Engineering carbon nanotubes for sensitive viral detection

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ABSTRACT

Viral infections have been proven a severe threat to human beings, and the pandemic of Coronavirus Disease 2019 (COVID-19) has become a societal health concern, including mental distress and morbidity. Therefore, the early diagnosis and differentiation of viral infections are the prerequisite for curbing the local and global spread of viruses. To this end, carbon nanotubes (CNTs) based virus detection strategies are developed that provide feasible alternatives to conventional diagnostic techniques. Here in this review, an overview of the design and engineering of CNTs-based sensors for virus detection is summarized, followed by the nano-bio interactions used in developing biosensors. Then, we classify the viral sensors into covalently engineered CNTs, non-covalently engineered CNTs, and size-tunable CNTs arrays for viral detection, based on the type of CNTs-based nano-bio interfaces. Finally, the current challenges and prospects of CNTs-based sensors for virus detection are discussed.

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1. Introduction

The increasing number of viral diseases with unknown origins has become a real threat in recent decades, ultimately harming global public health [1,2]. The probabilities of emerging and re-emerging diseases triggered by viral infection are continuously increased, including Coronavirus disease 2019 (COVID-19) [1,3], Middle East respiratory syndrome coronavirus (MERS-CoV) [4,5], severe acute respiratory syndrome (SARS) coronavirus [6], Ebola virus [7], dengue virus (DENV) [8], influenza viruses (mainly influenza A virus subtype H5N1) [9], and human immunodeficiency virus (HIV) [10] (Fig. 1). Viral infections have become a more severe issue with the increase in population density, owing to the robust capability of reproduction and infection of viruses [11–13]. The World Health Organization also proposed that early detection could prevent the spread of the virus by rapidly deploying appropriate countermeasures [14]. Thus, the need to detect different diseases at their early stage is exponentially growing to maintain society's sustainable health. Meanwhile, the increasing demands for virus monitoring and effectively controlling the spread of disease indicate the requirement for rapid and sensitive virus diagnostic devices. The progress in emerging biosensing technology displays excellent potential for the early detection of viruses like biomarkers [15], succeeding in generating an improved, rapid, and accurate screening of various biomarkers through biosensors. Because of the outstanding sensitivity and specificity, biosensors display promising potential for the accurate and quantitative detection of viruses [16,17]. Furthermore, the performance of biosensors has been significantly enhanced by the advancements in the biochemical mechanism of viruses, transduction systems, and strategies of engineering nanomaterials.

Usually, most discovered viruses, ranging from 20 to 300 nm in size, comprise an RNA or DNA genome covered by a protective protein shell or capsid [22–24]. In viruses, the capsid protein that
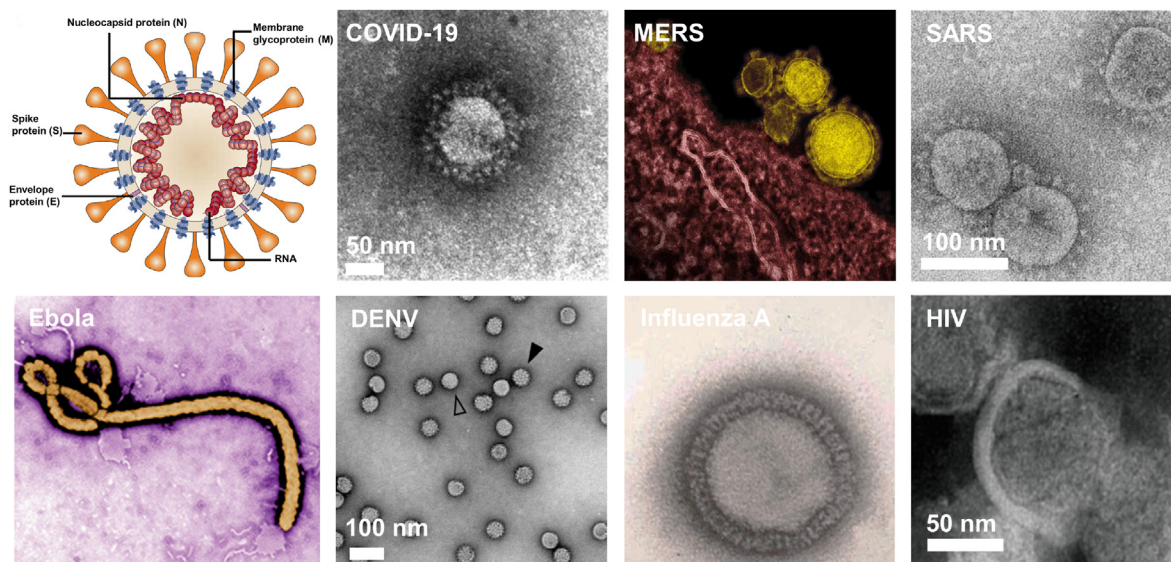

Fig. 1. Schematic presentation of coronavirus. Reproduced with permission from Ref. [6]. Morphology of COVID-19. Reproduced with permission from Ref. [3]. Transmission electron microscope image for MERS. Reproduced with permission from Ref. [4]. Electron micrograph of the SARS virus that was cultivated in Vero cells. Reproduced with permission from Ref. [6]. Transmission electron microscope image for Ebola virus. Reproduced with permission from Ref. [18]. Transmission electron microscope image for DENV. Reproduced with permission from Ref. [19]. Electron micrograph of the influenza A virus. Reproduced with permission from Ref. [20]. Electron micrograph of the HIV. Reproduced with permission from Ref. [21].

makes up the viral outer coat and the nucleic acid contains genetic information inside the coat (Fig. 1) [16]. These components can be targeted in biochemical measurement, where the specific target determines the type of biochemical interaction used in it. Based on the viral biochemical mechanism, varieties of virus detection approaches have been developed, including enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), next-generation sequencing (NGS), and electronic and optical transducers [25]. These methods are widely used for virus detection and show excellent specificity. Although these methods present excellent performance, they also have unavoidable limitations, including high cost, time-consuming, and complicated procedures. Therefore, fast and sensitive viral biosensors have been developed to overcome these limitations for attenuating the threat caused by viral diseases.

Biosensors, based on biochemical and physical interactions, have been developed for the sensitive, specific, and rapid detection of viruses. According to the types of affinity reagents and viral targets, the affinity interactions-based virus biosensors are divided into four main categories: antibody-, DNA-, antigen-, and cell-based biosensors (Fig. 2) [12]. The primary biochemical mechanism for selective binding of capsid proteins is based on the antigen-antibody interaction [26], which means the unique antibodies with specific target binding sites can be used to selective and sensitive detect viral proteins. In the view of nucleic acid, the viral nucleic acids can be measured with complementary oligonucleotide sequences based on the principle of nucleic acid hybridization [27], which maintains high sensitivity and selectivity toward the combination of viral target nucleic acid. The designed complementary aptamers are single-stranded oligonucleotides (ssDNA and ssRNA) (~20−40 bases in length) [12], which can recognize target viral antigens via three-dimensionally preferred orientation with high selectivity and affinity. To specifically recognize the target, antibodies or aptamers are immobilized on the sensor surface to form the bioreceptor-based biosensors with retained reactivity. However, the surfaces of most biosensors are difficult to modify, and the conductivity of biosensors is poor after the modification of biorecognition molecules.

Carbonaceous nanomaterials have been widely regarded as highly attractive biomaterials due to their multifunctional nature, facile surface modifications, and incorporation into existing biomaterials which could supplement their potential applications in biotechnology [28−32]. Among them, carbon nanotubes (CNTs) are unique carbon allotrope, which is constructed by carbon elements with hollow cylindrical tubes consisting of carbon, high aspect ratio (~1000), and sp^2 hybridization [26]. Other carbon allotropes, such as fullerene (C_{60}) and graphene [29,33], have also revealed the unique combination of physical properties that stems from their macromolecular structures. Moreover, the macromolecular structures consist of all three hybridizations sp^3, sp^2, and sp, depending on the nature of allotropes. CNTs, another cylindrical form of sp^2 hybridized carbon atoms arranged in single or multiple coaxial tubes of hollow graphitic sheets, have attracted much attention from the scientific community over the last few decades due to their unique mechanical, chemical, electrical, and optical properties [34−37]. CNTs have strong conductivity, reactivity and possess intrinsic physicochemical properties regardless of their shapes and size. Single wall carbon nanotube (SWCNT) and multi-wall carbon nanotube (MWCNT) are the two major configurations of CNTs, which have been used in a variety of diagnostic applications through electrochemical and optical sensing techniques [26]. As an excellent platform for biomolecules immobilization, CNTs provide a facile route to transduce the signals associated with the recognition of analytes, metabolites, or disease biomarkers.

Based on the advantages mentioned above, CNTs have been widely used in sensing systems to detect analytes and biological species (DNA, RNA, proteins, peptides, bacteria, viruses, etc.) [14,26,38]. With the development of biochemistry and related disciplines, varieties of strategies have been developed in engineering CNTs (e.g., covalent modification, non-covalent modification, and size-tunable array processing) to enhance the performance of viral detection [39]. These bioreceptors show apparent affinity with biological molecules [16,26], so they are used as sensitive and selective recognition elements. Meanwhile, CNTs are excellent transducers that can collect and convert the signal into a more detectable physical signal [25], allowing the targets to
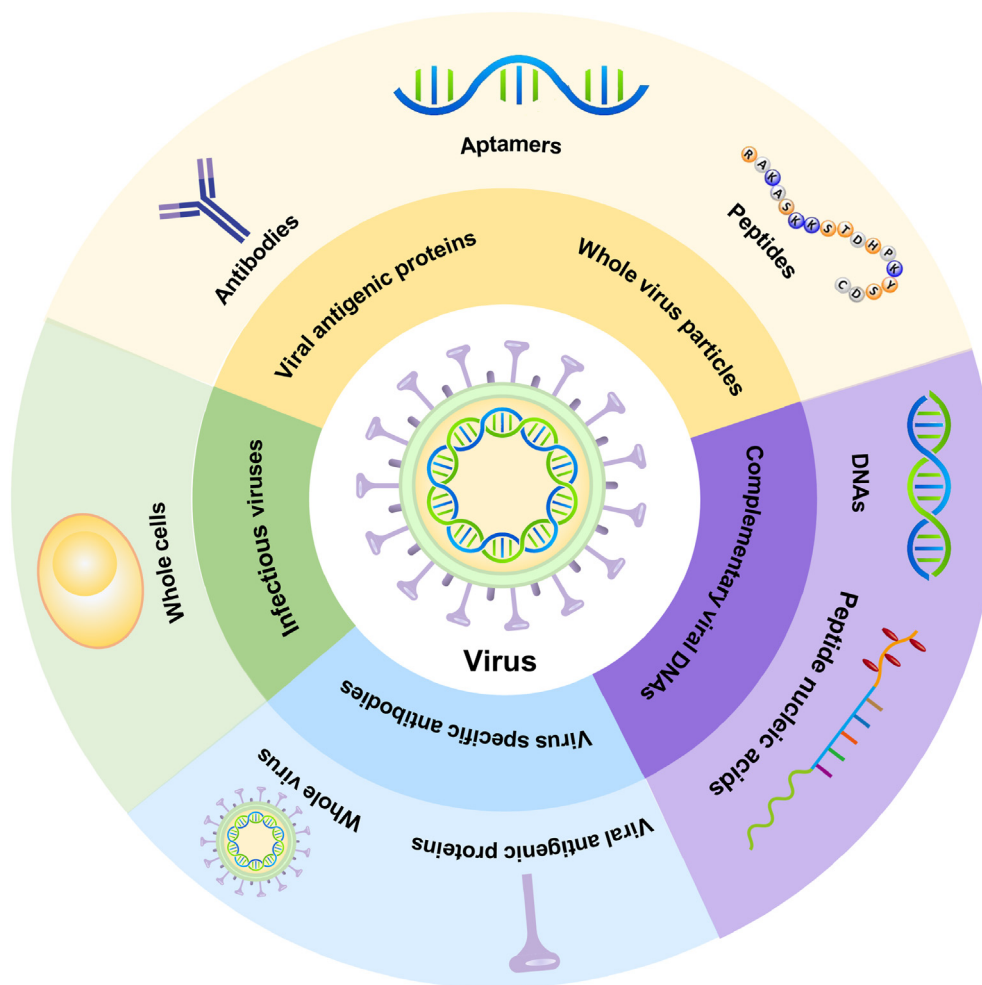
Fig. 2. Schematic of affinity reagents with their corresponding viral targets.

be detected via the interaction between the recognition element and biological species. According to the difference in physical signals, different CNTs-based biosensors can be divided into electrical signal sensors, optical sensors, acoustic signal sensors, thermal sensors, and so on [40,41]. The application of CNTs has also been expanded to biomedical applications, photoacoustic imaging, protein separation, and point of care devices [10,26]. The novel biosensing methods based on CNTs present the ultrasensitive detection of viruses, suggesting high application prospects in future disease diagnosis. This review will provide an in-depth progress report focusing on the current progress and advantages of novel CNTs-based biosensors for viral detection and discuss the promising prospects in future disease diagnosis.

2. Fabrication and functionalization of CNTs

CNTs are elongated nanometric-tube-shaped materials consisting of sp^2 hybridized graphite. Depending on the conditions of CNTs synthesis, different classes of CNTs such as SWCNTs, double-walled CNTs (DWCNTs), and MWCNTs with open or closed terminations can be obtained. There are three main routes to fabricate CNTs: Arc discharge, laser ablation, and chemical vapour deposition methods [42,43]. CNTs have attained much attention in developing biosensors for detecting viral species due to their extraordinary physicochemical properties such as higher surface-to-volume ratio, excellent electrical conductivity, electrochemically stability,

intrinsic photoluminescence, and superior mechanical strength [44]. However, since pure CNTs do not have a good attraction toward biological species, usually the functionalization of CNTs with bioreceptors (oligo- or polynucleotides, proteins, cells, microorganisms, or nanoparticles) is required. In terms of CNT-based biosensors, CNT acts as a high surface area transducer, enhancing real-time detection.

Two approaches to functionalizing CNTs have been commonly applied, such as covalent and non-covalent (Fig. 3A and B) CNTs surface functionalization [45,46]. Usually, covalent functionalization occurs via the chemical oxidation of CNTs, followed by bioreceptor immobilization. The direct covalent functionalization can deform the prefect structure of CNTs, which may result in insufficient transducing activity. However, the covalent functionalization approach was reported to enhance the solubility of highly hydrophobic CNTs in water and organic solvents [47]. The esterification or amidation of the carboxyl groups of oxidized CNTs to facilitate the immobilization of bioreceptors has been reported as well. The recombinant dengue envelope (DENV3E) proteins functionalized MWCNTs were developed via covalence [48]. The covalent functionalization was carried out using a diimide-activated amidation method, which was based on the covalent binding NH_2 of DENV3E protein to carboxylic groups on the surface of MWCNTs in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDAC) as a binder. At the same time, NHS was added to stabilize the reaction.
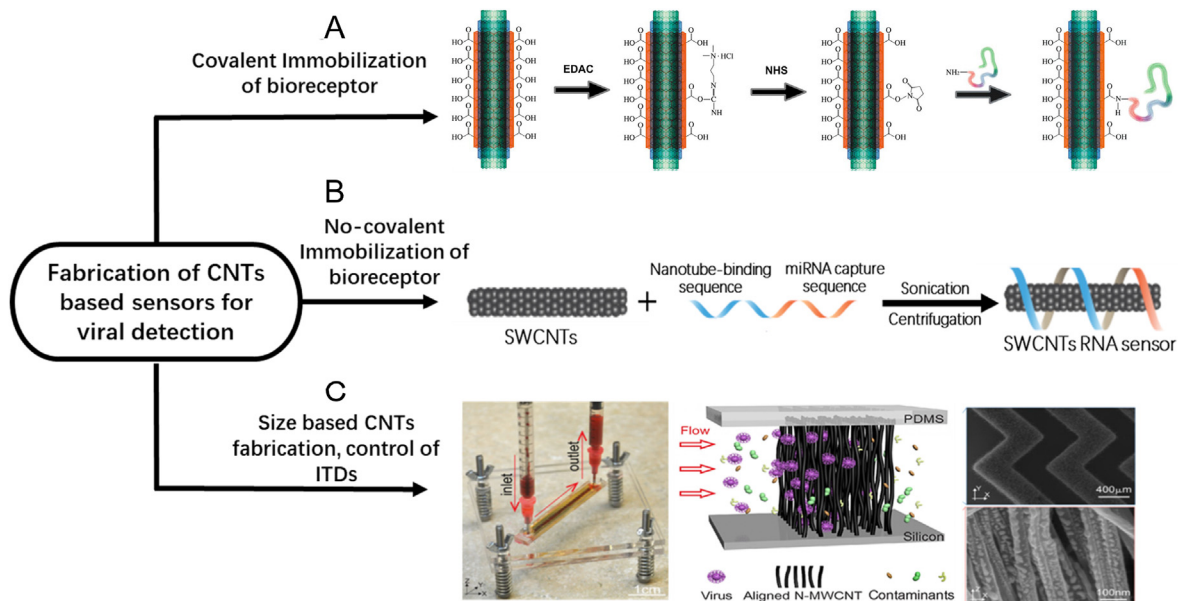
Fig. 3. Main routes for the fabrication of CNTs based sensors for viral detection. (A) Example for the covalent immobilization of bioreceptor on the surface of CNTs, DENV3E protein was immobilized on CNTs surface using the diimide-activated amidation process. EDAC: 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; NHS: *N*-hydroxysuccinimide. Reproduced with permission from Ref. [48]. (B) Example of non-covalent immobilization of bioreceptor on CNTs surface by ultra-sonication and ultracentrifugation protocol. Reproduced with permission from Ref. [41]. (C) Example for CNTs based sensors for size-based viral detection, ITDs CNTs arrays were controlled within 22−720 nm range to detect a diversity of virus sizes. Reproduced with permission from Ref. [25].

Non-covalent functionalization (e.g., π-π interactions, Van der Waals forces, and physical adsorption) is used to immobilize bioreceptors on CNTs surfaces without significantly modifying the structure or proprieties of CNTs, such as degradation of CNTs surface or loss the conductivity. The biosensor device fabricated by anti-avian metapneumovirus (*anti*-aMPV) antibody functionalized SWCNTs/multi-polymers was reported [49]. SWCNTs/multi-polymers were fixed onto Cr/Au coated silicon wafer via a non-covalent layer-by-layer self-assembly technique. *Anti*-aMPV antibody species were then immobilized on the device surface. Moreover, the CNTs based field effect sensor device was designed by coating the as-prepared homogeneous and transferable CNTs thin films in the presence of poly(methyl methacrylate) on Au/Cr coated silicon thermal oxide wafer [50]. Afterward, CNTs thin film blocks bridging the electrodes were constructed using negative photoresist and photolithography. In order to enhance the selectivity towards M13-bacteriophage and avoid the unwanted sorption of other species on the surface of the sensor, the CNTs sensor was equilibrated in phosphate buffer solution (PBS) buffer. Then, CNTs thin film blocks were decorated with *anti*-M13 bacteriophage antibodies. This antibody CNTs based sensor device was used to detect approximately 550 model label-free viruses, wherein its sensitivity was five orders higher than free-CNTs antibody sensor device. Furthermore, the gold nanoparticles (AuNPs) functionalized MWCNTs composite was fabricated to detect the swine influenza virus [51]. Firstly, the AuNPs were conjugated with aptamer or anti-hemagglutinin antibody. Thiol (SH)-linker was used to conjugate AuNPs and aptamer. The conjugation of AuNPs and anti-HA antibodies was carried out via 3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) method. Afterward, AuNPs-aptamer or AuNPs-antibody conjugated probe was immobilized onto MWCNTs.

Ultra-sonication followed by ultracentrifugation can also be used to functionalize CNTs non-covalently. The highly photoluminescent DNA functionalized SWCNTs were used for the fast optical detection of HIV in serum through non-covalent synthesis [41,52]. DNA was composed of a single oligonucleotide sequence having two domains, including a $(GT)_{15}$ nanotube-binding sequence (to impart the stability of CNTs) and a miRNA capture sequence, which was non-covalently bound to the surface of SWCNTs. The DNA-SWCNTs sensor was constructed by simple ultra-sonication of SWCNTs with DNA oligonucleotides, followed by ultracentrifugation.

Size-based detection (Fig. 3C) using CNTs-based biosensors has also been reported to isolate viruses of different sizes. In this case, the functionalization of CNTs by a bioreceptor is not required. Matching the intertubular distance between CNTs assays, viruses can be captured by them without specific labels. According to this principle, the carbon nanotube size-tunable enrichment microdevice (CNT-STEM) efficiently enriches and concentrates viruses collected from field samples, potentially providing a powerful method for novel and emerging virus discovery [25]. The CNT-STEM was fabricated based on nitrogen-doped CNTs arrays decorated with AuNPs for the fast detection and identification of viruses [14,25]. The aligned CNTs arrays were designed via the vertical growth of N doped MWCNTs building blocks on Fe-thin film using the aerosol assisted chemical vapour deposition method. Firstly, Fe film was formed on a prime silicon wafer that was the main responsible for the catalytic growth of N doped MWCNTs with herringbone configurations. A low-cost, efficient stamping-based method was developed to pattern the catalytic Fe NPs instead of lithography and metal deposition techniques. Additionally, depending on the thickness of Fe film, this stamping process allowed to control of the intertubular distances of N doped MWCNTs arrays; intertubular distances (ITDs) within 22−720 nm were obtained, covering a considerable diversity of virus sizes, which could make the capture and identification of unknown virus strains.

3. CNTs-based nano-bio interface for biomarkers detection

In the last three decades, immense technological development

for diagnosing viruses has taken place in the field of virology. Detecting various disease biomarkers, especially viruses and their dynamics, is essential for diagnostic and therapeutic aspiration. Thus, nano-arrays, protein arrays, nano-pore technology, nano-particles as gadgets in immunoassays, and nano-biosensors are integral parts comprising nanotechnology platforms [53]. The progress in CNTs-based nano-interface platforms has had great potential for the early detection of these biomarkers, resulting in an improved, rapid, and accurate screening using biosensors. The CNTs-based biosensors specifically interact with an analyte and retain direct spatial contact with physical, chemical, optical, and electrical transduction systems to obtain a measurable signal [54]. Moreover, new nanotechnology is emerging as a potent means to improve the performance of CNTs-based bio-recognition interfaces [55]. The advancements in new synthetic approaches have led modern material science to deliver high efficacy of smart "nano-materials" used as an interfacial medium. Nanomaterials possess unique physical and chemical properties like high stability, high drug loading with a high aspect ratio, and low toxicity in biomed-ical applications. Nanomaterials produce the synergistic effect of catalytic activity and biocompatibility to accelerate the signal transduction and amplify the bio-recognition actions with specif-ically designed signal tags, leading to a highly sensitive biosensing platform [56]. By exploiting the advantages of nanomaterials, which are being developed with new emerging technologies, the sensitivity and stability of the detection techniques can be signifi-cantly enhanced [57,58]. Therefore, a great diagnostic accuracy with low detection limits achieved by such methods has greatly improved the performances of point-of-care devices, making them accessible at the patient's bedside. Furthermore, the scientific and technological interests in nanomaterials greatly facilitate the application of CNTs-based nano-bio interface in detecting various biomarkers, including viruses.

The development of nanomaterials has revolutionized bio-sensing due to their enhanced electrical, optical, chemical, and magnetic properties. Moreover, metallic nanomaterials and hybrid materials have been integrated with CNTs to improve the perfor-mance of CNTs-based nano-interface in biosensing. Over the past few decades, varieties of composites combined CNTs with metallic nanomaterials are the area of extensive research in biosensing. Given these factors, the nanomaterials based on transition-metal oxides, including iron (Fe), molybdate (Mo), zinc (Zn), and copper (Cu) oxide, as well as bi-metallic NPs or alloys such as Au nickel (AuNi), Au copper (AuCu), and Cu cobalt (CuCo) are considered to be the excellent alternatives comparably with pure noble metals [56,59]. These composites are considered desirable platforms in biological and chemical sensing applications as they are highly sensitive and possess rapid response. Hybrid materials, which consist of a variety of communities such as organometallics, soft matter, and polymers, metal-organic frameworks (MOFs), sol-gel, catalysis and surfaces, nonporous and mesoporous materials, bio-materials (aptamers, antibodies, enzymes, and DNAs, etc.) are another important class which has been explored since long in biological applications. They are biocompatible and can catalyze biological signals, and many of them can mimic molecular func-tions, making them an attractive choice in biotechnology [60−62]. The improved electrocatalytic performance of these hybrid nano-materials can be further achieved with different morphologies and sizes. After incorporating with CNTs, they can enhance the sensi-tivity of the target biomolecules up to hundreds of orders [63]. Hence, the CNT-based composites can improve the catalytic activ-ity, stability, and analytical performance in biomarkers detection.

Besides, the presence of edge-defect sites on the CNTs surface plays a vital role in communicating with the sensor surface and biological molecules, which are surrounded deep inside the peptides. Because of the small size and high aspect ratio of CNTs, they can easily approach the electroactive sites of these molecules. Moreover, the biological molecules can be interacted with CNTs either covalently onto an oxidized surface or non-covalently through electrostatic interaction, π-π stacking, van der Waals force, and hydrophobic or hydrophilic methods [34]. In addition, the superconductive nature of CNTs can enhance the electron transfer and amplify the signal obtained in the biosensing or bio-recognition process. Thus, massive research on CNT-based elec-trochemical biosensors has been reported to measure ions, me-tabolites, and protein biomarkers [64]. The CNTs-based nano-bio interface for biomarker detection can be fabricated by covalently modified CNTs, non-covalently modified CNTs, and unmodified CNTs for viral detection (Fig. 4). CNTs have a great potential to be utilized in optical sensing platforms; however, the number of studies that exploit the optical properties of CNTs for biosensing is small compared to electrochemical or electrical properties. One of the interesting phenomena of CNTs is the quenching ability, which is a sequential process of an absorbed photon (light) that excites the electron (in CNTs) and then results in recombination (fluorescence photon). Thus, the quenching phenomenon of semiconducting SWNTs is particularly interesting for biosensing. Unabsorbed by biological tissue, near-infrared radiation (NIR) can be used for biosensing within biological samples, organisms, and intra- or extracellular matrices [28,65,66].

4. Engineering CNTs for viral detection

CNTs can be engineered by many materials, including bio-materials, metallic nanomaterials, polymers, and hybrid nano-materials, due to the surface functional groups, π-π conjugated structure, and high aspect ratio [26]. CNTs are primarily used as labels or carriers, which can remarkably enhance the detection capacity of viruses. However, the functional groups on CNTs are few. Therefore, researchers have developed many methods to modify CNTs, which significantly extends the application of CNTs in sensitive virus detection. The engineering process of CNTs is ob-tained via covalent grafting, physical adsorption, and entrapment to form the CNTs-based nano-bio interfaces [26]. After the modi-fication, the CNTs-based nanocomposites are immobilized by the bio-recognition elements such as aptamer, antibody, antigen, ssDNA, and RNA for specifically recognizing viruses [67]. According to the type of CNTs-based nano-bio interfaces, we classify the viral biosensors into three groups, covalently engineered CNTs, non-covalently engineered CNTs, and size-tunable CNTs arrays for viral detection. The performances of CNTs-based nano-bio in-terfaces for viral detection are summarized in Table 1.

4.1. Covalently engineered CNTs for viral detection

CNTs inherently hold a high aspect ratio, excellent mechanical and electronic properties, outstanding optical, good environmental stability, etc., making them attractive for signal enhancement in various fields [26,33,80]. However, bare CNTs do not show notice-able affinity to biomolecules, so they need to be modified with bioreceptors, containing antibody, antigen, aptamer, ssDNA, RNA, and even whole biological tissues [26]. These have a compelling affinity with biomolecules, so they regard as the bio-recognition elements. In order to maintain the stability and reliability of viral biosensors, the bio-recognition elements need to be covalently modified on the surface of CNTs through the functional groups on CNTs, such as carboxyl, amino, and hydroxyl. The covalent immo-bilization of bio-recognition element is employed owing to the reaction between CNTs and amino, or carboxyl functional groups of the bio-recognition elements using cross-linkers EDC and NHS. The
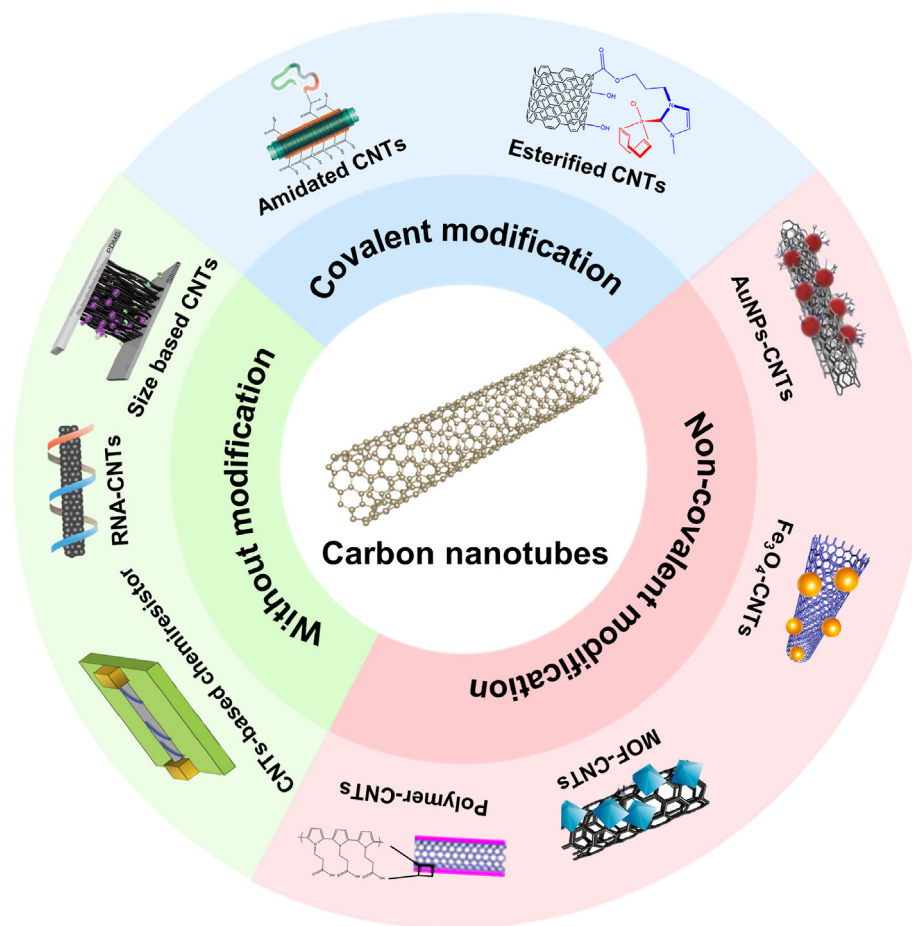
Fig. 4. Schematic illustration of the strategies for CNTs engineering and the CNTs-based nano-bio interface for biomarker detection.

Table 1
Summary of CNTs-based nano-bio interface for viral detection.

Type	Modified material	Target	Recognition element	Linear range	LOD	Ref.
Covalence	DNA probe, HCV core antibody	HCV core antigen	HCV core antibody	0.25−300 pg mL^{-1}	0.01 pg mL^{-1}	[27]
	HA, HBc antigen	*Anti*-HBc	HBc antigen	1−6 ng mL^{-1}	0.03 ng mL^{-1}	[68]
	RNA aptamer	HIV-1 Tat	RNA aptamer	0.2−1000 nM	600 pM	[40]
	Ethylenediamine	DENV NS1 protein	*Anti*-NS1	40−2000 ng mL^{-1}	12 ng mL^{-1}	[69]
Electrostatic interaction	Au NP	H3N2	Antibody	50-10000 PFU mL^{-1}	50 PFU mL^{-1}	[70]
	Au NPs	H3N2	Antibody	10-50000 PFU mL^{-1}	3.4 PFU mL^{-1}	[71]
	Au NP, MNP	H1N1	H1N1 antibody	1 fg mL^{-1}-1 µg mL^{-1}	2.16 fg mL^{-1}	[72]
	NiCo$_2$O$_4$/CoO	HIV-1 DNA	DNA probe	0.1−20000 pM	16.7 fM	[73]
	CS	HIV-p24	MIPs	0.1−2000 pg mL^{-1}	0.083 pg mL^{-1}	[74]
	SiO$_2$-HRP, CS	HIV-p24	*Anti*-HIV-p24	0.5−8500 pg mL^{-1}	0.15 pg mL^{-1}	[39]
	Poly(allylamine)	DENV NS1	*Anti*-NS1	0.1−2.5 µg mL^{-1}	0.035 µg mL^{-1}	[10]
π-π stacking	Polyaniline	*Anti*-HPV-16	HPV-16-L1 peptide	10−50 nM	490 pM	[75]
	Polypyrrole-NHS	DENV NS1 antibody	Dengue toxin	1 pg mL^{-1}-10 µg mL^{-1}	1 pg mL^{-1}	[76]
	Pyr-NH$_2$	DENV	Heparin	840-8.4 × 10^5 TCID$_{50}$ mL^{-1}	840 TCID$_{50}$ mL^{-1}	[8]
	DNA probe	H5N1 DNA	DNA probe	2−2000 pM	/	[77]
	DNA probe	Influenza A virus DNA	DNA probe	1−10000 pM	1 pM	[78]
	DNA probe	H5N1 DNA	DNA probe	0.01−20 µM	9.39 nM	[79]
Size-tunable CNTs	DNA probe	HIV RNA	DNA probe	/	/	[41]
	/	H5N2	/	/	1 EID$_{50}$ mL^{-1}	[25]

EDC/NHS coupling is used to activate carboxyl on CNTs or bio-molecules for immobilizing bio-recognition element through amide bonds [67]. According to these physical signals (current, optical absorbance, heat, etc.), different CNT-based biosensors have been developed [38]. Generally, the CNTs or CNTs-based materials are applied to detect viruses to improve their electrical conductivity and sensitivity. Then, they are integrated into portable miniaturized sensing devices for their small size and electronic properties and utilized in fluorescence sensing platforms based on the fluorescence resonance energy transfer (FRET) [10,79]. Herein, we will focus on the covalently engineered CNTs for viral detection owing to their excellent performance and wide application.

The main methods of virus diagnosis include detecting antigen (Ag), host antibodies (Abs) made against different viral proteins, nucleic acids of the virus, and the whole virus [12]. As an essential component of the virus, antigen, which can promote an immune response from the infected host, is a promising biomarker for the reliable and accurate diagnosis of viruses. The ELISA, as a classic method, has been widely used for the quantitative detection of viruses with high specificity and sensitivity [27,75]. However, ELISA presents some inherent limitations, such as long analysis time, complex operating procedures, high sample consumption, and expensive instruments. Hence, alternative methods need to be developed with faster responses, easy to use, low cost, lower detection limit, high sensitivity, and repeatability. Compared with other types of immunosensors, CNTs-based electrochemical immunosensors have displayed great competitiveness in detecting viral antigens with superior analytical performances.

Due to their outstanding electronic properties, large surface area, and chemical properties, various CNTs-based electrochemical immunosensors have been developed to detect viral antigens with high sensitivity [69,73,81]. These immunosensors are generally constructed via immobilizing a capture antibody on the surface of the electrode, which is then allowed to combine with its corresponding antigen. Some researchers have focused on the excellent mechanical and electronic properties of CNTs to improve sensitivity and faster responses of biosensing devices [82,83]. Ma and co-workers reported a strategy using CNTs as a nanocarrier (Fig. 5A) [27], which combined with DNA hybridization chain reaction (HCR) to amplify the signal for the detection of hepatitis C virus (HCV) core antigen. The modified electrode was constructed by the composites of graphitized mesoporous carbon-methylene blue. Moreover, Au NPs were electrodeposited on this electrode for immobilizing HCV core antibody (Ab1). To create a secondary antibody layer, a bridging DNA probe (BP) and secondary antibody were attached to MWCNTs-COOH, a biotin-tagged signal DNA probe (bSP) and auxiliary DNA probe (AP) were bound with BP via

HCR, then HRP as redox enzyme was linked to DNA probes through the biotin-streptavidin system (MultisHRP-DNA-CMWNTs). HCV core antibody (Ab2) was labeled on MultisHRP-DNA-CMWNTs, enabling the immunosensor to obtain detection signals at low analyte concentrations. Under optimized conditions, the proposed immunosensor suggested an excellent linear relationship in the concentration of HCV core antigen concentration ranging from 0.25 pg mL^{-1} to 300 pg mL^{-1} with a low limit of detection (LOD) 0.01 pg mL^{-1}. This immunosensor provides a reliable method to obtain ultra-low LOD through covalently engineered CNTs.

Similar to antigens, antibodies are also significant biomarkers for rapid and convenient diagnoses of viruses [76]. Antibodies, which are the earliest serological biomarkers distributed in the blood during virus infection, are produced by the immune response of the infected host caused by antigens [75]. After acute virus infection, the antibodies can be detected during the recovery period and remain for the whole life after infection. Furthermore, this biomarker may be associated with the viral infection without obvious symptoms, and patients are asked for early screening before starting therapy [68]. Hence, antibody testing is valuable and has become mandatory in serological assays. Antibody screening relies on ELISA and electrochemiluminescence immunoassay after virus infection [68]. However, these techniques are time-consuming, high costs, and complex operations. Electrochemical biosensors have been developed to analyze antibodies qualitatively to overcome these limitations. They are even considered competitive candidates for point-of-care testing in diagnostics because of their excellent advantages [40]. Some CNTs-based electrochemical biosensors have been proposed for accurately detecting antibodies [75,68]. Cabral et al. used hyaluronic acid (HA)-CNTs film to bind proteins in an electrochemical immunosensor for detecting antibodies to hepatitis B (*anti*-HBc) (Fig. 5B) [68]. The synergic effect of HA-CNTs enabled a large number of antigens to be immobilized on it and increased the electron transfer with high diagnostic sensitivity. The achieved linear range of the immunosensor was ranged
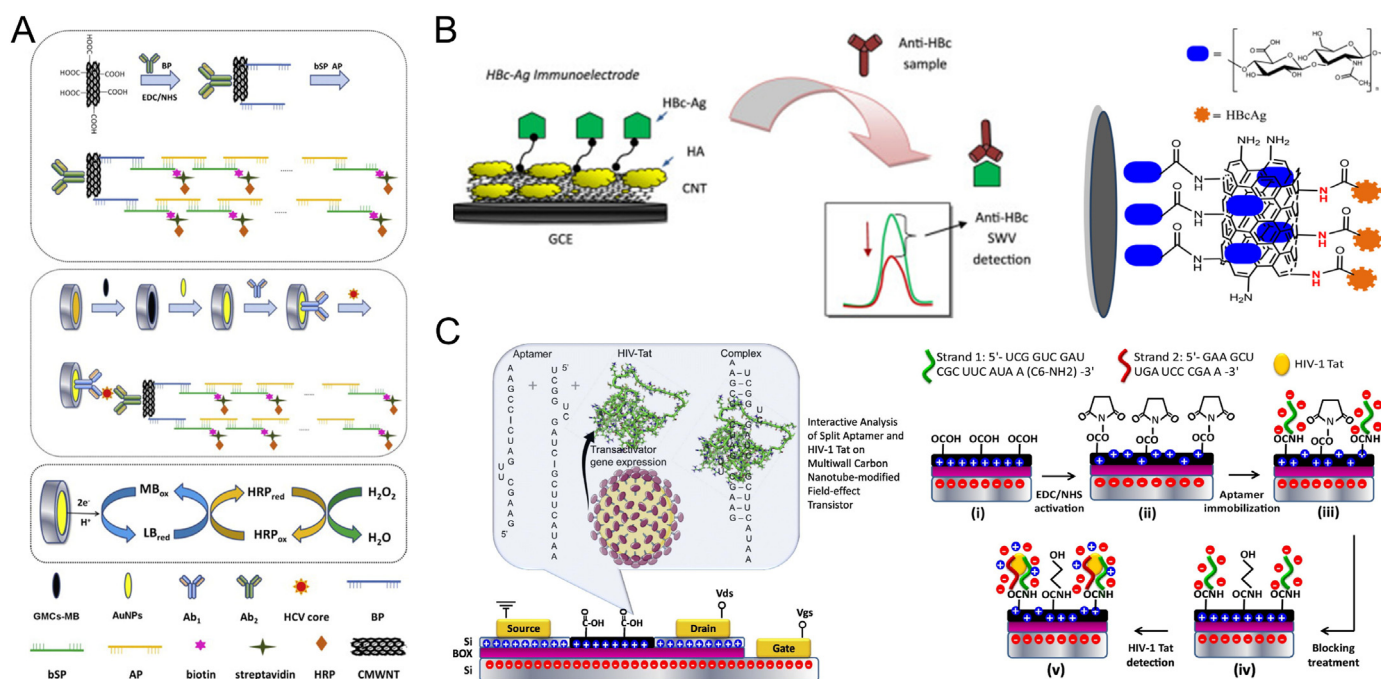

Fig. 5. (A) Preparation of the multis HRP-DNA-CMWNTs-Ab2 bioconjugate and fabrication procedure for the HCV immunosensor. Reproduced with permission from Ref. [27]. (B) Schematic representation of the HA-CNT and immobilization of the HBc antigen. Reproduced with permission from Ref. [68]. (C) Interactive analysis of split aptamer and HIV-1 Tat on multiwall carbon nanotube-modified field-effect transistor and its construction. Reproduced with permission from Ref. [40].

from 1 to 6 ng mL^{-1} with a LOD of 0.03 ng mL^{-1}. Ultimately, the advantages of this electrochemical biosensor, such as rapid analysis and non-incubation with antibodies, indicated that the CNTs-based immunosensor was a promising tool for *anti-HBc* assay.

Unlike antibodies, some regulatory proteins are also indispensable to viruses for mediating early-stage infection, regulating early stages of the viral life cycle, and regulating transcription and replication [51]. These regulatory proteins are usually used for monitoring viral replication and detecting viruses at earlier stages compared with the antibody [40]. Numerous CNTs-based electrochemical approaches have been reported to measure regulatory proteins recognized by antibodies, proteins, peptides, and aptamers [40,51]. Fatin et al. designed a CNTs-based field-effect transistors (FETs) device for the determination of human immune deficiency virus-1 (HIV-1) Tat protein recognized by split RNA aptamer (Fig. 5C) [40]. The split RNA aptamer was immobilized on MWCNTs-COOH, and HIV-1 Tat was quantified by electrical measurement through the current signal (Ids) over a gate voltage (Vgs) for the interaction between split RNA aptamer and HIV-1 Tat. The fabricated device displayed an excellent sensitivity towards HIV-1 Tat with a LOD of 600 pM. This immunosensor exhibited promising prospects for other target analytes and biomarker types and great potential for clinical applications.

The covalently engineered CNTs are highly stable, and most of them are used in the electrochemical detection of viral nucleic acids, especially DNA. In electrochemical DNA biosensors, the CNTs or their composites were firstly modified on electrodes with different materials under ambient conditions [9,84]. Then, the probe DNA was grafted on the surface of CNTs or their composites via the interactions between the groups in probe DNA and CNTs-based materials [40,41]. Next, the target DNA was introduced to combine with probe DNA through DNA hybridization forming the sandwich or sandwich-based structure [26]. At last, the signal changes attributed to DNA hybridization are collected by related equipment, obtaining the concentration information of viral DNA. Besides the large surface-to-volume ratio and excellent conductivity of CNTs, they can be easily modified with many chemical ligands, biomolecules, and other materials [26]. These significant features of CNTs are appropriate for viral DNA detection systems. Before binding with probe DNA, CNTs were usually functionalized with boiling HNO$_3$ to generate the carboxylic groups [85], allowing CNTs to have functional groups connected to other molecules through chemical reactions. Some works directly modified the CNTs on the electrodes and then grafted probe DNA on the surface through chemical reactions toward viral DNA detection [85,86]. Li et al. described a novel label-free electrochemical DNA biosensor for hepatitis B virus (HBV) DNA [86]. The MWCNTs-COOH were modified on 4,4′-Diaminoazobenzene (4,4′-DAAB) functionalized glassy carbon electrodes via carbodiimide chemistry mediated by EDC and NHS. Consequently, this electrochemical DNA biosensor displayed excellent specificity and chemical stability for HBV's DNA sequences. Taken together, the covalently engineered CNTs are used for improving the performance of biosensors is an efficient strategy for sensitive viral detection.

4.2. Non-covalently engineered CNTs for viral detection

Due to the lack of sufficient functional groups, CNTs are non-covalently modified by other nanomaterials, such as metallic nanomaterials, sol-gel, polymers, MOFs, and hybrid materials. The high aspect ratio and π-π conjugated structure of CNTs ensure that CNTs can be modified by other materials through non-covalent interactions (electrostatic interaction, π-π interactions, Van der Waals forces, and physical adsorption) [26]. The non-covalently CNTs-based nano-bio interface is mainly fabricated by

electrostatic interaction and π-π interactions, which significantly enlarges the application of CNTs in sensitive virus detection. In general, the CNTs are firstly modified by different nanomaterials via electrostatic interaction or π-π interactions [8]. Then, the bioreceptor is grafted on the surface of the CNTs-based composite via the interactions between the groups in the bioreceptor and composite. Moreover, the bioreceptor can be directly combined with CNTs through π-π stacking interaction without a label [52]. In terms of the classification, the non-covalently CNTs-based nano-bio interfaces have been presented into electrostatic interaction mediated CNTs-based nano-bio interface, π-π stacking interaction mediated CNTs-based nano-bio interface, and bare CNTs interface.

4.2.1. CNTs-based nano-bio interface engineered by electrostatic interaction for viral detection

The CNTs functionalized with COOH and OH groups usually display a negative charge in water [26]. Thus, CNTs can combine with various positively charged materials through electrostatic interaction, containing metal ions, metallic nanomaterials, metal oxide nanomaterials, positively charged polymers, and positively charged proteins, etc. The metal-based materials are positively charged in water because metal ions are positively charged [70]. Simultaneously, the soft matter, polymers, and biomaterials are positively charged in water due to the NH$_2$ group. The modified materials are robustly attached to CNTs through electrostatic interaction and other non-covalent interactions. Therefore, the electrostatic interaction is a reliable mechanism for the modification of CNTs. After engineering by electrostatic interaction, the CNTs-based nano-bio interface will be combined with bioreceptors for virus detection.

Acting CNTs as a nanocarrier, the optical sensors have also been investigated for detecting the whole virus, based on the composite of Au NPs and CNTs (AuCNTs) via electrostatic interaction. Lee et al. explored a novel optical sensor for influenza virus detection owing to plasmon-assisted fluoro-immunoassay (PAFI) (Fig. 6A) [70], which was based on the plasmonic resonance energy transfer (PRET) phenomenon between Au NPs and CNTs assisted by quantum dots (QDs). During the construction of the PAFI-based sensor, Au ions (Au^{3+}) were adsorbed on the surface of multi-walled CNTs through electrostatic interaction to form AuCNTs. Next, antibodies against the influenza virus were grafted on the AuCNTs, as well as cadmium telluride quantum dots (CdTe QDs). This whole virus sensor exhibited superior performance in clinically isolating influenza viruses ranging from 50 to 10,000 PFU mL^{-1}, with a LOD of 50 PFU mL^{-1}. Similarly, they also reported another work on a colorimetric biosensor of influenza virus based on the AuCNTs hybrid composite [71]. The AuCNTs hybrid materials displayed enhanced peroxidase-like activity, which could catalyze the oxidation of 3, 3′, 5, 5′-tetramethylbenzidine (TMB) by H$_2$O$_2$, and the reaction solution turned blue color. The linear response of this whole virus sensor was up to 10 PFU mL^{-1} in human serum. As a result, the LOD of the colorimetric biosensor was 3.4 PFU mL^{-1}, 385 times lower than the conventional ELISA (1312 PFU mL^{-1}). Furthermore, the sensitivity of this method was 500 times greater than commercial immunochromatography kits. Hence, electrostatic interaction is an effective method to fabricate CNTs-based nano-bio interfaces.

Because of the superior electronic properties, the CNTs-based composites are used to fabricate electrochemical sensors for virus surveillance [87,74]. Cheng et al. combined MWCNTs and Au NPs through electrostatic interaction to construct an electrochemical biosensor for Enterovirus 71 virus (EV71) determination [87]. This biosensor was used to directly monitor virus strains according to the testing of clinical samples in real life. Ultimately, this work obtained good selectivity with the presence of interferents and low
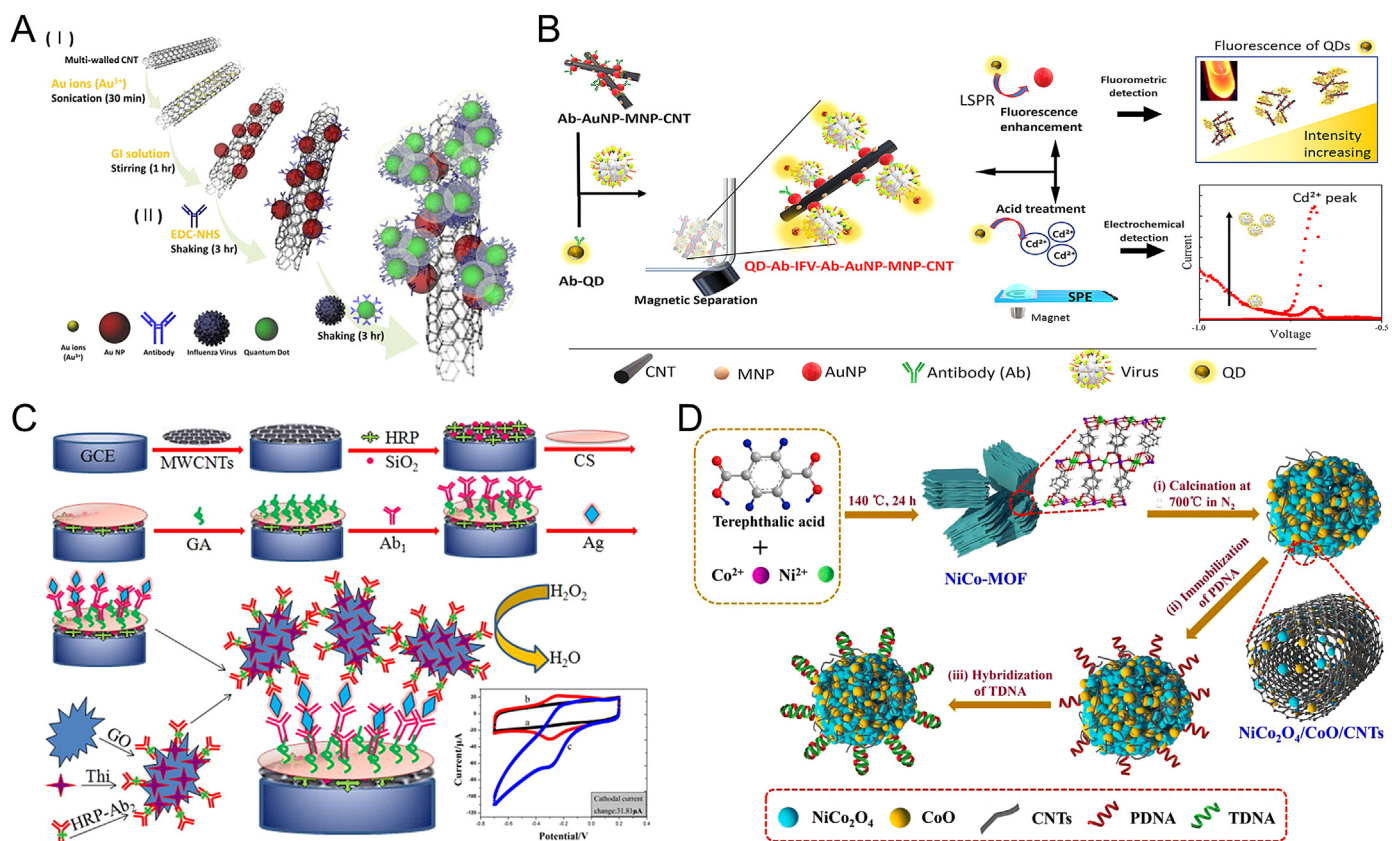
Fig. 6. (A) (I) Synthetic scheme for the preparation of Au nanoparticle decorated CNT nanostructures (AuCNTs) and (II) the process of influenza virus detection by using PAFI, non-scalable. Reproduced with permission from Ref. [70]. (B) Schematic of the optical and electrochemical IFV detection method using plasmon nanocomposites and QDs. Reproduced with permission from Ref. [72]. (C) Schematic representation of the preparation of immunosensor array. Reproduced with permission from Ref. [39]. (D) Schematic diagram of the fabrication procedure of the NiCo₂O₄/CoO/CNTs-based assay for detecting HIV-1 DNA, including (i) the fabrication of the NiCo₂O₄/CoO/CNTs-based assay, (ii) the immobilization of the probe DNA, and (iii) the detection of the HIV-1 DNA. Reproduced with permission from Ref. [10].

LOD for EV71. Besides, Takemura et al. used the localized surface plasmon resonance (LSPR) effect between nanoparticles to develop the dual-signal virus detection (Fig. 6B) [72]. In the dual-signal virus detection system, the CdSeTeS QDs were acted as optical and electrochemical signal-generating materials. The nanocomposite consisted of AuNPs, magnetic nanoparticles (MNPs), and highly conductive CNTs, and then conjugated with antibodies to recognize the target virus. After binding this target virus in a sandwich structure, the AuNPs were used for enhancing the fluorescence signal of QDs through the LSPR mechanism. Owing to its magnetic properties, the MNP was utilized to separate the analyte captured in the sandwich structure from the solution. In addition, the CdSeTeS QDs were regarded as the two signal generators with a long fluorescence lifetime and high dispersibility in the solution. Consequently, the increase of the fluorescence intensity and current values of this virus detection method was concentration dependent even in human serum. This biosensor exhibited excellent LOD, 2.16 fg mL^{-1} for optical detection and 13.66 fg mL^{-1} for electrochemical detection. These results demonstrated that the dual-signal virus detection method was reliable and stable.

Wang and co-workers modified the composite of MWCNTs and (3-Aminopropyl)triethoxysilane (APTES) by electrostatic interaction on an interdigitated electrode (IDE) surface to combine aptamers and antibodies for the measurement of hemagglutinin [51]. Through the sandwich patterns, this sensing system showed high sensitivity towards hemagglutinin detection. In addition, the LOD was estimated to be 10 fM for aptamer, and it was 1 pM for antibody. Moreover, the high-performance system exhibits

promising prospects for the point-of-care system for viral detection. Meanwhile, CNTs can combine with positively charged polymers through electrostatic interaction, such as chitosan (CS). Ma's group proposed a strategy for whole virus detection. The MWCNTs were firstly covered by CS through electrostatic interaction. Then, the novel molecularly imprinted polymers (MIPs) were constructed on the surface of CS and MWCNTs for the measurement of human immunodeficiency virus p24 (HIV-p24) [58]. The whole HIV-p24 was used as the template, acrylamide (AAM) acted as a functional monomer, N, N′-methylene bisacrylamide (MBA) served as the crosslinking agent, and ammonium persulphate (APS) as initiator. The reported whole HIV-p24 biosensor could specifically recognize the target and suggested a wide linear detection range from 1.0×10^{-4} to 2 ng mL^{-3} with a LOD of 0.083 pg mL^{-3} (S/N = 3). Furthermore, this biosensor achieved satisfactory results for the detection of HIV-p24 in real human serum samples. Fang et al. designed a multienzyme amplification strategy for electrochemical immunosensor to measure HIV-p24 (Fig. 6C) [39], in which enzyme encapsulated in MWCNTs-silica as a matrix and the MWCNTs were coated by CS. To enhance the sensitivity, the horseradish peroxidase-labeled HIV-p24 antibody (HRP-HIV-p24) was linked to graphene oxide (GO) and thionine (TH), and HRP was efficiently encapsulated in the silica matrix as well. Consequently, the sandwich electrochemical immunosensor showed high sensitivity to HIV-p24 in a concentration range of 0.5 pg mL^{-1} to 8.5 ng mL^{-1} with LOD of 0.15 pg mL^{-1}. These electrochemical biosensors developed by the composites of CNTs and polymers are facile approaches for viral detection, which may be further improved by

incorporating CNTs with other polymers.

MOFs are a kind of emerging porous materials formed by co-ordination between metal ions or ion clusters and organic ligands. Hence, MOFs can be modified on CNTs through multiple non-covalent interactions, such as electrostatic interaction. Binding with bioreceptors, the composites of MOFs and CNTs are also used for virus detection. Jia and coworkers reported that a novel CNT-based composite was used to form a viral DNA sensor to test the HIV-1 DNA (Fig. 6D) [10]. This novel composite comprising $NiCo_2O_4$ spinel, CoO, and metallic Co/Ni nanoparticles was pyrolyzed from a bimetallic NiCo-based metal-organic framework (NiCo-MOF) and embedded with CNTs ($NiCo_2O_4/CoO/CNTs$) under high temperature. The probe DNA was immobilized on $NiCo_2O_4/CoO/CNTs$ because of its strong bio-affinity. This viral DNA sensor presented superior performances, and its linear range was from 0.1 pM to 20 nM with an ultralow LOD of 16.7 fM. In conclusion, these CNTs-based nano-bio interfaces engineered via electrostatic interaction simplify the detection of viruses and improve their sensitivity.

4.2.2. CNTs-based nano-bio interface engineered by π-π stacking for viral detection

Besides the electrostatic interaction, the π-π stacking interaction, which is based on the π-π conjugated structure of CNTs, is another important interaction for the modification of CNTs. Varieties of compounds with π electrons can bind with CNTs through π-π stacking interaction, especially the compounds containing pyrene rings [8]. According to the pyrene-linker, the CNTs can be further functionalized by bioreceptors, which significantly expands the application of CNTs in viral detection. The CNTs-based nano-bio interface engineered by π-π stacking interaction is further decorated by bioreceptors. To date, various detection techniques have been developed for virus detection, such as PCR-based testing, ELISA, plaque assays, and sensors [88]. Most of these detection techniques require complex sample preparation procedures, including viral isolation, extraction, purification, and amplification of respective biomolecules [12]. However, the CNT-based determination of virus is much simpler in sample preparation, which shows promising potential in point-of-care testing based on lab-on-a-chip devices. Moreover, the functionalized CNTs by π-π interaction further simplify the immobilization process of bioreceptors. Due to their excellent mechanical and electrical properties, CNTs are particularly suitable for the electronic detection of viruses with low cost and high sensitivity.

In virus surveillance, the explosive growth of CNTs-based methods has benefitted from the inherent properties of CNTs [41]. Researchers have explored large quantities of CNTs-based sensing platforms for the virus, including portable microfluidic platforms, miniaturized electrical devices, modified electrode-based sensors, and optical sensors [25,87]. The CNTs-based biosensing interface constructed by π-π interaction is an important field of viral detection. Wasik et al. used heparin to functionalize the SWCNT network chemiresistor to detect the dengue virus with high sensitivity and antibody-free (Fig. 7) [8]. In this chemiresistive biosensor, heparin, instead of antibody, is recognized as the biorecognition molecule to detect the virus. The 1-pyrenemethylamine (Pyr-NH₂) was firstly adsorbed onto the SWNTs via π-π interaction. Next, the carboxyl groups of heparin were cross-linked to primary amine groups on the Pyr-NH₂. The biosensors exhibited excellent performance for detecting dengue type 1 virus in PBS and DENV isolation in cell culture. A LOD of 8.4×10^2 $TCID_{50}$ mL^{-1} (~8 DENV/chip) was obtained to measure DENV with only 10 μL sample in 10 min. The electronic biosensors based on SWCNT achieve important progress in point-of-care detection and monitoring pathogens with sylvatic cycles. In addition, they also reported another work that a label-free
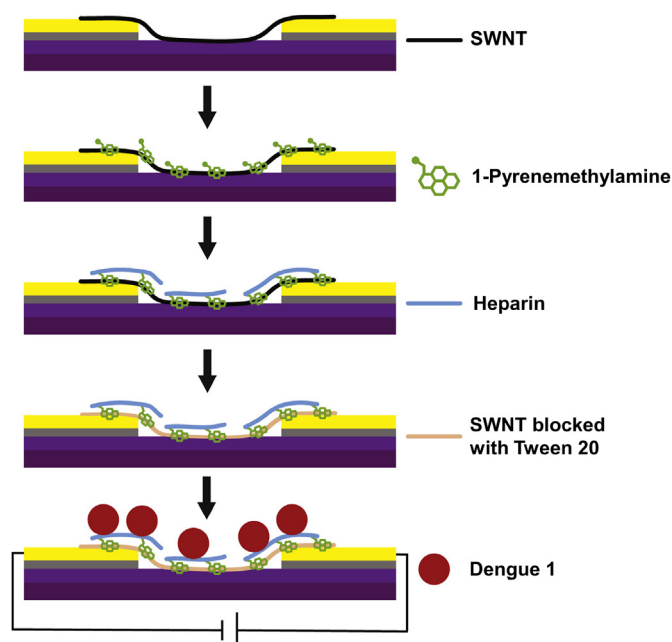

Fig. 7. Functionalization schematic representation of the fabrication of the chemiresistor used for detection of Dengue virus. Reproduced with permission from Ref. [86].

chemiresistive immunosensor was fabricated to detect the DENV non-structural protein 1 (NS1). The dense network of self-assembled SWNT was integrated on the gold microelectrodes, and then the 1-enebutyric acid (Pyr-COOH) and 1-Pyrenebutyric acid *N*-hydroxysuccinimide ester (PBASE) were adsorbed onto the SWNTs via π-π interaction. Next, the anti-dengue NS1 monoclonal antibodies were cross-linked to PBASE on the SWNTs. The proposed immunosensor presented a quantification range of ~1 ng mL^{-1} to 1000 ng mL^{-1} of NS1 in artificial human saliva. Liu et al. proposed a sensitive electrochemical sensor for the detection of avian influenza virus (AIV) H5N1 DNA with hybrid nanomaterial [9]. The hybrid nanomaterial was constructed by MWNTs, polypyrrole nanowires (PPNWs), Au NPs, and the probe DNA, which was immobilized onto it via Au−S bond. This composite offered a porous structure with a large surface area, highly electrocatalytic activities, and electronic conductivity. The proposed viral DNA sensor exhibited an excellent linear range from 5.0 pM to 1.0 nM (R = 0.9863) with a detection limit of 0.43 pM. Therefore, the π-π stacking interaction is also a reliable strategy to construct the CNTs-based nano-bio interface for detecting viruses.

4.2.3. CNTs immobilized bioreceptor through π-π stacking for viral detection

Most biomolecules have π electrons from the benzene ring and its derivatives, which allow bioreceptors to directly bind with CNTs through π-π stacking interaction without additional modification. DNA, RNA, and peptides can be decorated on CNTs via π-π interaction while maintaining the ability to recognize biomarkers. Generally, DNA and other small oligonucleotides are potential disease biomarkers to diagnose, monitor, and stratify disease states [41,52]. However, the genetic materials of most viruses are RNA. Both endogenous and exogenous RNAs strands found in viruses are useful for the rapid diagnosis of relative infectious diseases, and their detection principle is also based on nucleic acid hybridization as same as DNA [41]. The exogenous RNAs are cell-free oligonucleotides in biofluids such as serum and urine [52,89], which are promising biomarkers for the detection of cancer and many other

diseases. Furthermore, the rapid and quantitative detection of endogenous viral RNAs is very significant for diagnosing infections before symptoms appear, the same as monitoring the disease's course. Recently, some CNTs-based methods have been explored to detect RNA in biological fluids such as serum and urine [41,52,90,91].

Harvey et al. designed an engineered carbon-nanotube-based sensor that could optically quantify the hybridization events of microRNA and other oligonucleotides in real-time (Fig. 8A–F) [52]. A single DNA oligonucleotide, which contained a nanotube-binding sequence ($(GT)_{15}$) and a miRNA capture sequence, was bound to CNTs through π-π stacking interactions (Fig. 8A). The mechanism of the sensor was based on the competitive effects between the displacement of both oligonucleotide charge groups and water on the nanotube surface, resulting in a response similar to solvent-induced discoloration. The sensor worked through single-molecule sensor elements and was multiplexed by using multiple nanotube chirality. The sensor could detect nucleic acids in whole urine and serum and non-invasively measure DNA and microRNA after implantation in live mice (Fig. 8E and F). After immersing the filled capillary into buffer containing RNA, the implantable device in vitro displayed an excellent detection threshold below 10 pmol. Moreover, the limit of detection of this device implanted in mice was measured down to 100 pmol. Additionally, they further used

this CNTs-based optical sensor for the detection of single-strand RNA from HIV in complex media (Fig. 8G) [41]. The probe DNA oligonucleotides were firstly modified on CNTs via π-π interaction. Then the liberated RNA hybridized to the probe DNA, freeing space on the SWCNTs surface. Next, the denatured viral proteins could bind to the freed space on the SWCNTs surface, eliciting an enhanced blue-shifting response. Under the condition of 50 mg mL^{-1} bovine serum albumin (BSA) treated with 1% sodium dodecyl sulfate (SDS), the concentration of target miR-19 DNA diluted with GT_{15}miR19 was ranged from 10 to 1000 nM generating a wavelength shift response. This work indicated that the CNTs-based point-of-care optical detection method of viruses exhibited promising application in viral nucleic acids determination.

To meet the needs of fast and mobile analysis requirements in possible threatened areas, the high integration, low-power, and portable miniaturized sensors seem to be suitable and useful [38]. Hence, various potential biosensors have been developed to satisfy these demands, including lab-on-a-chip, chemiresistor-type biosensors, FETs, and so on [92,93]. Fu's group developed CNT-based chemiresistor-type sensors to detect the AIV subtype H5N1 DNA [77]. To achieve susceptible and rapid label-free detection, these viral DNA sensors were constructed by semiconducting SWCNTs (sc-SWCNTs) and nitrogen-doped multi-walled CNTs (N-MWCNTs). The probe DNA was attached to CNTs via π-π interaction. These
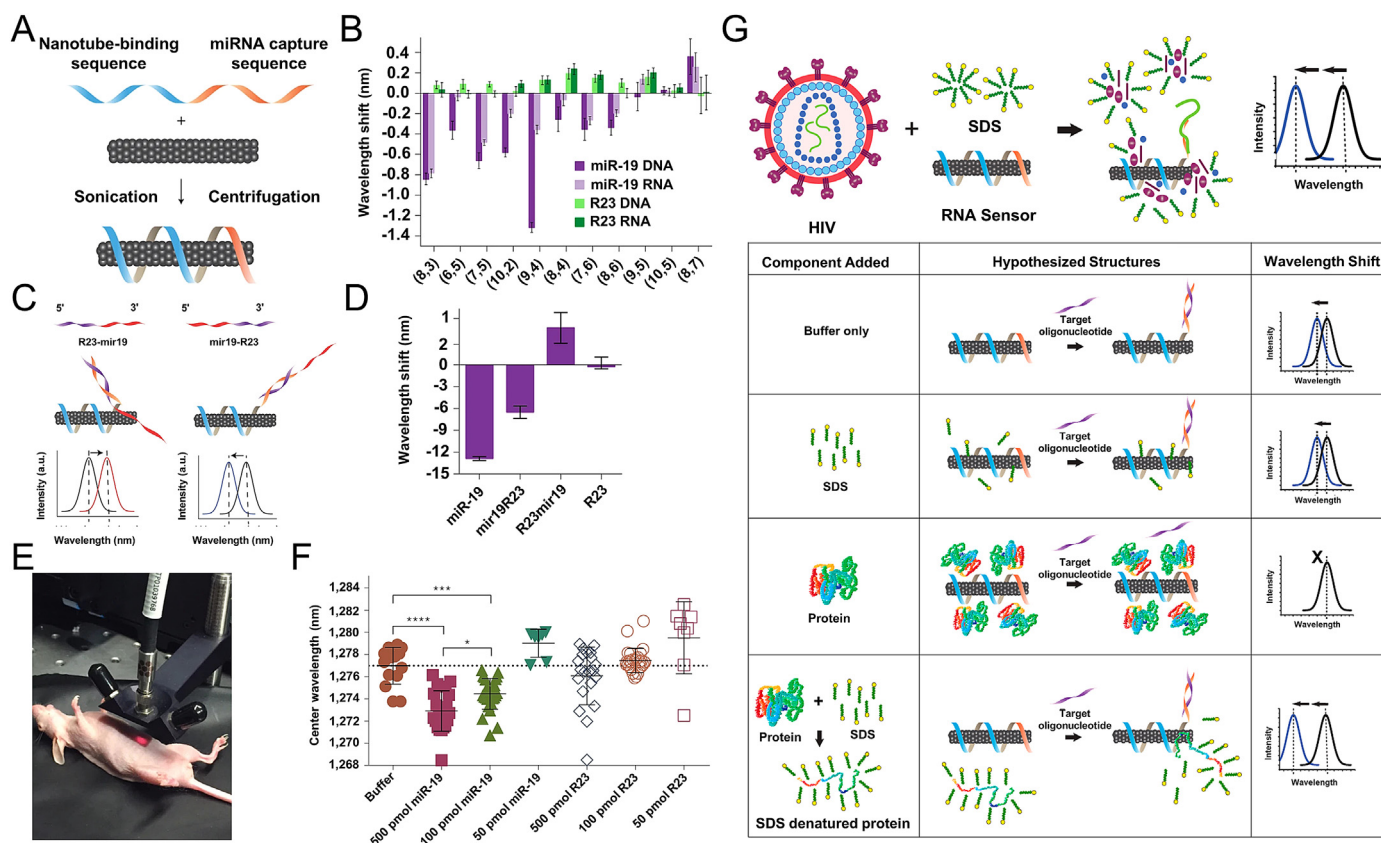

Fig. 8. (A) Construction scheme of the miRNA sensor complex, consisting of a single DNA oligonucleotide containing a nanotube-binding sequence (blue) and a miRNA capture sequence (orange) that is non-covalently bound to the carbon nanotube surface. (B) Response of the GT_{15}mir19 sensor to analyte DNA or RNA with the miR-19 sequence or a control sequence (R23), for each nanotube chirality (n,m). A positive wavelength shift denotes a red-shift in the emission peak, and negative values denote a blue-shift. (C) Cartoons depicting an experiment designed to assess orientation of partially complementary sequences, including predicted sensor responses. (D) Response of (8,6) nanotubes on interrogation of the GT_{15}mir19 sensor with partially complementary oligonucleotides. All error bars represent the standard deviation for three technical replicates. (E) Image of the near-infrared probe system measuring the nanotube response in a live mouse. (F) Response of implanted sensor ((8,7) nanotubes) device to 500, 100 and 50 pmol of miR-19 RNA or R23 RNA injected intraperitoneally into mice (3–4 measurements per mouse; 3 mice per group). R23 (50 pmol) was slightly red-shifted compared with the buffer-control. Reproduced with permission from Ref. [52]. (G) Model depicting HIV RNA detection. Reproduced with permission from Ref. [41].

chemiresistor-type sensors displayed the detection range from 2 pM to 2 nM in 15 min. Besides, Tran et al. reported a novel carbon nanotubes field-effect transistor (CNTFET) based DNA sensor to detect influenza A virus DNA [92]. The probe DNA was immobilized on CNTs by simple physio-sorption. This viral DNA sensor revealed an excellent performance in response time that was less than 1 min with high reproducibility. Moreover, the DNA sensor possessed a wide linear range from 1 pM to 10 nM with a low LOD of 1 pM. This virus biosensor exhibits high sensitivity and good stability, which is a promising method for viral detection.

CNTs also display broad light absorption spectra and are considered useful receptors for fluorophores in FRET systems, with a high signal-to-noise ratio and low fluorescence background [77]. Owing to the optical property of inorganic QDs, the interaction between QDs and CNTs has been intensely investigated QDs, in which QDs were acted as energy donors [77]. The functionalized MWCNTs can strongly quench the fluorescence of CdSe QDs, and CdTe QDs can also be effectively quenched by the oxidized SWCNTs (oxCNTs). Based on these fluorescence quenching mechanisms between CNTs and QDs, some biosensors were proposed to measure DNA with high sensitivity and accuracy. Tian et al. reported a simple and sensitive DNA biosensor for H5N1 DNA detection based on the FRET from QDs to oxCNTs [79]. The CdTe QDs were modified with ssDNA as donors, which could wrap around individual CNTs generating stable complexes through π-stacking interactions between CNTs sidewalls and aromatic nucleotide bases. Then the fluorescence of QDs was effectively quenched. However, the interaction between double-stranded DNA (dsDNA) and CNTs was weaker than that of ssDNA. Thus, the fluorescence of QDs could not be quenched in the above case. The proposed viral DNA sensor presented a linear range from 0.01 to 20 μM with a LOD of 9.39 nM [79]. Although the CNTs immobilized bioreceptor through π-π stacking can further simplify the viral detection, this method may reduce its sensitivity and narrow the range of analytes.

4.3. Size-tunable CNTs arrays for viral detection

Generally, most discovered viruses' size ranges from 20 to 300 nm, which provides reliable evidence for the vertically aligned CNTs arrays to isolate viruses of different sizes [24]. Nowadays, the diagnostic methods of viruses recognized by antibodies or probes mainly include direct detection of viruses by isolating them in cell culture, identifying viral nucleic acid or antigen, and serological tests for detecting virus-specific antibodies [24]. However, virus culture requires at least 2−10 days of enrichment to provide statistically relevant information. It presents a challenge to emerging viruses or unidentified strains. To accurately match the size of different viruses, the intertubular distance ranging between CNTs can be engineered in the range of 17−325 nm by adjusting the thickness of the iron catalyst thin film [25]. Using the size-tunable CNTs arrays, the nanomaterial-integrated microfluidic device can efficiently enrich and concentrate viruses collected from field samples without label and virus amplification [14]. Furthermore, the size-based capture strategy enables us to rapid and real-time quantificational detection of pathogens. Hence, this unique and powerful method provides a promising platform for discovering novel and emerging viruses, contributing to the control and eradication of viral infectious diseases.

Yeh and co-workers proposed a series of hand-held devices for capturing viruses integrated the vertically aligned carbon nanotube (VACNT) into point-of-care devices [14,24,25]. These microfluidic devices achieved label-free and high throughput virus capture by applying physical size-based exclusion. One of their work showed that a unique CNT-STEM was successfully constructed for efficiently enriching and concentrating viruses from field samples (Fig. 9) [25]. The robust arrays of aligned CNTs were integrated into tunable devices that were able to isolate different sizes of viruses. This device could effectively trap/concentrate viruses within a three-dimensional (3D) porous system by controlling the intertube distance of CNTs. The proposed CNT-STEM significantly improved virus isolation rates by at least 100 times and detection limits. Furthermore, the novel device was successfully used to identify an emerging avian influenza virus strain [A/duck/PA/02099/2012(H11N9)] and a new virus strain (IBDV/turkey/PA/00924/14). The selectivity of CNT-STEMs could be improved by decorating with biomolecules and other chemical groups, and the capability of rapid pathogen detection and real-time quantification could be enhanced after integrating a detection system with it.

Overall, the CNTs-based methods illustrate significant potential in rapid pathogen detection and a real-time quantification for whole virus detection, due to the extraordinary physical and chemical properties [26,93]. To overcome the technical barrier, the CNTs-based sensing platforms are promising in virus surveillance and discovery. In the future, modeling and predicting the outbreak of zoonotic diseases will be more viable and reliable because of the improvement of the monitoring system and data resolution.
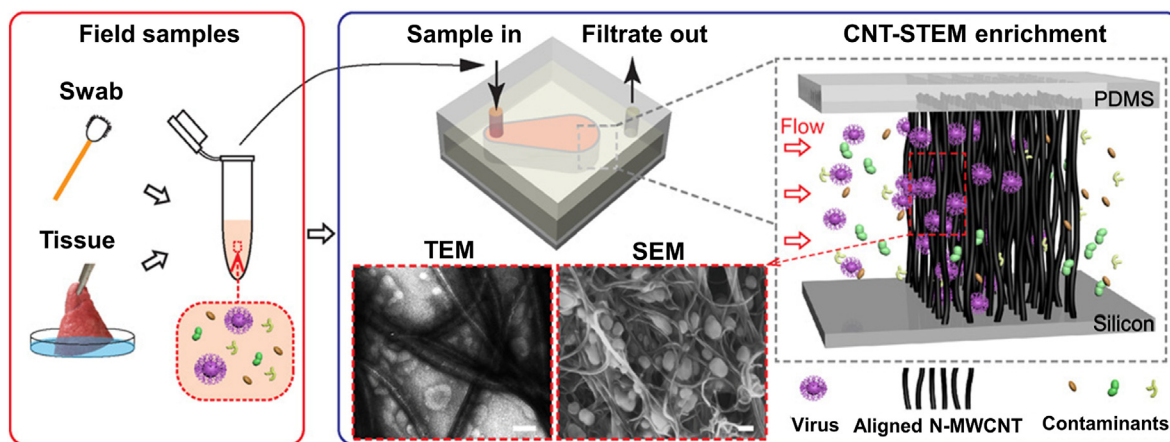

Fig. 9. The working principle of virus enrichment and concentration from field samples. Left: The field viruses (purple spheres) sample is collected from a cotton swab or a tissue sample. Right: The supernatant of the field sample flows through the CNT-STEM, and the viruses are enriched in the device. Reproduced with permission from Ref. [25].

4.4. Current challenges and outlook

In this review, we have summarized the engineered carbon nanotubes for the formation of sensing platforms to detect viruses. The recent advancement in engineering CNTs can change the landscape of the viral detection and therapeutic scenario. However, the debate on the efficacy, precision, reliability, and generic model of the nanomaterials applied for the sensing is undergoing to find the optimal solution. Carbon nanomaterials have been widely used in biomedical applications because of their multifunctional nature and ease in surface modifications that enhance the biophysical properties of existing biomaterials on physical incorporation [94,95]. Among them, carbon nanotubes are unique carbon allotrope, constructed by carbon elements with hollow cylindrical tubes consisting of carbon, high aspect ratio (~1000), and sp^2 hybridization. The physicochemical, optical and chemical, mechanical, and electrical properties of the CNTs define the potential applications and role in sensing viral genomes, proteins, and other viral cellular biological materials. Thus, it is necessary to tune the properties mentioned above of engineered CNTs to increase the detection's efficacy and precision.

Many viruses make the latent state where they remain inactive within the host cell [96–98]. It is difficult to detect the virus by a simple screening approach until the virus becomes active. Therefore, it is challenging to design nanomaterials that can detect/sense the virus in its active and non-active states. Consequently, we emphasize developing the CNTs to directly sense the genetic materials of virus-like DNA and RNA via simple and low-cost detection screening methods. The CNTs can be engineered by different methods, including covalent bonding, non-covalent modification, and size-tunable arrays to form the nano-bio interface. Due to intriguing physical properties, the engineering CNTs show promising potential in the chips and devices for viral detection. Mainly, the modification can be achieved through non-covalent interactions between CNTs and other nanomaterials. Furthermore, the EDC/NHS chemistry and click chemistry can also be used for the modification to produce material at the bulk level. One other challenge in the CNTs-based viral biosensors is their stability and accuracy in complex sample matrixes [99–101]. The limitations in the performance of CNTs-based viral biosensors may be overcome with the application of antifouling materials, such as synthetic peptides, polyethylene glycol, and zwitterionic polymers.

The challenge in designing a general sensing device for all viruses persists, and selectivity issues are raised in practical applications. The efforts can be devoted to figuring out the generic design strategies, which at least should be used across the globe. However, CNTs have the potential in detecting the virus because of their large surface area, known chemistry, and especially electrical properties, which are needed for the sensing application. Although the CNTs-based viral biosensors are promising in the future due to their high sensitivity and long stability, their convenience and signal availability is also crucial during global pandemics. To tackle this issue, wearables and wireless communication will be the trend for viral detection [67], which will allow decision-makers to quickly obtain analysis results and give a timely decision in viral diagnosis.

In December 2019, the unknown strain of coronavirus emerged as a real threat to humanity [22,23], which had several times more transmission propensity than existing viruses. Its fatalness and mutation in the genetic material and early detection have become the challenge for scientists to design the remedial platform. The deficiency in the sophisticated techniques based on quite expensive instrumental infrastructure in developing countries could hamper containing the viral transmission. It could remain a threat to developed nations as well. Therefore, we acclaim that CNTs can be used as one of the promising nanomaterials to design the detection kits and devices for the early detection of the coronavirus 2019. Finally, the continuity in research on nanotechnology for virus detection will lead to novel platforms that could remarkably change how viral infections can be detected at their early stage in the clinics.

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.

Acknowledgments Declaration of competing interest

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