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Nanotechnology in the COVID-19 era: Carbon-based nanomaterials as a promising solution

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic has led to collaboration between nanotechnology scientists, industry stakeholders, and clinicians to develop solutions for diagnostics, prevention, and treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections. Nanomaterials, including carbon-based materials (CBM) such as graphene and carbon nanotubes, have been studied for their potential in viral research. CBM unique effects on microorganisms, immune interaction, and sensitivity in diagnostics have made them a promising subject of SARS-CoV-2 research. This review discusses the interaction of CBM with SARS-CoV-2 and their applicability, including CBM physical and chemical properties, the known interactions between CBM and viral components, and the proposed prevention, treatment, and diagnostics uses.

1. Introduction

This century has witnessed no other global emergency as critical as the Coronavirus Disease 2019 (COVID-19). Vaccines have successfully controlled this pandemic, nevertheless, as a result of the typical viral capacity to quickly adapt and mutate, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has infected almost 670 million individuals worldwide (January 2023) [1]. The current variant of concern (VoC) Omicron has more than 30 mutations in the spike protein, the outer and first protein encountered by cells and surfaces interacting with the virus. Omicron has also transformed the pathogenic mechanism by using a different cell entry route, i. e reducing cell syncytia and favoring a cellular transmembrane serine protease 2 (TMPRSS2)-independent endosomal entry [1,2].

To control this continuously evolving microorganism, both in terms of structure and mode of infection and spreading, nanotechnology scientists and industry stakeholders have worked with clinicians to create solutions for diagnostics, prevention and treatment [3].

Actually the ongoing SARS-CoV-2 pandemic has highlighted the importance of nanomaterials science in offering new tools for antiviral research (Fig. 1 from Ref. [4]): nanomaterials can limit viral spreading and environmental contamination; nanosensors are extremely sensitive in diagnostic and finally, nanocarriers can be exploited for treatment and vaccine design.

Among nanoparticles, graphene and more generally carbon-based materials (CBM) have been widely studied in the last 15 years in the field of microbiology. CBM unique mechanisms of interaction with microbial species have initially attracted a broad interest as a possible answer to the antibiotic resistance emergency, and the studies conducted before 2020 have served as a valuable experience for SARS-CoV-2 studies [5–8]. Mechanisms of bacteria-killing by CBM involve reactive oxygen species (ROS) generation or membrane disruption [9] and even if viral particles are smaller (−100 nm vs microns) and lack metabolism, or have a different outer envelope structure compared to bacteria or fungi, we have learned, as nanomaterials scientists, concepts about in vivo protein corona formation [10,11], nanoparticle stability and immune interactions beneficial for SARS-CoV-2 fighting [12–14].

Analyzing literature data on graphene, the primarily studied member of the CBM family, before 2019 and during the last three years of pandemics, we observe a sharp increase in the study of viruses and graphene, graphene sensors or material for personal protective equipment production (Fig. 2). CBM-based sensors in diagnostic are highly advanced and some available sensors might just be modified for SARS-CoV-2 specific antigens.

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In this Review, we will discuss the role of CBM nanomaterials in SARS-CoV-2 research. We will start with the physicochemical characteristics of the SARS-CoV-2 particles, especially size and charge that influence the interaction with cells and with CBM family members, which are an impressive catalog of size and chemistry. We will then examine the described mechanisms of interaction of CBM and SARS-CoV-2 proposed mainly in the last three years of groundwork. Finally, we will report the main applications of cbm in the fields of prevention, screening, diagnostics, and treatment designed explicitly for SARS-CoV-2 and analyze the market for this type of materials. We highlight that other Reviews, that will be mentioned in the text, have focused on CBM and viruses in general. Universal knowhow offered by nanotechnology science will play a critical role in the prevention, diagnosis, and treatment of future viral outbursts.

2. SARS-CoV-2 physicochemical properties and variants

A detailed comprehension of the SARS-CoV-2 genetic and structural properties is a precondition for ensuring successful medicinal and diagnostic tools based on nanomaterials.

SARS-CoV-2 dimensions are comprised between 60 and 140 nm[16], and the capsid has the Coronaviridae typical morphology (Fig. 3 from Ref. [15]). SARS-CoV-2 is an enveloped, positive-strand RNA virus, with distinctive spikes (26–61 in number [16]), about 9–12 nm long, that create the viral corona [15,17]. SARS-CoV-2 RNA genome encodes approximately 27 proteins with common possible roles, and the remaining ones with putative roles.

The SARS-CoV-2 outer charge and geometrical arrangement are of particular interest to study its specific behavior when interacting with nanomaterials.

The SARS-CoV-2 structural proteins are the small envelope (E), matrix and membrane proteins (M), nucleocapsid (N), hemagglutinin-esterase (HE), and spike (S) glycoprotein [15]. The main roles of the E and M proteins are to build the viral three-dimensional structure, differently, N proteins assemble in the core with the RNA. The S protein plays a main role as the outer layer glycol-molecule and is assembled in trimers that bind receptors and mediate fusion with cell membrane via the two functional subunits named S1 and S2. The S receptor-binding domain (RBD) that binds the angiotensin-converting enzyme 2 (ACE2) on the human cell membrane is in the S1 segment, while the merging of the virus with the host cell membrane is regulated by the bent conformation of the S2 structure. In the original viral strain, also TMPRSS2 processes the S protein, enabling virus–host membrane interaction [18].

Scopus publications	Total/year	Num/Total	Increase% (2022-23/2019)
Graphene			121%
Graphene Coronavirus and/or SARS			9600%
Graphene Virus			792%
Graphene Bacteria			141%
Graphene Sensor			138%
Graphene PPE and/or face mask			733%

Fig. 2. Literature data on graphene before and after SARS-CoV-2 pandemics from Scopus database. Search has been done in Scopus (January 2023, Publication type: Article). Each point represents the following year: 2019; 2020; 2021; 2022–2023. Words in the first column have been searched in Title-abstract-keyword. Num/total refers to the number of publications per year on the total publications about graphene. Percentage increase (Increase %) has been calculated comparing publications of 2022–2023 and 2019. (A colour version of this figure can be viewed online.)

More than ten variants of SARS-CoV-2 have been reported so far, with mutations associated to elusion of the body's natural immune defenses and antibody recognition. In 2022, Omicron became the primary circulating variant and the only VoC [1].

All variants contain the D614G mutation, that enhances both the viral replication and infectivity [1] by increasing the spike protein processing [19]. However, there is no evidence that D614G is related with COVID-19 disease severity or with the SARS-CoV-2 escape from the immune system [1].

Omicron exhibits over 30 mutations along the S structure, primarily in epitopes in the RBD region recognized by immunoglobulins, which might explain why vaccine-induced immunity is less effective [1,20]. One more possible explanation for Omicron's quick transmission, is its ability to enter cells through an endosomal pathway that isn't dependent on TMPRSS2. In this way, the virus can more effectively infect cells in the supralaryngeal apparatus, that have lower expression levels of

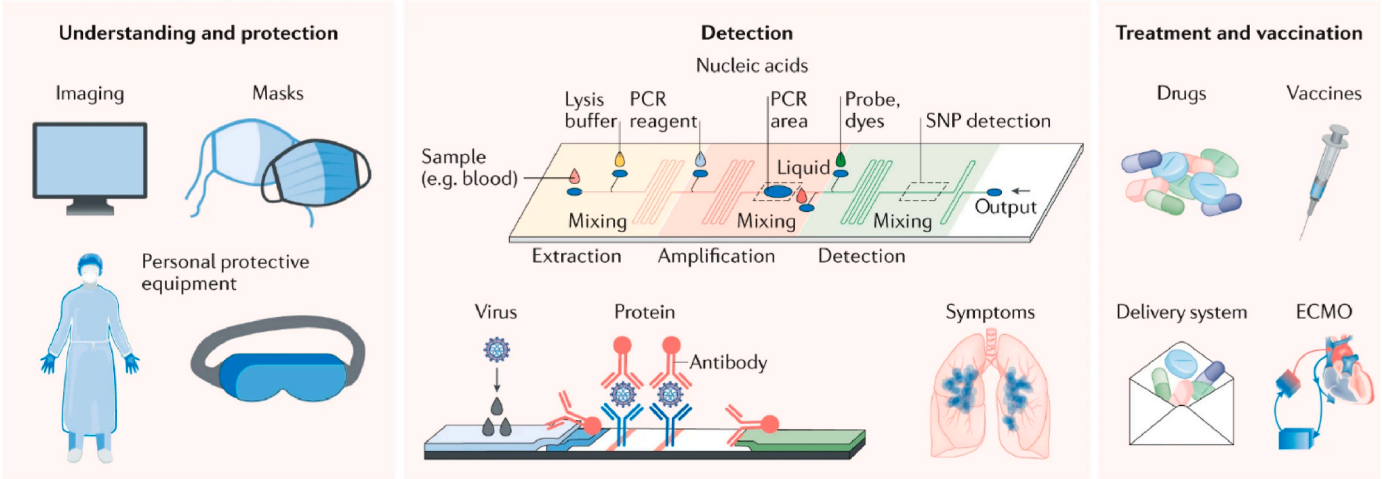

Fig. 1. Material science helps in the creation and improvement of protective equipment, and supplies techniques and methods for analyzing SARS-CoV-2, such as high-resolution imaging, polymerase chain reaction (PCR) for detection of single nucleotide polymorphism (SNP) as well as protein analysis for virus detection. Furthermore, material science can be employed for the development of vaccine and delivery systems, as well as providing advanced materials for medical instruments like filters for extracorporeal membrane oxygenation (ECMO) machines. Modified with permission from Ref. [4]. (A colour version of this figure can be viewed online.)

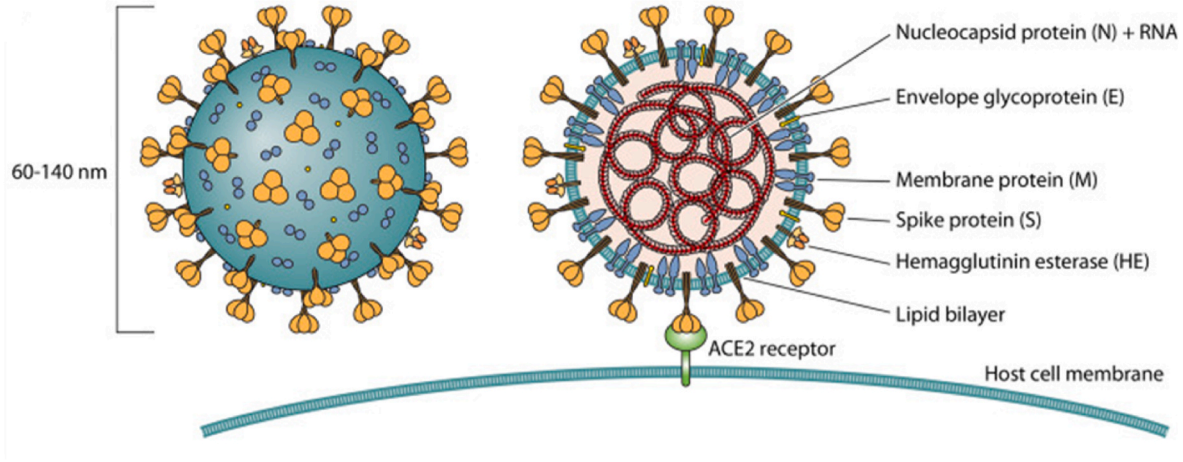

Fig. 3. Diagram of the SARS-CoV-2 virion. Reproduced with permission from Ref. [15]. (A colour version of this figure can be viewed online.)

TMPRSS2 [1,21]. From the respiratory upper tract, the virus can be readily scattered and transmitted [22]. On the other hand, the localization implies a less severe disease, which might also due to the less efficacy in interferon response antagonism [23].

The interaction of antimicrobials with microbes, such bacteria, is influenced by the outer structure of the cell membrane both in terms of electrostatic attraction and cell thickness [24]. For example, the silver nanoparticles (negative charge) interact more strongly with the positive residues of the integral membrane proteins on the bacteria surface and cause alteration in structural integrity or physicochemical changes that lead to cell death [25]. The outer surface parameters are also crucial for antiviral agents, thus it is fundamental to observe the physicochemical features of the SARS-CoV-2 virion, which have been resumed in Table 1 from Ref. [16].

The knowledge of the S structure and electric charge distribution on SARS-CoV-2 is essential for the analysis of possible interactions with CBM, given its fundamental role in the adsorption process on surface [16]. It is known that the exposed part of the S protein is electrically positive, while the rest of the protein is negative. The Omicron mutations have collected positive charges in areas exposed to solvents, particularly at the interface for binding of the ACE2 receptor, which has a complementary electrostatic surface. On the other hand, the interfaces between Omicron and neutralizing antibodies have comparable positive charges. Beside the charge distribution at physiological pH (7.4), it was reported that in the endosomal compartment, SARS-CoV-2 evades the neutralizing antibodies through a pH-dependent conformational masking [26].

Table 1
Physicochemical properties of SARS-CoV-2 reproduced and modified with permission from Ref. [16].

Quantity (unit)	Value
sVirion core part diameter (nm)	91 ± 11
Membrane thickness (nm)	5 ± 1
Core surface area (nm [2])	2.6×10^4
Virion diffusion coefficient (m^2s^{-1})	2.7×10^{-10} Air
	5.4×10^{-12} Aqueous media
S protein	
Molar mass (kg mol^{-1})	141.2
Density (kg m^{-3})	1.35×10^3
Molar volume (nm [3])	1.7×10^3
Equivalent sphere diameter (nm)	15
Diffusion coefficient (m^2s^{-1})	3.3×10^{-11}
Length (nm)	24 ± 9
Number per virion	26–61
Surface concentration (nm [2])	$1–2.3 \times 10^{-3}$
Cross-sectional area at the top (nm^{-2})	97–110
Coverage at the core (dimensionless)	0.097–0.25

Regarding the charge-mediated stability on different solid surfaces, SARS-CoV-2 survives more on plastic and stainless steel than on copper and cardboard. Viruses adsorb to surfaces through two main mechanisms, van der Waals and electrostatic interactions. Viruses tend to be hydrophobic, thus are attracted to metal surfaces (e.g., gold and stainless steel) because of mainly van der Waals and hydrophobic forces. Hydrogen bonding plays a key role in this case, and when surfaces are covered by an aqueous thin film. The bond strength is high in the presence of –O–H···O bonding, particularly in pH environments where the carboxylic acid on the virus is deprotonated (pH > 4).

Due to the large size of virus particles and variety of surface proteins, there are multiple positive and negative patches in the pH range 5–8. Therefore, $–NH_2$, $–NH_3^+$, –COOH, and $–COO^-$amino acids groups of S protein drive adsorption onto the solid surfaces through double electrostatic interactions and hydrogen bonding based on the surface characteristics.

Fig. 4, from a recent Review about SARS-CoV-2 adsorption on surfaces, outlines the possible interactions that can occur among capsids and materials interfaces varying pH and chemical groups. At pH values below the isoelectric point (for many viruses below 7 [27]), the overall charge of SARS-CoV-2 is positive, given that both the carboxylate and amine groups are protonated, and hydrogen bonding would be formed to hydroxyl-containing surfaces such as wood, cotton, or paper (Fig. 4A). At pH above the isoelectric point (Fig. 4B), the outer surface is deprotonated and therefore negative, accordingly, lower virus adsorption occurs. At higher pH, negative charge interacts strongly with cations that create a thinner double layer and lower repulsion forces, and again possible hydrogen bonding is formed to surface hydroxyl groups, which results in increased adsorption [28]. On surfaces coated with water, the virions form robust interactions through hydrogen bonding with the water layer. The water molecules can also occupy the spaces between closely positioned viral particles up to a distance that is determined by the humidity level [28].

3. Carbon nanomaterials family: size, shape and biological identity

The size, shape and charge of nanomaterials heavily determine the nature of their interaction with biological entities (microbes and eukaryotic cells) and in vivo distribution [29,30] (Fig. 5 from Ref. [31]). These interactions and in vivo outcomes are also influenced by the biological identity that CBM after absorption of macromolecules on their surface in body fluids, the so-called biomolecular corona [31]. The biomolecular corona of proteins, lipids, and carbohydrates dramatically

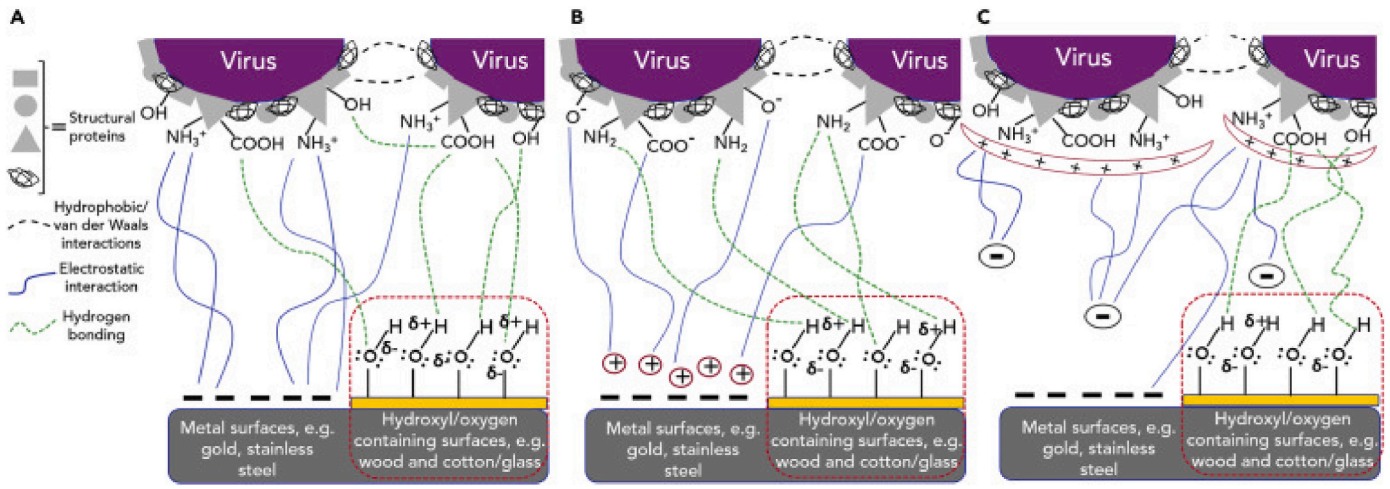

Fig. 4. Molecular Interactions of SARS-CoV-2 on several surfaces Interfaces (A) below the isoelectric point; (B) above the isoelectric point in presence of external ions; (C) below the isoelectric point in the presence of potential chemistries with negative surface charge. Reproduced with permission from Ref. [28]. (A colour version of this figure can be viewed online.)

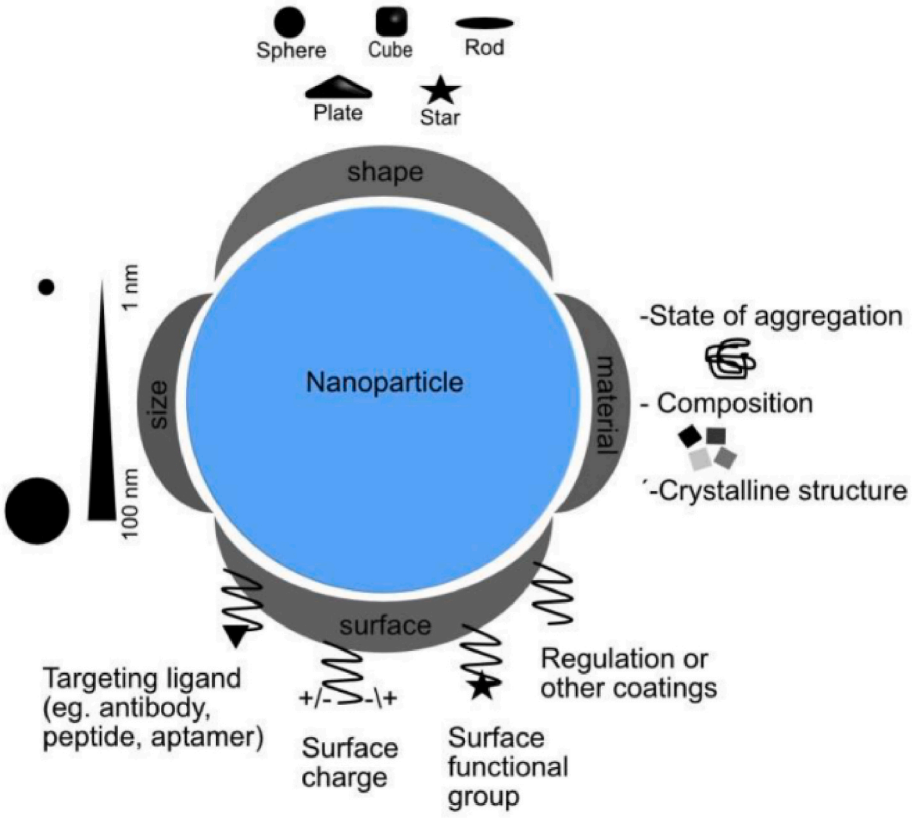

Fig. 5. Nanomaterial features that influence interaction with biological systems. Reproduced with permission under the terms and conditions of the Creative Commons Attribution (CC BY) license from Ref. [31]. (A colour version of this figure can be viewed online.)

changes the surface of nanomaterials causing an increase or decrease in internalization, toxicity, and antimicrobial activity as well as colloidal stability over time [32].

In this Chapter, we will compare the shape and size features of CBM family members that influence interactions with SARS-CoV-2 discussed in Chapter 3. For discussion on how the in vivo effects might be influenced by the intermediation of the biomolecular corona on the surface of CBM, we refer to specific literature on corona formation on graphene and derivatives [11,33,34], carbon nanotubes [35], and other members of the CBM family [10,36,37].

The CBM family comprises several geometries from the approximately spherical nanodiamonds and fullerenes, up to the *famous* bidimensional carbon flake, graphene (Fig. 6) [38]. The size of CBM ranges from the very small fullerene C60 and carbon dots up to the micrometric length of carbon nanotubes and lateral size of graphene.

Fullerene C60 is a highly symmetrical sphere (diameter of ~1 nm) of carbon atoms. It can be synthesized by laser or heat-induced evaporation of graphite, or by direct bottom-up chemical synthesis from small

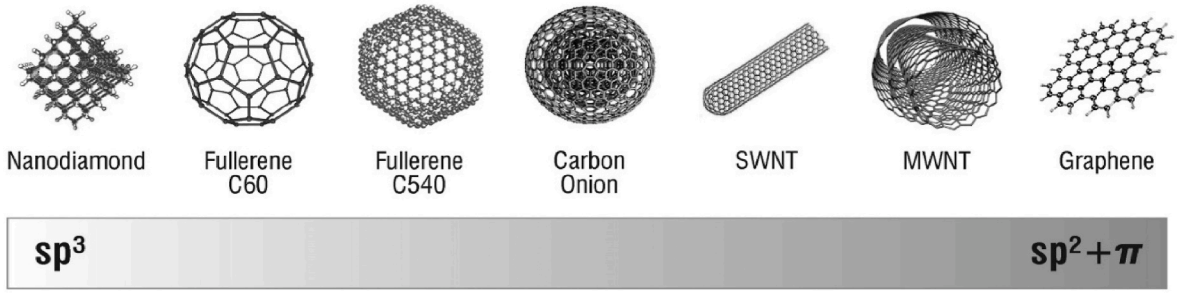

Fig. 6. An overview of carbon nanomaterials. Reprinted with permission from Ref. [38] Copyright (2015) American Chemical Society.

aromatic molecules. Although insoluble in water, C60 can be functionalized with hydrophilic surface groups and antibodies for selective targeting. The C60 nanometer-sized molecules possess various unconventional capabilities for imaging and drug/gene delivery, together with the photoexcitation capability that allows the transfer of stored energy to the surrounding oxygen molecules creating ROS [38].

Besides fullerenes, the sp2 carbon atoms can also form single-walled carbon nanotubes (SWCNTs) and multiple-walled carbon nanotubes (MWCNTs) where each "wall" is a single graphene sheet rolled up into a nanocylinder. The length of CNTs is in the micrometers range with a diameter between 10 and 100 nm [39,40]. The carbon nanotubes are metallic or semiconducting and have a band gap energy according to the direction along which the graphene sheet rolls up with respect to the 2D honeycomb lattice, and the diameter of the tube. Several biomedical imaging applications have been demonstrated for SWCNT especially, since they absorb photons in the visible (400−750 nm) and near-infrared (NIR) window NIR-I (750−1000 nm) windows, for photothermal and photodynamic therapy and as fluorophores. Aside from this, CNTs have also been reported to possess exceptional mechanical properties that allow for tissue scaffolding, and interesting chemical properties that make them efficient delivery carriers for nucleic acids [38].

Graphene is an atomically thin nanomaterial that consists of hexagonally arranged carbon atoms with sp2 hybridization in two dimensions, with a large surface area (from nm [2] to μm^2), high mechanical flexibility, and capability of chemical functionalization. There have been an increasing number of studies on the use of graphene and graphene oxide (GO) for various biological and medical applications including biosensing, imaging, and therapy. A wide spectrum of biomolecules, including glucose, DNA and cholesterol, have been successfully detected with high sensitivity using graphene sensors [41]. Besides the electronic properties of graphene, the distinctive optical properties of GO allow for biomedical imaging and photothermal therapies. The large surface area of graphene family materials, along with the delocalized π-electrons on its surface, have made graphene and its derivatives good candidates for loading and delivering drugs. Graphene also has excellent mechanical properties, including superior elasticity and high flexibility, allowing the graphene to conform to any substrate with an arbitrary shape and reinforce the structure and morphology of engineered tissues [38].

Carbon dots or graphene quantum dots resemble graphene but have a size below 10 nm and various degrees of oxidation. Carbon dots have fluorescence in a broad range from deep ultraviolet, to the NIR. The fluorescence peak emission wavelength can be tuned allowing a wide range of imaging applications in vitro and in vivo as well as drug delivery, and photodynamic therapy due to their small size and easy penetration of cells [38].

Given their small size, carbon dots have been applied for analysis of SARS-CoV-2 cell entry process by creating pseudovirions for imaging by fluorescence microscopy [42,43].

Nanodiamonds (ND) are an emerging class of new carbonaceous nanomaterials with many fascinating optical, mechanical, and chemical properties. Unlike all the other classes of nanomaterials consists of sp3 carbon atoms and a size comprised between 2 and 10 nm. ND are used for bioimaging and therapy purposes, being highly photostable, highly biocompatible, and nontoxic [38].

Other less-studied geometries include Carbon Onions and Carbon Nanocones [44,45]. Carbon onions are carbon particles with a size below 10 nm and a closely spherical shape made of fullerene-like carbon shells [46]. Applications of Carbon Onions include tissue engineering [47] and drug delivery for brain targeting [48].

Carbon nanocones are conically shaped carbon nanoparticles firstly synthesized by vapor condensation of carbon atoms on a graphite substrate [45]. Different numbers of pentagons can arrange from the seed from which it grew: disks (no pentagons), five types of cones (one to five pentagons), and open tubes (six pentagons). Nanocones have been employed as nanofiller in polymers [49] having high surface area, electrical conductivity, glass transition temperature, thermal and mechanical properties, specific capacitance, and photovoltaic properties.

For small nanoparticles, the larger the surface-volume ratio the higher their toxicity, and so the probable mode of interaction with microbes [25]. The higher area-to-volume ratio characteristic of non-spherical nanomaterials crucially influences the generation of ROS, the nanomaterial distribution in biofilms and their activity in viscous body fluids [29,50,51]. Size and shape have been crucial also for the synergistic effects of silver nanoparticles and drugs [52]. Shape-related antimicrobial properties have been reported for different nanomaterials, including carbon, silver and gold nanomaterials, though studies on shape relationship with antiviral activity are more focused on bacteria rather than viruses. Indeed non-spherical nanomaterials, having sharp edges and a high aspect ratio generate local stress and membrane rupture in bacteria [29,50,51].

As for any nanomaterial to be used in living organisms, water solubility needs to be maintained mainly by surface functionalization. Fullerenes are typically covalently functionalized through chemical reactions directly with the carbon atoms in the sp2 carbon shell, using a library of standard chemical reactions. CNT and graphene, both of which feature continuous graphitic honeycomb, can be either covalently or noncovalently functionalized. Carbon dots are by nature rich in –OH and –COOH functional groups, which can easily form hydrogen bonds with water molecules and thus have good solubility, however PEG can increase their biocompatibility. ND, on the other hand, are similar to carbon nanotubes and graphene in that both noncovalent and covalent functionalizations [38]. To increase the stability of 2D materials, also proteins like bovine serum albumin can be used as a dispersant agent.

It is worth mentioning that the instability of CBM like graphene or graphene oxide has been exploited for the so-called trapping mechanism: the complete enwrapping of viral or bacterial particles/cells to avoid the spread in the environment. This mechanism has been demonstrated also for graphene oxide interaction with SARS-CoV-2 [53].

4. Mechanisms of SARS-CoV-2 inactivation by CBM

Because viruses do not possess metabolic or signaling abilities, their replication relies entirely on the functions of the host cells. Upon attaching to the cell, SARS-CoV-2 gains entry and releases its viral RNA. Within the cell, the virions control the macromolecular machinery to produce RNA and synthesize structural proteins, which then assemble and are released from the host [4].

The opportunities for blocking viral infections include the uptake/penetration targeting, by interfering with the cell metabolism, critical for viral assembly [54]. In this chapter, we will discuss first the interference of nanomaterials with viral proteins, then we will move to the damaging of viral structure by ROS generation and finally, we will describe the nanomaterials useful to target the human immune response.

4.1. CBM interfering with viral structure in solution and on surfaces

Studies of CBM interaction with viral proteins, especially the exposed S protein, are essential for diagnostic, chemical functionalization, and medical purposes. Indeed CBM might induce protein denaturation after adsorption and rearrangement of buried residues [55,56].

Graphene and GO represent the most studied materials of the CBM family. Yan and colleagues have examined graphene effects on the spike protein of wild type (WT) and Omicron variant in the two states reported for this protein, the open and closed states in solution [57]. When the spike protein is in the closed state, three RBDs (S1 subunit) are in the down conformation, whereas in the open state, one or two of the three RBDs are in the up conformation and can bind to ACE2 [58].

In the closed state, graphene can insert into the region between the RBD and the *N*-terminal domain in wild type and Omicron variants, keeping the RBD in the down conformation [57]. In the open state, graphene can hamper the binding of up RBD to ACE2 in WT, but in Omicron variant, it has little impact on up RBD or can either stimulate the down-to-up transition of down RBDs. This may increase the infection ability of Omicron. However, it should be pointed out that the size of the graphene flakes is important in this mechanism.

When the size of graphene is 5.0×5.0 nm^2, compared to 3.0×3.0 nm^2, differences were not significative [57]. The same authors hypothesize that very small graphene flakes (1.0×1.0 nm^2) can bind everywhere in the spike protein, with a small effect on its function.

However graphene quantum dots, that can be considered the tiniest graphene flakes, might block viral entry and viral enzymes if functionalized with triazole heteroatom and co-doped [59]. Also carbon quantum dots attached with α-defensin HNP1 or cathelicidin LL-37 are able to inhibit the virions intake hindering RBD binding with ACE2 [60] and carbon quantum dots activated with boronic acids are able to interact and inhibit human Coronavirus [61].

On graphene surfaces, both RBD and whole S protein have been studied. The RBD interaction is irreversible and based on quick π−π stacking and hydrophobic interactions. Residue PHE486 with benzene ring has stronger adsorption force and the maximum contact area. Graphene significantly affects the secondary structure of RBD, especially the three key sites of binding with ACE2, GLY476, PHE486 and ASN487 [62].

S-protein secondary structures display only minor changes with only one α-helix of the RBD transformed into a turn after interaction with graphene. The authors concluded that although no significant changes have been observed in the secondary and tertiary structure of the S-protein, the feasibility of the changes in the quaternary structure of the spike protein trimer should not excluded [63].

Graphene is unstable in solution and tends to aggregate into multilayers. Molecular docking studies have shown that seven layered graphene, that has an increasing number of edge sp3 –type carbon, providing greater curvature, further increases the surface reactivity responsible for high binding efficiency of SARS-CoV-2 virions [64]. Therefore the effect of graphene edges or planar surfaces seems quite different on the S protein, however on graphene deposited on surfaces, the availability of edges might be increased by laser printing, magnetic field, or plasma-enhanced chemical vapor deposition techniques that reorientate flakes [65–68].

Another study analysed the interaction of graphene, P-doped graphene, and functionalized p-doped graphene with SARS-CoV-2 spike proteins and ACE2 receptors [69]. A marked effect was observed on p-doped graphene since the envelope membrane is essential to maintain the entire architecture, the effects on lipids have been evaluated by the same group using dipalmitoylphosphatidylcholine (DPPC) bilayer in molecular dynamics simulations. Graphene-based materials without difficulty pierce the capsid and translocate through it thanks to the ion channels charged groups [69].

Moving to experimental results with graphene derivatives, GO nanosheets are able to inactivate SARS-CoV-2 using a two-step mechanism, (i) the adsorption of the positively charged spike of SARS-CoV-2 on the negatively charged GO surface and (ii) then the neutralization/inactivation through decomposition of the viral protein. In this sense, the GO, thanks to the oxygen groups on the surface, has proven to be more effective than its reduced counterpart rGO [70].

GO has affinity towards the spike protein, ACE2 receptors and spike-ACE2 complex. However, GO interferes more sharply with the viral spike and the ACE2 before binding to the virus ligand. Based on this in silico examination, when cells were exposed to GO prior to viral treatment, pronounced viral inhibition was observed compared to a post-infection protocol in vitro [71]. Similarly, De Maio et al. demonstrated a trapping mechanism of GO flakes that remove viral particles in solution [53] (Fig. 7 from Ref. [53]).

GO modifications also interfere with viral envelope: different lengths of alkyl chain have been attached to GO to determine the inhibition of feline coronavirus and SARS-CoV-2 and an alkyl chain greater than C9 can disturb coronavirus replication by destabilizing its envelope [72].

Theoretical studies have demonstrated that fullerenes are potential inhibitors of SARS-CoV-2 thanks to the number of interactions established with the spike protein and the ACE2. Fullerene C48 represents the most efficient nanomaterial per se due to the flattened shape which confers a larger inhibitory surface. The adsorption of oxygen on fullerene increases the noncovalent contacts and creates increased hydrogen bonds which stabilize the various complexes while decreasing the binding energies [73].

A comprehensive study on the five major targets of SARS-CoV-2 (S protein, RNA directed RNA polymerase, Main protease, Papain-like protease, RNA binding domain of Nucleocapsid protein) and fullerene or carbon nanotubes has been conducted by Skaryacian and colleagues using molecular docking [74].

Carbon nano fullerene (C60) has an important molecular specificity for all tested targets interacting with four aminoacidic residues present at the recognition domain of Spike glycoprotein. An RNA polymerase - C60 docking model displays interactivity along the helix and beta-strand regions.

By analysing the conformation and orientation of Carbon nanotubes into possible SARS-CoV-2 binding sites several putative associations have been proposed: 11 residues of the Spike glycoprotein, essential for structural integrity, interact with the carbonaceous material, while the material binds eight residues of the binding site of RNA-dependent RNA polymerase. Five residues close to the Lopinavir and Ritonavir recognition domains in the main protease show better binding energy with possible development of drug. Three out of the ten interacting residues of papain-like protease have a largely reported interplay with nelfinavir and remdesivir conventional drugs. In another theoretical study, it has been demonstrated that SWCNTs might interact with the RBD, reducing the intra-hydrogen bonding, and increasing the water-exposed region by altering tertiary structure [75].

Patel and colleagues have tested the main protease of SARS-CoV-2 and the spike RBD complexed with its receptor ACE2 binding to MWCNTs of different morphologies (zigzag, armchair and chiral). The

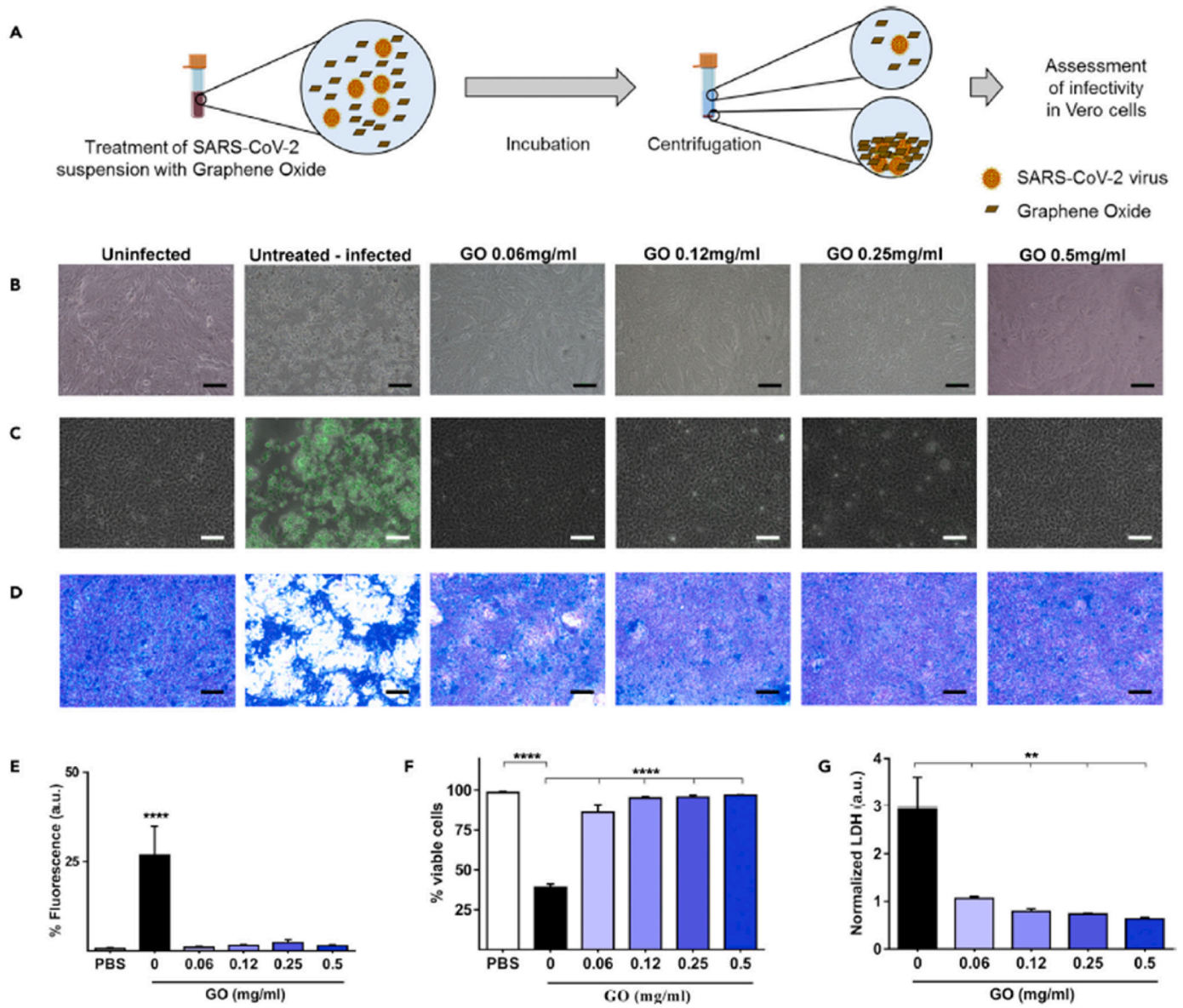

Fig. 7. The trapping mechanisms of GO in solution allow to precipitate SARS-CoV-2 particles (A). With the addition of low concentration of GO, VERO cell monolayer integrity is restored, as is visible from optical microscopy (B), fluorescence microscopy (C) and crystal violet staining (D). Data on retrieved fluorescence, cell viability and lactate dehydrogenase (LDH) confirm that infectivity is inhibited by GO trapping (E-F-G, respectively). Reproduced with permission from Ref. [53]. (A colour version of this figure can be viewed online.)

data indicate that MWCNTs interact with the active sites of the main protease along with ACE2 receptors. The highest free binding energy was observed for the armchair with SARS-CoV-2 for both hollow and bamboo-shaped MWCNT for the SARS-CoV-2 spike RBD-based ACE2 receptor [76].

Interaction of CBM with other viruses have been recently discussed in comprehensive reviews [6,7].

There is currently a lack of studies concerning nanoonions, nanocones or nanodiamonds interactions with SARS spike protein to our knowledge. However, nanodiamonds have been conjugated with antibodies for diagnostic purposes, as discussed below [77].

4.2. *Physical sterilization and viral damage by reactive oxygen species*

Physical methods (irradiation, X-rays, and Photodynamic therapy (PDT)) can directly damage viral components, mainly nucleic acids, as shown in Fig. 8 from Ref. [78] or generate ROS that can destabilize viral components [9].

De Maio et al. demonstrated sun-mediated viral inactivation on graphene 3D-printed medical devices [79], also Huanget al. have shown that laser-induced graphene under low solar irradiation has high virucidal efficacy against coronaviruses [80]. Similarly, graphene films in nonwoven fibers of face masks can inactivate SARS-CoV-2 under sun irradiation [81] and masks can be reused after light treatment [82].

Lastly, photodynamic therapy is a recent methodology for the inactivation of native microbes. The PDT effect occurs when a photosensitizer and O_2 are exposed to light; hence, PDT represents a local treatment limited to specific infection sites. Once exposed to visible light, photosensitizer compounds react with O_2 to produce ROS. The genetic material of the viruses can be disrupted by PDT as photosensitizers may bind or intercalate with viral nucleic acids. Viral proteins naturally endure structural adaptations, such as protein cross-linking. CBM represent excellent photosensitizers for PDT, together with recent materials MXenes [83–86]. The easy optical transition between the loosely held p bands of CBM carbon bond mainly contributes to the absorption of light [87]. Fullerene C60 and functionalized GO have been

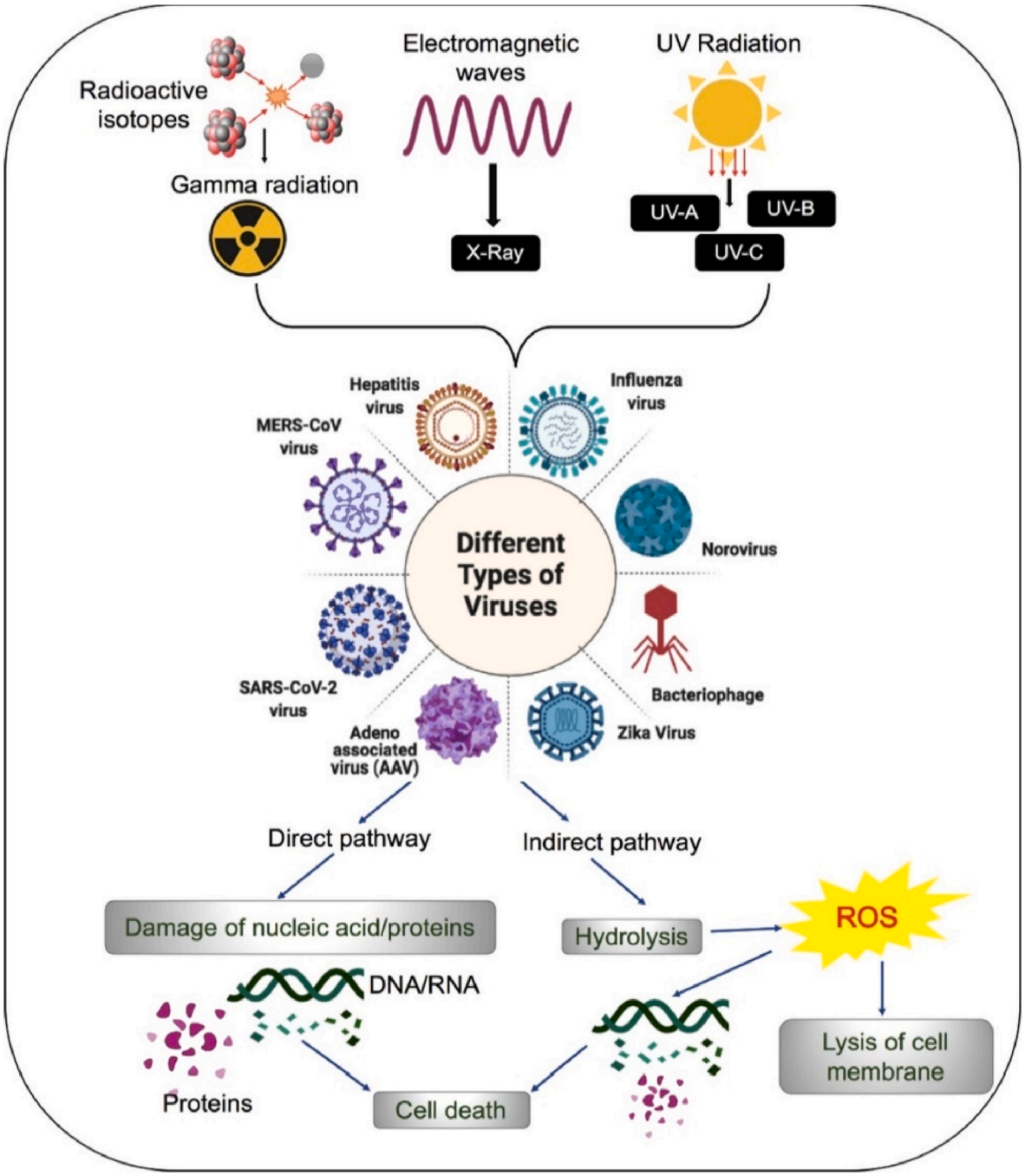

Fig. 8. Physical methods to combat viruses. Reproduced with permission from Ref. [78]. (A colour version of this figure can be viewed online.)

used for antiviral PDT [86,88]. Beside viral inactivation PDT can be used to modulate immune response [89–91]. However, ROS formation may also damage many cellular organelles and processes, ultimately interrupting the normal physiology of cells.

Thus, moving the cellular redox homeostasis, by means of drugs to a more reduced status could encourage viral proliferation. On the contrary, higher oxidizing levels could suppress the viral replication but increase the host damage [54]. Indeed SARS-COV-2 is also a stress inducer in vivo and the combination of oxidative stress and release of pro-inflammatory cytokines contributes to damage of tissues observed in the pathogenesis of COVID-19 patients [92].

5. CBM vaccines and immunotherapies

Vaccines continue to be the most effective strategy to defend the population against viral infections, since they induce the production of distinct antibodies [93].

The process of designing a vaccine involves the discovery of an antigen, an adjuvant that amplifies the immune response elicited by the antigen, and an appropriate delivery mechanism [4]. Nanomaterials used for vaccine delivery are developed to augment the uptake by antigen-presenting cells (APCs), and/or achieve controlled or sustained release of the antigen for optimal presentation [94].

Nanocarriers can protect antigens from proteolytic degradation and allow a sustainable release profile. Nanodelivery platforms serve as a long-lasting depot of antigen to boost the immune system, and facilitate

APC uptake. Antigens that have large surface areas are more effective at interacting with APCs owing to their diverse surface properties, such as charge, hydrophobicity, and ability to interact with receptors. Conversely, small protein antigens are poorly internalized and presented by APCs.

In addition, nanocarrier surface modification with ligands or antibodies targeting pattern recognition receptors can enhance antigen delivery to specific APCs through active targeting. Finally, nanocarriers allow co-delivery of immunostimulatory components along with antigens to achieve a synergistic effect [95].

In addition to the delivery uses, nanomaterials have an intrinsic immunomodulatory activity that makes them potentially applicable as adjuvants [95]. Their nanoscale size influences Inflammasome and complement activation, and immune cell recruitment [96].

The utilization of nanomaterials as vaccine adjuvants has been increasingly explored for immune protection and immunotherapy against infectious diseases and malignant cancers. Nanomaterials enable dose-sparing (using less antigen or requiring fewer immunizations), create a wide-ranging antibody response against pathogens that undergo antigenic drift or variation, and offer quick and long-lasting protection. Adjuvants can be classified as either immunomodulatory molecules, non-immunostimulatory delivery systems (for enhanced antigen presentation), or a combination of both, depending on their function and application. Only a small proportion of candidates, such as alum (aluminum salts), squalene-in-water emulsions, virosomes, and AS04 (monophosphoryl lipid A preparation plus alum), have been licensed or utilized in clinical trials.

The primary methods of immunization for human vaccines consist of the oral, nasal, intramuscular, intradermal, intraperitoneal, and intravenous administration. The size and surface properties of nanoparticles are the predominating factors controlling their behaviours in biological barrier transport, tissue and cellular uptake and the induction of immune responses [95].

During intranasal or aerosolized immunization to boost mucosal and lung immunity, the deposition and distribution of nanoparticles in the respiratory tract is governed by diffusion due to displacement when they collide with air molecules. Nanoparticles of 10–100 nm are mostly deposited in the alveolar region; and nanoparticles of 1–10 nm in diameter in the tracheobronchial region. Once deposited, nanoparticles appear to transfer to extrapulmonary sites and target different organs readily. In contrast, large particles are rarely transferred and are instead cleared by mucociliary movement or phagocytes [95]. This should be taken into account considering the different distribution in the respiratory tract of the variant Omicron. Upon intradermal injection, nanoparticles are more efficient at overcoming biological barriers than microparticles, this is true in general for all biological barriers but there isn't a consensus on a specific size [95,97]. Intravenous nano-adjuvants or nanoparticles that bypass organ barriers at the site of administration will enter the circulation. It has been suggested that the mechanism of hepatic uptake is mediated by the protein corona, that induces alterations in blood circulating time.

The induction of an adaptive immune response requires the transportation of antigens to secondary lymphoid organs, such as lymph nodes and spleen, and the size of the antigen is a crucial factor in this process. Particles ranging from 20 to 200 nm can effectively penetrate the initial lymphatic vessels, where the junctions between endothelial cells that line the vessels are permeable. However, the lymphatic capillaries that are closer to the lymph node have a more restrictive structure, permitting only particles smaller than about ~5 nm to pass through specialized narrow channels directly into the lymph node. Particles measuring between 200 and 500 nm cannot passively enter the lymphatic vessels but require the aid of dendritic cells (DCs) to be transported into the lymphatic system. As antigens with dimensions of 20–200 nm may freely drain to the lymphatic capillaries, designing vaccines within this size range is imperative for the facilitation of direct interaction with B cells in the secondary lymphoid organs, and thus activation of a potent immune response.

Antigen retention by DCs is also affected by nanoparticle size while particle shape does not appear to play a significant role in localization to and activation of B-cells, though certain shapes are preferentially taken up over others by cells of the peripheral immune system [96].

Beside in vivo distribution, data on immune interactions of carbonaceous material are contrasting [98]. A significant effort to systematize the data on CBM immunomics has been done recently by the G-IMMUNOMICS and CARBO-IMmap projects [99]. Data have been recently summarized on a review from Azelvedo and colleagues [12], whose scheme is reported in Fig. 9.

CBM may activate the immunological system useful for immunotherapy that engages the immune system to kill tumor cells or vaccine design [32].

Here we list some interesting data concerning using CBM in immune control for vaccination; in many studies the adjuvant effect has been demonstrated using Ovalbumin (OVA) as an antigen.

Ultrasmall GO-supported gold nanoparticles (usGO-Au) have been proposed as immune adjuvant and can efficiently stimulate RAW264.7 cells to secrete tumor necrosis factor-α. In vivo, usGO-Au@OVA can also promote robust OVA specific antibody response, $CD8^+$ T cells proliferation, and different cytokines secretion, therefore, inducing potent humoral and cellular immune responses [100].

Modulating the formation of DC–T-cell synapses may greatly increase efficacy of DC vaccines, used for cancer and infectious diseases. The GO has size dependent effect on DCs and on the creation of synapsed between DC and T-cells: GOs with diameters >1 μm (L-GO) demonstrate strong adherence to the DC surface, inducing cytoskeletal reorganization while relatively small GOs (≈500 nm) are predominantly internalized by DCs. Furthermore, L-GO enhances DC–T-cell synapse formation. L-GO acts as a "nanozipper," facilitating the aggregation of DC–T-cell clusters to produce a stable microenvironment for T cell activation. Importantly, L-GO-adjuvanted DCs promote robust cytotoxic T cell immune responses against S of SARS-CoV-2, leading to >99.7% viral RNA clearance in infected mice infected [101].

A novel Hepatitis E virus (HEV) vaccine was created utilizing chitosan-modified nano-GO (GO-CS) as an adjuvant to support HEV antigen P239 protein (GO/CS/P239): GO/CS/P239 vaccine can promote immune cells to produce more IgG antibodies and cytokines, which were able to stimulate the organism to produce stronger cellular and humoral immunity [102].

Polyethyleneimine-functionalized GO nanoparticles showed high antigen-loading capacities and superior immunoenhancing properties after adsorption of influenza hemagglutinin (HA). These formulations induced significantly enhanced and cross-reactive immune responses at both systemic sites and mucosal surfaces in mice after intranasal immunization [103].

Carnosine GO adjuvant loaded with CpG molecule and RBD protein antigen-induced the production of high titre anti-SARS-CoV-2 RBD antibody neutralizing SARS-CoV-2 in mice within 2 weeks [104].

A DNA vaccine together with a hydrophobic immune adjuvant (R848) was delivered using Thiolated low-molecular-weight polyethylenimine (TPEI1.8) crosslinked with 4-aminothiophenol-modified GO (TGO). This system significantly enhanced the DNA transfection, the expression of the costimulatory signal, and the level of antigen presentation to MHC class I DCs for their activation and maturation [105].

Chitosan (CS)-functionalized GO (GO-CS) nanoadjuvant significantly activates RAW264.7 cells and stimulates cytokines secretion [106].

To avoid possible GO-mediated oxidative stress and inflammatory reaction at the site of injection, Carnosine (Car) was used as antioxidant to decorate ultrasmall GO flakes. OVA@GO-Car generates strong and long OVA-specific antibody response, increase lymphocyte proliferation efficiency, and enhance $CD4^+$ T and $CD8^+$ T cell activation. The presence of Car in GO also probably contributes to enhance the antigen-specific adaptive immune response through modulating the expression

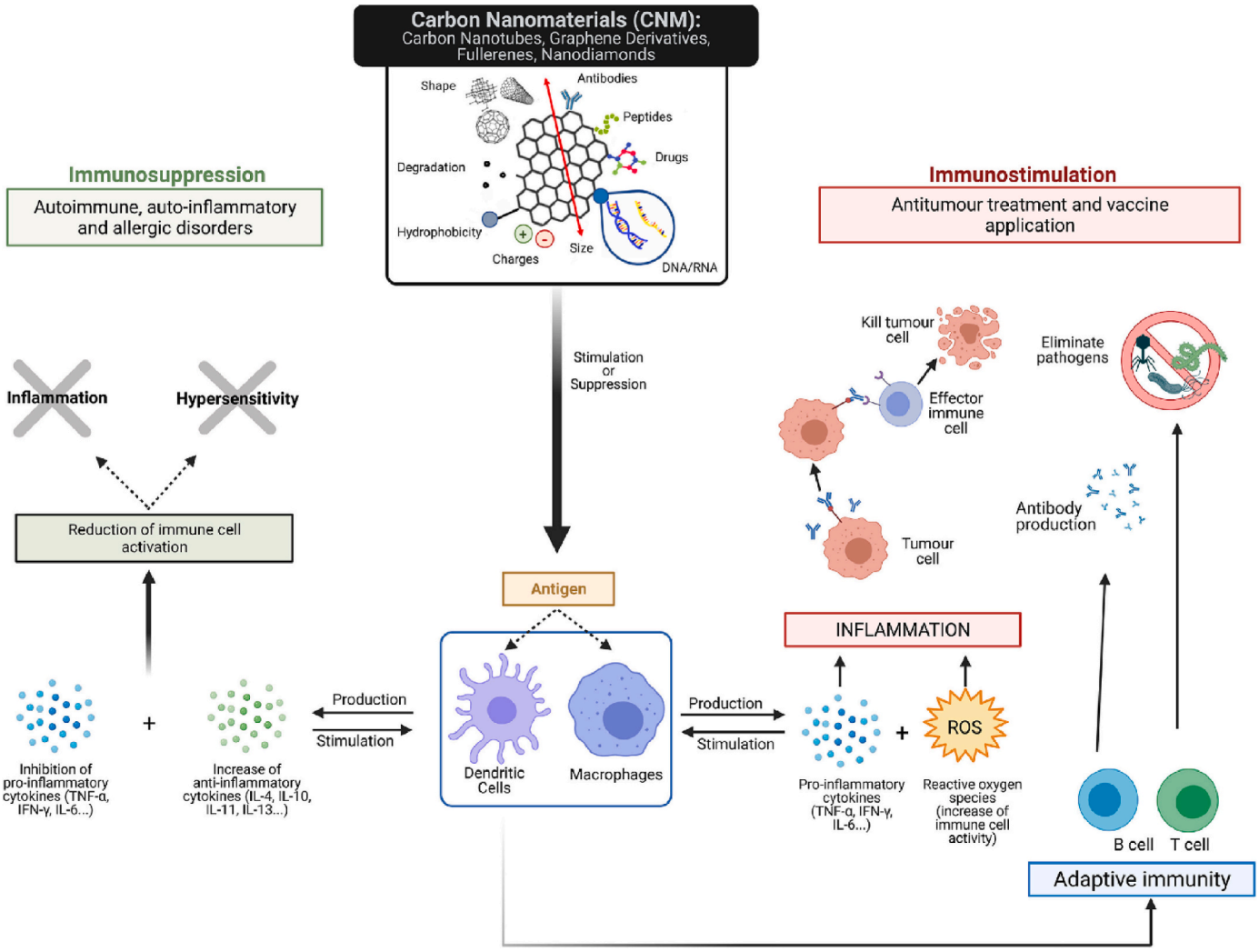

Fig. 9. A summary of immunosuppressive and immunostimulative properties of carbon Reproduced with permission from Ref. [12]. (A colour version of this figure can be viewed online.)

of cytokines. After modification with carnosine, histological damages in lung, muscle, kidney, and spleen became significantly weaken [107].

GO was used as adjuvant for immunotherapy using urease B (Ure B), a specific antigen for *Helicobacter pilori*, as the model antigen. Polyethylene glycol (PEG) and polyethylenimine (PEI) were used to create GO-PEG-PEI that worked as a positive modulator of DCs maturation and enhanced their cytokine secretion through the activation of multiple toll-like receptor pathways. Moreover, this GO-PEG-PEI was an effective antigen carrier to effectively shuttle antigens into DCs. Compared with free Ure B and clinically used aluminum-adjuvant-based vaccine (Alum-Ure B), GO-PEG-PEI-Ure B induces stronger cellular immunity after intradermal administration [108].

Lentinan (LNT), a β-1,3-glucohexaose with β-1,6-branches that is extracted from the mushroom Lentinus edodes, can bind to various immune receptors [109].

GO grafted with LNT facilitates antigen uptake in macrophages and improved the efficiency of antigen application in vitro. GO-LNT/OVA sustained a long-term immune responses and boosted the levels of IgG thanks to increased amounts of antigen uptake by cells [110]. Similarly LNT-MWCNTs rapidly entered dendritic cells and carry large amounts of antigen with upregulation of DCs maturation markers [109].

Beside GO, a series of studies are available also for CNT as adjuvants [111]. CS-MWCNT encapsulating *Hericium erinaceus* polysaccharide (HEP), an immunostimulant promoted the expression of MHCII, CD86, F4/80 and gp38 in mice peritoneal macrophages. Moreover, CS-MWCNT-HEP immunized mice significantly lengthened IgG immune response and cytokines levels [112].

Phospholipid-PEGylated single-walled carbon nanotubes (PL-PEG-SWCNTs) were applied as a safe co-adjuvant for the commercial recombinant hepatitis B virus vaccine to enhance induction of monocyte-derived dendritic cells differentiation and activation in vitro as an immune response initiator cell to prompt a long-term immune response after a single dose injection [113].

B cells incubated with acid-functionalized single-walled carbon nanotubes (OVA-AF-SWCNT) internalized more OVA than the B cells incubated with free OVA with a higher antibody response was highest in the group where ovalbumin coupled to AF-SWCNTs was used for immunization comparable Freund's adjuvant [114].

Cytosine-phosphorothioate-guanine oligodeoxynucleotides (CpG ODN) are immunotherapeutic agents and vaccine adjuvants. SWCNT functionalized with PEI and alkylcarboxylated PEI (AL-PEI) have been tested as delivery systems for CpG ODN. The results showed that all nano-adjuvant formulations had a strong influence in the up-regulation of IFN-γ and IL-4 in parallel with high IgG1-IgG2a isotype antibody titres in mice. In particular, SWCNT-AL-PEI nano-adjuvant formulation generated a balanced Th1/Th2 immune response with more biased toward Th1 response without exhibiting any inflammatory and toxic effects [115].

To enhance the stability and immunogenicity of the protective antigen (PA) of Bacillus anthracis, MWCNTs have been proposed as a nanocarriers. After the second booster, anti-rPAD4 IgG level in MWCNTs-rPAD4 groups was significantly higher compared to group immunized with Freund's adjuvant [116].

Multihydroxylated fullerene has been proven as an efficient adjuvant for human immunodeficiency virus DNA vaccine and HCV: a relatively low dose was sufficient to promote both humoral and cellular immune responses to antigens and reduce the usage of antigen [117].

ND-based adjuvants have been proposed as a rapid and versatile platform for antigen conjugation, utilizing peptides common to different pathogenic strains and making this strategy a good candidate for a "ready-to-use" vaccine. Initiation of an inflammatory reaction with a resulting immune response is based on the ability of living organisms to entrap nanostructures such as ND with neutrophil extracellular traps (NETs) formation. Coronavirus peptide homological for MERS-CoV, fusion inhibitor, was conjugated to nanodiamonds and used to induce neutrophilic driven self-limiting inflammation. The resulting adjuvant was safe and did not induce damage at the site of injection. Animal immunization displayed an elevated grade of antibodies [118].

The feasibility of utilizing ND to deliver NH_2-PLGA nanoparticle-encapsulated fig polysaccharides (FP) for strongly enhanced immune responses showed that NDs-PLGA-FP/OVA could promote antigen uptake and lymphocyte proliferation, increase the expression levels of MHC II, CD80 and CD86, and upregulate the ratio of Th1/Th2 cells in immunized mice. NDs-PLGA-FP/OVA could also upregulate the IL-17 signaling pathway for further immunological enhancement. NDs-PLGA-FP/OVA induced increased TNF-α, IFN-γ, IL-4, and IL-6 cytokine secretion and the levels of OVA-IgG antibodies [119].

Quaternized cationic carbon dots derived from biquaternary ammonium salt (BQAS-CDs) bound to the negatively charged OVA to form BQAS-CDs-OVA nanocomplexes dramatically enhance the uptake of antigen by APCs. The BQAS-CDs-OVA nanocomplexes significantly increase the anti-OVA IgG2a and IgG2b levels and keep a significant level of the OVA-specific IgG1 antibody, inducing both robust Th1- and Th2-type immune responses and stimulating the proliferation of OVA-specific $CD4^+$ and $CD8^+$ T cells [120].

Besides the cell interaction control, the development of adjuvants necessitates a comprehensive understanding of the specific virus's infection and immune activation mechanism [4].

SARS-CoV-2 infection's pathophysiology can lead to an aggressive inflammatory response and might cause an extended activation of the immune response leading to hypercytokinemia and polyorgan dysfunction syndrome (as summarized in Fig. 10 from Ref. [121]).

Nanomaterials may therefore be applied to control the immune system as (i) boosters/adjuvants or (ii) as cytokine storm [4] inhibitors. Indeed MWCNT and fullerenes present a direct influence on immunomodulation, especially fullerenes C60 which has a proven capacity to scavenge free oxygen radicals in their cage structure, reducing ROS generation. This effect can lower the release of inflammatory and/or allergic mediators [12]. Similarly, carbon dots can act as ROS scavengers, preventing related oxidative damage and pro-inflammatory response [12].

6. High technology readiness level applications of CBM for SARS CoV-2 pandemics

Beside the use as adjuvants, which requires approval for in vivo administration and further elucidation of systemic effects and accumulation, diagnostic devices and high-touch surfaces based on CBM have a higher technical readiness level. In this section, we discuss the proposed applications of the last years.

6.1. Carbon nanobiosensors for SARS-CoV-2 detection

A comprehensive and updated review concerning molecular biology and antigen test available and approved from FDA has been recently written by Tali and colleagues [15]. Although highly sensitive in detecting SARS-CoV-2 infection, RT-PCR techniques are complex and require time to produce the diagnostic result. Rapid antigen tests are also used, but they sometimes are inaccurate. To address these challenges, there is a growing need for more efficient and economical diagnostic tools. Biosensors have proven to be a viable solution for detecting the virus, and with the advancements in artificial intelligence and Internet of things, compact diagnostic assay have been designed possessing a great degree of reactivity, precision, and rapidity, along with a very small threshold of recognition [123]. As a consequence of these innovations, also led to the ideation of on-body transportable devices for quick virus detection and recognition by continuous monitoring of individual medical conditions.

CBM are extremely versatile with broad sensing properties. In terms of electrical conductivity, while fullerene C60 is insulating, SWNT exhibit long mean free paths (microns) for electron transport, and semiconductor SWNTs and MWNTs show features of diffusive transport. Finally graphene has the best electrical conductivity in plane [124–126].

The specific surface area and consequently the capacitance, broadly varies along CBM family: CNTs depending on the number of walls and the diameter have surface area values from 50 to 1315 $m^2\ g^{-1}$. While graphene, considering both sides, has a predicted specific surface area of 2630 of $m^2\ g^{-1}$ [127]. The specific surface area influences also the quantity of ligands (S protein, nucleic acids, ACE2, S antibodies) available for reaction.

While further research is necessary, the improvement of compact systems like fluorometric, and conductometric SARS-CoV-2 detectors based on CBM is underway, as is visible from the applications listed in Table 2.

6.2. Protective equipment and environmental control of SARS-CoV-2 spreading

Antimicrobial substances and coverings have diverse applications, such as preventing enteric viruses on food packaging and surfaces that come into contact with food, and preserving personal health with products and PPE. (Fig. 11 from Ref. [122]).

A recent Review reported the most viral contaminated surfaces in hospital settings, which include tray tables, monitors, bed rails, computer keyboards, computer mouse, toilet bowl rims and toilet seats [152].

The specific properties required vary depending on the application; for example, materials used in food production must be non-toxic, while those used in public transportation must be stable, durable, and non-flammable. Despite having the ability to specifically interact with SARS-CoV-2 components (see Chapter 3), to the best of our knowledge, studies on disinfectant addition with CBM are still lacking, probably for the uncertainty of hazardous effects and the cost compared to alcoholic solutions. Conversely approved nanomaterial-based disinfectants contain silver and/or copper nanoparticles formulations and titanium and silver zeolite nanomaterials [153]. Concerning large surfaces such as walls and floors, data on graphene nanoparticles and CNT antifouling properties as paint components might be used for the analysis of performance against viruses [154].

Table 3 recapitulates the practical applications of CBM materials and coatings that limited SARS-CoV-2 infectivity. So far, all SARS-CoV-2 PPE studies have been focused on graphene, likely because it is less expensive compared to other CBM and can be deposited on large surfaces. Also, applications demonstrating efficacy are all focused on face masks, though it is likely that any fabrics can be used to create other PPE devices such as lab coats. We highlight that other applications that showed promising results on other microbes are not included in the table, but can be found in recent broad Reviews [122,155,156].

Several companies including Bonbouton, Zen Graphene Solutions Ltd., Directa Plus PLC "Guardian G-Volt", Planar TECH & IDEATI,

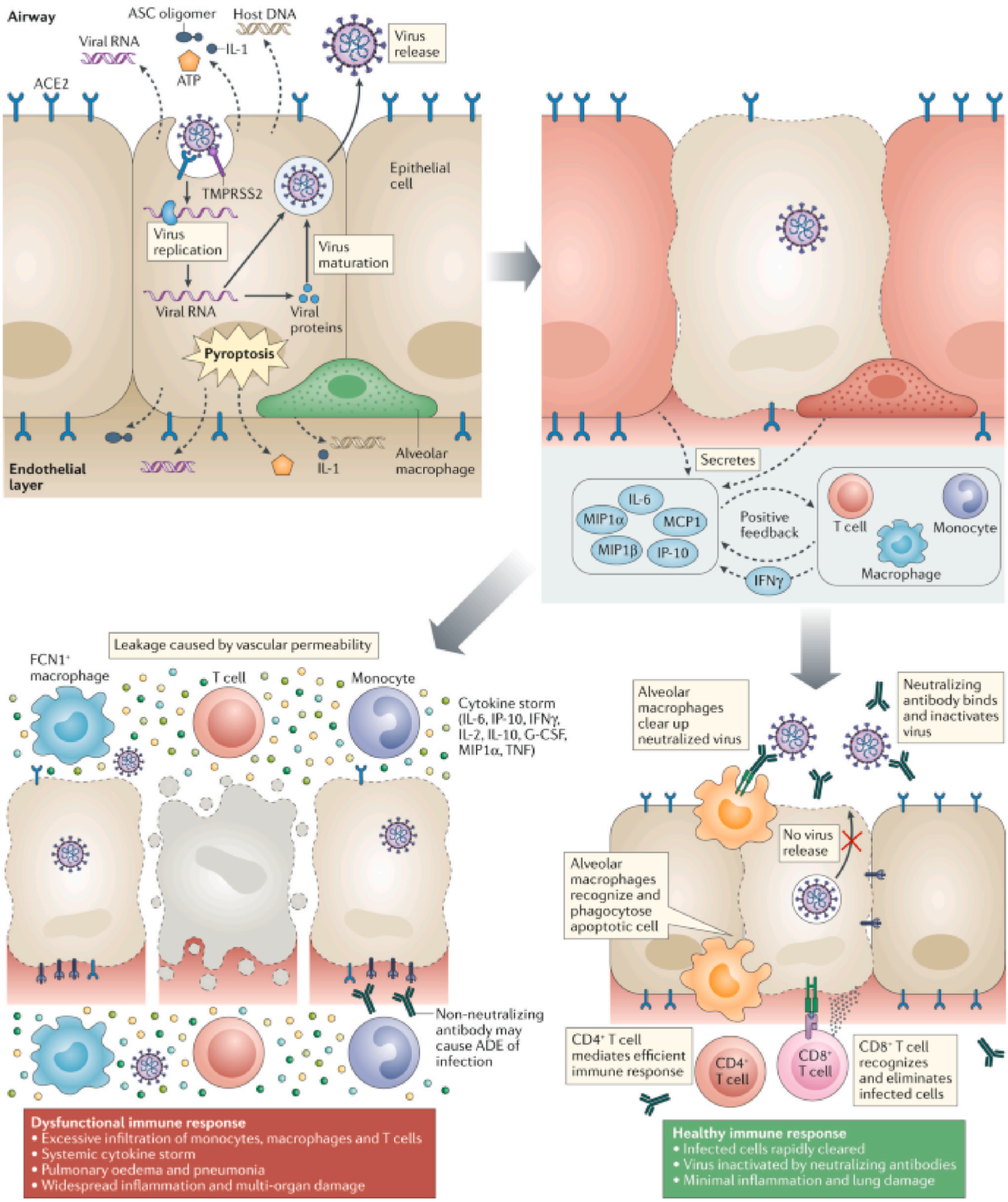

Fig. 10. When SARS-CoV-2 invades cells that express the ACE2 and TMPRSS2 proteins, the virus replicates inside the cells and releases new viral particles, causing the cells to undergo pyroptosis and release damage-associated molecules such as ATP, nucleic acids, and ASC oligomers. These molecules are then detected by neighboring cells, which trigger the release of pro-inflammatory cytokines and chemokines. The presence of these molecules attracts immune cells such as monocytes, macrophages, and T cells to the site of infection, which promotes inflammation. In a dysfunctional immune response, this process can lead to the accumulation of immune cells in the lungs, resulting in an overproduction of cytokines and significant tissue damage. This can cause a cytokine storm and multi-organ failure. Neutralizing immunoglobulins block viral infection, and alveolar macrophages recognize neutralized viruses and apoptotic cells, clearing them through phagocytosis. Cytokines such as G-CSF (granulocyte colony-stimulating factor) and TNF (tumor necrosis factor) play an essential role in this process. Overall, the interplay between the virus, the immune system, and various cellular responses is complex and critical to understanding the pathogenesis of COVID-19. Reproduced with permission from Ref. [121]. (A colour version of this figure can be viewed online.)

Fig. 11. Hospital surfaces and nanotechnological solution studied. Reproduced with permission under the terms of the Creative Commons CC BY license, from Ref. [122]. (A colour version of this figure can be viewed online.)

Redcliffe Medical Devices Inc., together with Universities such as Israel and Indian Institute of technology, are now commercially producing graphene-based face masks [155]. The use of self-cleaning properties of graphene via sunlight mediated process or electrochemical sterilization [161] might both serve as a low-cost and environmentally friendly solution for face mask and air filter recycling [79–82]. Also, laser induced graphene scribing process might reduce possible leakage of nanomaterials in the wearer and/or the environment [162].

The monitoring and tracking of viral spread can be also obtained by environmental sensors: in 2018, a textile screen-printed biosensor based on a GO transduction film was developed for the detection of influenza A virus H1N1. The sensor was integrated with fabric and was aimed to track the virus before disease manifests [163].

Carbon nanotubes and graphene are among the most promising materials for the adsorption of a wide range of environmental organic and inorganic pollutants. In fact, these nanomaterials have shown better capabilities than other more commonly used sorbents such as active carbon, clays, and zeolites as they can establish stronger physical and chemical interactions with pollutants, allowing for rapid adsorption. Furthermore, the possibility of chemically modifying the surface allows controlling the selectivity of the material for certain species rather than others. During the adsorption process of organic molecules different forms of interactions can occur simultaneously such as hydrophobic interactions, π–π hydrogen bonding interactions and electrostatic interactions.

The graphitic structure present on the surface of carbon nanotubes and graphene due to poor polarity has a strong affinity with hydrocarbons (such as hexane, benzene, cyclohexane) rather than with polar molecules. Through the functionalization of the nanomaterial, on the other hand, there is usually a tendency to introduce groups containing oxygen on its surface, thus decreasing the useful surface for the adsorption of non-polar substances in favor of polar species. This strategy has been used for example to control the adsorption and for the removal from industrial waste of dyes, heavy metals, phenols of synthetic origin such as bisphenol A, endocrine disruptors, pesticides, and antibiotics of phenols on the surface of nanotubes and graphene [164]. CBM-based membrane filters have a higher surface area, oxygen groups, and have improved corrosion resistance than standard adsorbents and for these reasons are extremely promising for wastewater treatment [165].

The colloidal stability of GO and the multifunctionalities of oxygen groups on its surface are responsible for a mechanism of trapping small compounds and salts, nucleic acids [166], protein [167], viruses [53] and even large bacteria [168], that can be exploited for the decontamination of waters.

The trapping effect of SARS-CoV-2 has been demonstrated for bare GO [53,71], however functionalization of GO has been also proposed for the same application. As an example, reduced GO nanoparticles functionalized with iron and cetyltrimethylammonium bromide have been synthesized to absorb SARS-CoV-2 and other viruses from the environment [169].

High-performance air filters have been made using nano-fibers as well as metals, and CBM, as reviewed recently by Mallakpour et al. [5]. However, there are few filters made by CBM tested for viruses and specifically for SARS-CoV-2. Laser-induced graphene filter can capture contaminants and microorganisms and have self-cleaning properties by Joule-heating reaching >300 °C [162]. VirusWall is a commercial medical device that filters air through a laser-induced graphene membrane launched in the market in 2021 (https://ieeexplore.ieee.org/document/9359386). Propylene filters coated with graphene can inhibit bacteria and SARS-CoV-2 passage and be integrated in 3D-printed face masks [160].

It has been reported that air filter paper with a high filtration efficiency made of wood fiber filter paper covered by MWCNTs can remove small-size pollutant particles [170]. Also CNT-made electrically conductive filters can be actively self-sanitized by thermal flashes via resistive heating to temperatures >80 °C that entirely deactivate beta-coronavirus and adenoviruses [171].

7. Market aspects

The potential market of CBM products for pandemics could be significant with opportunities in the production of PPE such as masks, gloves, and protective suits, as well as in the production of diagnostic and decontamination devices.

In evaluating the impact of CBM on the global economy, it is necessary not only to think about the absolute number of devices sold but also about the best performance and efficiency of nanomaterials such as graphene, fullerene, or nanotubes and the environmental impact of these materials [172].

WHO has estimated that 3.4 billion masks end up in the trash every day (global data), together with 140 million test kits, which have the potential to generate 2600 tons of non-infectious waste (mainly plastic) and 731,000 L of chemical waste [173]. A recent study appeared in Environmental Advances revealed that a large part of the masks ends up in water (almost 5500 metric tons of plastic every year with an

Table 2
Summary of CBM materials applied for SARS-CoV-2 detection.

CBM	Conjugated molecule (probe)	Detection technology	Ref
Au-decorated-graphene	Phosphorodiamidate morpholino oligos that recognize RdRp gene	Field-effect transistor	[128]
GO decorated Au/fiber Bragg grating	S glycoprotein	Surface plasmon resonance	[129]
Graphene nanoplatelets on filter paper	thiol-modified ssDNA-capped nano-Au particles for selective targeting of the nucleocapsid phosphoprotein	Electrochemical biosensor	[130]
GO/Au-based composite electrode	–	Screen-printed electrodes	[131]
Graphene electrodes patterned on a polyimide substrate	SARS-CoV-2 S1 protein and specific antibodies for the detection of Nucleocapsid protein (NP), specific immunoglobulins against SARS-CoV-2 spike protein (S1-IgM and S1-IgG)	Electrochemical biosensor	[132]
rGO on 3D nanoprinted electrodes	S protein	Electrochemical biosensor-smartphone	[133]
Graphene	Anti SARS-CoV-2 antibodies	Field-effect transistor	[134]
Cy5-labeled (GT)6 ssDNA SWCNT	ACE2	Fluorescence	[135]
GO	Anti SARS-CoV-2 antibodies	Interdigitated capacitive biosensing	[136]
Graphene/CNT	Peptides binding RBD of the Spike protein	–	[137]
(PEG)—phospholipid heteropolymers adsorbed onto near-infrared (NIR) fluorescent SWCNTs	–	NIR Fluorescence	[138]
rGO Au nanoparticles and nano-islands	ACE2	Fluorescence	[139]
Fluorescent ND	Anti-SARS-CoV-2 antibodies	Spin-Enhanced Lateral Flow Immunoassay	[77]
Laser-scribed graphene (LSG) sensor coupled with gold nanoparticles	ACE2	Smartphone electrosensor	[140]
Graphene	Anti-Spike antibody/ ACE2/ACE2-Fc	Field-effect transistor	[141]
n-printed carbon electrode modified with electrodeposited Graphene Quantum Dots and polyhydroxybutyric acid	RBD	Electrosensor	[142]
Dual-color carbon dot	Antisense oligonucleotides for SARS-CoV-2 RNA	Aggregation in solution and fluorescence emission	[143]
Carbon quantum dots	S protein	Aggregation in solution and fluorescence emission	[144]
Single-walled carbon nanotube	anti-SARS-CoV-2 spike protein antibody (SAb) and anti-nucleocapsid protein antibody for S and N antigen respectively	Field-effect transistor	[145]
CNTs/WO3-screen printed electrodes	Virus imprinted chips	Impedimetric biosensor	[146]
MWCNTs screen-printed electrode	methylene blue (MB), antibodies against SARSCoV-2 spike protein (SP), a bioactive layer of chitosan (CS) and protein A (PrA).	Voltametric and Impedimetric biosensor	[147]
Polyethylene terephthalate film functionalized with SWCNT	Anti-spike antibodies	Immunoresistive biosensor	[148]
SWCNT screen-printed electrodes	Redox-tagged DNA aptamer binding the RBD domain	Electrochemical sensor	[149]
gold nanoparticles (GNp) and thionine (Th) are immobilized on carboxylic acid functionalized SWCNT	Anti-spike antibodies	Electrochemical sensor	[150]
SWCNT Single-stranded DNA	SARS-CoV-2 nucleic acids	Bandgap near-infrared photoluminescence	[151]

Table 3
Application of CBM materials on medical surfaces and PPE against SARS-CoV-2.

CBM Material	Application (surface/PPE)	Ref.
Coal derived octadecylamine-functionalized nano-GO	Polyethyleneterephthalate fabric	[157]
Graphene/Graphene Curcumin	Cotton/Polyester Fabrics	[158]
Graphene-PLA	3D-printed respiratory valve	[79]
Graphene/Graphene Oxide	Cotton and non-woven polyurethane	[53]
Graphene nanosheet-embedded carbon film	Non-woven fiber mask	[159]
Functionalized graphene	Propylene filter for face masks	[160]

optimistic downward estimate), also highlighting how a single mask could release up to 173,000 plastic microfibers per day into the oceans, with possible damage from obstruction following ingestion by aquatic animals, and toxicological effects due to the conveyance of chemical contaminants. and organic [174]. The presence of sub-micrometric plastic, capable of crossing biological barriers, is also worrying. The impact of the enormous number of polluting materials due to the pandemic has therefore made the protection of the environment and water one of the major concerns of society and with an enormous socio-economic impact [175].

The global water treatment market is experiencing strong growth, driven by the growing needs of agriculture but also by new sectors such as seawater desalination and water treatment waste [176]. As for the global market, in the year 2021 reached a value of 164.24 billion dollars and is estimated to be worth 211 billion dollars in 2025.

Also in this market, CBM can be a game changer in the control and purification of water and the environment which are strongly compromised by the exponential increase in the use of devices for the pandemic that do not yet envisage the use of a circular economy.

Given the continual growth of medical care demand for graphene, by 2027 the related business is expected to encounter a 39% yearly progression and reach a volume of almost 3 M of dollars [155]. Interestingly Galante and colleagues point out that a twenty times less expensive production of graphene can be obtained from coal rather than graphite [157].

8. Perspectives and challenges

Material scientists have learned much in the last three years of pandemics. On one side, nanomaterial technologies have improved observing viruses [177], mimicking viral strategies used to hijack cells or evade immune responses. Indeed, several distinct viral traits such as size and surface, multivalent ligands, glycosylation, charge, stimuli responsiveness (pH, ROS and enzymatic triggers), and the sequential interactions with cellular receptors might help creating nanomaterials with better pharmacokinetics and delivery advantages [178].

Materials science has also created thousands of new solutions to quickly respond to pandemic diseases by creating devices that detect viral proteins, point-of-care diagnosis and monitoring methods, and treatment and vaccination strategies [172].

Given the risk for new zoonoses and/or spreading of drug-resistant species and the rapid mutation of viral variants with diffusion in the community, a multidisciplinary approach designed by both nanomaterial scientists and biotechnologists is necessary. Among nanomaterials, CBM have been synthesized in a variety of shape, sizes and functionalized and tested in many different biological systems in the last 15–20 years.

On one hand, the CBM high surface area, the possibility of functionalization, and the high sensitivity in diagnostics will serve as a starting block for innovations for new pathogens. On the other hand, the biotechnological synthesis of peptides recognizing the latest variant or small RNAs replicating viral genome must be combined with CBM platforms to ensure specificity against new pathogens [137].

As an example, synthetic neutralizing peptides have been screened for the inhibition of SARS-CoV-2 interaction with cells, have a smaller molecular weight and are more economical to produce compared with antibodies [179]. These peptides might be easily combined with CBM diagnostic platforms already existing. In Fig. 12, a possible workflow for new sensors development, used for experimental procedures by Badhe et al. [137], is shown.

Similarly, given the synergistic effect demonstrated by CBM and drugs [180,181], it would be interesting to evaluate the combined effects of CBM with broad-spectrum antiviral compounds such as rhodamine and thiobarbituric derivatives [182].

CBM might also be useful for the treatment of secondary bacterial and fungal infections that are responsible for the death of many COVID-19 patients [172,183,184].

Importantly, since the distribution of nanomaterials in vivo strictly depends on their size, the treatment can be designed to target higher or lower respiratory tract according to viral tropism during intranasal or aerosolized immunization to boost mucosal and lung immunity [95]. This should be considered given the different distribution in the respiratory tract of the new variant Omicron [185].

Modern artificial intelligence techniques might also offer new compounds for treatment by analyzing the available data on COVID-19 [186] or by predicting new epitopes or evolution of viral species [187].

In this sense, five possible scenarios have been described recently [188].

The first possibility, less probable, is the lack of any further evolution of the SARS-CoV-2 S-protein. A second possibility is based on possible point Mutations, Insertions/Deletions, and/or Intra-SARS-CoV-2 recombination creation of new variants. As long as the virus continues to circulate in the environment, the risk of the appearance of variants is latent.

The third possibility is represented by the occurrence of intratypic recombination between SARS-CoV-2 and other Sarbecoviruses. This scenario requires zoonotic transmission and a co-infection that allows the recombination between the two viruses. Forth possibility: intertypic recombination between SARS-CoV-2 and viruses from other beta-CoV subgenus. A structural protein region from SARS-CoV-2 passes to an animal or human CoV of another Beta-CoVs subgenus. Due to the adaptation, the protein undergoes rapid divergence, and the recombined virus is different to parental. The possibility 3 and 4 occurred for influenza A H1N1/pdm2009 where there was co-infection (with H1N1 classical swine + H1N1 avian + H3N2 seasonal human + H1N1 Eurasian swine viruses) that recombined and generated a new virus. Therefore,

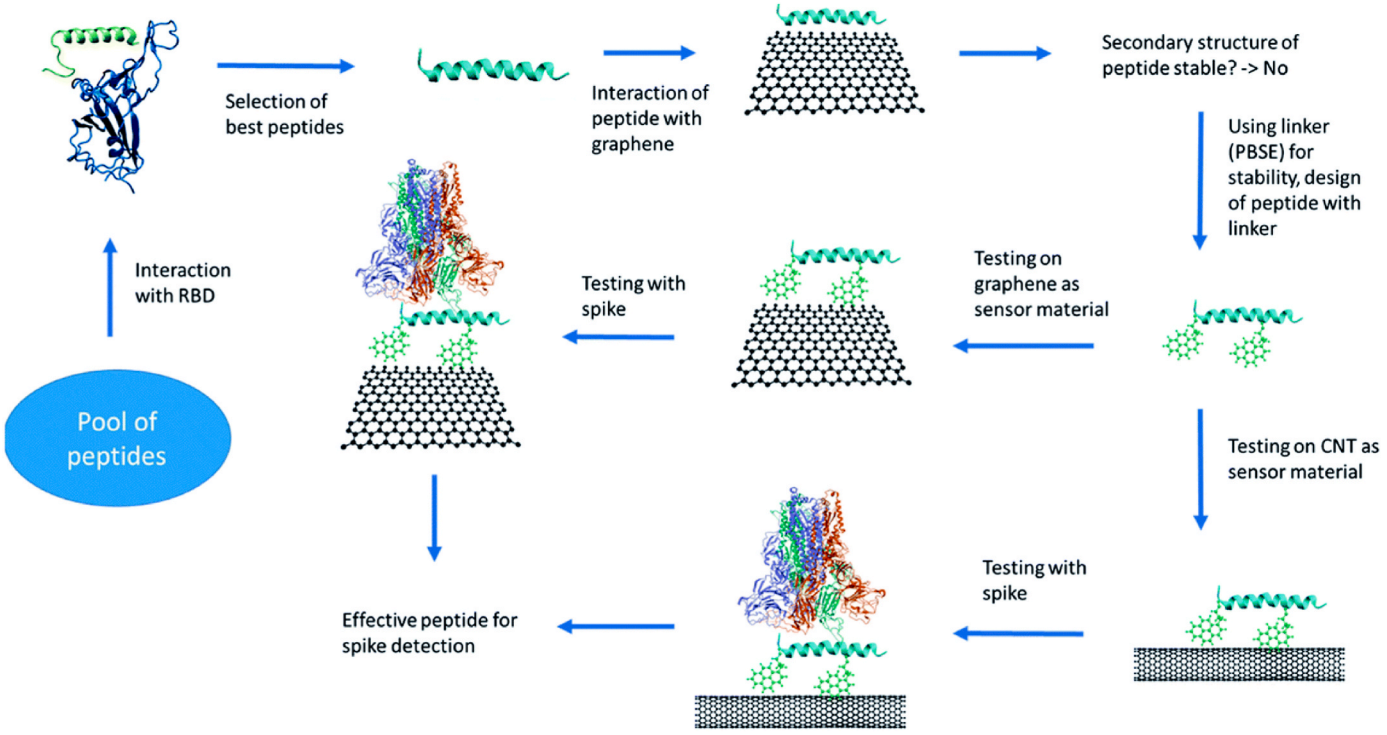

Fig. 12. The protocol of peptide design and testing creation of CBM sensors. Reprinted with permission from Ref. [179]. Copyright 2021 American Chemical Society. (A colour version of this figure can be viewed online.)

this eventuality requires at least two viruses be circulating at the same time and also infect a host at the same time (co-infection).

Possibility 5: Accessory open reading frame acquisition by non-homologous recombination of SARS-CoV-2 with other coronaviruses or even other viruses/hosts or even via de novo gene birth. These evolutionary processes have already been observed in beta-genus CoVs and as a result, the molecular biology of the recombinant virus changed.

As already stressed out, virtually all the advances made in the CBM field, not only the last 3 years' efforts, will serve as a response to any pandemic of the future, no matter whether a sensor has been developed for a nonviral protein as long as the recognizing probe is specific and changeable.

It is noteworthy to underlight the fundamental role of scientists in elucidating the immune and more in general the blood kinetics of the CBM nanomaterials for the creation of new treatments and vaccines. Both for immunostimulation necessary for vaccination or immune suppression of COVID-19 generated cytokine storm.

Finally, engineered sensors coupled with smartphone devices will offer the availability to leverage pharmacy and hospital overcrowding allowing a point-of-care low-cost diagnosis.

A global multidisciplinary network focused on the communication of advancements in nanomaterial field, biotechnology and immunology can achieve coordinated detection, protection, containment, and therapy in the future.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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