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Carbon-based nanomaterials for viral infection management

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Jinming Yu,[1] Chaiyaporn Kuwentrai,[2] Jian-Dong Huang,[2,3,a)] and Chenjie Xu[1,a)]

AFFILIATIONS

[1]Department of Biomedical Engineering, City University of Hong Kong, 83 Tat Chee Avenue, Kowloon, Hong Kong SAR, China
[2]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, 21 Sassoon Road, Hong Kong SAR, China
[3]Institute of Synthetic Biology, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, 1068 Xueyuan Avenue, University Town, Nanshan, Shenzhen 518055, China

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[a)]**Authors to whom correspondence should be addressed:** chenjie.xu@cityu.edu.hk and jdhuang@hku.hk

ABSTRACT

Carbon-based nanomaterials such as graphene and nanodiamonds have demonstrated impressive physical and chemical properties, such as remarkable strength, corrosion resistance, and excellent electrical and thermal conductivity, and stability. Because of these unique characteristics, carbon nanomaterials are explored in a wide range of fields, including the diagnosis and treatment of viruses. As there are emerging concerns about the control of virus including Middle East respiratory syndrome virus (MERS), severe acute respiratory syndrome coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), this review highlights the recent development of carbon based-nanomaterials for the management of viral infections.

I. BACKGROUND OF VIRAL INFECTION AND NANOMATERIALS

The SARs-CoV-2 infection has become one of the most serious threats to human health and society. This outbreak highlights the urgent need for developing effective and efficient detection and treatment methods. Currently, viruses are detected via antigen or antibody detection assays (ELISA, immunofluorescence, immunoperoxidase), hemagglutination testing, nucleic acid recognition (polymerase chain reaction), and genomic sequencing.[1] Most of these conventional methods are time-consuming, labor-intensive, and costly (Table I). Fast, accurate and cost-efficient techniques, such as nanomaterial-based methods, are required for the rapid and large-scale pathogenic detection.[2] In recent years, we have witnessed great development of nanomaterials that have shown promises in meeting the needs of biomedical applications.[3,4] Nanomaterials are materials from which at least one dimension has the scale of 1–100 nm. They are unique in that they have extremely small sizes, huge surface area to volume ratios, tunable optical emissions, strong mechanical properties, and superparamagnetism. Because of their small size, nanomaterials can easily interact with extracellular and intracellular biological substances, enabling the development of novel medicine (i.e., nanomedicine). Their unique optical, magnetic, and electric properties allow the development of relevant devices for disease diagnosis and medical imaging. There are over 28 Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved nanomedicines so far, and above 60 other nanoparticle technologies that are still pending FDA/EMA approval.[5] Common nanomedicines include Epaxal (Crucell) for Hepatitis A vaccination and Inflexal V (Crucell) for Influenza vaccine; both nanoparticle vaccines are liposome-based making them highly efficient for penetrating tissues and cells to induce protective immune responses against virus. Interestingly, Alnylam developed and marketed Patisiran/ONPATTRO, an siRNA-delivering lipid-based nanoparticle intended for silencing gene induced expression of transthyretin, associated with hereditary transthyretin amyloidosis.[6]

Not surprisingly, their success in the above applications has brought the attention from the infectious disease field. For example, recent development of RNA vaccines against SARs-CoV-2

TABLE I. Comparison of traditional virus detection techniques and carbon nanoparticle detectors.

Detection methods	Detection time (excluding antigen/protein/DNA preparation)	Detection accuracy	Cost of device
Enzyme-linked immunosorbent assay (ELISA)	Moderately fast (3 h to 6 h).	Extremely high sensitivity and good selectivity for specific antibodies in sera.	Inexpensive platform. However, antibody and antigen proteins are costly.
Hemagglutination assays	Relatively slow (4 h to 2 days).	High sensitivity and good selectivity for red cell agglutination.	Inexpensive platform. However, antibody and antigen proteins are costly.
PCR and genomic sequencing	Relatively fast process depending on the DNA fragment length. However, specific primers may take time to be synthesized.	Highly accurate detection of DNA sequences.	Machine is costly. However, repeated use of machine is enabled over long term. Primers have relatively low cost.
Carbon-based quantum dots	Extremely fast (1 min to 5 min).	Moderate sensitivity and selectivity.	Relatively inexpensive platform.
Carbon nanotubes	Relatively fast (5 min to 1.5 h).	High sensitivity and good selectivity.	Inexpensive platform. Immobilized antibody and antigen proteins are costly.
Graphene	Relatively fast (30 min to 2 h).	Moderate sensitivity and selectivity.	Relatively inexpensive platform.

virus involves the use of lipid nanoparticles.[7] In general, the roles of nanomaterials in medicine are roughly classified into three groups (detection, prevention, and treatment). The usage of nanomaterials is to facilitate fast detection with high sensitivity and selectivity,[8] prevention of virus attachment or recognition,[9] and the eradication of virus before their contact with human being through physical, chemical, and biological properties of nanomaterials.[10]

Carbon-based nanomaterials comprise of fullerenes, nanodiamonds, carbon nanotubes, graphene and its derivatives, and carbon-based quantum dots (CDots).[11] They own impressive mechanical, thermal, electrical, optical, and chemical properties (Table II). For example, they have broad-range one-photon property (single photon adsorption), good biocompatibility, and are ease for functionalization. Carbon based-nanomaterials also contain an intrinsic two-photon fluorescence property in the long wavelength region (near-infrared II); this property permits them to be used for deep-tissue optical imaging. Furthermore, their high conductivity, chemical stability, and fast electron-transfer rate make them exceedingly fit for biosensing applications.[12] This review highlights the recent development of carbon-based nanomaterials and discusses their potential and encouraging diagnostic and therapeutic applications against infectious diseases (Fig. 1). The goal is to provide an alternative thinking about the management of infectious diseases from the field of nanotechnology.

II. GENERAL PROPERTIES AND SYNTHESIS OF CARBON-BASED NANOMATERIALS

A. Carbon-based quantum dots

Carbon-based quantum dots comprising of graphene quantum dots (GQDs) and carbon quantum dots (CQDs, C-dots, or CDs) have sizes that are lower than 10 nm. Different from the bulk carbon, carbon-based quantum dots have excellent water solubility and good luminescence signals. Compared with traditional semiconductor quantum dots and organic dyes, they are better in terms of chemical inertness, high resistance to photobleaching, and low toxicity.[13] The last but not least, carbon-based quantum dots have good electronic properties as either electron donors or acceptors. All these make them suitable in applications in biomedicine, catalysis, optronics, and sensors.

Carbon-based quantum dots can be prepared or synthesized via "top-down" and "bottom-up" approaches including chemical ablation, laser ablation, electrochemical carbonization, microwave ray irradiation, and hydrothermal/solvothermal treatment.[14] Keys in this synthesis process are to avoid carbonaceous aggregation, to achieve size control and uniformity, and to enable surface modification. For example, we synthesized 15 nm GQDs with the green emission (497 nm) from Vulcan CX-72 carbon black by being refluxed with concentrated nitric acid.[15] Synthesized GQDs contained plenty of carboxyl and hydroxyl groups on the surface. In another study, the hydrothermal approach (Hummer's method) was used to make 5 nm GQDs with blue emission (430 nm).[16]

B. Carbon nanotube

Carbon nanotubes (CNTs) are hexagonal arrangements of carbon atoms that have a diameter of 1 nm and length ranging from 1 to 100 μm.[17] There are two types: single-walled nanotubes (SWCNTs) and multi-walled nanotubes (MWCNTs). Notably, the structure of SWCNTs is similar to those of graphite, whose chemical bonding is constituted entirely of sp^2 bonds. This bonding structure has even higher strength than the sp^3 bonds found in diamond and provides CNTs with their exceptional strength, flexibility, and resistance to fracture. In addition, CNTs exhibit excellent

TABLE II. Comparison of synthesis, properties, and viral applications of various carbon nanomaterials.

Carbon nanomaterials	Synthesis techniques	Properties	Viral applications	Reference
Carbon-based quantum dots (CDots)	Chemical ablation, laser ablation, electrochemical carbonization, microwave ray irradiation and hydrothermal/ solvothermal treatment.	Excellent water solubility, good luminescence signals, chemical inertness, high resistance to photobleaching, low toxicity, good electronic properties.	Treatment and detection.	13 and 14
Carbon nanotubes	Carbon arc-discharge technique, laser-ablation technique, and the chemical vapor deposition (CVD) technique.	Exceptional strength, flexibility, resistance to fracture, and good electrical properties	Detection and prevention.	17 and 18
Graphene and derivatives	Exfoliation and cleavage of natural graphite, CVD, plasma enhanced CVD (PE-CVD), electric arc discharge, micro-mechanical exfoliation of graphite, epitaxial growth at electrical insulating surfaces, opening up CNTs and reduction of GO using various solutions.	Large surface area, high electrical conductivity, high thermal conductivity, exceptional mechanical stiffness and adaptiveness to chemical modification.	Treatment and detection.	21–25
Nanodiamonds	Detonation events, high-energy ball milling of pressurized high-temperature diamond microcrystals, plasma-assisted CVD, laser ablation, ion irradiation using graphite, and ultrasound cavitation.	Disperse uniformly and stably in water, high stability, high strength, good thermal conductivity, high refractive index and enhanced resistivity.	Treatment	26–29
Fullerenes	Electrical arc vaporization, combustion, laser ablation of graphite and pyrolysis.	Superconductivity, ferromagnetism, anti-HIV bioactivity and optical limiting effects.	Treatment and detection.	60

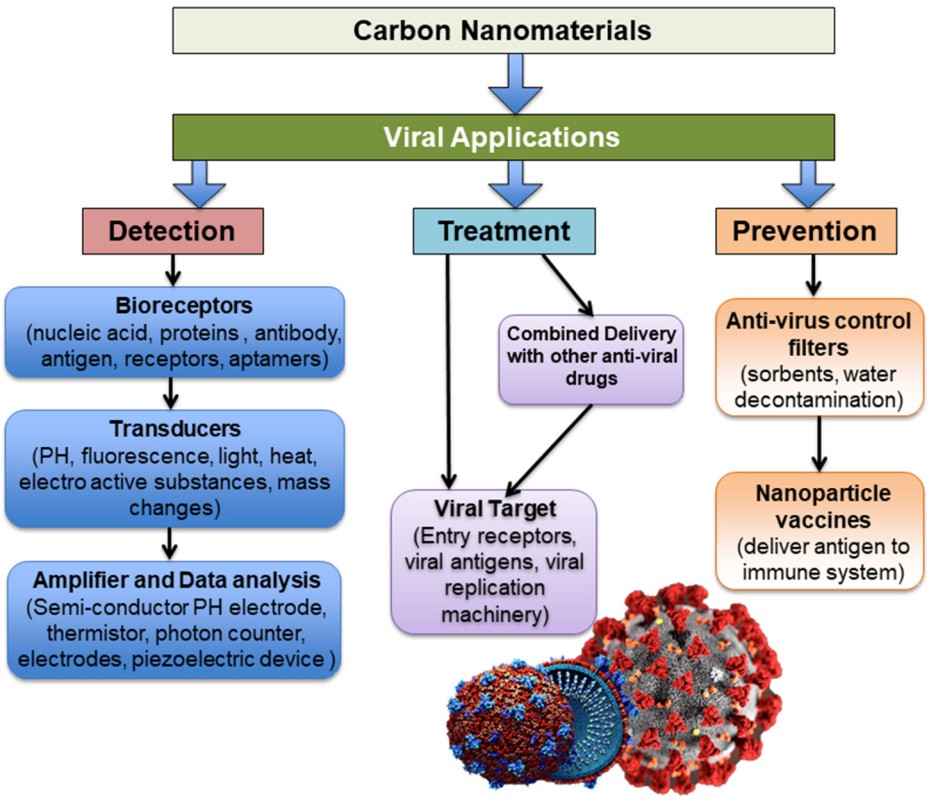

FIG. 1. Carbon nanomaterials for virus management.

electrical properties. They behave as metals or semiconductors depending on tube diameter and the chirality.[18]

CNTs are synthesized by three major techniques including the carbon arc-discharge technique, laser-ablation technique, and the chemical vapor deposition (CVD) technique. Notably, etching agents, such as CO_2 and H_2O, are necessary components for aerosol synthesis of CNTs. It was reported that adding small amounts of CO_2 and H_2O vapor into the reactor could extend the length of synthesized CNTs. Methods affected by these etching agents include Fe particle's vapor nucleation and thermal decomposition of ferrocene vapor.[19] In another study, laser ablation synthesis by a double-pulse Nd:YAG laser was performed at optimal wavelengths of 355 or 1064 nm to synthesize CNTs.[20]

C. Graphene and derivatives

Graphene is composed of a single layer of sp^2-hybridized carbon atoms arranged in a honeycomb structure with the C—C bond exhibiting a length of 0.142 nm. It is considered as a wonder material due to its impressive physical properties, such as large surface area, high electrical conductivity, high thermal conductivity, and exceptional mechanical stiffness.[21] Graphene derivatives are graphene with chemical modification, which are to meet the needs of specific interests. Graphene oxide (GO) is one of the most studied derivatives that contain carbon–oxygen bonds such as hydroxyl, carbonyl, and carboxyl groups. Different from graphene, GO is highly hydrophilic and more important for biomedical applications.

Graphene may be synthesized by various methods including exfoliation along with cleavage of natural graphite, CVD, plasma enhanced CVD (PE-CVD), electric arc discharge, micromechanical exfoliation of graphite, epitaxial growth at electrical insulating surfaces, opening up CNTs and reduction of GO using various solutions.[22] For plasma enhanced chemical vapor deposition, methane is an effective H_2 source for high quality graphene synthesis and saturates the nucleation density when the plasma power is above 120 W.[23]

GO is synthesized by the oxidation of graphite via the addition of various chemicals, such as potassium chlorate plus nitric acid (Brodie and Staudenmaier method) or potassium permanganate plus sulfuric acid (Hummers method).[24] A study showed that GO could be synthesized from natural flake graphite using the Hummers method (liquid oxidation followed by chemical reduction with NH_3H_2O aqueous solution and hydrazine hydrate).[25]

D. Nanodiamonds

Nanodiamonds (NDs) are monocrystalline forms of diamond with a particle size below 100 nm. They consist of a diamond core and amorphous carbon layers. In the core, there are sp^3 C—C bonds, while the surface of NDs is covered by sp^2 C—C bonds. The most unique feature of NDs is the existence of various oxygenic functional groups on the surface, thus NDs can disperse uniformly and stably in water. Other unique properties of NDs are high stability, high strength, good thermal conductivity, high refractive index, and enhanced resistivity.[26] In the last decade, researchers also discovered fluorescent NDs by generating point-defects in the diamond structure (i.e., color centers). For example, Vlasov *et al.* generated a silicon vacancy in the 1.6 nm NDs to provide the stable fluorescence emission.[27]

NDs are mainly synthesized by detonation events. However, there are also other synthesis methods such as high-energy ball milling of pressurized high-temperature diamond microcrystals, plasma-assisted CVD, laser ablation, ion irradiation using graphite, and ultrasound cavitation. Detonation events of explosives (60/40 ratio of TNT/hexogen) in a steel chamber of 1.6 m^3 have led to the synthesis of black powdered product containing NDs and other substances like graphite and amorphous carbon. Structural characterization by various techniques, such as x-ray diffraction spectroscopy, energy dispersive spectroscopy, transmission electron microscopy at high resolutions, Fourier transform infrared spectroscopy, Raman spectroscopy and differential scanning calorimetry, are critical for determining the efficiency of ND synthesis.[28] Another study used high-energy Kr ion irradiation (350 ± 50 MeV Kr ions) of fine-grain polycrystalline using an Argonne tandem linear accelerator system (ATLAS) and acid dissolution to produce NDs at room temperature.[29]

III. CARBON-BASED NANOMATERIALS FOR THE MANAGEMENT OF VIRUS

A. Detection

A biosensor typically contains biological active components that are incorporated into an equipment that enables the conversion of biochemical signals into measurable signals.[30] Specifically, there are (1) a bioreceptor (e.g., antibody, aptamer, nucleic acid) enabling in the selectivity and specificity of the equipment, (2) a transducer (e.g., electrode, fluorophore) promoting the physical or chemical changes after sensing of analytes, and (3) a signal-processing unit (signal output). Since the biomarker may sometimes be found at very low concentrations, the sensibility, reproducibility, and stability of transducers are critically important. Due to the unique properties described above, carbon-based nanomaterials are perfect candidates for developing transducing components. Here depending on the signals generated by the transducers, we group their applications in virus detection into three sub-groups.

1. Optical biosensors

The optical sensors work by detecting changes in light emission during target–detector interaction.

CDs or carbon nanoparticles (CNPs) exhibit optical specifications with respect to fluorescence, chemiluminescence, electrochemiluminescence, phosphorescence, up-conversion of photoluminescence, and photo-stimulated electron transfer activity. Achadu *et al.* developed a fluoro-immunoassay system for detecting influenza virus (H1N1 and H3N2), composing of magnetic-derivatized plasmonic molybdenum trioxide quantum dots (MP-MoO_3 QDs) and fluorescent graphitic carbon nitride quantum dots (gCNQDs).[31] Both nanomaterials were coated with specific antibody against influenza. Under the presence of the virus, a core-satellite immunocomplex was formed between Ab-MP-MoO_3 QDs and Ab-gCNQDs. The MP-MoO_3 QDs steadily generated plasmonic-induced elevation of the gCNQDs fluorescence upon escalating concentrations of influenza virus. This whole device produced a detection time of 10 min and detection limit of

0.25 pg/ml and 0.9 pg/ml for Influenza virus A/New Caledonia (20/99/IVR/116) (H1N1) in de-ionized water and human serum respectively. Furthermore, clinically isolated influenza virus A/Yokohama (110/2009) (H3N2) was sensed within the detection range of approximately 45–25 000 PFU/ml. In another case, Shojaei *et al.* developed a complex fluorometric immunoassay which consisted of anti-Citrus tristeza virus (CTV) antibody conjugated cadmium-telluride QDs (QD-Ab) and 25 nm CNPs coated with the coat protein of CTV (CP-CNPs).[32] When QD-Ab and CP-CNPs were mixed, the QD fluorescence was quenched by the CNPs. While in the presence of the target (i.e., CTV) in the samples, the CP-CNPs were displaced by free CPs leading to the recovery of fluorescence intensity of the QDs. Such a system provided a detection limit of 220 ng/ml of CTV.

CNT-based optical biosensors typically rely on either the quenching activity of CNTs over conventional organic quenchers or the near-infrared photoluminescence from semiconducting SWCNTs. Tian *et al.* devised a biosensor for H5N1 detection based on the quenching effect of CNTs.[33] Briefly, they synthesized a fluorescence resonance energy transfer system using QDs and CNTs. QDs modified with ssDNA acted as the fluorescence donor. Initially, the fluorescence of QDs was quenched by CNTs due to their complexation. Upon the recognition of the target DNA, this complexation was weakened that restored the QD fluorescence. Harvey *et al.* designed SWCNT-based RNA optical sensors for detecting intact HIV in serum (characterized by wavelength shifts) within minutes.[34] SWCNTs were modified with the DNA oligonucleotide sequence (GT)15-(T)15 DNA, which would hybridize to the polyadenylation elements of HIV RNAs. Sodium dodecyl sulfate (SDS) was used to disrupt the virus, denature the viral protein, and liberate the RNA genome. The denatured proteins interacted with the CNTs upon hybridization, leading to a greatly enhanced blue-shift.

Similar principles have been explored on the graphene and its derivatives as well. Kim *et al.* developed a biosensor using reduced GO (rGO) that can serve as an effective distance-dependent fluorescence quencher.[35] They hybridized a single-strand aptamer possessing a fluorophore at 5′-end and a Black Hole Quencher-1 (BHQ1) on 3′-end with a complementary oligomer consisting of BHQ1-modified 5′-end. The aptamer targeted interferon-gamma (IFN-γ) specifically here. The whole complexes were anchored to rGO through two BHQ1. The presence of IFN-γ induced the complexation between single-strand Aptamer, which displaced the double-stranded structure into two individual strands. Thus, two denatured strands, as well as the fluorophore, became close to the rGO surface. This quenched the fluorophore, result in an "off" signal. This sensor allowed the specific detection of IFN-γ at the concentration range of 0.1 ng/ml–10 μg/ml in buffer and human serum. Alternatively, Zhang *et al.* designed silver nanoclusters (AgNCs)/GO-based fluorescence sensor for detecting HIV genomic DNA via hybridization chain reaction (HCR).[36] In this case, GO conducts adsorption for capturing the hairpin probes along with the selective fluorescence quencher. There are two partially complementary DNA probes, hairpin probe 1 (H1) and hairpin probe 2 (H2) as well. After adding of $AgNO_3$ and $NaBH_4$, the AgNCs were produced at the H1 and H2 probe terminals. Without HIV DNA, HCR could not be triggered. The hairpin probe shielded AgNCs attached to the GO surface that quenched fluorescence of the AgNCs. In the presence of target, H1 and H2 assembly happened via HCR, producing a long chain of H1/H2 complexes. Consequently, the HCR product (AgNCs nanowires) could not adsorb at GO surfaces and produced a strong fluorescent signal depending on the target's concentration.

Different from the above three materials, NDs are mainly used for labeling and tracking. Pham *et al.* modified fluorescent NDs with the viral protein, rA27 (a recombinant envelope protein of vaccinia virus). This allowed the targeting of glycosaminoglycans (GAGs) on cell membrane.[37] The small size and fluorescent properties of NDs permitted the understanding of the virus–host interactions during the infectious stage. Trinh *et al.* complexed fluorescent NDs and bacteriophages through streptavidin and biotin interaction. NDs served as the fluorophores to visualize the interaction between phages and bacteria.[38]

2. Electrochemical biosensors

Electrochemical biosensors conduct sensing of analytes by determining electrical responses generated from electrochemical reactions between analytes and functional electrode surfaces within the sensor. The concentrations of analytes tend to linearly correlate with sensor responses for practical applications. Electrochemical biosensors are extremely sensitive, possess high signal-to-noise-ratios, and provide rapid response times. Carbon-based materials have a diverse application potential. They also are chemically inert and affordable to be used as electrode substances for electrochemical biosensors.

Carolina *et al.* established CNT-screen printed electrodes (CNT-SPE) immunosensor for the detection of non-structural protein 1 (NS1) from Dengue virus.[39] This sensor was made by dispersing carboxylated CNTs in carbon ink to prepare a SPE and then covalently immobilizing anti-NS1 antibodies at the CNT surface. In the measurement, the sensors were incubated with the NS1 samples and then with anti-NS1 that was labeled with horseradish peroxidase (anti-NS1-HRP). The electrochemical response was achieved by the peroxidase catalyzed reaction of hydrogen peroxide and anti-NS1 coupling, and was accordingly resolved by chronoamperometry. Palomar *et al.* modified a gold electrode with a CNT/gold nanoparticles nanocomposite.[40] Dengue toxin was detected by gold nanoparticles, which immobilized Dengue antibody by covalent bonding. Ferri/ferrocyanide [Fe (II/III)] ion was utilized as the signal reporter. After recognition of the Dengue antibody and the toxin, the electrode's surface would be blocked, drastically reducing the Fe (II/III) redox current. Thus, detecting the sensitive change of the ferrocene-labeled probe electrochemical signals would enable transduction of target hybridization activity.

Similar to CNTs, graphene can be used to achieve the electrochemical detection too. Muain *et al.* immobilized Hepatitis B virus core antigen (HBcAg) on gold nanoparticle-decorated rGO (rGO-en-AuNPs) nanocomposite.[41] The biosensor can be used to detect anti-HBcAg in the electrolyte solution by the impedance method. Briefly, the electrolyte solution consists of 5 mm potassium hexacyanoferrate $[K_3Fe(CN)_6]$ that acts as the redox probe and 0.1M potassium chloride (KCl) that acts as the support electrolyte. The electrochemical response demonstrated that the electron transfer resistance was linearly related to the concentration of

anti-HBcAg, ranging from 3.91 ng/ml to 125.00 ng/ml, and the lowest detection limit was 3.80 ng/ml at 3 σ/m. Huang *et al.* developed an electrochemical biosensor with a sandwich-type immunoassay for avian influenza virus H7 (AIV H7).[42] The device consists of gold electrodes coated with gold nanoparticles and graphene nanocomposites (AuNPs-G). It is worth noting that the surface of gold nanoparticles was further modified by incorporating H7 monoclonal antibody (MAbs). Another component of this system is silver nanoparticle-graphene (AgNPs-G) whose surface was immobilized with H7-polyclonal antibodies (PAbs). In the detection, AIV H7 bound to MAbs-AuNPs-G-electrodes first. Then PAb-AgNPs-G was added to form the sandwich structure. Finally, gold electrodes with the complexes were placed in the KCl solution with a platinum wire auxiliary electrode (counter electrode) and a saturated calomel reference electrode (SCE). Linear sweep voltammetry (LSV) was conducted for recording the stripping currents needed for AIV H7 detection.

3. Field-effect transistor (FET) biosensors

Field-effect transistors are a form of semiconductor apparatus that work by current flowing from source to drain electrodes. The semiconductor channel that lies between the source and drain is modulated by the electric field generated by a gate electrode's voltage. Specifications of electrical FET biosensors may be implemented by changing different adhesive biomolecules within the system. Both CNTs and graphene are commonly used for producing FET-based biosensors.

Mandal *et al.* developed a device consisting of a rectangle-shaped block of semiconducting CNT spanning a pair of Au source/drain electrodes (100 μm wide). There was no gate electrode in this device. CNT was coated with the M13-pIII antibodies that specifically bind with the pIII coat protein of M13 bacteriophage. Under the presence of M13, the specific antibody-virus (M13-pIII antibody) binding, the source-drain current decreased significantly (>20%). This device allowed the selective detection of 550 M13 viruses.[43] Fu *et al.* developed the chemiresistor DNA sensors using semiconducting SWCNTs (sc-SWCNTs) and nitrogen-doped multi-walled carbon nanotubes (N-MWCNTs) for avian influenza virus (AIV) subtype H5N1.[44] In these sensors, long CNTs (>5 μm) are positioned between the Cr/Au interdigital electrodes to allow a single CNT to be connected to the electrodes. The CNTs were functionalized with DNA probe sequences that have been non-covalently bound to sidewalls. These chemical resistance DNA sensors can accurately detect the H5N1 complementary DNA target sequence of avian influenza virus at a concentration of 2 pM–2 nM. The working mechanism is attributed to the electrical conductivity change either to the electron doping by DNA bound to the CNT sidewall or to the change in Schottky barrier on CNT/metallic-lead interface. Besides phase and influenza virus, CNT based FET biosensors are also used for dengue virus detection. For instance, Waski *et al.* constructed a SWCNT-based heparin (viral receptor analog) modified chemical resistance to detect the whole dengue virus.[45] The biosensor consisted of a SWCNT network chemical resistor that is functionalized with heparin, instead of using an antibody, which serves as a biomolecule for viral recognition. The SWCNT network chemical resistance sensor was fabricated on the patterned interdigital gold electrode by the self-assembly method. Heparin was covalently attached on the SWCNT surface. The virus would bind to heparin and cause the increase of resistance of the electrodes. This chip-based biosensor had a detection limit of ∼8 virus/chip. It was sensitive to detect the presence of dengue virus but unfortunately not Influenza H1N1.

Similar to CNTs, graphene can be used to build FET biosensors as well. Afsahi *et al.* built a FET biosensor using single layer graphene for Zika virus detection.[46] The graphene was then functionalized by the target, anti-Zika NS1 mouse mAb 6B1 antigens. The C-Response Sensorgram (capacitance of biosensor towards the liquid) was used to monitor the binding of virus and the biosensor. Jin *et al.* used similar strategy to develop a FET biosensor for the detection of inactivated Ebola virus.[47] An equine antibody targeting the virus glycoprotein was immobilized on reduced graphene oxide-modified FET surface. Different from Afsahi's work,[46] this work measured the shift of Dirac voltage during the binding of ebola virus and antibody.

The current coronavirus pandemic (SARS-CoV-2) has been posing a serious threat to global public health. Reliable laboratory diagnosis of this virus is the first step toward effective preventive intervention. Seo *et al.* demonstrated that graphene and its derivatives could be used to make biosensors for detection of COVID-19 (Fig. 2).[48] Their device consisted of anti-SARS-CoV-2 spike protein antibodies immobilized on graphene sheets that recognized SARS-CoV-2 spike protein. FET sensor utilized PBS buffer as the electrolyte to modulate an effective gating effect. This biosensor detected the SARS-CoV-2 based on alterations in channel surface potential and the consequential effects on the electrical response. The device exhibited the detection limit of 16 pfu/ml in culture medium and 2.42×10^2 copies/ml in clinical samples.

B. Treatment

Viruses rely on infecting host mammalian cells to conduct genome replication and generation of new virus particles.[49] The infection process is a major part of the virus life cycle therefore viral treatments target this stage. Current replication inhibitors comprise of antiviral drugs designed to interfere with viral replication and intracellularly prevent production of new virus particles.[50] Conversely, entry inhibitors block virus particles extracellularly to combat infection. These aim to decrease viral loads along with improving prophylactic or therapeutic endpoints. Carbon nanomaterials exhibit low to moderate cytotoxicity and specific antiviral actions.[51] They work by either directly interacting with the virus, (also via photo-induced mechanisms) or as platforms for delivering other antiviral substances.

Huang *et al.* synthesized benzoxazine monomer derived Cdots (BZM-CDs) as a broad-spectrum antiviral drug.[10] BZM-CDs could directly attach to virion surfaces, and thus block the first step of virus–cell interaction. They found that BZM-CD treatment could prevent the cell infection by flaviviruses (JEV, ZIKV and DENV) and non-enveloped viruses (porcine parvovirus, PPV and adenovirus-associated virus, AAV). Barras *et al.* discovered that the boronic acid or amine functionalization on Cdots was critical to prevent the entry of herpes simplex virus type 1 (HSV-1).[52] In another independent study, Aleksandra Łoczechin *et al.* confirmed

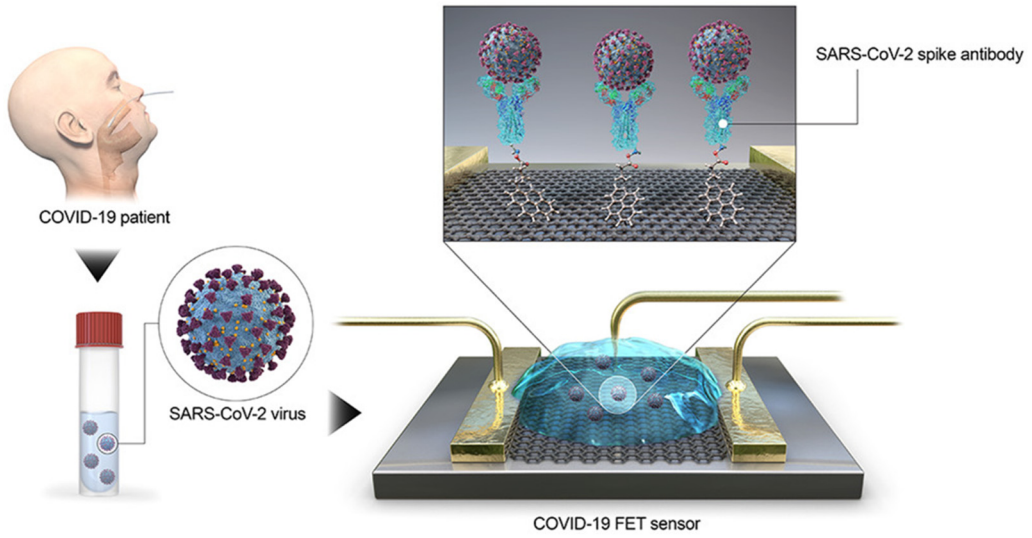

FIG. 2. FET biosensor for the detection of SARS-CoV-2 in human nasopharyngeal swab specimens. Reproduced with permission from ACS Nano **14**(4), 5135–5142 (2020). Copyright 2020 American Chemical Society.[48]

this observation. They explored the usage of 7 different CQDs made of different methods for inhibiting the HCoV-229e through inhibition of human coronavirus (HCoV-229E) infections.[53] The most effective CQDs were either made from boronic acid derivatives or coated with amine groups. Another interesting report examined the anti-viral activity of positively-charged, 2,2′-(ethylenedioxy)bis(ethylamine) (EDA)-Cdots and non-charged 3-ethoxypropylamine (EPA)-Cdots. This group studied the infection of two strains of human norovirus virus-like-particles (VLPs), GI.1, and GII.4 VLPs. Both types of Cdots effectively inhibited both strains of VLPs' bindings to histo-blood group antigens (HBGA) receptors from human cells. However, the positively-charged EDA-Cdots proved to be more efficient.[54] Taken together, Cdots/CQDs execute their anti-viral functions mainly through blocking the antigens on the viral particle surface. The surface charge and functional groups control the efficiency of this process. Roy *et al.* made use of NDs as the carriers for the anti-HIV-1 drug (efavirenz).[55] This system showed excellent drug dissolution profile (approximately 5–10 ng/ml greater dissolution for ND-drug complex compared to free-drug), transmigration through the blood brain barrier in vitro (~450 ng/ml greater transmigration for ND-drug complex compared to free-drug at day 2), and therapeutic efficacy (significantly reduced number of HIV-1 infected macrophages from over 8000 pg/ml for untreated group, 2500 pg/ml for free drug to below 1500 pg/ml for ND-drug complex by day 7).

Yang *et al.* reported a sulfonate GO system that were modified with β-cyclodextrin (CD) and curcumin. Through the tissue culture infectious dose assay and immunofluorescence assay, this functional GO provided effective inhibition of RSV infections. It works through three possible mechanisms: directly inactivating viruses, blocking viral attachment, and interfering with virus replication.[56] Deokar *et al.* explored the photothermal antiviral properties of graphene by taking that sulfonated magnetic nanoparticles functionalized with rGO (SMRGO) as a hot plate surface for herpes simplex virus type 1 (HSV-1) capture and destruction under irradiation. The captured HSV-1 became non-infectious after SMRGO irradiation and average infection percentage reduced from 65.62% without irradiation to 0% after near-infrared light irradiation.[57]

C. Prevention

As everyone knows nowadays, the best way to prevent illness is to avoid being exposed to the virus. Before the development of the vaccines, any strategy to minimize the exposure to the virus is welcomed. Estevez *et al.* showed SWCNT could act as a filter to efficiently remove bacterial and viral microbes from water.[9] The filter was a polyvinylidene fluoride (PVDF)-based microporous membrane (5 μm pore size) sheltered by a thin layer of SWCNTs. SWCNT filters had depths of 2.0 to 6.0 μm. When the water containing T model virus particle (MS2 bacteriophage) ran through the filter using a peristaltic pump, the virus could be completely removed (no remaining plague forming units detected at filter outlet) based on size exclusion or sieving. Later, the same group further developed an anodic MWCNT micro-filter for removal of MS2 viruses.[58] MWCNT filters were made of 5 μm PTFE membrane and MWCNTs that had diameter distribution of 17 ± 9 nm along with a length distribution of 91 ± 21 μm. The solution with virus ran through filters under the peristaltic pump as well. However, previous work purely depended on the sieving to remove the bacteria and virus. This new system has an integrated electrolysis component. Concomitant electrolysis on the filters during filtration led to significantly elevated viral inactivation. At applied potentials of 2 and 3 V, the electrochemical MWCNT filter decreased the viral numbers in the effluent lower than the detection limit.

IV. CONCLUSION AND PERSPECTIVE

As we are observing, infective diseases continue to provoke global risk to the public health. Despite the development of biology and electronic devices in the past 50 years, our capabilities to cope the pandemic including the large-scale and fast detection and the development of vaccines are obviously insufficient. There is a great need for multidisciplinary collaboration to prepare the humankind for any future outbreak.

Materials science is one of the fast-developing fields and offers numerous potentials for revolutionizing the medical industry. As we discussed in this article, carbon nanomaterials, one representative new type of materials are highly promising for the virus management. They ease diagnostic processes via various platforms by conducting direct real-time sensing of biomolecule targets. They block the entrance of virus to the cells to prevent infection. They can also be used to remove the virus from the water.

Although it does not seem to be far away before we bring the carbon-based sensors/medicine/purifier from bench to our real life, there are a few things to notice in the following process. The immobilization methods of nanomaterials and the incorporated biological components should be standardized to improve precision during virus detection/targeting. The protocols reported in most of the articles are individually developed. The lifetime of the biosensor/medicine/purifier may be considerable. Another important consideration is the clearance of carbon nanomaterials. Although Singh *et al.* revealed that functionalized SWNT linked with ^{111}Indium are excreted as intact nanotubes by renal excretion, CDots and CNTs may accumulate in the reticuloendothelial system (RES), which could prevent renal uptake.[59]

Finally, the cost is also critical. The research field has aimed to produce accessible, precise, real-time, portable and recyclable devices to detect viruses. The development of next-generation carbon based nanomaterials for virus treatment devices must also be safe, cheap, and efficacious to treat the infection. In conclusion, carbon-based nanotechnology is positioned to provide a better life.

AUTHORS' CONTRIBUTIONS

J.Y. and C.K. contributed equally to this work.

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DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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