoptosis. Moreover, histological examinations of biopsy samples of patients who died from COVID-19 revealed an increased alveolar exudate due to the extended neutrophil and monocyte infiltrate in lung capillaries with fibrin deposition, probably leading to difficulties in gas exchange. Through nanomedicine, we envision therapeutic approaches aimed at targeting specific immune subpopulations to avoid these complications, and different nanomaterials have already been explored for their specific impact on different immune cell subpopulations.[82,83,86] Octadecylamine-functionalized and dexamethasone-adsorbed nanodiamond promotes anti-inflammatory and proregenerative behavior in human macrophages *in vitro*.[101] A low dose of this functionalized nanodiamond also reduced macrophage infiltration and expression of proinflammatory mediators iNOS and tumor necrosis factor (TNF)-α in mice. Overall, these results suggest that nanodiamond particles may be useful as an inherently immunomodulatory platform.

Nanosystems can enhance the specificity/efficiency of immunosuppressant delivery to target immune cells, with consequent reductions in drug dose, drug distribution to nontarget tissues and organs, and possible side effects.

Finally, the indiscriminate systemic suppression of the immune system may increase the susceptibility to sepsis due to underlying secondary bacterial infections that can exacerbate critical conditions in patients, causing death.[102] Risk factors for mortality include acquired bacterial infections by opportunistic organisms and primary pathogens. Using nanocarriers to achieve targeted delivery of immunosuppressive drugs, or the specific and controlled inhibition of only a specific immune cell subpopulation, can play a critical role in limiting such complications.

The fast and complete removal of pro-inflammatory cytokines from the bloodstream has been shown to increase survival significantly in patients with early stage sepsis. Adsorption of cytokines from serum by extracorporeal perfusion through porous carbons is one of the most promising ways for their selective, quick, and complete removal from blood circulation. Hierarchical carbon materials with tuned porosity have shown effective adsorption of many cytokines, including IL-6 and even the largest ones, such as TNF-α.[103] Based on their demonstrated outstanding performance in removing sepsis-associated pro-inflammatory cytokines from blood, mesoporous carbon adsorbents with hierarchical structure, tuned pore size, and surface chemistry, as well as graphene with open and accessible surfaces[104] have significant potential to quickly remove inflammatory cytokines associated with CRS and to prevent mortality arising from an uncontrolled inflammatory cascade, thereby providing enough time for the defense mechanisms of the human body to fight the virus.

Photodynamic Inactivation of SARS-CoV-2. In addition to drug- and vaccine-based antiviral strategies, photodynamic therapy (PDT) stands as a unique approach to inactivate SARS-CoV-2. Using a light-based method, PDT attacks target cells *via* the excitation of photosensitive agents, called photosensitizers (PSs), with radiation characterized by a wavelength corresponding to its absorption spectrum to generate reactive oxygen species (ROS) in the presence of oxygen, which ultimately results in cell death. Photodynamic therapy is primarily used for the clinical treatment of various oncological disorders.[105] It was not until the 1970s that PDT was first used clinically against viruses,[106] exploiting ROS production to damage virus proteins,

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nucleic acids, and—if present—lipids.[107] Even though there are research efforts for PDT-based virotherapies against different viruses, including herpes simplex virus, human papilloma virus, and human immunodeficiency virus,[106−109] clinical use of PDT is limited due to hydrophobicity of PSs, poor target specificity, and limited tissue penetration ability.

Most PSs are hydrophobic and aggregate in aqueous solutions, affecting their photochemical and photobiological properties.[106,110] For this reason, Lim *et al.* have proposed a promising approach for photodynamic inactivation of viruses with NPs, developing sodium yttrium fluoride ($NaYF_4$) upconversion NPs (UCNs) with zinc phthalocyanine PSs grafted onto their surfaces. Unlike most PSs, these UCNs are coated with polyethylenimine (PEI), which render them hydrophilic and easier to manipulate. These UCNs showed antiviral activity against Dengue virus serotype 2 and adenovirus type 5, which were used as models of enveloped and non-enveloped viruses, respectively.[110] MXenes[111,112] are a large family of 2D transition metal carbides, nitrides,[113] and carbonitrides[114] that exhibit unique electronic, optical, and catalytic properties. They have the general formula $M_{n+1}X_nT_x$, where M is an early transition metal (Ti, Zr, V, Mo, *etc.*), X is C and/or N, T_x represents the surface functional groups (=O, −OH, −F, −Cl), and n = 1−4.[115,116] Some examples include $Ti_3C_2T_x$, V_2CT_x, and Nb_2CT_x, with over 30 stoichiometric compositions already synthesized with more than 100 predicted. Biocompatible MXenes, such as $Ti_3C_2T_x$, are hydrophilic and are among the most efficient light-to-heat transforming materials.[117] The plasmon resonance extinction maxima of $Ti_3C_2T_x$ is at 780 nm, enabling the use of near-infrared (IR) light for PDT. Several other MXenes have absorption maxima in the IR range and have shown outstanding performance in PDT and theranostic applications.[118]

Fullerene and graphene are also good candidates for virus inactivation by PDT and have proved to be effective against Semliki Forest virus (SFV), vesicular stomatitis virus (VSV), HSV-1, HIV-1, mosquito iridovirus (MIV), and influenza A virus (IAV), as well as the phage MS2.[107] In addition, several 2D nanomaterials, including graphene-based materials, MXenes, black phosphorus, graphitic carbon nitride, tungsten disulfide, and molybdenum disulfide, have been reported to improve the efficacy of PDT considerably for cancer treatment.[56,57] Therefore, determining if such nanomaterial-based PDT protocols could be exploited to inactivate SARS-CoV-2 is of great interest.

Biomimetic Engineering of Nanodelivery Systems: Artificial Viruses in the Making. In an effort to engineer the next generation of nanoscale vectors, scientists have moved from using inorganic components aimed at obtaining inert structures to utilizing biological building blocks that are able to convey additional functionalities to the resulting construct. To cope with the complexity of the body and to evade the multiple layers of defense that tissues and organs have, it is critical to rely on the ability of certain materials to interact with, rather than to eschew, the biology of our body. Every NP system conceived to date faces one common fate: whether injected, inhaled, ingested, or absorbed through our epithelia, all will at some point come into contact with the mixture of fluids and organic compounds that comprise the body. Under such conditions, every material reacts in a unique way according to the conditions they individually face (*i.e.*, the tissue or body region they are in), their composition (*i.e.*, organic or inorganic), and their physical properties (*i.e.*, size, shape, surface charge).[119] Inorganic NPs can function as globular protein mimics because of their similar size, charge, shape, and surface features that can be chemically functionalized to resemble proteins. These similarities can be used in biotechnology to control virus pathways or cell receptor interactions with NPs.[120]

Among the many attempts, the legendary accomplishments, and the epic failures, we could list thousands of different NPs, differing from one another thanks to the creative endeavors of their designers. Despite their remarkable differences and researchers' endeavors to make them one of a kind, they all aim to achieve one goal: to deliver in a specific way one particular form of payload, while remaining as unnoticed as possible by the body's defense mechanisms. For everyone who has made an effort to create their own version of such a silver bullet, it has come to mind that nature in its incredible variety had already invented a few ingenious solutions to this problem. In the world of nano-based drug delivery, one entity dominates as the quintessential example of precision, efficiency, and stealth: the virus. Not by chance, these two worlds share many features that span from the physical laws that govern their assembly and stability to the chemical similarities in their overall composition.[121]

Historically, the field of nanomedicine and the global endeavor to generate NPs for drug delivery arose from one of the greatest struggles in medicine: gene therapy. At the core of that approach was the idea that viruses could be used as Trojan horses to deliver the correct sequence of the gene into the cells that harbored the mutated copy. In order to identify the virus that offered the best delivery service, a cadre of viral strains and species were tested, adapted, and engineered to fit the aims and hit the targets. It took decades of trial and error, of progressive adjustments, and a few tragic mistakes to identify the viruses that could provide the ideal backbone to develop viral vectors able to ferry genetic cargo into the target cell.[122] In the midst of that global challenge, nanotechnology offered a safer and more controllable alternative: to generate bespoke structures that could replace viral vectors and do the same job, delivering a payload from the point of injection to the site of action.

Fast forward a few decades, and the promises made by both worlds seem to have finally become reality, with a number of active clinical trials, some clinical success stories, and a few commercial products in the market space. Interestingly, the two worlds seem to have maintained a safe distance so as to avoid any collision or dangerous proximity. Exchange of ideas between the fields of gene therapy and nanomedicine is limited, and the potential for disciplinary growth through knowledge exchange has remained elusive to scientists in both fields.[5] Many scientists have suggested that nanotechnologists could find inspiration in the mechanisms devised by viruses to elude immune surveillance, to overcome biological barriers, and to deliver their genetic payload with high specificity. Similarly, gene therapists would find high-tech solutions to their scalability and safety issues in looking at the new generations of biomimetic particles being generated.

The principles of biomimicry and bioinspiration have been used to design and to engineer drug-delivery technologies that reproduce or recapitulate biological materials, for what pertains to not only their structure and chemistry but also, more importantly, their functions. In drug delivery, surface recognition and nanoscale interactions between materials and biological entities are key to the success of the delivery strategy, and the use of biological building blocks such as membrane proteins has been proposed as a way to convey targeting and shielding moieties simultaneously.[123] One can only hope that

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the recent events and global attention that viruses are capturing in the scientific world will spur a renewed interest in finding ways to adapt viral features and mechanisms of action to the world of NPs. Increased focus in this field would be useful to create virus-like NPs able to circulate in the blood system, overcoming the endothelial barrier, and to deliver their therapeutic payload with high efficiency.[124]

Interference with Cellular Uptake, Immobilization, and Inactivation of the Virus Outside of the Host Cell. Nanomaterials can be synthesized with a high specific surface area of a few hundred square meters per gram. Therefore, dependent on the surface properties, nanomaterials efficiently adsorb biomolecules and form a so-called biomolecular corona. This passive, nontargeted adsorption might be utilized to bind viruses, provided that the selected nanomaterial is relatively biocompatible. Viral surface proteins are often modified by sugar moieties or encompass positively charged amino acid patches that bind to lectins or glycosaminoglycans (GAGs) of heparan sulfate (HS), respectively.[32] Robust interactions of virus particles with these host receptors is ensured by multivalent binding, which is likely why single-molecule inhibitors often are not capable of efficiently perturbing this key event but multivalent NPs are superior to block binding of different viruses to the host cell.[125]

Gold NPs capped with mercaptoethanesulfonate are effective inhibitors of HSV type 1 infection as they mimic cell-surface-receptor heparan sulfate and, therefore, competitively bind to the virus. Interestingly, polyvalent sulfated Au NPs inhibit virus binding to the host cell dependent on their size. Nanoparticles of diameters equal to and larger than the virus diameter (in this case, the stomatitis virus) more efficiently inhibit the binding to cells than smaller particles. Most likely, larger NPs efficiently cross-link virions, whereas smaller NPs simply decorate the viral surface.[126] Papp *et al.* found that gold NPs decorated with SA effectively inhibited the binding of influenza virus to the target cells. In this case, viral recognition *via* its surface protein hemagglutinin of SA on the host cell membrane was a prerequisite for cellular entry.[127] More recently, Cagno *et al.* reported antiviral NPs (Au and iron oxide core) with long and flexible linkers mimicking HS that strongly bind and inactivate viruses such as respiratory syncytial virus *in vitro* and *in vivo* in a lung infection model and even led to irreversible viral deformation.[53] Hence, there is ample evidence that biocompatible, functionalized NPs can act as broad-spectrum antivirals. Notably, the receptor-binding domain of the spike S1 protein of SARS-CoV-2 binds not only to ACE2 but also to heparin[128] and, thus, might be targeted by similar approaches as outlined above.

There is ample evidence that biocompatible, functionalized nanoparticles can act as broad-spectrum antivirals.

One of the most recent strategies to inhibit viral uptake is based on administration of recombinant ACE2 to inhibit binding competitively *via* the spike S1 protein.[21] Knowing that multivalency is key to block virus–host interactions reliably, researchers have speculated that a nanostructured carrier could not only improve delivery and cargo stability but also might dramatically enhance binding strength.[129]

Speeding up the Nanomedicine-Based Approaches for COVID-19 by *In Silico* Analysis. Currently, repurposing drug molecules is a key strategy for identifying approved or investigational drugs outside the scope of the original medical indication that can be used to fight COVID-19.[130,131] There are various advantages to this strategy, including already-established safety profiles, fast transition to clinical studies, and less investment needed, compared to the process of developing an entirely new drug.[132,133] Therefore, these advantages have the potential to result in less risky and more rapid returns on investment in the development of repurposed drugs, benefits that are particularly important during pandemics. In addition to rapid diagnosis, making recommendations to physicians about rapid treatment methods can save the lives of many people. Combining *in silico* tools such as molecular docking, molecular dynamics, and computational chemistry with large drug databases provides a great advantage in selecting "possible candidates" from among thousands of pharmaceutically active substances (Figure 3). *In silico* analyses should be supported by

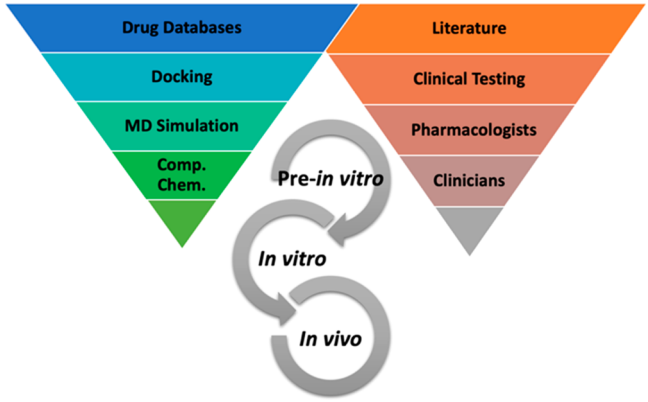

Figure 3. Schematic of how *in silico* analysis can be used to select candidate drug molecules for clinical studies. MD, molecular dynamics.

the literature, expert opinions (pharmacologists and clinicians), and, when possible, preclinical and clinical findings. After selecting the best candidates following *in silico* analyses, detailed *in vitro* and *in vivo* experimentation should be undertaken prior to clinical studies. Recently, various drug-repurposing studies have been published to assist in the global COVID-19 pandemic response.[134−136] Such studies aim to identify whether already-approved drugs have the capacity to interact with viral proteins or receptors on host cells.

In nanomedicine, computational models have recently garnered attention; such work may help to identify how nanomaterials interact with biological systems and to determine how the efficacy of these nanotherapeutics could be improved. Computational models indicate how NPs are taken up by healthy cells or tumor cells, enabling better predictions regarding the pharmacokinetic and pharmacodynamic properties of these materials.[134] For example, Lunnoo *et al.* used a coarse-grained molecular dynamics (MD) simulation to observe the internalization pathways of various Au nanostructures (nanospheres, nanocages, nanorods, nanoplates, and nanohexapods) into an idealized mammalian plasma membrane.[137] Other studies have simulated how different NPs can target tumor cells and deliver drugs.[138,139] Therefore, *in silico* approaches that are currently used for drug repurposing, including molecular docking, molecular dynamics, and computational chemistry, constitute valuable tools to aid preclinical and clinical studies of nanomaterials directed for disease treatment. Considering the urgent need for nano-

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medicine against the current pandemic, *in silico* analyses may be especially useful in guiding the rational design of new NP formulations required to fight SARS-CoV-2.

NANOTECHNOLOGY TOOLS TO DETECT SARS-CoV-2

Standard procedures for detecting the virus from nasopharyngeal and/or oropharyngeal swabs have been reviewed recently and are primarily based on reverse transcription polymerase chain reaction (RT-PCR).[140] Here, we would like to mention some preliminary ideas on nanotechnology-based assays to monitor the presence of SARS-CoV-2. A simplified test and variants thereof to detect viral proteins (*e.g.*, HIV or influenza virus) without the need for expensive equipment is based on the color change of Au NPs bound to antibodies. Similar to the enzyme-linked immunosorbent assay (ELISA) antibodies coupled to Au NPs will form a tertiary complex with the viral antigen and a capture antibody, thereby leading to the immobilization and agglomeration of NPs, which shifts the color from red to blue.[32] Such simple, low-cost procedures could be of value in regions with low-resource medical infrastructure, as found in developing countries. For rapid, on-site detection, the development of graphene-based field-effect transistor (FET) biosensing devices coupled to a specific antibody against SARS-CoV-2 spike protein was recently reported.[141] Dual-functional plasmonic biosensors combining the plasmonic photothermal (PPT) effect and localized surface plasmon resonance were also recently developed and could be used as a cost-effective and fast alternative to RT-PCR. Here, Au nanomaterials coupled to complementary DNA sequences are used to sense hybridized cDNAs of SARS-CoV-2.[142]

Nanobiosensors are a valuable alternative to conventional laboratory equipments for clinical and environmental analyses.[143] Usually, nanobiosensors combine the excellent electrical and optical properties of nanomaterials with biological or synthetic molecules used as receptors to detect selectively any kind of analyte. The detection of whole cells (*e.g.*, cancer cells) using electrocatalytic properties of Au NPs toward hydrogen evolution has been reported.[144] This cell-sensing device is based on the reaction of cell surface proteins with specific antibodies conjugated to Au NPs. The same detection technique can also be applied to the detection of viruses, taking advantages of the known antigens and available antibodies. Recently, as mentioned above, a FET sensor (modified with graphene sheets) that uses a specific antibody against SARS-CoV-2 spike protein was reported to detect SARS-CoV-2 in culture medium (limit of detection, LOD: 1.6×10^1 pfu/mL) and clinical samples (LOD: 2.42×10^2 copies/mL).[141]

> Nanobiosensors are a valuable alternative to conventional laboratory equipments for clinical and environmental analyses.

Researchers have also demonstrated solid-phase isothermal recombinase polymerase amplification (RPA) for the detection of *Citrus tristeza* virus (CTV) for plant disease diagnostics. Gold NPs linked with DNA strands on top of an electrode were used to detect *in situ* amplified CTV (RPA assay for amplification of the P20 gene, 387 bp) using electrochemical impedance spectroscopy (EIS) in a $Fe(CN_6)^{4-}/Fe(CN_6)^{3-}$ redox system, being able to detect 1000 fg μL^{-1} of nucleic acid quantitatively (Figure 4).[145]

Paper/nanomaterial-based sensors,[146,147] in general, and, particularly, NP-based lateral-flow devices that are observed with the naked eye or operated through a smartphone are now the most reported testing platforms for the analysis of COVID-19-related biomarkers.[148] Nanopaper[147] and nanochannels[149] may also offer cost-efficient alternatives for detection of viruses and related biomarkers. Nanomaterials are already being used in theranostics applications. Although the field of nanomaterial applications in nanotheranostics is still in its infancy,[55] a thoughtful review of the performance characteristics of known nanomaterials may open new avenues of investigation, even for COVID-19-related applications (for both diagnostic and therapies, including vaccines).

NANOTECHNOLOGY TOOLS TO INACTIVATE SARS-CoV-2 IN DIFFERENT ENVIRONMENTS OUTSIDE THE PATIENT

SARS-CoV is highly stable at room temperature and at 4 °C, but it is inactivated by ultraviolet light at 254 nm, highly alkaline or acidic conditions of pH >12 or pH <3, respectively, or by brief (e.g., 5 min) heat treatment at 65 °C. SARS-CoV-2 is expected to be similarly sensitive.[150] Several human coronaviruses can be inactivated by classical disinfectants, including bleach, ethanol, povidone-iodine, chloroxylenol, chlorhexamide, and benzalkonium chloride,[151] so we expect similar inactivation with SARS-CoV-2. The virus stability on surfaces depends on the composition of the infected material, with inactivation in <3 h on printing and tissue paper, in <2 days on treated wood and cloth, in <4 days on glass and banknotes, and in <7 days on stainless steel and plastic.[152] Conversely, active viruses can remain on the outer layer of a surgical mask even after 7 days.[152] The surface and aerosol stability of SARS-CoV-2 is comparable to that of SARS-CoV-1,[153] with both viruses remaining viable in contaminated aerosols for more than 3 h. Infectious SARS-CoV-1 and SARS-CoV-2 remain viable up to 72 h after inoculation on plastic and stainless steel, whereas both are inactivated on copper in less than 4 or 8 h, respectively, and on cardboards in less than 24 and 8 h, respectively.[153] Therefore, the stability of both viruses is similar, and we can hypothesize that surface treatments with NPs that proved to be effective for SARS-CoV-1 could possibly also be effective for SARS-CoV-2.

Nanotechnology can offer alternative methods to classical disinfection protocols used in healthcare settings, which typically rely on chemical-based disinfection using hydrogen peroxide stream or metal-ion-coated surfaces, biological-based strategies including probiotics or biosurfactants, or physical strategies such as irradiation with ultraviolet (UV) light. Nanotechnology may offer pathways to the development of self-disinfecting surfaces that would avoid contamination of the healthcare and housekeeping staff.

> Nanotechnology may offer pathways to the development of self-disinfecting surfaces that would avoid contamination of the healthcare and housekeeping staff.

The methods proposed here for virus inactivation encompass the use of NPs and nanomaterials known for their intrinsic

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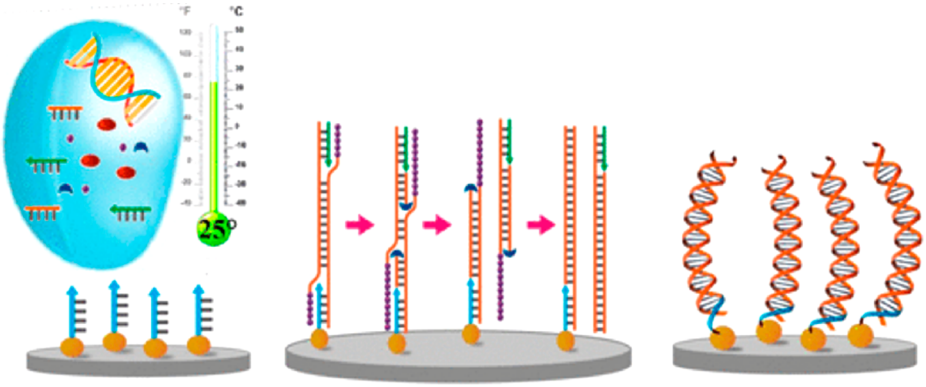

Figure 4. Schematic of recombinase polymerase amplification-based *Citrus tristeza* virus detection using gold-nanoparticle-modified DNA strands and electrochemical impedance spectroscopic detection. Reprinted from ref 145. Copyright 2019 American Chemical Society.

antipathogenic properties, such as metal-based NPs and graphene, or for their ability to inactivate viruses, bacteria, fungi, or yeasts either photothermally or *via* photocatalysis-induced ROS generation.

SARS-CoV-2 Inactivation by Nano-Based Tools. Silver, copper, and zinc show intrinsic antimicrobial properties and are already used in medical equipment and in healthcare settings. For instance, Ag is used in wound dressing and in urinary and intravascular catheters. It is advantageous to use NPs composed of these metals rather than bulk materials or the metal ions themselves because NPs release the toxic metal ions slowly and progressively right where the antimicrobial action is needed and because NPs can accumulate within cells without being expelled by specialized efflux pumps. The antimicrobial property of Ag has been used since ancient times for medical applications[154] and more recently in commercial products such as silver zeolites in paints[155] and in food trays[156] as biocide. The antiviral efficiency of Ag NPs has been demonstrated in a variety of viruses, including HIV-1,[157] monkeypox virus,[158] bacteriophages UZ1 and MS2,[159,160] murine norovirus MNV1,[159,160] HSV,[161] HBV,[162] and, recently, in porcine epidemic diarrhea virus (PEDV).[163] Antiviral properties of Ag NPs arise from three different mechanisms. First, Ag(0) NPs dissolve and release some toxic Ag(I) forms (including Ag^+ ions), which could be responsible for their antiviral activity. As a soft metal, Ag shows strong affinity toward sulfur, and therefore, it interacts strongly with thiols from small molecules such as cysteine or glutathione or with sulfhydryl groups in the active sites of many enzymes. Ag(I) may interact with surface proteins of viruses or accumulate in host cells and further interact with thiol-containing enzymes that are involved in virus replication, thus hampering their functions. This hypothesis was proposed by Zodrow *et al.* to explain the antiviral property of Ag NPs for bacteriophage MS2 and by De Gusseme *et al.* in response to MNV-1 exposed to Ag NPs.[159,164] Moreover, Ag_2S nanoclusters (NCs) with diameters of 2.5 and 4 nm showed effective inhibition of PEDV replication in Vero cells *via* inhibition of the synthesis of viral negative-strand RNA and of virus budding from the cells, but not by preventing their anchorage on cell membranes or their intracellular penetration. Exposing cells to Ag^+ ions at the same concentration did not inhibit virus replication, which led the authors to conclude that the antiviral property of Ag NCs was independent of the release of Ag(I).[163] However, the mechanisms by which Ag^+ ions and Ag NCs enter into cells are different and, consequently, their local distribution and handling within cells would also be different. This difference could lead to different modes of toxic action for Ag ions and Ag NCs toward the viruses that have infected cells. For instance, Ag NCs may aggregate in intracellular areas where vital steps of the viral cycle are performed, such as protein or genome production or assembly of nucleocapsids before their release into the extracellular space, whereas Ag(I) could aggregate in other areas of the cells or be rapidly eliminated. Second, the antiviral efficiency of Ag NPs would derive from physical interaction of Ag NPs with the surface of viruses, which would impede their docking on host cells and limit their infectivity. This mechanism was demonstrated by Elechiguerra *et al.* for HIV-1 exposed to 1−10 nm Ag NPs[157] and by Orlowski *et al.* for HSV-2 exposed to 13, 33, and 46 nm Ag NPs coated with tannic acid.[161] Elechiguerra *et al.* found that the optimal size of Ag NPs was around 10 nm, with larger or smaller NP sizes showing weaker physical interaction with the virus. In contrast, Orlowski *et al.* found that the larger the NP, the more effective its blocking was of virus attachment to host cell. The same mechanism, combined with the release of Ag(I), was also proposed by De Gusseme *et al.* to explain the reduced infectivity of MNV-1 virus when exposed to 11.2 nm biogenic Ag NPs.[159] Finally, this docking of Ag NPs on the surface of viruses could be associated with the local release of ROS from the Ag NP surface, which would damage the envelope and/or membrane of the virus. Ag NPs are already used in wound dressings, catheters and other medical equipment; their use could also be envisaged to confer biocidal properties to paints used in healthcare settings, or to air filters or face masks. Ag NPs loaded on filters show effective antiviral activity against bacteriophage MS2, which drops with dust loading.[165]

The antimicrobial activity of Cu has also been known since ancient times,[166] and surfaces containing a significant amount of Cu have demonstrated their efficacy to inactivate viruses. Murray *et al.* showed the efficacy of Cu against poliovirus in 1979.[167] More recently, the efficacy of Cu was demonstrated on the HuCoV-229E coronavirus; the effectiveness of Cu to inactivate other forms of coronaviruses suggests potential similar efficacy against SARS-CoV-2.[168] Whereas HuCoV-229E persists for more than 6 days in an infectious state on smooth surfaces (Teflon, polyvinyl chloride, ceramic tiles, glass, stainless steel), it is inactivated in less than 60 min on brasses containing at least 70% Cu or Cu−Ni alloys containing at least 90% Cu.[168] When incubated on Cu-containing surfaces, the viral genome becomes fragmented, ensuring the irreversibility of inactivation.[168] The proposed inactivation mechanisms include both toxicity toward virions of Cu ions released from the Cu-containing surface and

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attack of viral proteins and lipids by ROS generated from Cu reacting with exogenous hydrogen or molecular oxygen through Fenton-like or Haber Weiss reactions.[166] Likewise, both SARS-CoV-1 and SARS-CoV-2 are inactivated on Cu surfaces in less than 4 h, whereas they persist for 48−72 h on plastic and stainless steel and less than 24 h on cardboard.[153] In this case, the main inactivation mechanism is also proposed to be damage to viral proteins and lipids by Cu ions and ROS, in particular, envelope proteins.[153] Using Cu brasses or Cu-containing alloys rather than stainless steel would provide effective antimicrobial surfaces (doorknobs, bed rails, *etc.*) in healthcare settings. Supported catalysts composed of Al_2O_3 impregnated with Ag and Cu to form Ag/Al_2O_3 (5% Ag) and Cu/Al_2O_3 (10% Cu) also inactivate SARS-CoV virus in less than 5 and 20 min, respectively, which would be useful for air disinfection.[169]

Using Cu brasses or Cu-containing alloys rather than stainless steel would provide effective antimicrobial surfaces (doorknobs, bed rails, *etc.*) in healthcare settings.

Cu and CuO NPs have also been shown to release Cu ions when in contact with live cells.[170,171] The large surface that NPs develop due to their small size endows them with a reactivity higher than that of their bulk counterpart and would fasten the kinetics of Cu ion release. The use of nanostructured Cu surfaces would further enhance their antimicrobial activity. Moreover, these NPs could inactivate viruses if sprayed on contaminated surfaces or loaded onto textile fabrics to confer antimicrobial properties (masks, blouses, *etc.*). Indeed, CuO-impregnated masks have shown remarkable anti-influenza virus (H1N1 and H9N2) activity under simulated breathing conditions,[172] and the activity of these materials toward SARS-CoV-2 should be investigated. The viral disinfectant properties of Ag NPs and CuO NPs is further enhanced when they are combined with Fe as bimetallic particles, due to coupled redox reactions between the two metals.[173]

In addition to metal NPs, graphene derivatives have also shown promising viral inactivation properties.[174] For example, graphene oxide (GO) sheets and sulfated GO derivatives have been found to be effective against herpes simplex virus type-1 (HSV-1) infections, with viral binding and shielding as the two putative main inhibitory mechanisms.[175] Thermally reduced graphene oxide (rGO) sheets functionalized with biocompatible hyperbranched polyglycerol (hPG) and then sulfated have also been generated as graphene-based heparin biomimetics.[176−178] Sulfate-rich polymers like heparan sulfate and its equivalent soluble counterpart heparin are widely known as broad antiviral agents,[179,180] but their use is limited due to their anticoagulant effects. Sulfated rGO-hPG sheets were found to be effective at inhibiting orthopoxvirus and herpesvirus strains, particularly in the early stages of the infection, although they could not prevent cell-to-cell spread. Additional antiviral activity of graphene derivatives has been attributed to the negative surface charges and sharp edges of the individualized sheets, as the electrostatic interactions promote binding with the positively charged virus particles. Negative charges on sharp-edged single-sheet GO and rGO were shown to bind and to suppress the infection of pseudorabies, PEDV, EV71, and H9N2 viruses.[181,182] This mechanism suggests that potentially similar antiviral effects could be offered by other negatively charged, sharp-edged 2D nanomaterials such as $Ti_3C_2T_x$ MXene, which has shown promising bacterial inactivation effects against both Gram-positive and Gram-negative species due to similar hypothesized mechanisms.[118,183]

Graphene derivatives linked to virus-specific antibodies have also been adopted in antiviral platforms based on antibody-mediated binding and sensing mechanisms, which have been shown to capture a number of viral species successfully including rotavirus, avian influenza virus subtypes H5 (AIV H5) and H7 (AIV H7), and influenza virus H1N1.[184−187]

Photothermal Inactivation of SARS-CoV-2. Another example of the use of noble metals for disinfection is the ability of Ag and Au NPs and nanorods to induce heating when illuminated at optimal wavelength, corresponding to the plasmon resonance condition, in a process called plasmonic photothermal treatment.[188] This property is currently being evaluated by nanomedical researchers as a method for killing cancer cells with Au NPs because Au NPs are considered much less toxic than Ag NPs. By tuning NP size and shape, it is possible to emit intense heat under solar irradiation of Au NPs and to inactivate viruses, as demonstrated by Loeb *et al.* with bacteriophages MS2 and PR772 exposed to Au nanorods and nanocubes or to surfaces coated with such NPs.[189] Close contact between NPs and the pathogen is necessary for the process to be effective, which supposes that NPs adsorb onto their surface. Elsewhere, Nazari *et al.* used femtosecond pulsed laser irradiation on Au nanorods to inactivate murine leukemia virus (MLV).[190] Here, inactivation did not require contact between Au NRs and viruses, and the addition of ROS scavengers did not reduce the inactivation effect, suggesting that neither heat nor ROS generation accounted for the observed effect. The authors propose that the underlying mechanism is plasmon-enhanced shockwave generation, which alters virus membrane and/or surface groups and, therefore, reduces virus binding and fusion with the host cell.[190]

Inactivation of SARS-CoV-2 by Photocatalytic Nanoparticles. Photocatalytic NPs offer another possible approach to the inactivation of SARS-CoV-2. The most described NP in this category is titanium dioxide (TiO_2), which shows photocatalytic properties when illuminated under UV light, is considered inert, has low toxicity, and is not susceptible to photocorrosion.[191] TiO_2 is currently used in paints and lacquers,[155] in self-cleaning windows, and for water purification.[192] TiO_2-containing paints have also been envisaged for purifying ambient air because photocatalytic TiO_2 successfully removes volatile organic compounds (VOCs) when exposed to UV light. However, recent findings show that VOC disruption is associated with the release of toxins in the air, which questions the prudence of TiO_2-doped paints for air purification purposes.[155] If effective, the use of TiO_2 photocatalysis for SARS-CoV-2 inactivation would be particularly useful for surface decontamination using TiO_2-doped paints, aerosol decontamination using air filtration filters and ventilation systems impregnated with TiO_2 that can be exposed to UV light, and for wastewater treatment.

The underlying mechanism of this photocatalytic process relies on the excitation of an electron from the valence band (VB) of the photocatalytic material to the conduction band (CB) when exposed to UV light, which leaves a positive hole (h^+) in the VB. The e^-/h^+ charge carriers migrate to the surface of the photocatalyst and initiate reactions leading to the production of ROS, including the superoxide anion, hydrogen

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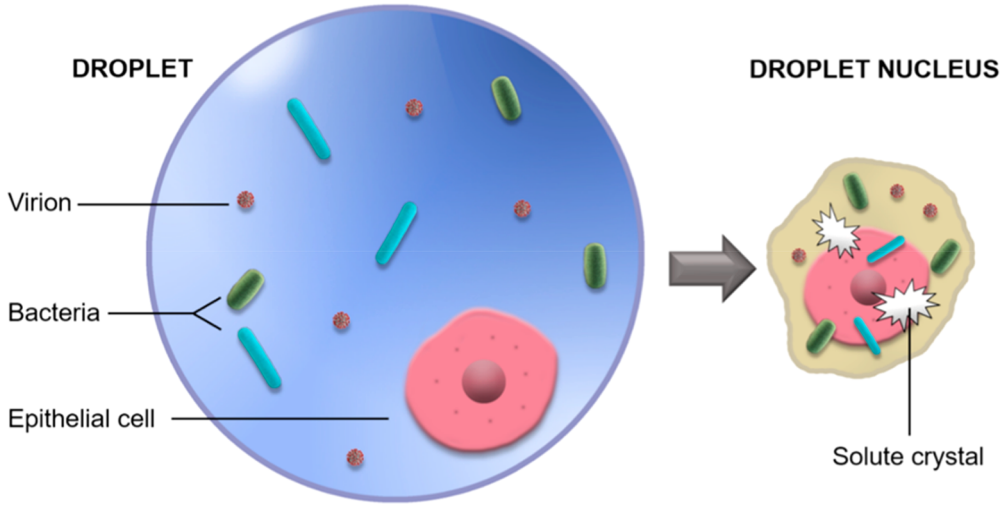

Figure 5. Droplets and droplet nuclei as important mechanism for transmission of infection. Liquid droplets containing SARS-CoV-2 virions originating from the respiratory tract of infected patients are emitted into the air and carry other materials including bacterial cells and epithelial cells. They are reduced in size by evaporation to small, dry particles resulting in droplet nuclei.

peroxide, the hydroxyl anion, and hydroxyl radical.[193] The production of hydroxyl radicals by the oxidation of water molecules on the photocatalysts' surface accounts for their disinfection activity, owing to their capacity to oxidize many organic constituents of microorganisms, such as lipid peroxidation, leading to damage to cell wall and cell membrane, protein alteration, and/or DNA damage.[193] Bare TiO_2 exposed to UV light is effective against a broad spectrum of Gram-positive and Gram-negative bacteria, including multi-drug-resistant strains but also against some fungi, viruses, and yeasts. As discussed by Bogdan *et al.*, according to some authors, viruses would be more susceptible to inactivation than bacteria.[194] Among viruses, some researchers have found that enveloped viruses would be more protected from photocatalytic inactivation than non-enveloped viruses, whereas other authors reported the opposite.[194] Only one article reported the usefulness of this inactivation strategy for treatment of SARS-CoV, using a photocatalytic titanium apatite filter (PTAF). This filter showed effective inactivation of SARS-CoV when exposed for 6 h to UV light.[195] One could also imagine that photocatalysts coupled to UV light could damage spike proteins and lead to decreased infectious capacity of the virus.

Because TiO_2 shows low solar light activity and a high recombination rate of electron−hole pairs, researchers have developed second-generation photocatalysts in which TiO_2 is used in combination with other components, such as metals. This new generation of photocatalysts shows high efficiency of inactivation of a wide range of bacteria and some viruses. Among them, S-doped and N-doped TiO_2 show photocatalytic properties when exposed to visible light and, therefore, would possibly be effective under interior lightning. The antimicrobial properties of these photocatalysts have been tested with a variety of bacteria, sometimes indicating good disinfection efficiency (for reviews, see refs 192 and 193), but to our knowledge, they have not been tested on viruses. Moreover, depositing some Ag NPs on the surface of TiO_2 NPs increases their antiviral efficiency against MS2 by means of increased production of hydroxyl radicals.[196] A Ag- and Cu-doped TiO_2 nanowire membrane is more active in eliminating bacteriophage MS2 from drinking water than are TiO_2, Ag-TiO_2, or Cu-TiO_2 membranes, both in the dark and when exposed to UV light. The underlying mechanism is thought to combine both enhanced photoactivity due to the lower band gap of (Ag, Cu)-TiO_2 than that of TiO_2[197] and antimicrobial activity of free Ag and Cu ions released into the treated water.[198] Another strategy to improve the antiviral capability of TiO_2 is by increasing its potential to absorb viruses, which has successfully been achieved by mixing TiO_2 NPs with SiO_2 NPs. Due to the large specific surface area of SiO_2, the mixture of NPs inactivated bacteriophage MS2 more effectively than did TiO_2 alone, in spite of reduced hydroxyl production.[199] Glass slides coated with TiO_2 doped with Pt show slightly better efficiency in inactivating aerosols containing influenza A (H3N2) virus than do surfaces coated with only TiO_2 when irradiated with UV-A,[200] owing to their increased oxidizing photocatalytic properties. Finally, as described by Byrnes *et al.*,[193] new photocatalytic materials that show efficient antibacterial activity have been developed and could be tested for the inactivation of SARS-CoV-2. These new materials include (among others) $BiVO_4$, $CuFeO_2$, $CuY_xFe_{2-x}O_4$, $LaFeO_8$, $CuMn_2O_4$, $ZnMn_2O_4$, $BaCr_2O_4$, $SrCr_2O_4$, $NiCo_2O_4$, $CuCo_2O_4$, $LaCoO_3$, and $La_{0.9}Sr_{0.1}CoO_3$. Importantly, before being used for SARS-CoV-2 inactivation, their nontoxicity should be ensured.

Nanotechnology-Based Solutions to Increase the Efficiency and Safety of Protective Devices. Cryoelectron microscopy (cryo-EM) studies show that SARS-CoV-2 virions are particles near the larger end of the NP size range (70−90 nm).[21,201] However, when dispersed into the air, the infectious particles exist as functionally larger particles. Initially, liquid droplets containing coronavirus virions originating from the respiratory tract of infected patients are emitted during normal breathing, forced expiration (*e.g.*, coughing and sneezing), or aerosol-generating medical procedures (*e.g.*, intubation and suctioning). Liquid droplets emitted into the air through these mechanisms originate from points throughout the respiratory tract and carry within them virions as well as other materials associated with the airways, including bacterial cells and epithelial cells (Figure 5). Droplets are emitted over a wide size range, and their potential viral burden is a cubic function of particle diameter (Figure 6). Thus, larger droplets have the potential to carry a significantly larger burden of virions according to their size and are substantially more hazardous

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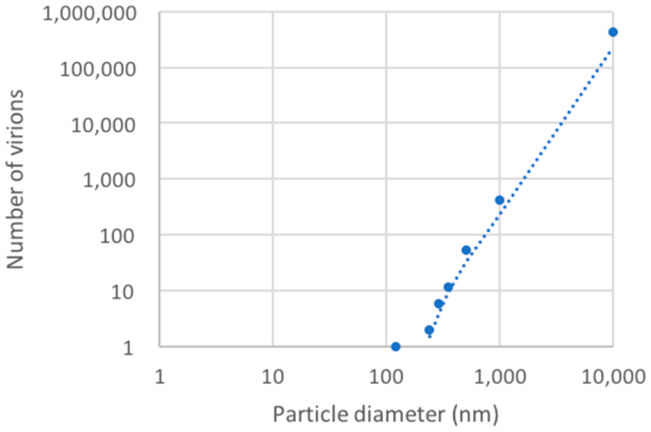

Figure 6. Maximum theoretical viral burden *versus* droplet nucleus size (nm).

than small droplets. Once emitted into the air, water from droplets immediately begins to evaporate. Water loss is associated with a rapid decrease in both particle diameter and terminal settling velocity (the equilibrium rate of fall of a particle in still air). The rate of evaporation of the largest droplets (>150 μm) is often insufficient to slow their swift descent in air, and they impact on nearby surfaces. However, the rapid water loss and sharp slowing of settling velocity of smaller droplets enables them to avoid a similar fate. Their constituent solid residues are instead drawn together during evaporation and cemented with dried respiratory secretions, and they remain aloft as droplet nuclei. Several epidemiological studies have supported the potential for droplet nuclei to be an important means of transmission for SARS-CoV-2.[202,203]

Assuming a median virion size of about 100 nm, a droplet nucleus of 1 μm diameter could contain up to 370 randomly packed virions. A similar 10 μm diameter droplet nucleus could contain up to 360,000. In practical terms, however, the size-defining element of a droplet nucleus is determined by the component item with the largest volume, which is often a bacterial cell or an epithelial cell. Thus, droplet nuclei in the 1–10 μm size range and above contain far fewer virions than this theoretical maximum.

Filter media, such as those used in N95 masks and in mechanical ventilation systems, consist of myriad interwoven fibers through which air is moved. Their purpose is to arrest particles as they move through the matrix. Filters capture particles chiefly by three mechanisms: impaction, interception, and diffusion. Impaction occurs when the momentum of a particle propelled toward a filter fiber prevents the particle from diverging around the fiber along the flow lines of the air stream, causing the particle to collide with the fiber. Impaction is the primary mechanism responsible for removing particles greater than 500 nm in diameter. Interception occurs when a particle diverges around a fiber along the flow lines of the airstream, the distance between the vector of the airstream and the centroid of the particle is smaller than the radius of the particle, and the particle touches the fiber. Interception operates efficiently on particles greater than 200 nm in diameter. Diffusion is the final important mechanism of particle removal, and it is most effective at removing very fine particles less than 200 nm, especially at low flow rates. Particles around 300 nm in diameter are least subject to these three removal mechanisms, and they are considered the "most penetrating" particles for a majority of filter types.[204]

When virus-laden droplet nuclei are deposited on filter media, they penetrate the filter matrix to different depths depending on their size characteristics: larger particles tend to become impacted or intercepted nearer the surface of the intake-facing side, whereas smaller particles penetrate more deeply into the fibrous matrix. In the case of filtering facepiece masks, cyclical breathing can cause changes in the physical characteristics of particles after they have been deposited. Humid exhaled air causes hygroscopic droplet nuclei to swell, becoming larger than they were when captured on filtration media. This size change can affect the ability of the filter fibers to retain particles and can lead to redistribution, shedding, or even breakthrough of particles.

From the standpoint of COVID-19, there are many opportunities for nanotechnology-based solutions to increase the efficiency and safety of air filter and mask devices.

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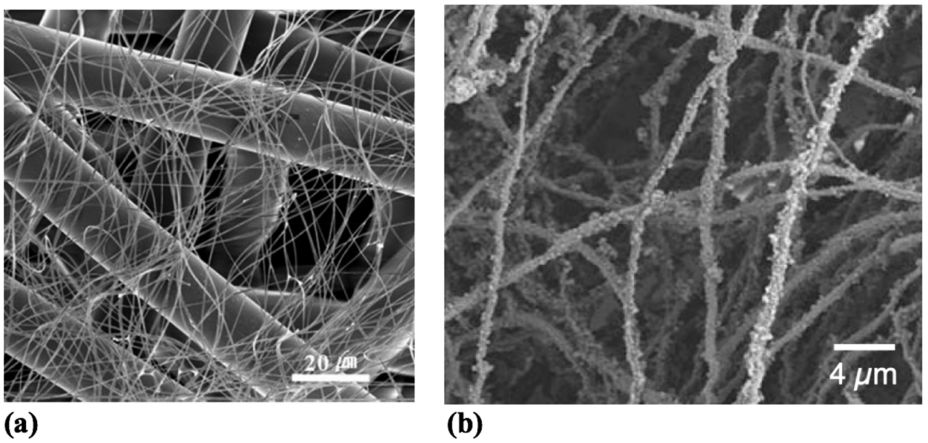

Figure 7. Scanning electron microscope images of electrospun nanofibers on polypropylene filter fabric (a) and titania-coated electrospun nylon nanofibers (b). Reprinted with permission from ref 206. Copyright 2010 Springer Nature.

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specific opportunities include (i) improving particle capture and retention characteristics, particularly, in the 300 nm diameter size range; (ii) reducing the effects of exhaled humid air on particle redistribution; (iii) rapid inactivation of membrane-bound microbes including enveloped viruses upon capture; and (iv) thin, high-efficiency filtration media for personal masks that are able to be reused repeatedly without loss of efficiency (*e.g.*, novel electrospun nanofibers). In this context, recent findings exploring the performance of several fabrics commonly used in cloth masks, alone or in combination, suggest that the combined mechanical and electrostatic effect observed in hybrids enabled enhanced performance with a filtration efficiency >80 and >90% for particle sizes <300 and >300 nm, respectively.[205]

Electrospinning is a technique that is widely used to produce nanofibers with diameters smaller than a micrometer (typically, ~100 nm). Even a micron-thin layer of nanofibers can capture the smallest droplets containing viruses and bacteria and prevent them from traveling through the mask. TiO_2-coated nanofibers deposited on a filter surface by the electrospinning process can capture submicrometer droplets and destroy the virus upon UV irradiation or under natural sunlight. After a micrometer-thick film of polyamide 11 nanofibers was deposited on polypropylene filter fabric, TiO_2 NPs were directly electrosprayed onto the nanofibers.[206] Scanning electron microscopy (Figure 7) demonstrated that nanofibers were uniformly coated by TiO_2 NPs without agglomeration. TiO_2-coated filters showed excellent photocatalytic and bactericidal activity and photo-induced hydrophilicity.

EMERGING NANOMATERIALS FOR THE FIGHT OF COVID-19

To prevent SARS-CoV-2 spread, proper PPE is critical for healthcare workers and the general public alike. Moreover, the development of face masks and other protective materials that can not only capture the aerosol droplets but also immobilize and kill the virus would be a major step toward preventing the spreading of COVID-19 and other infectious diseases. New nanomaterials can help to accomplish this function such as loading Ag NPs on these materials because they show effective antiviral activity against bacteriophage MS2 when loaded on filter surfaces.[165]

> The development of face masks and other protective materials that can not only capture the aerosol droplets but also immobilize and kill the virus would be a major step toward preventing the spreading of COVID-19 and other infectious diseases.

Graphene and Transition Metal Dichalcogenides. Graphene and layered transition metal dichalcogenides (TMDCs) have attracted enormous attention in the area of biomedical applications for diagnostics, therapeutics, safety/security, and environmental monitoring. Whereas pristine graphene has seen applications in biosensors devices, its derivative GO underwent a wealth of investigation for rapid detection, disinfection of pathogens, and enzyme assays, becoming a platform material for a variety of biomedical applications.[207−209] A decade ago, studies started to emerge where GO was employed for enzyme activity assays,[210] with the aim of using it as a platform material for viral helicase inhibition.[211]

Initial studies were performed with hepatitis C virus (HCV) NS3[212] helicase activity and severe acute respiratory syndrome coronavirus (SARS-CoV).[211] These studies were enabled by the evidence that single-stranded nucleic acids can adhere to the surface of GO through $\pi-\pi$ stacking interactions between the hexagonal graphitic units of GO and the nucleotides. Beyond therapeutics and diagnostics, graphene is also being pursued as an "engineering" material to enhance the barrier properties of masks, gloves, and gowns for medics against bacteria and viruses larger than 300 nm.[213] Contrastingly, MoS_2 nanosheets could be employed as a novel class of 2D nanocarriers functionalized with a variety of therapeutic and disinfection molecules.[214] They have demonstrated a loading capacity much higher than that of nanographenes and Au nanomaterials along with excellent physiological stability. Another advantage of several TMDCs is their ability to absorb light efficiently (more so than GO) in the near-IR region, with relatively deep penetrability into tissues and minimal phototoxicity, thus enabling different chemophoto-thermal treatments.[215]

> Beyond therapeutics and diagnostics, graphene is also being pursued as an "engineering" material to enhance the barrier properties of masks, gloves, and gowns for medics against bacteria and viruses larger than 300 nm.

Although 2D materials are mostly known in their planar sheet configuration, they can also form different morphologies such as nanoflowers, offering a very high surface area accessible to the virus. The petals are atomically thin, radiating from a common core and their dimensions can vary from tens of nanometers to about a micron. Atomically thin TMDCs—WSe_2,[216] WS_2,[217] $MoSe_2$,[218] and MoS_2[219] —have been obtained in this morphology when synthesized from chemical precursors in liquid phase at moderate temperatures (up to 300 °C). The syntheses are scalable, and the fact that they are directly grown and not exfoliated from bulk as 2D nanocrystals has the advantage of controlling the chemistry and crystal phase (from 2H to 1T).

This emerging variability of morphology of TDMCs is now attracting interest due to their high surface areas and edge reactivity. The high density of edges with dangling bonds underscores their ability to be readily functionalized with NPs and molecules. In addition, S and Se termination of the basal plane and edges can be particularly favorable to anchor biologically relevant molecules. Nanoflowers of TMDCs present attracting properties in nanomedicine applications because they could host a large number of molecules and NPs on their edges and thus can develop abilities to detect and to inactivate pathogens, to deliver molecules, and to interfere with cellular functioning.[220] Their stability in air and their availability as free-standing nanomaterials in addition to their strong substrate anchoring make them suitable for use in different environments such as in aerosols, on surfaces, in face masks, *etc.*, to detect and/or to inactivate the virus.

Two-Dimensional Carbides and Nitrides (MXenes). Among the emerging materials, MXenes are particularly promising for the development of coatings that are capable of

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capturing and inactivating viruses for use on face masks and other PPE.

MXenes are hydrophilic and they carry high negative charge (zeta-potential in solution is between −30 and −80 mV). As such, $Ti_3C_2T_x$ MXene has been shown to adsorb amino acids strongly[221] and may be able to bind strongly to viral spike peplomers and to immobilize the virus, thus deactivating it. It performs analogously to a strong magnet for proteins. Furthermore, MXenes have been shown to be photocatalytically active, meaning that once a virus is adsorbed onto the surface, it will be possible to apply light to degrade the adsorbate simultaneously.[222−224] MXenes are among the most efficient light-to-heat converters due to their plasmon resonance in the visible or IR range. For example, $Ti_3C_2T_x$ is excited by red light (780 nm plasmon resonance) and can be sterilized using a red/infrared lamp as well as solar light if the virus survives on the contact with the surface. A wide variety of MXenes—including $Ti_3C_2T_x$, $Ta_4C_3T_x$, Nb_2CT_x, and others—are biocompatible.[225−229] At the same time, some MXenes have shown antibacterial properties, likely due to the combination of their charge transfer ability and hydrophilicity.[183,230,231] Furthermore, it has been shown that the most common and least expensive titanium carbide MXenes have no negative ecological or toxicological impact on the environment.[232] Nanometer-thin coatings of single-layer MXene flakes on the exposed surfaces are worth exploring. Other new materials, such as metal oxides or metal−organic frameworks, deserve attention and should be explored as antiviral materials, as well, because they are also capable of releasing disinfectants from their pores.

In addition to the known pulmonary findings, it is estimated that 30−40% of hospitalized COVID-19 patients have evidence of kidney injury, and a significant percentage of those patients require renal replacement therapy (RRT) if their kidney function fails outright.[233] Kidney injury is an important predictor of mortality among those infected with COVID-19. Kidney function is essential to life: healthy kidneys filter the blood of harmful toxins, contribute to bone health, and maintain homeostasis of fluid and electrolytes.

When the kidneys fail, hemodialysis offers a life-sustaining therapy to prevent the buildup of uremic toxins that would otherwise result in death.[234] To perform hemodialysis, the patient's blood is passed through a filtration circuit that contains a semipermeable membrane ("dialyzer"). On the other side of the membrane, a balanced fluid ("dialysate") travels in the opposite direction to the patient's blood, dragging toxins and excess electrolytes across the membrane from blood into dialysate across their concentration gradients. The filtered blood is returned to the patient and the dialysate, once it passes through the filter, is discarded. Novel efficient sorbents for uremic toxins are critically needed to improve the efficiency of current technology, as well as to enable the development of wearable and portable dialysis technologies that could be critical to the care of COVID-19 patients. MXenes can regenerate dialysate by removing toxins that build up in the setting of kidney failure. Preliminary research demonstrates that Ti_3C_2 MXene is biocompatible and selectively adsorbs urea, a uremic toxin that is otherwise difficult to eliminate from dialysate, due to the presence of narrow slit pores between the negatively charged MXene sheets.[235] Thus, MXenes may be able to address key limitations of current ambulatory dialysis systems by offering efficient urea adsorption, small size, and light weight.[235] Experts have posited that MXenes might be a key technology in revolutionizing RRT delivery.[236]

RETHINKING THE FUTURE: ONE HEALTH, CONTAMINATIONS OF KNOWLEDGE, AND NANOTECHNOLOGY

The COVID-19 global emergency is making humans face unprecedented challenges. This new social scenario is necessitating collective thought as to where our actions are interconnected and interdependent, going beyond boundaries and cultural heterogeneity. The common interest, in the name of health as our primary need, must be addressed in the future having in mind the "One Health" concept,[237] relying on evidence that the well-being of humans is strictly interconnected with that of animals and the environment.

To address such a complex challenge, cooperation among diverse researchers with complementary expertise is required. The present challenge should be taken as an incredible opportunity to remind our globalized world that, as shown for other scientific contexts, multi- and interdisciplinary methodology involving transversal disciplines, promoting the exchange of knowledge among countries, and increasing diversity in teams all will be essential to achieve new and critical scientific solutions.[238]

In this view, nanotechnology is inherently a field in which scientists with incredible diverse backgrounds have converged in fruitful cooperations for multifaceted problems. Today more than ever before, nanotechnology is needed to lay new foundations toward counteracting the current global public health threat; preparing for possible new challenges, for instance, in infectious diseases; and rethinking a more sustainable future based on science.

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Notes

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Marie Carriere is a Principal Investigator in the Molecular systems and nanomaterials for energy and health laboratory at Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), in Grenoble (France). Her primary research interests are the toxicity and ecotoxicity of nanomaterials, environmental pollutants, and food additives. In this context, her studies are focused on DNA damage and repair, from damage recognition and the development of analytical techniques to detect and to quantify them with the highest sensitivity and selectivity, to genotoxicity assessment. A multidisciplinary approach is used, going from classical toxicity testing to medium-scale and high-content analysis and -omics approaches coupled with state-of-the-art microscopy and analytical techniques, including synchrotron-based methods and characterization of the physico-chemistry and fate of nanomaterials.

Laura Fusco received her B.Sc. in Medical Biotechnologies from the University of Milan (Italy) studying the effects of airborne particulate matter on human health. After receiving her M.Sc. in Medical Biotechnologies and Molecular Medicine from the University of Trieste (Italy), in 2018, she earned her Ph.D. in Chemistry from the same university (Prof. Maurizio Prato), with a project on the toxicological effects of graphene and graphene-based materials at the skin level, supported by the European Union H2020 Programme, integrating her research at the Karolinska Institutet (Prof. Bengt Fadeel), Sweden. Currently, she is Visiting Scientist at Sidra Medicine (Qatar) in the framework of the CARBOIMMAP H2020-MSCA-RISE project (L.G. Delogu coordinator) concerning the immune interactions of carbon nanomaterials. In the context of COVID-19, she studies the potential antiviral properties of various nanomaterials as well as the role of airborne particulate matter on the outbreak.

Ilaria Capua is Full Professor and Director of the One Health Center of Excellence at the University of Florida (United States). She is a virologist, known the world over for her ground-breaking research on influenza viruses, particularly avian influenza and for pioneering the open access concept in Science. She also was a Member of the Italian Parliament for over three years (2013−2016). She has authored over 220 scientific publications in peer-reviewed journals and has published scientific books on Avian Influenza and Newcastle disease as well as four books for the general public. She has obtained several awards including the Penn Vet World Leadership in Animal Health Award. She is active in the field of science communication and in promoting female leadership in the scientific arena. She regularly contributes columns and editorials to mainstream Italian press. Her research interests are related to the study of new approaches in infection disease in animals and humans.

Jose Angel Regla-Nava is a Postdoctoral Fellow at the La Jolla Institute, San Diego (United States). His research projects are mainly focused on the Dengue and Zika viruses. He graduated from Universidad de Guadalajara (Mexico) with a B.Sc. degree in Chemistry Pharmaceutical and Biology. He then obtained is M.Sc. in Molecular and Cellular Biology in 2010 and a Ph.D. in Biochemistry, Molecular Biology, Biomedicine, and Biotechnology (Molecular Bioscience) in 2015 from the Universidad Autonoma de Madrid, Spain. His Ph.D. work focused on the study of the identification of the Mechanisms Causing Reversion to Virulence in an Attenuated SARS-CoV for the Design of a Genetically Stable Vaccine.

Matteo Pasquali is the A. J. Hartsook Professor of Chemical & Biomolecular Engineering, Chemistry, and Materials Science & NanoEngineering at Rice University, where he also serves as Chair of the Chemistry Department, Houston (United States). He has been recognized by numerous awards in the field and also founded two companies, DexMat (smart carbon nanotube, CNT, materials) and NanoLinea (medical applications of CNT fibers). His laboratory is a key center for the scalable manufacturing and application of carbon nanotubes and graphene-based materials with enhanced mechanical, electrical and thermal properties. His research targets applications in wearables, energy transmission and harvesting, biomedicine, aerospace, and defense.

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Flavia Vitale is an Assistant Professor in the Department of Neurology, Bioengineering and Physical Medicine and Rehabilitation at the University of Pennsylvania (United States). She received her Ph.D. in Chemical Engineering at the Università di Roma "La Sapienza" (Italy), then completed her training in the Department of Chemical and Biomolecular Engineering at Rice University (United States) in 2015, where she was a R. A. Welch Foundation Postdoctoral Fellow. Dr. Vitale has received a number of awards, including the Graduate Research Fellowship, University of Rome "La Sapienza", the Taking Flight Award from CURE and the McCabe Fellow Award. Dr. Vitale research focuses on application of carbon nanostructures and MXenes to bioelectronic interfaces and biosensors.

Mehmet Altay Unal received his bachelor degree (2003) and M.S. (2006) from Ankara University Physics Engineering, Turkey, and Ph.D. (2016) degrees from the Ankara University Biotechnology Institute. He worked at the Department of Biomedical Engineering of Florida Institute of Technology, United States (2014−2015). Between 2011 and 2018, he worked at the Ankara University Department of Physical Engineering as a lecturer. He is currently lecturer at the Stem Cell Institute since March 2018. Dr. Unal's research mainly focuses on the development of cheap, next -generation biosensor devices, understanding protein dynamics and protein−ligand interaction, and developing new drug molecules. He is leading a drug repurposing project for COVID-19 in Turkey, which aims to screen drugs *in silico*.

Cecilia Mattevi is an Associate Professor and Royal Society University Research Fellow in the Department of Materials at Imperial College London (United Kingdom) since October 2012. Cecilia is a Fellow of the Royal Society of Chemistry, and she has been awarded an ERC-Consolidator Grant 2018 on 3D printing of nanomaterial inks for on-chip applications. Mattevi's group focuses on the precise synthesis of novel atomically thin 2D materials and their three-dimensional structuring *via* 3D printing in the form of miniaturized devices to address pressing challenges in energy storage, energy conversion, and biomedical applications.

Davide Bedognetti is the Director of the Cancer Research Department at Sidra Medicine (Qatar). Dr. Bedognetti received his M.D. and Ph.D. in Clinical and Experimental Oncology and Hematology from the University of Genoa (Italy). After completing his medical residency in Medical Oncology, he joined the Infectious Disease and Immunogenetics Section (IDIS) of the U.S. National Institutes of Health (NIH), where he completed his postdoctoral fellowship. Dr. Bedognetti's team employs high-throughput approaches to deconvolute the molecular network of host-tumor interactions, and to understand its relationship with treatment effectiveness.

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Ennio Tasciotti founded and directed the Center for Biomimetic Medicine and Musculoskeletal Regeneration as an Associate Professor of Nanomedicine and Orthopedic Surgery at the Institute for Academic Medicine. Sequently, he served as Director of the Center for Musculoskeletal Regeneration as Full Professor of Regenerative Medicine. He has wide expertise in applied science and translational research and a background in biology, biotechnology, and molecular medicine. His main research interests rely on nanotechnology, drug delivery, tissue engineering, and regenerative medicine. He is particularly interested in the development of new lines of research at the cross field of medicine and nanobiotechnology.

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