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Viral infection mitigations using advanced nanomaterials and tools: lessons from SARS-CoV-2 for future prospective interventions

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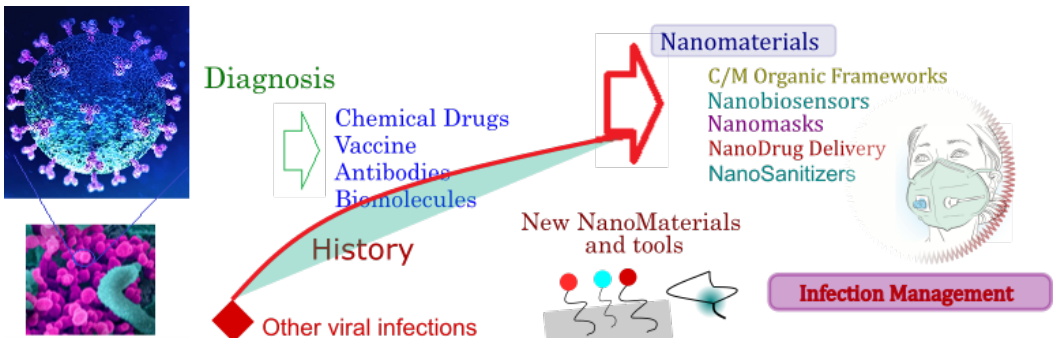
Review/Article

ABSTRACT



The emergence of recent corona virus SARS-CoV-2-led pandemic infection has generated the incessant demand for the evaluation and development of suitable advanced materials for controlling this and future unforeseen viral infections. The current nanoscience-based materials are being evaluated for possible appliances at different stages encompassing, fields locations for control, identification of virus spread, diagnosis of infection and potential therapeutic interventions by drug development. Assorted materials like carbon nanomaterials, metal nanoparticles, metal organic frameworks (MOFs), covalent organic framework (COF) materials, 2D materials, optical tweezers, artificial cells, etc. have been extensively investigated for the diagnosis, protection, and as therapeutics for viral infections. Herein, the existing materials and nanotechnological tools proposed or evaluated for controlling different viral infections and specifically, COVID-19 are deliberated. An insightful exploration of the advances in materials science, nanoscience and nanobiotechnology has been kept in core focus with perspective for controlling the similar type of infections in future.

Keywords: Nanomedicine, Biosensor, mask materials, smart materials, optics, viral infections, COVID-19, virus mutation

INTRODUCTION

The viral infections have a long history as human beings have been battling viruses even before the homo sapiens evolved in their current form. The viral infections have impacted the health of human beings in different ways at different times. Managing the infections caused by different viruses have been a cumbersome manifesto to humans due to the lack of ample availability of tools to combat the infections with disastrous impact on the survival. The severe viral infections that appeared at different times in history were responsible for a large number of deaths and also, caused socioeconomic problems. Because of the variety of viruses, their management or treatment has been a challenging task.

The human population has been impacted particularly in the last two decades with various severe viral infections where viruses originating from different animals (zoonotic viruses) caused widespread outbreaks that claimed thousands of lives. For example, the Ebola virus outbreak of West Africa in the year 2014-2016 killed up to 90% of the people infected with it,[1,2] making it the most lethal member of the Ebola virus family.[3] Similarly, current situation of ongoing pandemic of novel corona virus is equally devastating with even deadlier mutated virus evolving at present time; despite ultrafast vaccine development, it still poses a serious threat to humans because of its fast infectious nature along with lack of proper medication.

The current novel corona virus infects the respiratory tract with different level of illness in different people where symptoms vary from severe symptomatic to asymptomatic. The symptoms may vary from person to person with common cold to severe fatal

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pneumonia. Because of its fast-spreading nature, it has rapidly engulfed the whole world within 2-3 months of its first report in December 2019 and became a global health emergency. In corona virus family, more than a hundred corona viruses have been identified, most of which have been transmitted from animals such as camels, and bats to human beings. Generally, a genetic mutation in original strains makes them get transmitted and infect the human beings causing lethal diseases. In last two decades, these viruses were responsible for breathing and lungs-related infections.

In corona virus family, seven viruses have been known to cause infections in human beings, the major four viruses are 229E, OC43, NL63, and HKU1. These four viruses are known to cause mild diseases, even that undergo unnoticed. The remaining three viruses became prominent because of their lethal nature, the first viral infection caused by coronavirus was Severe Acute Respiratory Syndrome (SARS-CoV) which emerged in late 2002 and disappeared in 2004.[4] The second one is the Middle East Respiratory Syndrome coronavirus (MERS-CoV) which emerged in 2012 and still circulate among camels.[5] The third one is SARS-CoV-2 which is responsible for the current ongoing COVID-19 infection;[6] it appeared in December 2019, proliferated at a faster rate and caused different level of infections in all parts of the world.[7,8] As per the WHO dashboard, it has affected more than 200 million people, with more than 4 million deaths till August 2021, though, the real number is likely to be far higher.

In general, viruses do not have their cellular mechanism or system for their multiplication, so they utilize the cellular machinery of the host for their multiplication (progeny). During this process, they utilize the cellular machinery of different hosts, duplicating its genetic material RNA (or DNA), and thus have more chances of acquiring mutations. This way, during multiplication, it led to the generation of different variants or strains of virus. At the point of diagnosis and treatment of viral diseases, drugs or methods developed to combat one virus (or strain) may not work for other variants or strains in future infections because of these mutations.

In general, while identifying or combating a new viral infection, a randomized screening of different available viral drugs (for existing viral infections) is performed at initial stages. Here again, it became a big question mark because of differences in the genetic constitution, methods of multiplication and pathophysiology, whether a particular drug that is applicable to one type of virus will be applicable to other viral infections or will be able to combat any new viral infection. Moreover, many viral infections generate secondary immune system related inflammatory events as observed in the case of COVID-19; inflammatory cytokines are produced after the initial stage of infection. In some cases, this response can be excessive ('cytokine storm'), causing widespread tissue damage, septic shock, and leads multi-organ failure in patients.[9] So it becomes a difficult task to manage new viral infections and protection starts with (a) controlling the point of spread of infection, (b) inhibition at point of origin and medium through which virus spreads, and (c) putting different sorts of walls (barriers) and protecting human beings from infection.

Different materials, chemicals, nanomaterials, and technological tools help in the diagnosis, killing of the virus outside the hosts, protection from spread i.e. filtering the virus and then developing the drugs and drug delivery systems for controlling the infection in patient's body.[10] In this review, we have analyzed recent advances in nanomaterials and nanotools developed for controlling and identification of different viral infections along with promising new materials that would help in monitoring viral infection. A thorough analysis of currently available materials and nanotools would provide a perspective for future viral infections and would open-up new avenues for diagnosis, control, and treatment methods for viral infections.

VIRUS AND NANOSCALE

The viruses are the metastable particles that are produced by virus multiplication inside the living cell, whereas outside the living system, these act as neutral particles. Structurally, the virus contains genomic material (mostly RNA, few contain DNA as genetic material) in the center surrounded by a solid protective shell made up of protein known as capsid. With structural characteristics, most of the viruses vary in size from 20 nm to 250-400 nm while few viruses reach 500 nm size; recent coronavirus is ~70 nm to 80 nm in size. Because the virus size is in nanometer scale, these can be used as nanomolecular vehicles for drug/gene delivery applications. At the same time, the nanotechnological tools developed for the analysis of nanosized material can potentially be applied for the identification and mitigation of viruses.

The outer covering of the virus, the capsid, is made up of well configured proteins so that it provides a strong protective sheath to the virus when outside in the environment and it is flexible enough to get disrupted while in contact with the living cells. This outer envelope for capsid structure can be compromised with the application of physical means like UV radiations and few chemical sanitizers. The additional nanotechnology-based tools and materials have shown to be more efficient in controlling their spread or destroying the virus particles.[11]

MATERIALS FOR TRAPPING THE VIRUS ON SOLID SURFACE

The virus resides at different surfaces in the dormant form before causing any infection to the living system (animals or human beings). These surfaces could be hard surfaces like tables, door handles, etc. or soft materials like clothes and other fabric materials. The next generation surfaces should utilize the different materials chemistry to mitigate the viral spread. The fundamental design of different materials which can neutralize the virus needs to make use of the basic structural characteristic of advanced materials and nanotechnologically improved surface properties; materials should be capable of entrapping the virus indefinitely or should be able to destroy the virus functionality by altering the virus capsid. The following materials have shown promising properties in this context and could play a critical role in the development of advanced hard/soft surfaces:

Copper materials: Copper materials are well known for their antimicrobial activities since ancient times. In a recent study, it has been observed that copper containing materials are very efficient in inactivating the coronavirus; the material with smooth surface like Teflon, plastic, stainless steel retained the presence of coronavirus HuCoV-229E up to 6 days while the brass material containing 70% of copper inactivated the virus within 60 minutes.[12] Mechanistically, the copper containing material defragmented the viral genome material, thus leading to irreversible virus inactivation. The generation of reactive oxygen species (ROS) on the surface of copper material with reaction of oxygen via Fenton-like or Haber Weiss reactions, and its further interactions with protein and genome material of virus presumably causes the inactivation of the virus.[12] The fabrication of copper nanomaterial and their incorporation in fabric material like masks will further enhance the inactivation process due to the increased surface area on nanoparticle formation. The copper oxide CuO nanoparticles impregnated on the mask could enhance the inactivation of influenza H1N1 and H9N2 viruses.[13] With the observed antiviral properties of surface materials containing copper or other soft materials with copper nanoparticles will be effective in the inactivation of other viruses as well, and confers a point of evaluation and application of copper for future viral infections, in general.

Metal Organic Frameworks and Covalent Organic Frameworks: Metal organic frameworks (MOF) and covalent organic frameworks (COF) are three-dimensional network structure of organic molecules containing well defined cavities like zeolites and have found widespread applications in sensing[14] and delivery of drugs.[15] The COF have well-defined porous structures with uniform pore sizes (Figure 1). The COF pore size range from angstroms to nanometers depending upon the structural organic moieties. These materials have a large surface area owing to 2D/3D architecture due to the covalent combination of rigid building units with a different directional orientations of connecting units.[16] The organic structural units make it easy to introduce required functionalities on surface molecules towards development of specific applications. The MOFs are metal based organic frameworks with added advantages of metallic materials.

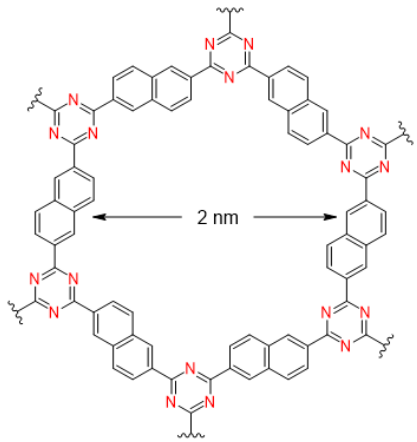

Figure 1. Representative structure of Covalent Organic Framework.

The photocatalytic property of selected COF/MOF provides a direction for light assisted denaturing of pathogens like virus and bacterial surface or destruction via other photo-thermal heating. The indoor surfaces coated with COF/MOF can thus inactivate the virus via photo destruction. It is noted that free radical, i.e. hydroxyl radicals generated with light and photocatalyst MOF, damages the exterior surface proteins (spike/capsid) of the virus. This inactivates the virus by removing the infectivity of the virus as it will not be able to bind on receptors due to altered spike units.[17] The specific pore sized architecture of MOF would be useful in the irreversible trapping of the different viruses depending on their size. These structures, in a way, could inactivate the virus and prevent it from spreading.

Materials conjugated with antiviral drugs: The antiviral drugs that directly binds to the virus envelop capsid proteins can be conjugated to the metal surface or on the surface of metal/non-metal nanoparticles for direct inactivation of the virus outside on the metal surfaces/fabric itself. However, this approach requires the synthesis and development of specific organic drug molecules that target the capsid proteins of the respective virus. The existing fusion inhibitor drug molecules would need to be re-evaluated for attaining the specificity for particular viral proteins.

Graphene: The single atomic layered sheets of graphite i.e., graphene is one of the important materials in the category of nanomaterials that finds numerous applications in diverse fields based on their unique physiochemical properties.[18–20] The graphene sheet surface functionalization chemistry has evolved to attach assorted active molecules for further tuning of its properties and applications thereof. They have also displayed interesting viral inactivation properties.[21] The graphene oxide and negatively charged sulphated graphene oxide derivatives are effective against herpes simplex virus type-1 (HSV-1) infections. These derivatives inhibited the viral infections by reducing viral binding and shielding as the probable mechanisms of viral infection progression.[22] In this context, thermally reduced graphene oxide (rGO) have been functionalized with hyperbranched polyglycerol (hPG) units which were further sulphated to fabricate the materials that resemble heparin.[23] Heparin is a mixture of sulphated carbohydrate polymers with varying lengths which is well known for its broad antiviral properties[24] but its usage is limited due to the anticoagulating beahviour of heparin. The heparin mimetic sulfated rGO-hPG sheets were found to be effective in inhibiting orthopoxvirus and herpesvirus strains, particularly in the early stages of the infection, although they could not prevent cell-to-cell spread. The enhanced antiviral activity of graphene or graphene oxide derivatives has been attributed to the negative charge surface and sharp edges of the individualized sheets; negatively charged surfaces promote binding with the positively charged virus particles via electrostatic interactions.[24] These electrostatic interactions restrain the virus and thus, inactivates towards further infection. The graphene oxide (GO) and reduced graphene oxide (rGO) with negative charges on sharp-edged single-sheet nanomaterials have been shown to bind and suppress the infection of pseudorabies, PEDV, EV71, and H9N2 viruses.[25,26]

Further, graphene and its derivatives have been functionalized with virus-specific antibodies that have been used for antiviral properties based on antibody-mediated binding and sensing mechanisms. The antibody incorporated graphene sheets have been shown to capture several viral species successfully including rotavirus, avian influenza virus subtypes H5 (AIV H5) and H7(AIV H7), and influenza virus H1N1.[27–29] Given these evidences, graphene could play a vital role in generating advanced antiviral surfaces.

MXenes: The metal halides with different architectural morphologies have intriguing properties and find application in various fields, ranging from electronics to biomedical applications.[30,31] The emerging materials referred to as MXenes are a broad family of 2D materials with halide compounds of metals (Figure 2). The MXene have been evaluated for their anti-microbial effect owning to the tunable surface charge and 2D architecture. As is the case with rGO, the negatively charged sharp edged sheet like nanomaterials comprising MXene have the potential to inhibit the growth of different microbes including viruses. Similar to this mechanism, potential antiviral effects could be offered by negatively charged, sharp-edged 2D nanomaterials such as Ti_3C_2Tx MXene, which has shown promising bacterial inactivation effects against both Gram-positive and Gram-negative species due to similar hypothesized mechanisms.[32]

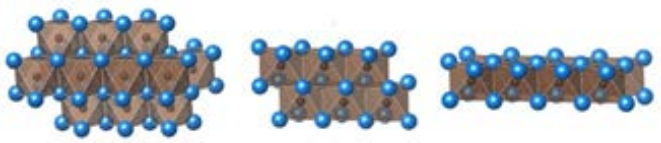

Figure 2. Representative structures of MXenes. Image Source: Wikipedia, CC4 license.

NANOTECHNOLOGIES FOR DESTROYING VIRUS IN THE ENVIRONMENT

Capturing the virus selectively or destroying it in space at high concentrations could be a step towards controlling the airborne or air mediated spread of viral infections. Numerous technologies can possibly be deployed to capture or destroy the virus in the space.

Virus trapping using optical tweezers

The optical tweezers are traps developed using the lights at different angles. This technique is utilized to trap the single cells, virus, nanoparticles and further investigation of morphologies and structure of such trapped particles. The optical tweezers use the momentum of photons to trap the microscopic objects in a contact-free environment and subsequently manipulate these objects in three dimensions.[33] This technique has been widely used in biology and nanotechnology to study solid surface structures, molecular motors, biopolymers and nanostructures. Though its application to study viruses has been limited due to their small size,[34] but with the development in fundamental trap designs and topologies, different viruses have been studied by researchers.[35] By using optical tweezers that can simultaneously resolve two-photon fluorescence at the single-molecule level, researchers have been able to show that individual HIV-1 viruses can be optically trapped and manipulated, allowing multi-parameter analysis of single virions in culture fluid under native conditions.[36] The studies of HIV virions with optical tweezers reflected that individual HIV-1 differs in the numbers of envelope glycoproteins by more than one order of magnitude, which implies substantial heterogeneity of these virions in transmission and infection at the single-particle level.[36] Analogous to flow cytometry for cells, the fluid-based optical tweezers technique may help in ultrasensitive detection, multi-parameter analysis and sorting of different viruses besides the study of other nanoparticles in biological fluids with single-molecule resolution. Hence, it has the potential to trap the SARS-CoV-2 in microfluids with possible surface proteins density analysis and alteration to attenuate the ability of a virus to spread[35] further via reduced virus-cell interactions.[37]

Laser beams to destroy virus

Laser rays are of high energy radiations sufficient to kill the microbes on exposure. Cleaning the material surface with laser light can reduce the amount of virus at the surface and thus, reduces the chances of spread of infection.

The different types of nanomaterials, especially, metal nanoparticles can further assist in the attenuation of virus density by localized heating on exposure to a particular wavelength light. This is addressed as photothermal inactivation of viruses and microbes.

Photothermal inactivation of virus particles

Ag and Au Metal Nanoparticles: The noble metals silver (Ag) and gold (Au) nanoparticles and nanorods can induce antiviral effects via heating when illuminated at an optimal wavelength corresponding to plasmon resonance. This process of heating, killing and modulating the behavior of cells, microbes, and viruses with light and nanoparticles is termed as plasmonic photothermal treatment.[38–40] This has been mainly used for the killing of cancer cells and nanomedicine has evaluated this strategy for clinical application in cancer therapy. Among the different nanoparticles, the Au nanoparticles are preferentially considered due to their less non-target toxicity compared to Ag nanoparticles. The advancement in the synthesis procedures for different nanoparticles has provided a good refinement towards tuning the synthesis of nanoparticles with different geometries and morphologies; this helps in fine tuning the end application of such nanoparticles including in plasmonic photothermal treatment. The intense heating by Au nanorods and nanocubes upon irradiation with solar radiations has been demonstrated for the inactivation of virus bacteriophages MS2 and PR772.[41] The more the proximity of Au nanoparticles to the virus, the enhanced effect of plasmonic heating/destruction would be. For this to happen, the adsorption of nanoparticles on the surface of the virus is considered the conducive requirement. Some other findings have proposed the involvement of plasmon-enhanced shockwaves in killing the virus as was observed in the inactivation of murine leukemia virus (MLV) with the femtosecond pulsed laser irradiation on Au nanorods.[42] In this case, the close contact of virus and nanoparticles was not required for inactivation. Further, the addition of ROS scavengers did not

alter the effect, which suggests that ROS is not involved in virus inactivation. It is proposed that shockwaves generated with plasmon of nanoparticles and radiation alter the outer membrane and surface proteins on the virus leading to virus inability to bind with host cells, thus, inactivating the virus.[42]

TiO_2 Enhanced Photothermal inactivation

TiO_2 is one of the nanomaterials that find extensive use in trapping or channelizing the light radiations. The TiO_2 acts as a sensitizer and finds wide-ranging applications in nano-solar cells.[43] The TiO_2 can in a similar way be combined with other nanomaterials or alone has the potential to generate the localized heating effect on irradiation with light, particularly in the visible region; inactivation of microbes and virus occurs in the same fashion as mentioned above for other Au or Ag nanoparticles.

Carbon nanotubes (CNTs) as photothermal sensors

The single-walled carbon nanotubes (SWCNT) and multiple-walled carbon nanotubes (MWCNT) are well known to generate thermal heating upon irradiation with Near Infra-red (NIR) radiations. The localized heat generation effect of CNTs has been used in materials development[44] as well as in different biological applications including killing of the cancer cells. The materials with incorporated CNTs can easily neutralize viruses with NIR irradiation of surfaces, an easy tool for commonly used hard surfaces e.g., instruments, door handles, public benches, etc.

MATERIALS FOR MASKS

Face masks have become a new norm while dealing with COVID-19 infections and other respiratory system infections that spread through air or droplets.[45] This has led to the task of identifying suitable materials that can selectively filter out the virus size particles. The research accelerated towards improving the quality and performance of existing face masks, e.g., by introducing properties such as antimicrobial activity and super-hydrophobicity. The quality of face masks design has parameters like filtration efficiency for particulate, bacteria, and viruses, and fluid resistance, differential pressure, flammability, and wear-design.[46] The adopted high-performance air filter materials for face masks should be able to capture particulate matter (PM), tiny particles including viruses, bacteria and other microbes with high efficiency while maintaining good air permeability. The commercial air filter masks for PM capture (mainly adopted for air pollution) are composed of a crisscross mat of randomly arranged polymer fibers or fiberglass with diameters ranging from several microns to tens of microns. These filters always function by passively trapping particulate matter and essentially depend on the porous structure of the fibrous membrane of the materials used. Generally, thick layers of densely packed fibers are used to achieve high filtration efficiency, but this also leads to decreased air permeability through a mask.

Based on the requirement of key factors that affect the functions of air filters i.e., fiber diameter, membrane thickness, and air permeability, different type of materials have been developed and evaluated for their applicability in the preparation of masks. Recently, Lui's group has developed transparent polyacrylonitrile (PAN) nanofiber for high efficiency towards air purification.[47] The fiber fabricated by electrospinning method has an average fiber diameter of ~200 nm and on evaluation for the capture of PM2.5 particles, the obtained nanofiber membranes displayed good optical transparency (up to 90%), high filtration efficiency (>95%), low-pressure drop (down to 132 Pa), and was light weight. The strong adhesion of PM to the PAN nanofiber surface and transparent thin filter makes it suitable for application for protection towards indoor air or can be incorporated into masks to improve its efficiency. The interesting results obtained from PAN nanofiber has led to the development of a variety of electrospun nanofiber membranes with different surface chemistry and mechanical or thermal properties using various polymers, polymer blends, or polymer composites with surface-functionalized inorganic nanofillers such as polyurethane,[48] polycarbonate,[49] poly(vinyl alcohol),[50] polytetrafluoroethylene,[51] polybenzimidazole,[52] polyacrylonitrile/polysulfone,[53] polypropylene/polyethylene,[54] polyurethane/polysulfonamide,[55] polyacrylonitrile/graphene oxide,[56] and polyacrylonitrile/MXene.[57] In addition to the electrospinning method, the needle-less electrospinning[58] and solution blow spinning[59] have also been applied for improving the effectiveness towards capture of the particulate pollutants. The 2D nanonets developed using electrospinning/netting technology have provided interesting mesh with an ultrafine diameter (<20 nm), high porosity, small pore sizes (<200 nm), and large specific surface area. The ultralight nanofiber-nets prepared by binary nylon 6-PAN having high coverage (>98%) of nylon nanonets and low packing density of PAN nanofibers (Figure 3)[60] resulted in well interconnected membranes having high filtration efficiency (99.99%) towards 300 nm aerosol particles and satisfactory quality factor (0.1163 Pa-1) under a high flow rate (90 L min-1). These 2D nanonets proved to be significantly superior to that of commercial glass fibers and melt-blown polypropylene fiber-based filtration membranes.

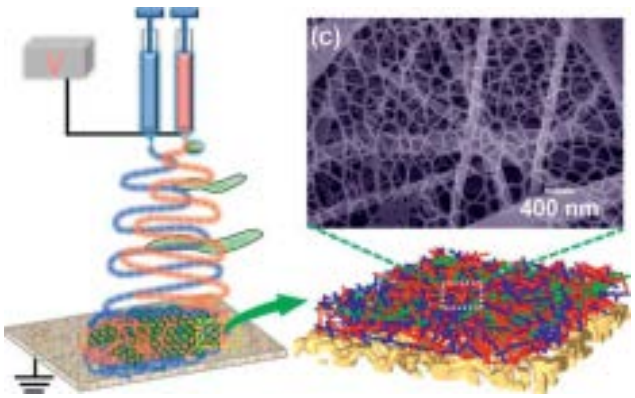

Figure 3. Electrospinning technology for nylon-6/PAN nanofiber/net membranes creation. Reprinted with permission from Ref. [60], copyright 2015, The Royal Society of Chemistry.

The passive filtration capability of simple fibers has been improved with the introduction of **Electret Membranes**, the active filtration members making use of charge for attraction of particles. In Electret membranes, the charge enhancing nanoparticles such as polytetrafluoroethylene, silicon nitride, magnesium stearate, titanium dioxide, boehmite, and SiO_2, are

incorporated via the in situ charging technology of electrospinning.[61,62] For example, the electrospun polyethylene/polypropylene bicomponent membrane incorporated with magnesium stearate (Figure 4) revealed the elevated surface potential of 4.78 kV and exhibited a high filtration efficiency of 98.94% towards PM2.5 with a low-pressure drop of 37.92 Pa and excellent dust holding capacity of 10.87 g m^{-2}.[61] Similarly, a polyvinylidene fluoride nanofibrous membrane doped with well-dispersed SiO_2 nanoparticles demonstrated a remarkable electret effect with a surface potential of 12.4 kV and high filtration performance towards particles with different sizes.[63] Another method, termed Corona charging, is also used to introduce charge under electrostatic potential but this has a drawback of rapid dissipation of surface charge leading to loss of filtration capacity of fibers particularly on contact with moisture or oil droplets under a hazy environment.[64] This problem is solved by the introduction of a triboelectric nanogenerator (TENG) with nanofibrous air filters for high-efficiency particulate removal.[65,66] TENG is a newly invented technology that is used for harvesting energy from various mechanical movements such as wind, water waves, and human motion.[67] Recently, a rotating triboelectric nanogenerator (R-TENG) enhanced the electrospun polyimide membrane for air purification has been developed by Gu and coworkers.[65] The

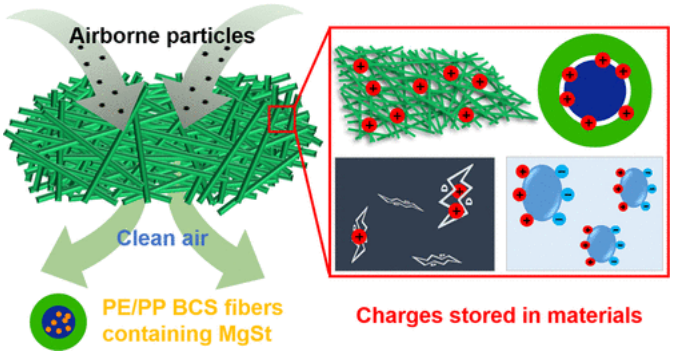

Figure 4. Magnesium stearate as charge enhancer in PE/PP nanofiber based electret filter. Reprinted with permission from Ref. [61], copyright 2019, American Chemical Society.

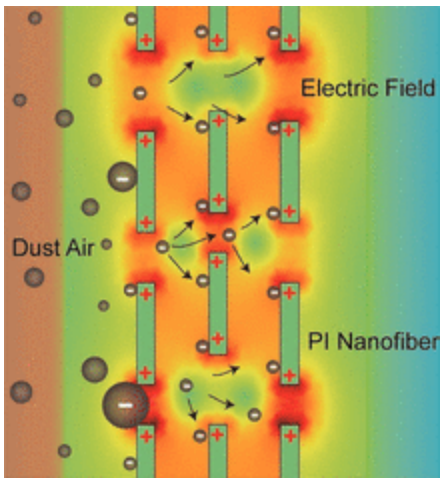

Figure 5. Image depicting the filtration process through R-TENG filter. Ref. [65], copyright 2017, American Chemical Society.

researchers used polyimide nanofibre membrane which was continuously positively charged by R-TENG, leading to greatly improved removal efficiency towards PM particles with diameters less than 100 nm (Figure 5).[65] This technology was further used for the development of a self-powered electrostatic adsorption face mask (SEA-FM) using an electrospun poly(vinylidene fluoride) membrane equipped with a TENG driven by human respiration,[66] providing the potential possibility for real life application of this technology.

Metal-organic frameworks (MOFs) are composed of transition-metal cations and coordinately bonded multidentate organic linkers and possess a porous crystalline structure.[14,16] The MOFs are materials with high porosity, the possibility of tunable pore size, having rich functionalities, and possess good thermal stability, and thus, hold great promise for applications as filtration materials.[68] Due to the light powder form of these MOF crystals, the MOFs based filtration materials are either grown on porous substrates or embedded in polymer fibrous membranes. Researchers have explored the interactions between MOFs and particulate pollutants using different design methods, like the one incorporating ZIF-8 nanocrystals in electrospun PAN membranes.[56] There are three proposed mechanism for the capturing of the particulate matter by the MOF-based filters: (i) entrapping the particulate matter on binding to the open metal sites on MOFs, (ii) capturing the matter via interacting with the functional groups on MOFs and/or polymers, and (iii) electrostatic interactions with MOF nanocrystals (Figure 6). The last factor of electrostatic charges is generated on MOFs due to the unbalanced metal ions and defects on the surface, which offers a positive charge to polarize the PM surface, leading to improved electrostatic adsorption of PM pollutants on the surface of MOFs. In a construct by Li's groups, the specific surface area of the PAN filter was dramatically improved from 115 to 1024 m2 g-1 after incorporation of 60 wt% ZIF-8 nanocrystals. The construct so developed i.e., ZIF-8@PAN filters exhibited high PM removal efficiencies up to 88.33% and 89.67% for PM2.5 and PM10, respectively, with an ultralow pressure drop of less than 20 Pa. Besides particulate matter, the cavities of MOF crystals can entrap the other materials as well such as pollutant gases. These MOF filters were found effective in selective capture of SO_2 when exposed to a stream of SO_2/N_2 mixture. The masks developed using MOFs and flexible fibers such as plastic mesh, glass cloth, metal mesh, nonwoven fabric, and melamine foam[69] showed very good particulate matter removal capacity along with improved thermal stability up to 300 °C. The long-term use analysis of efficiency of the ZIF-8@plastic mesh (Figures 7) indicated that it retained efficiency of >90% after 30 consecutive days of use. Following this, many different types of constructs have been developed such as multifunctional UiO-66-NH2 wrapped CNTs/PTFE filter with a high capture efficiency (99.997%) for ultrafine dust (diameter ~0.3 μm) and SO_2 adsorption,[70] flower-like hierarchical 2D assembled MOF on polypropylene microfibers filter with high PM removal performance (92.5% for PM2.5 and 99.5% for PM10), low-pressure drop (10.5 Pa at 25 L min−1), and superior stability after reuse for 12 cycles,[71] electrospun polyimide/ZIF-8 nanofibrous

membranes with superior thermal stability (up to 300 °C), good transmittance, and excellent mechanical properties for efficient PM2.5 capture (up to 96.6% with a 10 wt% ZIF loading).[72]

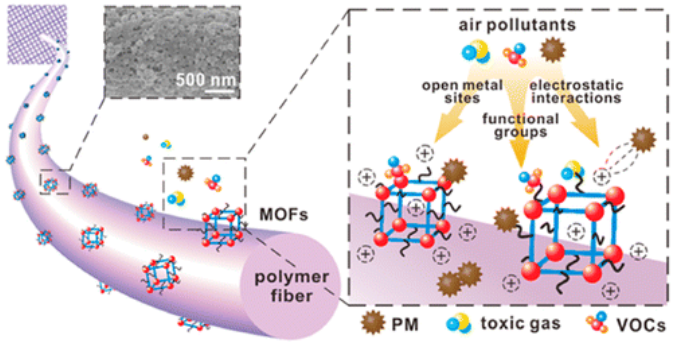

Figure 6 Representation of MOF-based polymer and filtration of air pollutants. Reprinted with permission from Ref. [73]. Copyright 2016 the American Chemical Society.

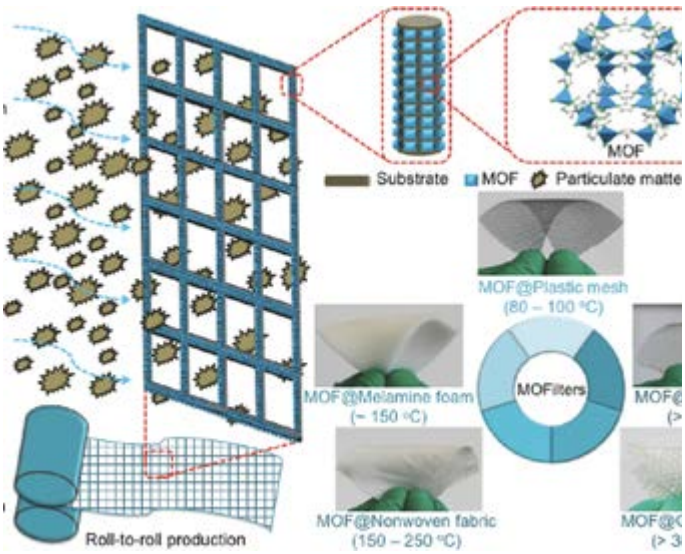

Figure 7. Representation of filtration materials prepared using MOF with roll-to-roll hot-pressing strategy. Reprinted with permission from Ref. [69]. Copyright 2017, WILEY-VCH.

In addition to particulate filtration capacity, the materials of the masks need to be equipped with biocidal products such as antibacterial, and antiviral products to keep the masks functional for a longer time. A wide range of antimicrobial agents, such as natural products and synthetic medicinal compounds, nanoparticles of metal and metal oxide, metal-organic frameworks (MOFs), graphene, and its derivatives, have been investigated to impart air filters with biocidal properties. Many natural compounds and synthetic drug molecules can be incorporated into the mask's fibers to induce the respective antimicrobial property. Nanoparticles of different metals and metal oxides such as silver (Ag),[74–76] silver compounds (Ag+),[77] titanium dioxide (TiO_2),[78] zinc oxide (ZnO),[79,80] aluminum and aluminum oxide (Al_2O_3)[81] have been incorporated into various filters for antimicrobial properties. The copper and copper oxide nanoparticles endowed with antimicrobial properties[82] have the potential for application in SARS-CoV-2 mitigation (discussed above). The nanoparticles show a synergetic antimicrobial effect in combination with other biocidal agents, such as carbon nanotubes.[76] The 2D materials such as graphene and MOF are known to have antimicrobial properties (discussed earlier in this article) and have the potential for incorporation into masks materials for enhanced performance. Many other 2D materials, such as MoS_2[83,84] and graphitic carbon nitride (g-C_3N_4),[85] have antimicrobial properties and can potentially be explored for masks as well.

Nano-based sanitizers

The sanitizer materials are effectively used for killing the infective agents and serve as a shield for self-infection as well as for the spread of infection. Broadly the sanitizers have two categories: (1) Surface sanitizers – meant for application on different solid surfaces (disinfectants) and (2) Hand sanitizers – meant for removing the infective germs from the hands. Each category has a wide variety of chemicals and compositions. Most hand sanitizers have alcohols as base compositional material. The surface sanitizers are either in-built materials for the solid surfaces (like door handles, tables, benches, faucets, tools etc.) or liquid, gel sanitizers used for disinfection of solid surfaces.

The nanomaterials including metal nanoparticles have been adopted for application in these sanitizers. The antimicrobial materials based on nanoparticles and nanomaterials (2D and other nanomaterials) discussed earlier for masks materials, also have the potential applications in sanitizers.

Nanomedicinal technologies/nanomaterials for entrapping of virus in throat and lungs

The trapping and reducing the viral load when in the throat and lungs are major targets for respiratory infections as is the case with corona virus. In this upper respiratory part (lung/throat), the nanomaterials as drug delivery agents for the constant release of drug molecules have the potential in the treatment of respiratory viral infections; such drug designing for virus infection meant to target the SARS-CoV-2[86–88] and other corona virus is in preliminary stage.[6] Once the potential drug molecules are approved for corona-virus infection treatment, the methods and materials that already have been approved or evaluated for other viral infections,[89–98] would be potentially deployed for enhanced drug delivery targeting throat and lungs infections.

Nanomedicine for reducing secondary/consecutive effects of infection (cytokine storm control)

The viral infections generally can induce secondary metabolic syndromes like SARS-CoV-2 infection, the cytokine storm is a prominent secondary symptom observed and which even proved lethal in some cases. These secondary infections can last for months, even, in some cases for years. The drugs to control these secondary metabolic syndromes vary based on symptoms of individual patients and their infections. The nanotechnological materials, in a similar way, would be valuable in the controlled delivery of drugs for controlling the secondary symptoms.

NANODIAGNOSTICS DEVELOPMENT

The detection and diagnosis of the viruses in diverse settings need different methods for precise identification and confirmation. The detection of virus in air, solid surfaces, clothes, other fabric materials, involve direct characterization methods while the diagnosis of viral infection in the human body involves various serological tests and biomedical procedures. The virus and infection identification targets either the viral proteins or the genetic materials RNA/DNA. Each method has its unique background science, tools, and protocol procedures for proper identification of the respective virus. As viral infections have been impacting the human population at different times, the science of detection and diagnosis of respective virus and viral infections has been in continuous development. New procedures, tools and methods have been introduced with the advancement in materials and nanosciences.[99] Scientists have been able to modulate the existing methods on emergence of any new virus and infection as was seen in the present Covid-19 pandemic.

The understanding of genetic conposition and proteins present on the virus provides the background about the applicability and development of the respective diagnostic methods. The coronaviruses have RNA as the genetic material (RNA viruses). Systematic nomenclature places the coronaviruses in order: nidovirales; family: coronaviridae; and subfamily: coronviridae.[100] The recent infective SARS-CoV-2 virus has different structural and functional proteins. The structural proteins are the body constituting proteins of SARS-CoV-2 and these include spike (S) glycoprotein of globular structures present of the surface, small envelope (E) proteins present in the outer capsid, matrix (M) protein present in the inner core of virus, nucleocapsid (N) protein surrounding the genetic material, and there are several other accessory proteins. The SARS-CoV-2 spikes (S) are responsible for the majority of interactions of the virus with the host cellular membrane and cause infection in the cells via receptor-binding mechanisms. As the spikes are main responsible proteins for adhesion to host cells receptors (known as angiotensin-converting enzyme 2 (ACE 2)); therefore, these spike proteins are frontline targets for the development of therapeutics and diagnostics tools (biosensors).[101] The spike proteins are glycoproteins[102] and have high affinity towards lectin proteins. These high affinity interactions can potentially be used in the development of biosensors using lectins as substrate.[103] The other proteins present in SARS-CoV-2, such as the M and E proteins perform other functions e.g. envelope E protein are required for the assembling the virus capsid. Similarly, the matric M protein is required for the transport of nutrients across the membranes and also helps in the formation of the envelope. Some proteins are involved in obstruction of the host immune response like N and E protein. There are several other proteins that have unknown functions. The specific protein of SARS-CoV-2 is used as biomarkers for diagnosis, for instance the spike proteins are leading antigen biomarkers that are used for the diagnosis of Covid-19 disease; similar detection methods were developed earlier for the diagnosis of SARS using the S and N proteins.[104]

In COVID-19, diverse diagnostic, and testing kits/assays, such as rapid test kits deploying enzyme-linked immunosorbent assay (ELISA)-based immunoassays, thermal screening guns, point-of-care (POC) tests and real-time reverse transcriptase polymerase chain reaction (RT-PCR), have been used for the detection of SARS-CoV-2 via characterization of the cellular and antibody responses to viral infections. The RT-PCR and chest-CT imaging proved to be the reliable test for confirmatory diagnosis of Covid-19. The RT-PCR is based on the synthesis of cDNA from viral genomic RNA via amplification and has served as the gold standard for the identification of Covid-19 infection. Loop mediated isothermal amplification (LAMP) technique has emerged as a better sensitive, specific detection alternative method to RT-PCR. It is because the LAMP technique uses specific primers along with a selective Bst DNA polymerase enzyme having the capacity of chain displacement activity under isothermal conditions, and thus, not requiring the thermocycler or electrophoresis equipment. It has been applied for the diagnosis of various viruses like MERS-CoV,[105] SARS-CoV, and influenza A.[106] In one study, the RT-LAMP was able to detect genomic RNA of SARS-CoV-2 in single step with a capacity to detect 100 copies of an RNA virus in respective reaction.[107] The immunoassays methods meant for detection of serum antibodies related to S or N proteins of SARS-CoV-2 using the protocol method of enzyme-linked immunosorbent assay (ELISA) and/or rapid lateral flow immunoassay (LFIA) besides the specific methods for IgM and IgG detection has been developed as rapid detection kits.[108]

However, these methods have some drawbacks and restrictions/limitations, including higher costs, non-specificity, false positive/negative responses, a longer duration of testing, along with being labor intensive. The currently employed diagnostic technique for the confirmation of COVID-19 infection is quantitative real-time polymerase chain reaction (qRT-PCR), however, it has its associated drawbacks as it is a labor-intensive and time-consuming technique as well as it cannot be easily used in remote areas or locations with limited resources. The RT-PCR is also known to have low sensitivity due to insufficient number of viruses in collected samples or sometimes due to inaccuracy in laboratory kits.[109] The rapid test kits using the ELISA based immunoassays have been used extensively in preliminary screening of infections, but they have the issues of false positive/negative cases. The Chest-CT, though reliable, but known to show the false diagnosis for the other infections with symptoms similar to Covid-19.[110] The researchers are always on lookout for the alternative methods for diagnosis like speedy alternative to RT-PCR, assuring confirmatory test alternative to rapid test kits.[111]

The recent molecular level genomic technology, **CRISPR** (*clustered regularly interspaced short palindromic repeats)* utilizes specific enzymes for gene editing via cleaving at specific loci with numerous applications.[15] The CRISPR based technologies are emerging to assist in the specific identification of genetic materials, including that of viruses at a very low concentration.[112] Gootenberg et al. utilized the distinctive properties of CRISPR-Cas enzymes for the development of a highly sensitive diagnostic technique for improved nucleic acid detection assisted with the lateral flow for visual readout. This

method, named SHERLOCK (specific high sensitivity enzymatic reporter unlocking), makes use of combined isothermal preamplification with Cas13 and is capable of distinguishing between various genetic fragments inputs that may differ by only a single nucleotide at very low concentrations.[113] Further, an improved version developed by the same group, SHERLOCK version 2 (SHERLOCKv2) have 3.5-fold increase in signal sensitivity by combining Cas13 with Csm6, an auxiliary CRISPR-associated enzyme with quantitative measurement of input as low as 2 attomolar and has been potentiated to detect the single stranded RNA of Dengue and Zika virus even with mutations in the liquid biopsy samples from patients along with visualization in lateral flow.[114] J.P. Broughton et al. have reported a CRISPR-Cas12 based lateral flow assay, DETECTR, for rapid detection of SARS-CoV-2 in the RNA extracts of the samples collected from respiratory swab.[115] This Endonuclease-Targeted CRISPR Trans Reporter (DETECTR) protocol can detect SARS-CoV-2 in less than 30 min with 3 step process involving RT-LAMP for 20 minutes, followed by use of CRISPR-Cas-12 for 10 minutes to distinguish SARS-CoV-2 RNA and finally lateral flow detection in 2 minutes.[115,116] Further evaluation by Alejandra group indicated the use of CRISPR-Cas-12 for the detection of SARS-CoV-2 RNA sequences at a low cost (1-2 USD/assay) with a detection limit of 10 copies/µl per sample.[117] The CRISPR-Cas-13 is reportedly used in the detection of SARS-CoV-2.[118] The CRISPR-Cas-13 use has also been implicated in therapy where this enzyme is used for destroying SARS-CoV-2 RNA sequences in infected human lung epithelial cells. The combinations of six crRNAs are capable of destroying up to 90% of corona virus in infected tissues.[119]

NanoBiosensors: The diagnostic tests using the serological fluids are based on the sensing the interactions of different types of bioreceptors such as nucleic acids (NA), immunoaffinity and protein (antigen, antibody).[120] The diagnostic signals in different **nanobiosensor** kits are based on electrochemical alterations, quartz crystal microbalance, change in impedance, and/or easily detectable signal due to optical change or surface plasmon resonance on interaction of various biomolecules or receptors (Figure 8).[121]

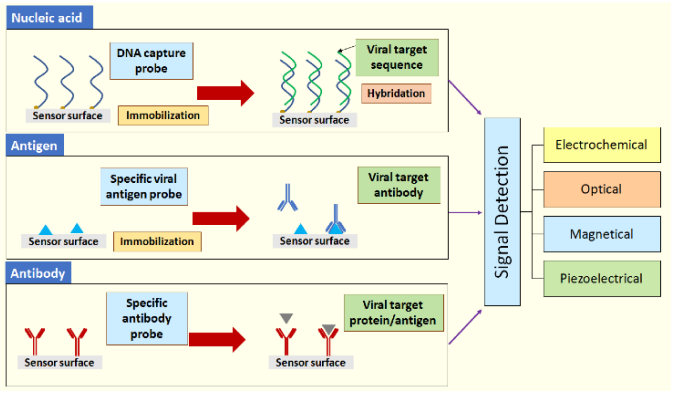

Figure 8. Summary of different methods and signal detection in biosensors meant for SARS and MERS coronaviruses. Reproduced from ref [122] Creative commons license CC 4 By.

Electrochemical nanobiosensors detect a change in electrical signal on the coupling of biological or biochemical interaction process transmission to an electrode transducer.[123] The electrochemical transducer signals i.e., amperometric, potentiometric, or impedance transducers[124] of nanobiosensors are used for the detection of pathogens and viruses. When the target molecule attaches to the electrode surface, it alters the electrical current that is transmitted through the nanostructure or nanomaterials, thus producing a signal in the nanobiosensor. Compared to optical or mass sensitization methods, the impedance biosensors are known to provide very sensitive detection and are thus, considered to be very ideal sensors for detection of proteins or DNA strands, along with their application in monitoring of the environment.[125] Electrochemical impedance spectroscopy (EIS) has emerged as an excellent tool for detection of the interactions between biological molecules in a non-destructive way. EIS has proved a better technique in comparison to differential pulse voltammetry (DPV), cyclic voltammetry (CV) and other electrochemical methods.[126] The signal generation used for the development of different nanobiosensors[127] for detection of different influenza viruses like Avian influenza virus (AIV) H7N9, H5N1, H7N7, and H7N9, the subtypes of influenza A virus are based on EIS, amperometry,[128] and cyclic voltammetry.[129] In these nanobiosensors, biological response on presence of virus/infection gets transferred to the signal detector via a transducer made up of different integrated or functionalized nanostructures, such as magnetic iron oxide nanobeads.[130] The ultrasensitive biosensor developed for influenza virus detection in saliva samples used boron-doped diamond equipped with antibodies, which performed exceptionally well with a detection limit of 1 fg/mL and accurate linear detection range of 1–100 fg/mL.[131,132] Various other electrochemical nanobiosensor constructs have been developed for the detection of influenza A virus (such as H1N1) where signal detection used different methods viz. EIS,[133] voltammetry,[134] amperometry,[29,128] or conductometry.[135] For the development of the Covid-19 nanobiosensor, the SARS-CoV-2 monoclonal antibodies were immobilized on a tin oxide electrode impregnated with Fluoride and Au NPs. This nanobiosensor measured the change in electrical conductivity on binding of SARS-CoV-2 spike antigen using different detection methods, such as differential pulse voltammetry (DPV) or cyclic voltammetry (CV) with good observed sensitivity of detection in the limit of 10 fM of corona virus SARS-CoV-2 antigens which further standardization gave a good linear detection in the range of 1 fM to 1 µM in standard buffer.[136] Similarly, an electrochemical nanobiosensor based on chronoamperometry and differential pulse voltammetry (DPV) using graphene oxide nanosheets immobilized with antibodies for H5N1 and H1N1 antigens showed good detection of these viruses with detection limits of 9.4 pM for H1N1 virus and detection limit of 8.3 pM for H5N1.[137] The SARS-CoV-2 spike protein serves as good antigen markers detection of Covid-19 infection. The biosensor based on bioelectric recognition assay (BERA) has been developed for direct detection of SARS-CoV-2 S1 spike antigens for the samples collected from green monkey kidney cell culture[138] with

a detection limit of 1 fg/mL and ultrafast detection within 3 min. The exciting results obtained from this novel biosensor with rapid detection with very low concentration have provided a leading edge in the possibility of fast and accurate detection of Covid-19 infections.[138] Further development in nanobiosensors for Covid-19 has provided enhanced electrical signals where spike S1 antibody inserted in the cell membrane of the electro-engineered cells were used. These results provide an optimistic impetus towards a portable diagnosis device with easy readings, simple handling with capacity to screen a large number of sample of SARS-CoV-2 antigens.[139] **Field-effect transistor (FET)-**based biosensors have been developed using graphene as base material for detection of biomolecules (DNA, Proteins etc.) with high sensitivity and same biosensors has been extended for detection of influenza virus (H5N1) genes via flow-through label-free detection method.[140] The graphene based FET biosensor so detect the influenza virus in the picomolar range with a detection range limit of 130 pM and 50 pM.[140] Similarly, another FET biosensor developed for the SARS-CoV-2 contained spike S protein antibodies immobilized on a sheet of graphene-based material (Figure 9)[141] and this nano-FET biosensor could detect the SARS-CoV-2 spike protein at a concentration of 1 fg/ml under laboratory test conditions in phosphate-buffered saline and ably detected virus at 100 fg/ml from real condition medical samples. This nano-FET biosensor construct has a capacity to selectively identify the SARS-CoV-2 in the laboratory culture samples (with good limit of detection ~1.6 × 101 pfu/ml) while in real time medical samples it could detect the virus with a limit of detection ~2.42 × 102 copies/ml in respective samples. This nano-FET biosensor with good observed sensitivity in Covid-19 virus containing samples along with no requirement of sample pretreatment or labeling indicates the successful application of these sensors for detection of specific viruses whereas various other materials can be investigated to further improve the signal-to-noise ratio and design improvement for use in the specific virus or multiple virus detection.

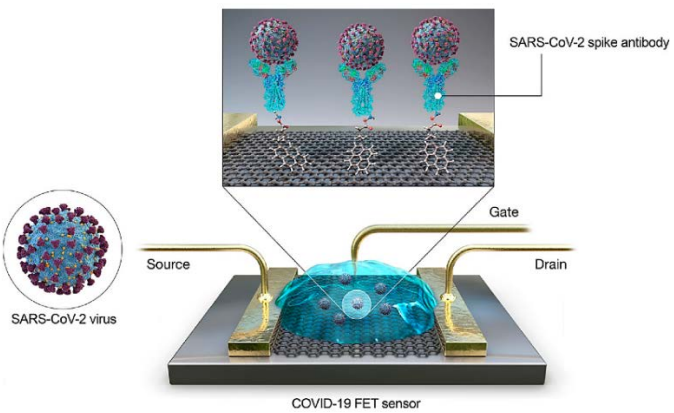

Figure 9. Representation of Spike antibody immobilized graphene for FET sensor for Covid-19 diagnosis. Reproduced from [141] with unrestricted reuse permission by ACS for Covid-19 work. Copyright © 2020, American Chemical Society.

The Optical nanobiosensors, the new photonic devices can be used for the detection of different type of signals based on energy changes, polarization change in molecules, absorption of radiation, photons from fluorescence, light scattering, decay time based, and/or change in phase of the system.[142] The optical nanobiosensors are the preferred and most common sensors as materials designing for signal based on the surface plasmon resonance,[143] and fluorescence principles is comparatively easy, along with the high capacity of optical nanobiosensors in the detection of the different viruses including the SARS-CoV-2 coronavirus.[144] A number of materials have been used for the construction of different type of optical nanobiosensors, mainly using the fluorescence, colorimetric or surface plasmon resonance (SPR) principles for the signals. The biosensors for influenza viruses included constructs of Au nanoparticles (Au NPs),[145] optical fiber SPR sensor,[146] Au chip,[147] Au micro-electrode modified with polypyrrole bearing ferrocene,[148] Au nanoparticles binding polypeptide (GBP)–fusion protein,[149] indium-tin-oxide (ITO) surface decorated with Au spike-like nanoparticle (hAuSN),[150] Antibody-Au nanoparticles,[151] Quintenary alloyed CdZnSeTeS quantum dots,[152] Ag@SiO2 NPs,[153] Liposome-based sensor[154] etc. The viral proteins and viral infection are frequently detected using fluorescence based photo-nanobiosensors.[155] For example, the detection of influenza virus H5N1 infection has been studied using an optical nanobiosensor developed based on fluorescence of CdTe quantum dots with a detection limit of 3ng/mL of virus concentration.[156] Chemiluminescence, like fluorescence, is the light emitted from the relaxation of excited electron of atoms and molecules. The chemiluminescence has a better resolution and sensitivity over other photo-methods. For example, a chemiluminescence sensor developed for the detection of Hepatitis B virus marker HBsAg have a good sensitivity to detect the marker at a very low (0.05 ng/mL) concentration, and thus showing the capability to detect the molecules at ten times lower concentration compared to a typical ELISA can detect in clinics and hospitals.[157] The optical nanobiosensors for SARS-CoV included materials constructs of gold nanoparticles (Au NPs),[158] poly(hydroxyalkanoate) (PHA) microbead,[159] green fluorescent protein (GFP),[160] graphene oxide (GO) sheet,[161] QDs-conjugated RNA aptamer on glass chip,[162] functionalized photonic nanocrystals.[163] The optical nanobiosensors for detection of MERS-CoV has been developed using Au nanoparticles,[164] and silver nanoparticles (Ag NPs).[165] Leading the information from the previous biosensors, the nanosensors for detection of SARS-CoV-2 have been developed. The nanobiosensor made up of Au nanoislands functionalized (Au NIs) with complementary DNA receptors has been developed using the localized surface plasmon resonance (LSPR) or plasmonic photo-thermal (PPT) signals on binding of SARS-CoV-2 nucleic acid with detection limit of 0.22 pM.[166] Another biosensor developed using AuNPs for colorimetric assay on binding of RNA sequence of SARS-CoV-2 has shown the detection limit of 0.18 ng/μL of RNA in a dynamic range of 0.2–3 ng/μL.[167] The AuNP colloids based colorimetric assay for the SARS-CoV-2 IgG-IgM combined antibody for blood samples has been recently developed for Covid-19 infection.[168]

Magneto-optic (MO) nanobiosensors are based on the combined properties of magnetic metal nanoparticles and their enhanced surface plasmon to provide an impetus to develop ultra-sensitive sensors.[169–171] The magneto-optic (MO) nanobiosensor platforms have shown exceptional characteristic properties such as detection with ultra-sensitivity at a faster rate with label-free probes, enhanced surface plasmons resonance by ferromagnetic metals/nanoparticles, easy construction using magnetic beads coated with a ligand and detection using magnetic field. Different type of materials have been developed for the construction of specific application oriented magneto-optic nanobiosensors. A nanobiosensor using Au/Fe_3O_4 decorated graphene has been developed for magnetofluoro-immunosensing of influenza virus (H1N1) with a detection limit of 7.27 fg/mL of virus concentration in deionized water.[172] Similarly, virus separation as well as plasmonic detection has been studied with plasmonic/magnetic graphene construct prepared with Au/iron oxides decorated graphene. The SARS-CoV-2 pseudo virus detection nanobiosensor has been prepared using magnetic nanoparticles coated on the polymer of poly(amino ester) with carboxyl groups (PC).[173]

Piezoelectric sensors convert the mechanical energy into electricity on exposure to analyte and are used in the detection of different biochemical entities. Depending upon their mode of functioning i.e., bulk wave (BW) and surface acoustic wave (SAW), the presence of any analytic entity affects the piezoelectric signal i.e. mechanical vibration of crystals get changed producing a variation in the electrical signal which indicates the presence of respective biochemical analytes/entities;[121] they help in detection of molecules without labeling, though have their limitation of complex measurements. These types of sensors have been applied for the detection of viruses in the past. The piezoelectric sensor i.e., a quartz crystal microbalance (QCM) sensor constructed on Au surface embedded with 3D nanowell has shown detection of influenza virus within 10 minute with a sensitivity of 2–4 HAU/50 µL.[174] Similarly, the piezoelectric immunosensor based on the mass detection have been developed for the detection of SARS-CoV.[175] The highly sensitive nanobiosensors for label-free real time detection using quartz crystal microbalance (QCM)-based method for oral swab have been developed for different type of viruses like influenza virus, SARS-CoV, and SARS-CoV-2.[176] These piezoelectric nanosensors with detection limits in ng range for viruses with high reliability makes them desirable tools for use in epidemics and pandemics.

Direct Imaging

Better optical, scanning, and other methods for direct detection of virus as a rapid kit's alternatives are needed. The Infra-red scanning probes and Nuclear magnetic resonance (NMR) probes could be the handy tools for precise identification of a particular virus, however, the presence of a very small number of viruses in the sample becomes one of the hurdles for clinical setting application. The Surface Enhanced Raman Spectroscopy (SERS) is a very effective spectroscopy technique that can be used for the detection of an analyte in a range of sub-atommolar quantities.[177,178] In the presence of gold nanoparticles (Au NPs), the Raman scattering is known to get enhanced a million folds.[179] The sensors comprising of metal organic frameworks (MOFs) on Au-nanorods i.e. MOF-5@Au-nanorods have been reported to show high accuracy and sensitivity in analysis of different analytes (figure 10).[180]

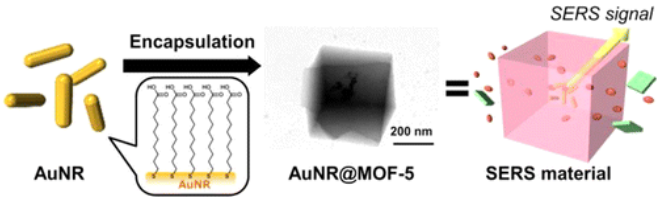

Figure 10. The SERS signal from Au-nanorods encapsulated on MOF-5. Reprinted from [180]. Copyright (2013) American Chemical Society.

There are few experiments towards an indication that selected different type of nanostructures can be used for the detection and diagnosis of viruses with a high limit of detection and sensitivity. The basis comes from the detection of selected analytes via distinct SERS signals on exposure to nanostructures, like the zeolitic imidazolate frameworks-8 (ZIF-8) have been developed using core-shell heterostructure of ZnO nanorods which can sense the different molecular scavengers such as H_2O_2, ascorbic acid and provide distinguished SERS signal with photoelectrochemical response on interaction with different analytes (Figure 11).[181]

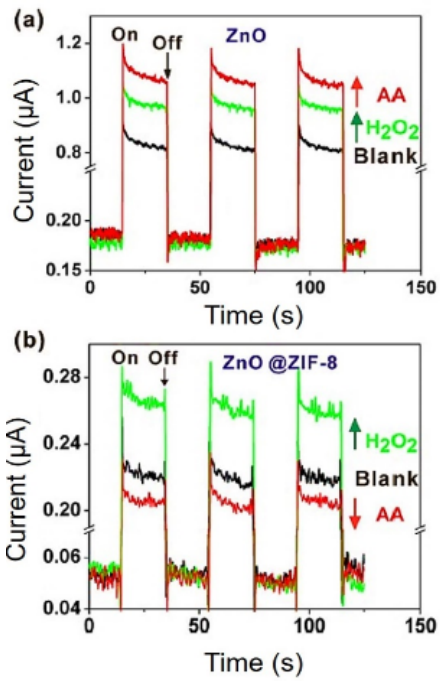

Figure 11. The H_2O_2 (0.1 mM) photocurrent signal on (a) ZnO nanorods (b) ZnO-nanorodes@ZIF-8. Reprinted from [181] with permission. Copyright (2013), American Chemical Society.

N. Rabiee et. al. proposed that similar nano-architectures can be used for the detection of different pathogens.[111] The nanoarchitecture includes incorporation of different optically active components on MOFs structure or impregnation on the

surface of MOFs and finally the development of an optical mechanism based on-off/off-on biosensor by conjugation of stimuli responsive linker on the surface.[111] In this postulate, the Au NPs would interact with disulfide bonds of surface proteins leading to disruption, to be followed by release of ozone from holes of MOFs. The released ozone assisted cleavage of cysteine bond of viral proteins would cause destruction of SARS-CoV-2 virus capsid leading to release of virus genetic material and media. The interaction of genetic material with AuNPs would provide the signal with change in intensity of SERS and thus the color of Au NPs will apparently change which can help in direct identification of virus in point of care (POC) settings (Figure 12).[111] In this method the optical nanoparticles impregnation on MOFs provide a signal on the interaction of virus and surface of nanostructure.

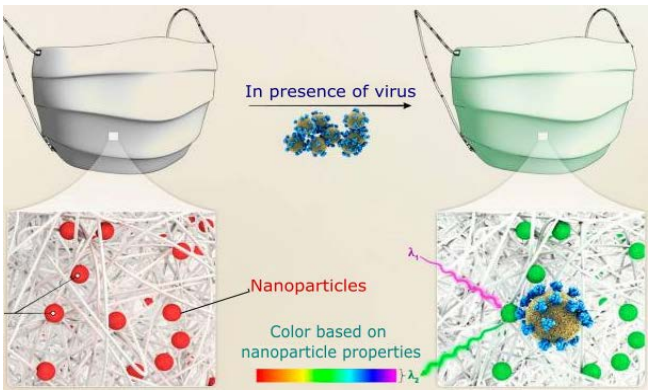

Figure 12. The proposed mask color change and SERS intensity of nanoparticles (NPs) on contact with SARS-CoV-2 virus. Reprinted from [111] Creative Commons License 4.0.

A simple optical biosensor (as discussed above) has potential of easy applicability in the point-of-care (POC) detection of different pathogens.[182] Further, signal enhanced SERS can provide a label free high sensitive technique for virus detection. The sharp bandwidth of Raman signal in SERS can be a better alternative for the fluorescent labels developed using quantum dots.[183]

VACCINE DEVELOPMENT

Vaccination is one robust method to control infectious diseases via the administration of mild antigenic materials to generate triggered adaptive or protective immunity in individuals to combat specific pathogens, particularly viruses. Vaccines have played an impressive role in controlling and elimination of fatal infections in past viz. smallpox, polio, measles, and hepatitis A. Continuous efforts are ongoing and have been remarkably successful to develop the vaccines for different other viruses such as HIV, Zika virus, influenza viruses (H1N1, H5N1), hepatitis C, Ebola virus and SARS-CoV.[184] Vaccine development has been the frontier emphasized field seen during the recent SARS-CoV-2 viral infection in a record time which was unimaginable a few years back.

The vaccines are developed by the inclusion of an inactivated or attenuated specific virus particles (first generation vaccines) or virus subunits - protein fragments (second generation vaccines) or genetic materials - mRNA, DNA fragments etc. (third generation vaccines). The recent second and third generation vaccines based on protein subunits or RNA/DNA have many advantages of cost effectiveness, higher care profile, and can induce immunity against selected pathogens, however, these also have their associated challenges such as weak immunogenicity, in vivo intrinsic stability, toxicity, and multiple dose requirements. There have been many advances to circumvent these challenges and the nano-based frontier constructs have assisted in the development of better vaccine formulations.

The nano size vaccine and nanodelivery vehicles for vaccines have the capacity to improve the efficacy of vaccines several fold, and because of the added advantages, the nano systems have recently been incorporated in vaccine development. The prolonged continuous release of antigenic materials from nanovaccine at various stages of immunogenicity induction at different time intervals have shown better and increased immunity generation compared to conventional vaccines.[185] The nanovaccines could entice the involvement of different immune cells in the generation of enhanced immunity (Figure 13).[185]

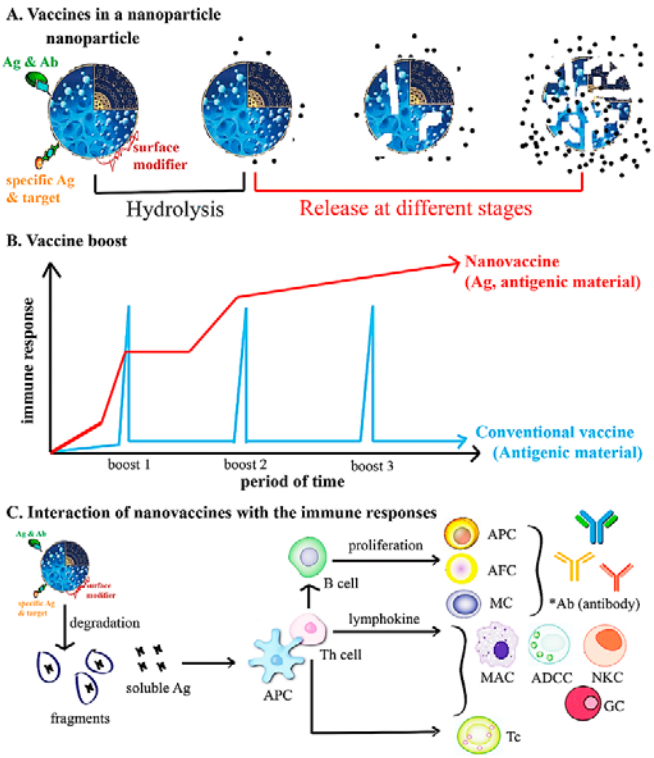

Figure 13. Nanovaccine effect on immune response generation. (A) Vaccines in nanoparticles facilitate controlled release. (B) One dose of Nanovaccines might be sufficient over many doses of conventional vaccines (C) Antigens released from nanovaccines may induce both humoral immunity (B cell responses) and cell-mediated immunity (helper and cytotoxic T cell responses). APC: antigen presenting cell; AFC: antibody forming cell; MC: memory cell; MAC: macrophage; ADCC: antibody-dependent cytotoxic cell; NKC: natural killer cell; Tc: cytotoxic T-cell; GC: granulocyte; Th: helper T-cell; IgG: serum immunoglobulin G. Reproduced from [185], Creative commons license (CC BY).

Nanoparticle or nanomaterials chosen for application in specific vaccine development depend upon the characteristic properties of respective nanomaterial. Accordingly, all different type of nanomaterials such as Quantum dots (QDs), carbon based nanomaterials e.g. Carbon Nanotubes, fullerenes, graphene, carbon black NPs; NPs of polymers such as chitosan, poly-lactide-co-glycolides (PLGA), poly-γ-glutamic acid (γ-PGA); non-metal NPs, metal/metal oxide NPs, silica NPs, liposomes, dendrimers, solid lipid nanocarriers, and virus like particles (VLPs) have been evaluated as drug carrier for molecular drugs, proteins/peptides, DNA/RNA, antibodies, and vaccines. For vaccine development, nanostructured materials may be utilized for antigen delivery (antigen nanocarriers) and/or may be used as adjuvants (helping as immunity booster) with interaction with immune cells, and thus assisting in the effective generation of a protective humoral immune response. In the continuous efforts to develop nanomaterials based vaccines for different viruses, the nanomaterials-antigen/adjuvant conjugates evaluated include AuNPs-viral plasmid DNA for HIV,[186] AuNPs-matrix protein 2 (M2e) for H1N1 influenza virus,[187] AuNPs-viral protein for Foot and Mouth disease virus (FMDV),[188] AuNPs-M2e/CpG for H1N1, H3N2, H5N1 influenza viruses,[189] Chitosan NPs-HBsAg for Hepatitis B virus,[190] Chitosan NPs-live virus for Newcastle disease virus,[191] γ-PGA NPs-Hemagglutinin (HA) for H1N1 virus,[192] VLPs-Nucleocapsid protein for Hepatitis virus,[193] Polypeptide NPs-Spike protein for SARS-CoV,[194] PLA/PLGA NPs-Hepatitis B surface antigen for Hepatitis B virus,[195] PLGA NPs-BPI3V proteins for bovine parainfluenza 3 virus,[196] and nanomicelles-mRNA for HIV-1[197] etc. having a different level of final outcomes towards the generation of varied immunogenicity against respective viruses.[11]

The background information regarding vaccines research for different viruses proved handy and boosted the early development of vaccines for Covid-19. Among the diverse emergent efforts ongoing for SARS-CoV-2 vaccine development, the approved vaccines for clinical use are based on either subunit (spike protein) like in Novavax (NVX-COV2373) (Novartis) or mRNA like the mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech). The nanostructures have integrally been used in these vaccines for enhanced immunity generation. In fact, two widely used mRNA based vaccines – mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) have utilized the lipid nanoparticles as the carrier.[198]

Novavax (NVX-COV2373) is a spike subunit protein-based vaccine that can be stored easily at 2 to 8 °C. This vaccine creation used a specific sequence of genetic materials i.e., RNA of SARS-CoV-2 that code or translates into spike protein S. The selected genetic RNA fragment was inserted into Baculovirus, and thus putting the spike protein genetic sequence in this virus genome will code the SARS-CoV-2 spikes proteins. This genomically modified Baculovirus was fused with Moth cells for further replication as well as translation. In this process, the Moth cells itself express or shoot out spike proteins on its surface. The Moth cells are harvested for the Spike proteins which assembles in the form of nanoparticles. Along with the spike proteins nanoparticles, the Novavax vaccine also contains M1 protein adjuvant, which helps to stimulate the immune response (Figure 14).

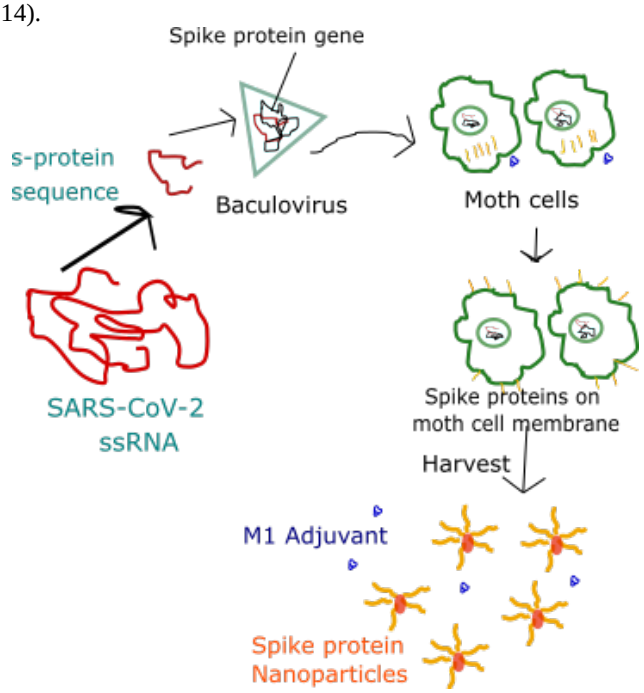

Figure 14. Schematic representation for Nonavax (NVX-COV2373) vaccine creation.

The Vector-based vaccines include the one developed by Johnson-Johnson and another by Astrazeneca vaccine. These both vaccines were developed by using adenovirus, the Astrazeneca vaccine has been developed by using the chimpanzee adenovirus and that of Johnson Johnson by using a human adenovirus.

The vaccines have been a boon in controlling infectious diseases in the past as well as at the present time, particularly the disease caused by virus pathogen. The nanomaterials have been successfully utilized for improved antigenicity of different vaccines and certainly, future vaccines development would need the advanced nanomaterials for the delivery or antigenicity development.

Virus mutations

The viruses utilize the cellular machinery of the host for their progeny and multiplication. When viruses infect a host to another and multiply during the process, they are prone to get a mutation in small ways. The recent, SARS-CoV-2 virus has developed its different variants because of the small mutations in the original Chinese virus. The independent lineage of corona virus established include Alpha (B.1.1.7), Beta (B.1.351), gamma (P.1), and Delta (B.1.617).[199] The variants originate because the virus adapts itself to evade the immune system of host, induced mutations during multiplication in host cells, and to evolve for fast infection and varied combination of these events.[200] The mutations responsible for variants may be similar gene alterations or at different loci. In case of SARS-CoV-2, the E484Q mutation of B.1.351 Beta variant and E484K mutation of P.1 Gamma variant are similar while both variants evolved independently (in different regions) towards enhanced infectivity and immunity evading.[199] The B.1.427/B.1.429 Epsilon variant has seen ‘double

mutation' referred to as L452R mutation. The B.1.617 (delta variant) have been observed in different countries including Australia, New Zealand, Turkey, Germany, United States, Nigeria etc. The respective mutations may bring the changes in the spike proteins and affect the binding on receptors which lead to increased/decreased infectivity. The current known variants of SARS-CoV-2 with different mutations have variance in infectivity rate and virulence, however, may not impact the immune response generated by different current vaccines substantially.[200,201] The fundamental information about mutations and associated structural changes in virus would assist in a suitable scenario for development of nanomaterials and tools for respective applications.

FUTURE PERSPECTIVE

With the emergence of new medical technologies and advancements in the field of science, it has been feasible to identify the cause of various severe infections. Infections with assorted viruses at different intervals have provided researchers the insight and opportunity to develop different tools to mitigate them. The development of these nano-tools and advanced materials helps to mitigate and control these suddenly emerging viral infections that can grow into pandemic quickly like recent covid-19. With these advanced tools, the mechanism of viral infection inside the body could be understood better along with the development of different drugs based on the underlying cellular-molecular mechanisms of viral infection progression and ultimately achieving success in controlling the viral infections to a large extent. The identification, treatment, and management of these infections with modern available tools would provide further ability to combat any suddenly appearing future infection. The extensive involvement of doctors, scientists, and engineers throughout the world today brought improved prospects for targeting the varying stages of transmission and different methods for infection control. The current tools available and developed so far would be further refined and would bring out new diagnostic and treatment methods, and thus, will be able to provide better solutions to mitigate any future viral infection.

CONCLUSION

Analysis of recent viral infections and further continuous development of various advanced materials has been possible with the new evolving technologies/tools in materials and medical sciences fields. The continuous research for sensitive biosensors has assisted in the development of new conjugates for the presence and detection of a virus on the surface as well as inside the human body. Similarly, the materials and concepts developed for various other diseases like cancer have also assisted in developing the preliminary drugs and vaccines for the COVID-19 disease and SARS-CoV-2 virus, whereas the fundamental new materials like graphene, carbon nanotubes, metal nanoparticles, metal/covalent-organic frameworks and associated properties provided the fundamental structural basis for the development of specific materials to mitigate this viral infection. The continuous development in materials and nanoscience would provide a better understanding and make available refined tools to fight any future infections.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

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