Recent trends and advancements in electrochemiluminescence biosensors for human virus detection

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ARTICLE INFO

ABSTRACT

Researchers are constantly looking to find new techniques of virus detection that are sensitive, cost-effective, and accurate. Additionally, they can be used as a point-of-care (POC) tool due to the fact that the populace is growing at a quick tempo, and epidemics are materializing greater often than ever. Electrochemiluminescence-based (ECL) biosensors for the detection of viruses have become one of the most quickly developing sensors in this field. Thus, we here focus on recent trends and developments of these sensors with regard to virus detection. Also, quantitative analysis of various viruses (e.g., Influenza virus, SARS-CoV-2, HIV, HPV, Hepatitis virus, and Zika virus) with a specific interest in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was introduced from the perspective of the biomarker and the biological receptor immobilized on the ECL-based sensors, such as nucleic acids-based, immunosensors, and other affinity ECL biosensors.

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1. Introduction

The rate of infectious diseases occurrence has been increasing despite all the developments in the healthcare systems and has not only affected humans but animals and plants as well. Among the pathogens responsible for these diseases, viruses have been found to play an essential role [1]. Throughout history, the evolution of viruses has co-occurred with that of humans, resulting in the death of millions of people due to several viral prevalence and epidemics [2]. The current pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), promoting coronavirus disease (COVID-19), is to blame for more than 4.5 million deaths worldwide. Like the new coronavirus, various undiscovered viruses could constitute future health threats and bring disaster to the global economy [3]. Therefore, the development of novel tools and techniques that provide sensitive, inexpensive, rapid, and accurate results seems inevitable for the future confrontation of these outbreaks and prevention of their catastrophic outcomes.

Biosensors are highly sensitive, selective, and accurate measurement systems to determine ultralow analyte concentrations in biological samples. In general, biosensors are considered as analytical devices, consisting of bio-recognition elements, signal transducers, and a detector with a digital output. The bio-recognition element interacts with the target, recognizes the

analyte through a reaction, and then the transducer translates the changes to a comprehensible signal measured by the digital detector. Due to the various types of transducers, biosensors can be classified as optical, thermometric, piezoelectric, electrochemical, and electrochemiluminescence (ECL) biosensors. Among them, ECL-based biosensors is a developing alternative tool for quantitative analysis of viruses thanks to the perfectly combined electrochemical and spectroscopic techniques [4–11].

Hence, this article reviews recent advances in ECL-based biosensors for virus detection, with a specific focus on respiratory viruses (Scheme 1). Previous reviews have covered essential advancements in the electrochemical-based biosensors for the detection of respiratory viruses [12], the contribution of biosensors in the detection of respiratory viruses [13], and multiple techniques and applications of biosensors in virus detection [14]; however, no review articles cover ECL-based biosensors with regards to virus detection. Therefore, we aim to fill the blank with essential background information about ECL-based biosensors in the field of virus detection.
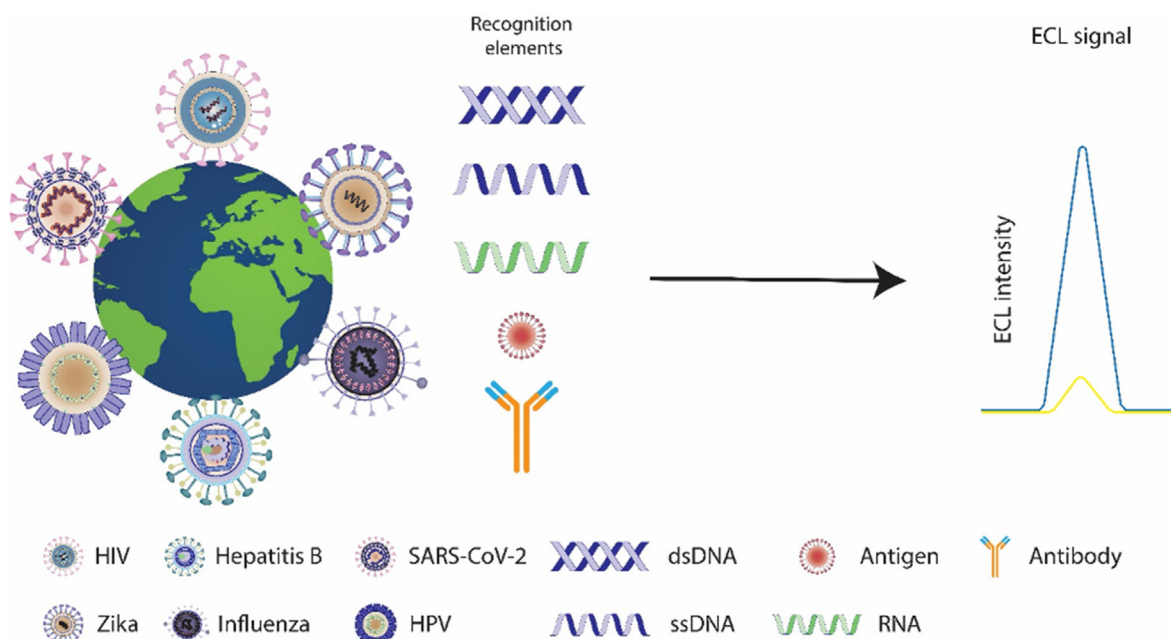
2. Electrochemiluminescence-based biosensors

Electrochemiluminescence, also called electrogenerated chemiluminescence, is one of the most widely used techniques for the emission of light from electrochemically excited ECL emitters via an efficient electron transfer. ECL has received enormous attention as a powerful tool in the biosensing field due to intrinsic strengths: rapid response, high sensitivity, simplified setup, a wide range of detection, flexibility, low cost, and miniaturized instrumentation [15,16]. In comparison with other optical-based analytical methods, the ECL process has some advantages: The light emission of ECL does not require an external source of light. Therefore, there is no background noise from the sample auto fluorescence or scattered light. Secondly, the potential applied at an electrode can control the ECL emission of light. Also, the ECL technique allows greater control over the emission position since the ECL emission is close to the electrode surface. This better control over the emission is advantageous for selectivity, sensitivity, imaging analysis, and multi-

analytes detection. Thirdly, some ECL reactants can be electrochemically regenerated at the electrode. This advantage increases the sensitivity of the technique, saves reactants significantly, and simplifies the instrument [17,18].

There are two main mechanisms through which ECL can be generated: annihilation and co-reactant mechanisms. Moreover, ECL can also be produced through hot electron-induced mechanisms and electrostatic chemiluminescence. In each mechanism, two species are produced electrochemically and undergo an electron-transfer reaction to create both a ground state and an electronically excited state, emitting light and relaxing to the ground state. In the annihilation ECL mechanism, radical species are produced from a single luminophore, while the co-reactant ECL mechanism requires electrochemical interaction between the emitter and a suitable coreactant [19–21]. In both mechanisms, the ECL-luminophore plays a significant part in changing electrical energy into radiative energy. Therefore, the sensitivity of the ECL biosensor specifically depends on ECL luminophores. Numerous ECL luminophores were synthesized in the past years, and several organic, inorganic, and nanomaterial systems can produce ECL [22]. Nevertheless, among the different emitting species commonly utilized in ECL biosensors, ruthenium complexes [23–27] and luminol [28–33] derivatives are the most popular ones employed due to their high solubility in an aqueous medium and the ability to use at a physiological pH in biological samples and also viral detection.

3. Virus detection

Many methods have been developed for detecting viruses. Biosensors have found enormous applications in virus detection, and it extends more sensitive, specific, fast, and reproducible results than conventional techniques like biochemical assays and immunoassays. Generally, biosensors are considered analytical devices that transform bio-related reactions into detectable signals and can be categorized according to their analytes or the reactions they measure. According to the analytes or reactions measured, biosensors for virus detection are categorized into 1,

Scheme 1. Electrochemiluminescence biosensors for human virus detection.

immunosensors that are based on antibody-antigen interaction; 2, genosensors that are dependent on gene sequences derived from viruses; and 3, whole virus biosensors.

3.1. Immunosensors

Immunosensors are a class of biosensors based on antibody-antigen-specific interactions. B-lymphocytes and plasma cells produce antibodies upon antigen contact. It is possible to detect viruses and infections relying on the subclass of antibodies due to their excellent specificity, extreme sensitivity, and high affinity [34,35]. For instance, in the case of SARS-CoV-2 infection, the immunoglobulin G (IgG) subclass of antibodies against N protein is detectable no later than four days after infection [36].

Immunosensors can be classified as both label-free and labeled in their sensing formats. Label-free immunosensors determine the antigen-antibody complex by detecting the physical changes induced by the emergence of other complexes. However, in the case of labeled immunosensors, the immunocomplex is determined by the measurement of the label. Among various types of virus antibody diagnostic technologies, enzyme-linked immunosorbent assay (ELISA) is the most popular one, providing recognition and quantification of various antigens. ELISA, like other types of immunoassays, is based on specific antibody-antigen interactions. However, in the past decade, various immunosensors have been developed to detect antibodies against viruses based on electrochemical and ECL techniques. For instance, a multichannel electrochemical immunoassay platform for quantitative detection of influenza A (H_1N_1) and SARS-CoV-2 viruses was developed [37]. Zhou and colleagues reported an ECL-based immunosensor employing a sandwich assay to detect human immunodeficiency virus type 1 antibody (anti-HIV-1) employing molecularly imprinted magnetic polymers as receptors [38].

3.2. Whole-virus biosensors

Whole viruses and their structural proteins can be applied as recognition elements. Different surface antigens in viruses' structures (e.g., proteins) can target various viruses. Upon cell lysis, proteins encoded via viral genomes emerge in blood circulation and can be detected upon the active replication of viruses [35]. In early diagnosis of COVID-19, the whole SARS-CoV-2, and its four structural proteins: spike (S) protein, envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, could be employed as targets. It should be noted that S and N proteins remain the most notable biomarkers in the COVID-19 early diagnosis [39].

3.3. Genosensors

Genosensors or deoxyribonucleic acid (DNA) biosensors detect the viral genome or specific gene sequences obtained from viruses. DNA, the genetic information carrier, is unique within every. Organism; therefore, this sensor is one of the most sensitive diagnostic tests routinely used to detect and identify viral diseases. The principle of genosensors depends on the stable immobilization of the nucleic acid (ssDNA or ssRNA) on the surface of the sensor to detect the target virus nucleic acid, based on nucleic acid hybridization [40]. The amount of probe immobilized on the ECL genosensors surface is straightly dependent on the availability of analyte binding sites. Consequently, the methods used for the immobilization of the probes are essential to verify the performance of genosensors. Overall nucleic acid-based ECL biosensors feature great stability, specificity, and sensitivity that through miniaturization can be used in the fabrication of POC devices for virus detection.

4. ECL biosensors for viruses detection

4.1. Respiratory virus

Two of the most well-known respiratory viruses, influenza virus, and coronavirus, are responsible for a large portion of morbidities worldwide. Determination of the viral genome sequence, protein structures, and their response to antibodies helps with the realization of the virus pathogenicity through which the development of appropriate and effective vaccines and therapies can be reached. Detection of these types of viruses helps with the decision-making in clinical trials, thus, here we discuss recent developments in their ECL-based biosensors.

4.1.1. Influenza

Influenza is a viral infectious disease that causes numerous medical issues and an enormous financial burden. The single-stranded antisense RNA virus encodes the proteins associated with the virus structure and functions. These enveloped viruses of the *Orthomyxoviridae* family, are classified into four genera, including influenza virus A−D (IAV, IBV, ICV, and IDV). IAVs and IBVs are of primary concern. The ICVs are endemic and can cause mild disease in humans, and IDVs primarily account for infections in cattle [41]. Hemagglutinin (H.A.), a surface glycoprotein, plays a significant part in the case of animal cell infections with influenza. Neuraminidase (N.A.), another viral surface protein, functions mostly as a virion releaser through the cleavage of virus-bound carbohydrates (sialic acids) from the cell surface [42]. Various ECL biosensors have been reported for the diagnosis of influenza viruses. Naoyoshi Egashira et al. [43] developed an ECL-based biosensor that employs a Ru complex encapsulated in an immunoliposome system. The sensor detects HA through hemagglutinin or antigen peptide immobilization on the surface of a working electrode made of gold. Then, the immunoliposome binds with hemagglutinin onto the working electrode through a competitive antigen-antibody assay. After destroying immunoliposomes, the Ru complex is adsorbed on the working electrode by heating, and ECL measurement is done. Hemagglutinin molecules of the influenza virus were determined in a concentration range of 3×10^{-14} to 2×10^{-12} g mL^{-1}. This level of sensitivity suggests that a limit of detection as low as 6×10^{-19} mol 50 µL^{-1} could be reached. The biosensor enables fast detection of hemagglutinin proteins in attomolar concentrations.

Also, in another work, Yumi Katayama et al. [44] reported the detection of influenza virus A (H_1N_1) using an ECL-based immunosensor that benefits from a tris (2, 2′bipyridyl) -ruthenium (II) encapsulated in an immunoliposome system. A competitive assay between the virus and HA is the principle behind the detection system that is immobilized on self-assembled monolayers (SAMs) through the liposome surface-bound antibodies immunoreaction. The first modified DTPA/HT binary SAMs on Au electrode, after fixing hemagglutinin peptide on activated DTPA, competitive reaction of immunoliposome and influenza virus done. They demonstrated significant improvement in sensitivity and accuracy by introducing binary SAMs instead of mono SAMs. The background signal decreased by 50%, and the sensitivity was higher than mono SAMs of dithiodipropionic acid (DTPA). This method features a double amplification of the ECL signal by liposome and adsorption of Ru complex onto Au electrode. The proposed sensor can determine the virus in the range of 2.7×10^2 to 2.7×10^3 PFU mL^{-1}. Recently, Luo et al. [45] proposed an immunomagnetic sensor for the detection of H9N2 avian influenza virus (H9N2 AIV) employing functional silica nanospheres as signal carriers and magnetic nanobeads (M.B.s). The virus detection is based on the formation of a sandwich assay. In this work, [Ru (bpy)$_3$]$^{2+}$ as

a luminophore and silica nanoparticles (SNPs) have been used for the amplification of the ECL signal. The functional silica nanospheres were prepared by embedding multiple [Ru (bpy) $_3$] $^{2+}$ in SNPs and further modifying with pAb, improving detection sensitivity as signal probes (Fig. 1). Monoclonal antibody (mAb) modified magnetic nanobeads (MBs) achieved the aim of specific capture and separation of H9N2 AIV in the system. Therefore, the combination of immunomagnetic separation and RuSi NPs made the method possible for practical application. The ECL-based immunosensor achieved a limit of detection as low as 14 fg mL^{-1} H9N2 AIV with a dynamic range of 25 fg mL^{-1} to 25 ng mL^{-1}, and the ECL signals by about 10^{-3} fold in comparison with the same concentration of [Ru (bpy)$_3$] $^{2+}$.

4.1.2. SARS-CoV-2

Since January 2020, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been spreading worldwide, bringing about the first documented coronavirus pandemic in history. The novel virus is known to cause coronavirus disease (COVID-19) associated with severe health problems, e.g., respiratory distress [46]. SARS-CoV-2 is a beta coronavirus capable of infecting both mammals and birds [47]. The virus belongs to the ssRNA virus group with a positive sense [46]. According to the high incidence and morbidity worldwide, rapid and sensitive detection of COVID-19 is of utmost importance. Three conserved viral sequences are found in the SARS-related genes: (1) RNA-dependent RNA polymerase gene (RdRp gene), (2) envelope protein gene (E gene), and (3) nucleocapsid protein gene (N gene) [48]. The gold standard detection method of COVID-19 is based on quantitative reverse transcription PCR (qRT-PCR), however, it is time-consuming and requires costly equipment [49]. Previously reported papers have discussed advancements in the development of the affinity sensors and immunosensors for the detection of the virus [50−53]. Most of the ECL-based techniques for this virus detection are based on Genosensor methods. Zhenqiang Fan and colleagues [54] reported the fabrication of an ECL-based biosensor that amplifies the signal by employing a DNA walker strategy for the detection of the SARS-CoV-2 RdRp gene. RdRp gene was used to trigger the entropy-driven reaction, the bandage was output, which in combination with the two single-stranded S$_1$ and S$_2$ formed a bipedal DNA walker. The modified Au-g-C$_3$N$_4$/GCE was applied to the ECL donor to combine PEI-Ru@Ti$_3$C$_2$@AuNPs-S7 probes as the ECL acceptor, and TDNAs got modified by hairpin structures to change the signal

by ECL resonance energy transfer (ECL-RET) (Fig. 2A). The proposed biosensor achieved a high sensitivity through the combination of a double amplification strategy, entropy-driven, and bipedal DNA walker. It can quantify the SARS-CoV-2 gene from 10 aM to 10 pM, and the detection limit was reported at 7.8 aM. Yao et al. [55] designed an ECL-based biosensor based on Au@Ti$_3$C$_2$@PEI-Ru (dcbpy) $_3^{2+}$ nanocomposites for the detection of the RdRp gene of SARS-CoV-2. As shown in Fig. 2B, the Au NPs were linked to the DNA and Ru (dcbpy) $_3^{2+}$ as the ECL emitter, was fixed on the Ti$_3$C$_2$ surface to improve the sensitivity of the ECL biosensor. Polyethylenimine (PEI) can bound to Ru (dcbpy) $_3^{2+}$ through an amide bond and as a co-reactant enhances the emission efficiency of Ru (dcbpy) $_3^{2+}$. Subsequently, the HP DNAs and swing arm-blocker were anchored on the Au@Ti$_3$C$_2$@PEI- Ru (dcbpy) $_3^{2+}$ nanocomposites surface via the Au−S bond possessed a strong ECL signal called "signal on" state. In the presence of the target DNA, the ECL biosensor could realize the transition from "signal-on" to "signal-off" condition. The intensity of the ECL signal decreased with the increasing concentration of the target. Based on this model, the ECL intensity change of the ECL biosensor could reflect different target DNA concentrations. The team of Fan [55] used DNA tetrahedron (TET) as a platform for the biosensor's construction to also detect the RdRp gene of SARS-CoV-2. They indicated an entropy-driven amplified ECL strategy for detection. The tetrahedral structure reduces non-specific adsorptions on the electrode surface, which significantly reduced the process of sensor preparation and made it more user-friendly. The enzyme-free entropy-driven reaction cuts on the expenses of expensive enzyme reagents and facilitates the realization of high-throughput screening of SARS-CoV-2 patients.

In another work done by Kai Zhang et al. [58] an ECL-based biosensor was designed for the detection of SARS-CoV-2. In this technique, the RNA-dependent RNA polymerase (RdRp) gene was detected using CRISPR-Cas12a and 3D-DNA walker as gene amplification methods, and a ruthenium complex was used as the anodic emitter of the ECL system. The detection of the gene is done in a 2-step process. First, DNA2/DNA6 duplex forms on the surface of the gold nanoparticle, and the second part of the system is an ECL sensor and CRISPR/Cas12a. The activated CRISPR/Cas12a cuts the single-stranded DNA that increases the ECL signal. They reported a linear range of 10 aM−500 aM and a detection limit as low as 12.8 aM. Zhang et al. [59] have reported the identification of the same gene (SARS-CoV-2 RNA-dependent RNA polymerase (RdRp)) using
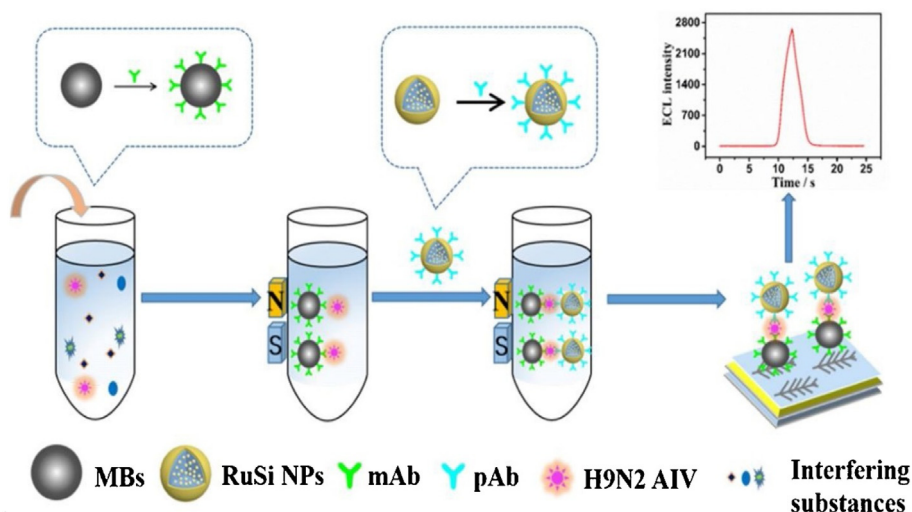

Fig. 1. Illustration of the immunomagnetic based ECL immunosensor for H9N2 AIV detection [45].
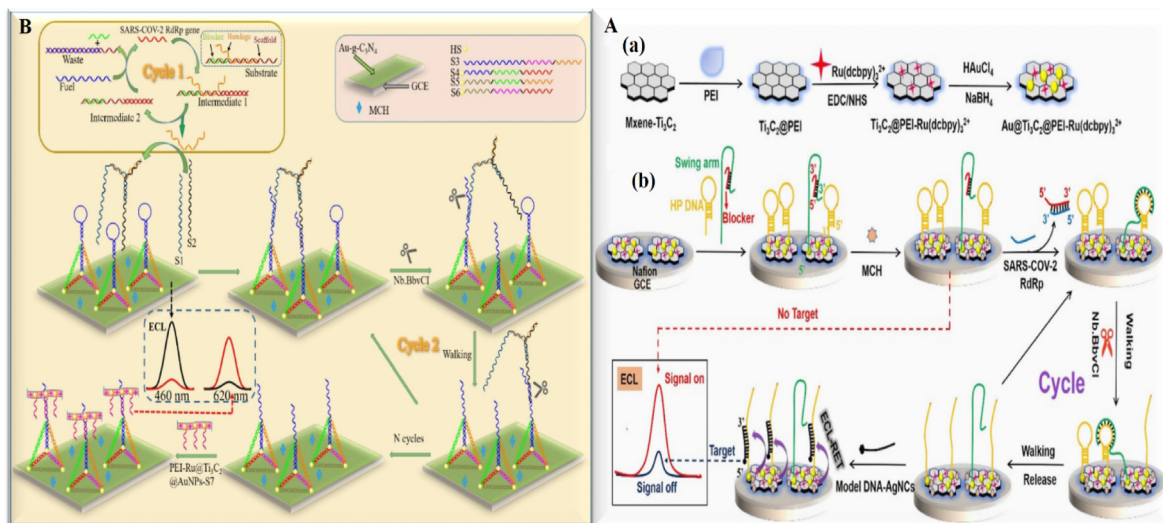
Fig. 2. A: Schematic of the double amplification strategy based on DNA tetrahedral ratiometric ECL-based biosensor for the assay SARS-CoV-2 RdRp gene [53]. B: Schematic Illustration of (a) Preparation of Au@Ti$_3$C$_2$@PEI-Ru(dcbpy)$_3^{2+}$ Nanocomposites; (b) based on Au@Ti$_3$C$_2$@PEI-Ru(dcbpy)$_3^{2+}$ Nanocomposites ECL Biosensor Detection of the SARS-CoV-2 RdRp Gene Combined Unipedal DNA Walker Amplification Strategy [55].

a pH engineered regenerative DNA tetrahedron and CRISPR-Cas12a as the amplification method (Fig. 3A). In this work, GCE was modified with Au-g-C$_3$N$_4$ as the ECL emitter and donor and the DNA-Ru as the acceptor, and pH was optimized at 10.0 because the

Fig. 3. A: Schematic of the pH-induced biosensor for the detection of SARS-CoV-2 RdRp gene [59]. B: Scheme of the ECL DNA biosensor development [60].

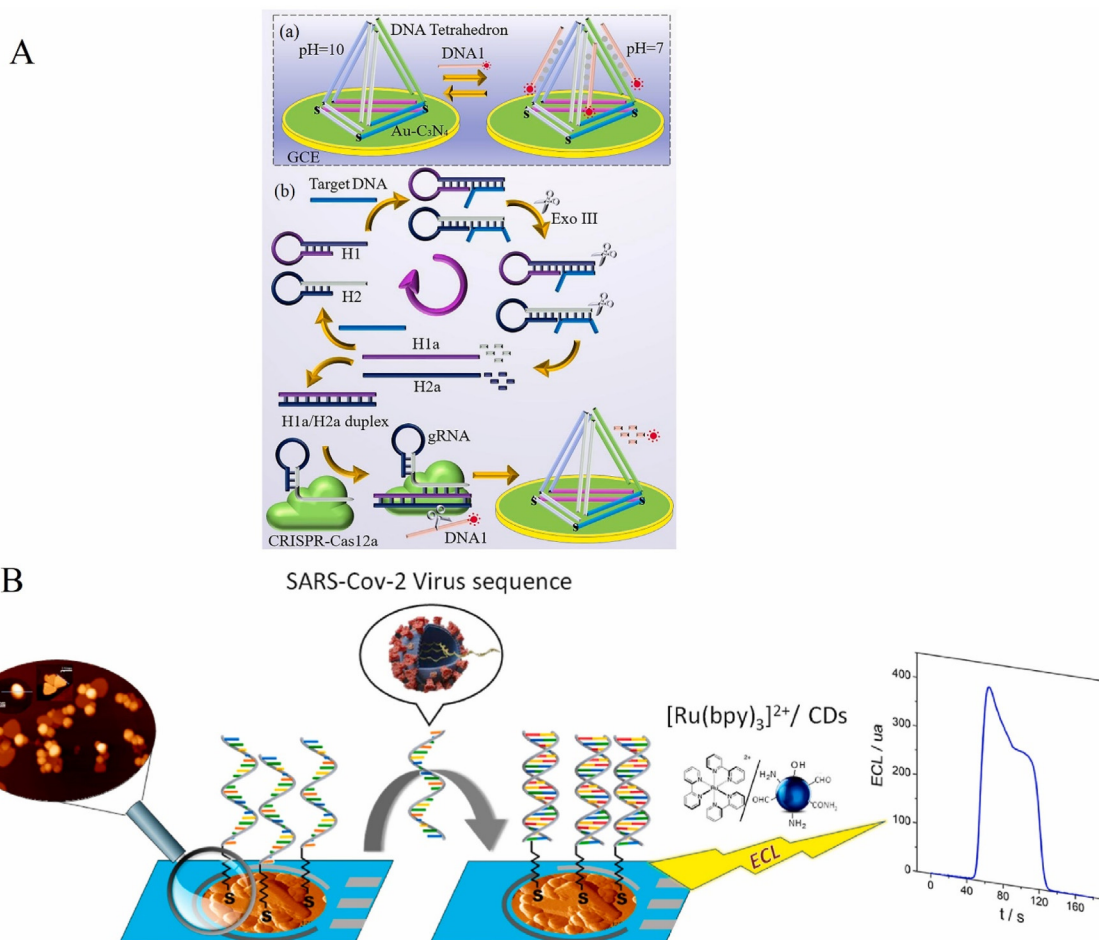biosensor can be regenerated at this pH. They showed that with the increasing concentration of the target from 0 to 1500 aM, the intensity of the ECL peak at 460 nm, which is the characteristic peak of Au-g-C_3N_4 decreases, and the peak at 620 nm increases drastically. The linear range was reported from 10 aM to 10 pM and the detection limit was found to be as low as 43.70 aM.

Laura Guti'errez-G'alvez et al. [60] recently developed an electrochemiluminescent nanostructured DNA biosensor for SARS-CoV-2 detection based on two distinct nanomaterials, gold nanomaterials (AuNMs) and carbon nanodots (CDs), for the development of an enhanced ECL DNA biosensor. CDs synthesized by green chemistry are used as coreactants agents in the $[Ru(bpy)_3]^{2+}$ anodic ECL, and changes in the ECL signal of $[Ru(bpy)_3]^{2+}$/CDs in combination with AuNMs nanostructures detect hybridization. In this work, SARS-CoV-2 was detected using the open reading frame 1 ab (ORF1ab) sequences as a model target. Fig. 3B shows the development of this ECL DNA biosensor. The first step is to use AuNMs to modify the surface of the AuSPE. Then, by immobilizing the thiolated capture probe on the AuNMs, the probe-target hybridization was performed to identify a specific DNA sequence of SARS-CoV-2. Finally, an ECL system was employed to identify and quantify SARS-CoV-2 specific DNA sequences by adding a mixture of [Ru (bpy)$_3$]$^{2+}$/CDs to the solution.

In a recent work by our team, we developed an ECL-based immunosensor for the detection of the virus [61]. Gold deposited GCEs were used as the working electrode. The surface of the electrode was further modified with MUA/MPA for the covalent immobilization of antibodies. The sensor benefits from a signal-on sensing strategy in which luminol is covalently attached to an Au-based nanocomposite working as the ECL reporter. The secondary SARS-CoV-2 specific antibodies attached to the nanocomposite, ensures the high specificity of the assay and lessens the possibility of false positive signals. A linear range of 10 ng mL^{-1} to 10 μg mL^{-1} with a LOD of 1.93 ng mL^{-1} was reached.

Moreover, Yingying Chen et al. [62] improved the sensitivity of the ECL biosensor through-reactant enrichment and used it to detect SARS-CoV2 Nucleocapsid Proteins. The combination of carboxyl-functionalized poly [2,5-dioctyl-1,4 phenylene] polymer nanoparticles (PDP PNPs) as an excellent ECL luminophore and β-cyclodextrin (β-CD)-Pt nanocomposites as ideal carriers of coreactants (TDBA), build an attractive ECL platform and shed light on the detection of the target. The GCE surface was modified with PDP PNPs to trap the first antibody (Ab$_1$) and capture the target and the secondary antibody complex (TDBA-β-CD-Pt@Ab$_2$). The obtained biosensor with a sandwich structure was able to detect SARS-CoV-2 Nucleocapsid Proteins with high sensitivity. Table 1 summarizes the various reported ECL biosensors for respiratory virus.

4.2. Human immunodeficiency virus (HIV) and human Papilloma virus (HPV)

Although human papillomavirus (HPV) and human immunodeficiency virus (HIV) can both be transmitted sexually, there's no medical link between the two conditions. However, the behaviors that put someone at risk of getting HIV can also raise the risk of getting HPV.

To date, more than 79 million people worldwide have been infected with HIV, and there are now approximately 37.7 million globally living with HIV. An accurate diagnosis of HIV is the primary way to control its spread, particularly in patients with the acute infection before the occurrence of seroconversion. ECL-based detection techniques can enable fast monitoring of disease analytes without the need for complex equipment.

The p24 antigen which is the HIV-1 capsid protein appears

earlier than the antibody in the case of HIV infection due to an explosive replication of the virus following acute infection and is correlated with highly infectious viremia. Thus, the p24 antigen can be used as a biomarker for early detection of HIV in its "window period."

Zhou et al. [64] developed an immunosensor for HIV-1 p24 analysis using Ru—SiO$_2$ NPs and gold-nanoparticle-decorated graphene. The as-prepared composite works as an ECL emitter and a carrier to immobilize the target antibody to build a sandwich-type ECL immunosensor through the antibody-antigen interaction. A high ECL signal was obtained due to the large amounts of Ru(bpy)$_3^{2+}$ molecules per Ru—SiO$_2$ nanoparticle. The composite with good conductivity and high surface area not only accelerated the electron transfer rate but also improved the loading of both ECL molecules and capture antibodies, which could further increase the ECL signal and result in high sensitivity.

HIV-1 Tat protein is considered another biomarker used in the early detection of HIV. Wang et al. [65] introduced an ECL-based aptasensor that uses Ti$_3$C$_2$T$_x$ MXenes modified with Imidazole Zinc -organic frameworks as an ECL emitter. To quench the ECL signal conductive carbon black combined with magnetic nanoparticles was used. The aptamers and their complementary sequence bonded covalently to the surface of the modified electrode.

A dual strategy technique for HIV detection was reported by Cai et al. [66]. They modified the surface of the ITO electrode with SnO$_2$ nanoflowers, and then the Au nanoparticles covalently bonded to which the HS-DNA was then linked. The target DNA then forms a three-chain structure in hybridization with the two other hairpins. A bipedal DNA walker with (abga fragments) was generated then through the cleavage of each clip by Exo III. The walker triggered cycle II and resulted in amplification of the target DNA, then target DNA was used to link the 3D CdSe QDs-DNA signal probes with numerous QDs to the electrode (Fig. 4), thus greatly enhancing the ECL signals and enabling an ultra-sensitive detection of HIV.

A non-enzymatic multiple amplified ECL-based biosensor was proposed by Wu and coworkers for the detection of HIV [67] CdSe/ZnS quantum dots were employed as the ECL luminophore and DNA functionalized magnetic beads were used to separate the target HIV DN. In the following, by adding another hairpin DNA modified nanospheres, a strand displacement amplification reaction resulted from the increasing binding sites between two hairpin DNAs. Based on strand displacement amplification, more nanospheres can be captured on the surface of magnetic beads through cycling reaction, which was beneficial for low-abundant biomarker detection. Finally, the magnetic particle was captured on a magnetic glassy carbon electrode surface and ECL signals were obtained in the presence of coreactant.

EuS nanocrystals have been used as ECL fluorophores by Babamiri and colleagues. Through polymerization of functional monomers, they managed to fabricate plastic antibodies around template molecules. The HIV DNA was used as the template molecule and phenylenediamine was employed as the functional monomer on the surface of an ITO electrode [68]. Cervical cancer ranks 4th in the most common cancers seen in women worldwide. Infections with human high-risk papillomavirus (HR-HPV) and HPV16 are amongst the most common causes of cervical cancers reported. Hence, early diagnosis of cervical cancer through monitoring HR-HPV genes has been adopted ubiquitously. E6 and E7, the two main oncogenic genes, are vital for viral replication with the latter having high genetic conservation making it an excellent biomarker for therapeutic interventions. Since HPV cannot be detected through cell culture techniques, its detection and identification mainly relies on molecular techniques. Among all detection methods, ECL-based detection techniques have been recognized as powerful and

Table 1
Summary of various biosensors for respiratory virus detection.

| Platform	ECL Luminophor	Type of Virus detection	target	Linear ranges	ECL pathway	LOD	matrix	Ref
Gold electrode	Ru complex	Immunosensor	Hemagglutinin (virus)	3×10^{-14} to 2×10^{-12} g mL^{-1}	Coreactant	10^{-14}		[43]
Au electrode/DTPA/ HT binary SAMs	Ru complex	Immunosensor	influenza virus A (H1N1)	2.7×10^2 to 2.7×10^3 PFU mL^{-1}	Coreactant	Not determined	Commercial H1N1	[44]
Au nanostructures (AGN)/ITO	Ru complex	Immunosensor	H9N2 avian influenza virus	25 fg mL^{-1} to 25 ng mL^{-1}	Coreactant	14 fg mL^{-1}	chicken liver, serum, and lung	[45]
PEI-Ru@Ti3C2@AuNPs	g-C$_3$N$_4$	Genosensor	SARS-CoV-2	10 aM to 10 pM	Coreactant	7.8 aM	human serum	[54]
Au@Ti3C2@PEI-Ru(dcbpy)$_3^{2+}$	Ru complex	Genosensor	SARS-CoV-2	1 fM to 100 pM	Coreactant	0.21 fM	human serum	[57]
DNA tetrahedron	Ru complex	Genosensor	SARS-CoV-2	1 fM to 100 pM	Coreactant	2.67 fM	human serum	[56]
PEI-Ru@Ti3C2@AuNPs	Ru complex	Genosensor	SARS-CoV-2	0 aM to 1000 aM.	Coreactant	12.8 aM	pharyngeal swabs samples	[58]
Au-g-C$_3$N$_4$/DNA tetrahedron	Ru complex	Genosensor	SARS-CoV-2	10 aM to 10 pM	Coreactant	43.70 aM	pharyngeal swabs samples	[59]
AuNMs and CDs	Ru complex	Genosensor	SARS-CoV-2	50.0 fM to 100.0 nM	Coreactant	514 aM	human serum	[60]
Gold electrode	Ru complex	Genosensor	SARS-CoV-2 ORF1 gene	0.1 fM to10 μM	Coreactant	0.1 fM	simulation samples (saliva and urine)	[63]
modified GCE	PDP polymer nanoparticles	Immunosensor	SARS-CoV-2	50 fg mL^{-1} -1.0 ng mL^{-1}	Coreactant	22 fg mL^{-1}	Serum Sample	[62]
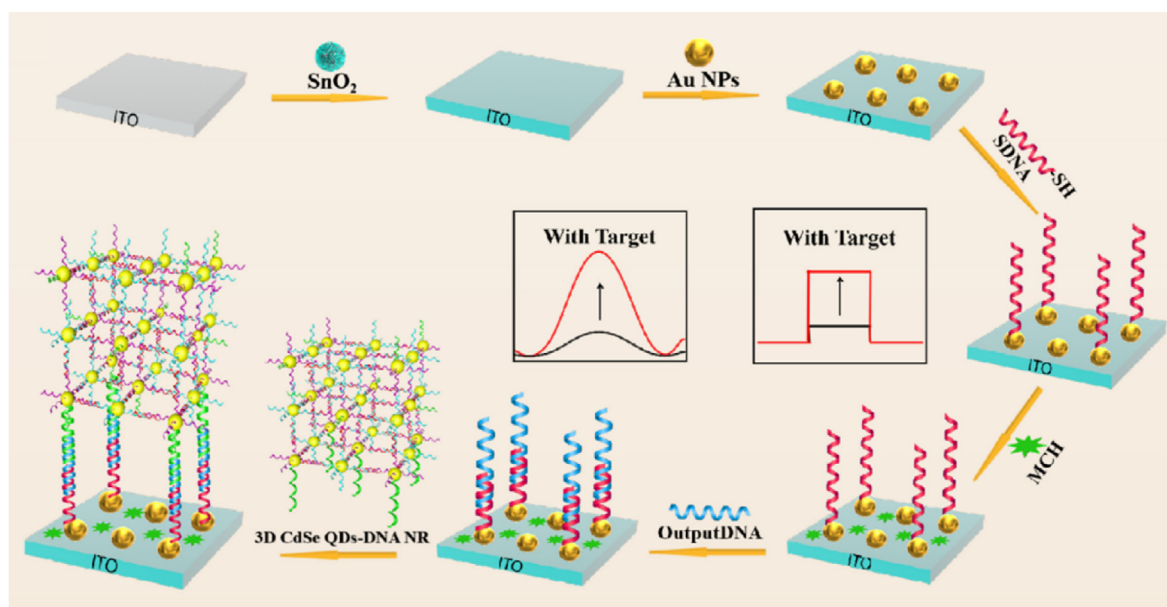
Fig. 4. Scheme of the ECL biosensing based on 3D CdSe QDs-DNA nanonetwork- SnO$_2$ nanoflower coupled with DNA walker multiple amplification for HIV detection [66].

promising analytical technique due to their distinctive advantages, such as rapidness, low background noise, and astonishing versatility. Hong et al. [69] introduced a split-type ECL technique that produced ascorbic acid through hydrolyzation of the conversion of alkaline phosphate to L-ascorbic acid 2-phosphate for the DNA hybridization reaction. For this, an amino-functionalized capture probes which is linked to the surface of carboxylic MBs[1], formed a sandwich structure via hybridization of HPV16 E7 and the biotin-labeled reporter probe.

After attraction between biotin-avidin in streptavidin-alkaline phosphatase and the biotinylated DNA complex, ascorbic acid was produced. Finally, through magnetic separation, a purified solution containing ascorbic acid was obtained. Based on ECL resonant transfer between AuNCs and MnO$_2$ NMs, the ECL signal of MnO$_2$/

AuNCs/GCE was decreased. The ECL signal recovered significantly after immersing the MnO$_2$/AuNC/GCE into the above solution due to the MnO$_2$ etching.

Most of the DNA-based ECL biosensors are fabricated by self-assembly of thiolated single-stranded DNA probes on the Au electrode surface. Due to this random assembly process, a significant discrepancy exists in the distribution of a modified DNA film on different electrodes, which directly affects the reproducibility of a biosensor. He et al. [70] worked on porous bovine serum albumin modified electrode to improve the self-assembly of the ssDNA probe's position distribution and spatial orientation. With the help of DNA amplification techniques in the presence of the target, the surface of the electrode accumulates abundant amplified DNA through reaction, which contains ds-DNA followed by bountiful Ru II complex as fluorophore insertion into grooves of ds-DNA fragments, and an ECL signal can be detected.

CRISPR/Cas systems, components of bacterial immune systems,

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[1] Magnetic beads

have gained enormous popularity in nucleic acid detections. Through the programmability of these biomolecular components, an enhanced and amplified ECL signal can be reached in the fields of biosensing. Leu et al. used Cas12a which improved specificity and signal amplification through part recognition mechanisms and *trans*-cleavage capability respectively [71]. In this work, L-methionine stabilized gold nanoclusters are used as ECL luminophores for the detection of HPV-16. Met-AuNCs modified electrode was used to achieve an original ECL signal and ferrocene-tagged thiolated single-strand DNA as non-specific ssDNA tethered on the surface of the modified electrode to quench the luminophore emission. In the presence of the target molecule, Cas12a activated and possessed *trans*-cleavage ability on ferrocene-tagged thiolated single-strand DNA with the help of the two-part recognition system, leading to the indiscriminate cleavage into short fragments. The recovered ECL signal under different concentrations of target HPV-16 DNA was used for the quantitative detection of HPV-16 in blood samples. Table 2 summarizes the variously reported ECL biosensors for HIV and HPV.

4.3. Hepatitis

Hepatitis viruses can be classified into 5 types including types A, B, C, D, and E. Hepatitis C virus (HCV) is responsible for several chronic liver diseases namely hepatocellular carcinoma, cirrhosis, and end-stage liver disease. HCV is a small single-stranded positive-sense RNA virus (+ssRNA virus) of the *Flaviviridae* family with a relatively small size (40−80) nm. It has six known genotypes and multiple subtypes amongst which genotype 1 is the most common worldwide. It is believed that there are about 71 million people worldwide infected with HCV. HCV can be diagnosed with various methods and among them, enzyme-linked immunosorbent assay (ELISA) and reverse-transcriptase polymerase chain reaction (RT-PCR) are the two most common detection methods. Hepatitis B virus (HBV) is responsible for a global chronic viral disease. The double-stranded DNA virus (dsDNA) belongs to the family of *Hepadnaviridae* with 257 million people worldwide being infected by it [72]. Immunoassays and polymerase chain reaction (PCR) are two of the reported assays mainly used to detect HBV. The comparison of the detection strategies has shown that electrochemical and electrogenereatedchemiluminescence provides a higher sensitivity in the analyte detection and a lessen dependency on nonspecific adsorptions [73]. The hepatitis B virus (HBV) is a DNA virus that replicates its genome via an RNA intermediate using reverse transcription 1 [74]. Hepatitis virus A (HAV) is a small, single-stranded positive RNA virus (+ssRNA virus) that can survive on hands and non-porous environments and various kinds of foods [75]. The hepatitis D (delta) viral agent, which is an infectious agent that needs hepadnavirus for propagation, contains a covalently closed circular single-stranded RNA genome of 1167 nucleotides. This genome encodes the proteins p_{24} and p_{27} that bind specifically to

antisera from patients with chronic hepatitis D infections [76]. Various ECL-based biosensors have also been adopted to detect different types of hepatitis viruses. Yang Liu et al. developed a distance-dependent Plasmon-enhanced ECL genosensors to detect the HCV gene, based on the amplification with hybridization chain reaction (HCR) [77]. The nonmetallic plasmonic MoS_2 nanosheets were employed to enhance the ECL signal of sulfur-doped boron nitrogen QDs (S-BN QDs). The distance-dependent plasmon-enhanced ECL were discussed with different length DNA chains. With the increased distance between MoS_2 nanosheets and S-BN QDs, the energy transfer effect was limited, and the surface plasma coupling effect was strengthened. As illustrated in Fig. 5A, each initiator can propagate a cascade hybridization event between alternate hairpins to form a long-nicked dsDNA with repeating units. To amplify the ECL signal of QDs, QDs were tagged on H2; MoS_2 nanosheets were connected to H1 on electrodes. In another research, a multiplex ECL DNA sensor was developed based on multicolor CdTe QDs and Au nanoparticles to determine hepatitis B virus (HBV) and hepatitis C virus (HCV) [78]. QDs were utilized as ECL luminophores and electrochemically reduced graphene nanosheets were employed to connect the luminophore onto GCE and enhance ECL intensity. After the introduction of target DNA, the capture DNAs on the surface of CdTe QDs hybridized with complementary target, and only the unreacted capture probes could hybridize with the complementary Au NPs-probe DNA. Au NPs could quench the ECL intensity of CdTe QDs due to the inner filter effect. Hence, target DNA_{HBV} and target DNA_{HCV} could be determined through monitoring the ECL DNA sensor based on Au NPs-probe DNA/target DNA/CdTe QDs-capture DNA/GNs/GCE composite film. The ECL signals of dual-color CdTe QDs increased with the increased concentration of target DNAHBV and target DNAHCV added with the limit of detection of target DNA_{HBV} and target DNA_{HCV} being 0.082 pM and 0.34 pM, respectively. In another effort to detect hepatitis C virus, an ECL genosensor was proposed to combine GQDs as a label and ECL signal source with site-specific recognition of BamHI endonuclease and bidentate chelation of dithiocarbamate ligands for enhanced the robustness of DNA immobilization on the surface of the gold electrode (Fig. 5B) [79]. BamHI endonuclease recognized the symmetrical duplex sequence and catalyzed the dsDNA cleavage, making the dsDNA fragments and the GQDs break off from the electrode surface. This resulted in a decreased ECL signal intensity. This signal-off ECL DNA biosensor employs hepatitis C virus-1b genotype complementary DNA (HCV-1b cDNA) as a model and displayed good analytical performance and a linear range from 5 fM to 100 pM with a detection limit as low as 0.45 fm. Recently, a novel multiple amplification strategies were reported for ultrasensitive near-infrared ECL immunoassay in $K_2S_2O_8$ solution for the detection of target procalcitonin (PCT) (Fig. 5C) [80]. The realization of this strategy is based on the antenna effect of Eu-MOF (EuBTC), and the high-efficiency catalysis of CoS_2 hollow triple shelled nano boxes (TSNBs). In comparison with

Table 2
Summary of various biosensors for HIV and HPV detection.

| Platform	ECL luminophor	Type of Virus detection	ECL pathway	Linear ranges	LOD	Matrix	Ref
ECL	RGO@Au composite	HIV Immunosensor	coreactant	10 ng mL^{-1} to 1 pg mL^{-1}	1 ng mL^{-1}	serum samples	[64]
ECL	Ti3C2Tx MXenes modified ZIF-8	HIV aptasensor	coreactant	1 nM 1 fM to	0.3 fM	Serum sample	[65]
ECL	CdSe QDs-DNA nano-network	HIV Genosensor	coreactant	0.5 μM to 5 fM,	2.4 fM	serum samples	[66]
ECL	CdSe/ZnS quantum dots @poly(styrene/acrylamide) nanospheres	HIV Genosensor	coreactant	50 nM to 0.5 pM	39.81 fM		[67]
ECL	EuS NCs	HIV Genosensor	coreactant	0.3 nM to 0.3 fM	0.3 fM	Serum sample	[68]
ECL	AuNCs	HPV Genosensor	coreactant	0.1 fM to 10 nM	0.06 fM	Clinical samples	[69]
ECL	Ru(phen)$_3^{2+}$	HPV Genosensor	coreactant	1 fM to 15 pM	7.6 fM	Clinical samples	[70]
ECL	AuNCs	HPV Genosensor	coreactant	10 nM to 1pM	0.48 pM	Blood sample	[71]
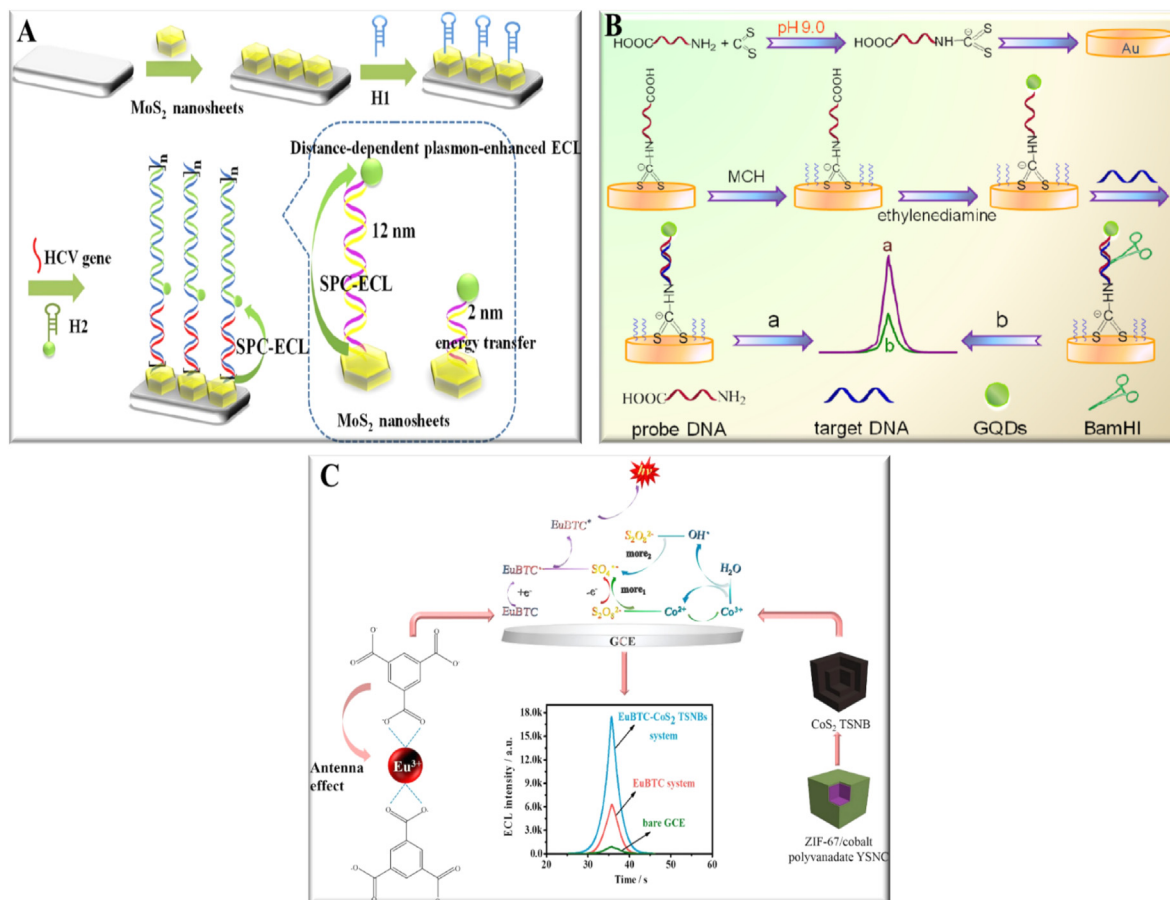
Fig. 5. A: The HCR-based sensing process and distance-dependent plasmon-enhanced ECL [77] BB. Schematic of the ECL-based biosensor based on GQDs combining with endo-nuclease cleavage and bidentate chelation [79], C: The mechanism illustration of the increased ECL by antenna effect and dual enhancement effect of CoS2 TSNBs [80].

the traditional ECL-emitters such as luminol, [Ru (bpy)$_3$]$^{2+}$, and noble metal catalysts, the Eu-MOF and CoS$_2$ make the ECL biosensor possess a low-cost advantage. This sandwich-type ECL biosensor has a near-infrared luminescence in 800−900 nm that does not damage the sample in the meantime. The strategy provides a feasible method for fearful bacterial infection, hepatitis B, and peritonitis. The limit of detection (LOD) for target procalcitonin (PCT) was calculated to be 3.65 fg mL^{-1} and a linear range of 10 fg mL^{-1} to 100 ng mL^{-1} was reported for the detection.

Moreover, Nikolaou and colleagues [81] recently suggested a new molecular biosensor for detecting Hepatitis B whole genome. The DNA sensor is based on a surface cooperative hybridization at a miniaturized gold electrode in conjunction with an ECL detection approach utilizing the [Ru (phen)$_2$dppz]$^{2+}$ complex. This PCR-free biosensor could detect both synthetic HBV genomes (SG ds-HBV) and samples collected from real samples (EG ds-HBV), with a detection limit of 0.05 μL^{-1} for extracted samples. In Table 3, various biosensors for hepatitis virus detection are summarized (see Table 4).

4.4. Zika virus (ZIKV)

Zika virus, is a single-stranded RNA virus that belongs to the family of *Flaviviridae* with strong neurotropic toxicity and terato-genicity [83]. The virus was first identified in 1947, and the name came from a forest in Uganda [84]. This virus can produce devas-tating consequences for the function of fetal development. Zika Virus spreads by infected mosquito bites and mother to fetus

transmission, sexual contact, or blood transfusion [87,89]. Zika's structure is tiled with a tightly packed coat of envelope proteins. The cryo-EM structure also revealed that an asparagine amino acid on the surface of this protein is glycosylated [90]. Recent techniques for Zika virus detection and diagnosis of its infections contain nu-clear acid-based assays, for example, quantitative polymerase chain reaction (QPCR), and immunoassays, such as neutralization tests or enzyme-linked immunosorbent assay (ELISA) [91] and ECL methods [92].

Acharya et al. worked on an immunoassay method to detect the Zika virus in human biological fluids [92]. They used polystyrene beads (PSB) with several ECL luminophores conjugated with anti-ZIKV monoclonal antibodies to form anti-ZIKV-PSBs. The rubrene/benzoyl peroxide (RUB/BPO) system was also chosen for the detection of viruses which is measured after further magnetic beads separation [71]. Their results indicated a linear range be-tween the ECL intensity and the logarithm of RUB concentration is from 0 to 104 PFU and the detection limit of anti-ZIKV-PSBs is 1 plaque-forming unit (PFU) in 100 μl of the sample. A platform for ultrasensitive detection of the zika virus based on a switchable ECL RNA method was developed by Yi-Wen Zhang and coworkers [93]. This platform surface was made from the metal-organic gel (AuNPs&gC$_3$N$_4$@Zr-MOG) and used a metal-organic framework (Fe-MIL-88 MOFs) as electrode surface and biofunctionalized the platform with DNA (Fig. 6A). Because of this, the ECL signal got enhanced. There was a direct relationship between the increase of ZIKV RNA concentration and the ECL signal. The linear range was reported from 0.3 nM to 3 μM, and the detection limit was 100 pM.

Table 3
Summary of various biosensors for hepatitis virus detection.

Platform	ECL Luminophor	Type of Virus detection	target	Linear ranges	ECL pathway	LOD	matrix	Ref
	Eu-MOF (EuBTC)	immunosensor	procalcitonin (PCT) ((hepatitis B))	(10 fg mL^{-1} -100 ng mL^{-1})	Coreactant	3.65 fg mL^{-1}		[80]
rGO-TEPA	Au@Pt Nanoparticles	immunosensor	HBsAg hepatitis B	0.25 pg mL^{-1} to 400 ng mL^{-1}	Coreactant	0.08 pg mL^{-1}	human serum	[82]
MoS2 nanosheets	sulfur doped boron nitrogen QDs (S-BN QDs)	Genosensor	hepatitis C virus (HCV) gene	0.5 pM to 1 nM	Coreactant	0.17 pM	human serum	[77]
polymer material	[Ru(bpy)$_3$]$^{2+}$ -Polymer	Genosensor	HBsAg gene of the Hepatitis B virus	102 aM−106 aM	Coreactant	100 aM	serum	[83]
Graphene nano sheets	CdTe QDs	Genosensor	DNA HBV and DNA HCV	0.0005−0.5 nM And 0.001−1.0 nM	Coreactant	0.082 pM and 0.34 pM	human serum	[78]
DTC-DNA/MCH/ ethylenedianmine/ GQDs	graphene quantum dots (GQDs)	Genosensor	hepatitis C virus-	5 fM to 100 pM	Coreatant	0.45 fM	Not mentioned	[79]
paper-based BPE	[Ru(bpy)$_3$]$^{2+}$	Genosensor	hepatitis B virus gene (HBV)	0.2 to 100 fM	Coreactant	0.2 fM	Serum	[84]
GCE/ABEI-PEI/ternary NCs/CS	N-(aminobutyl)-N-(ethylisoluminol) (ABEI)	Genosensor	HBV-related DNA	0.01−100 fM	Coreactant	down to 65 aM	human serum	[85]
poly(aniline-luminol)-MWCNTs	Luminol	Genosensor	hepatitis B virus	10^{-16}−10^{-7} M	Coreactant	2.4 × 10^{-17} M	Serum	[86]
Au electrode (CHI101)	(phen)$_2$dppz]$^{2+}$ complex	Genosensor	hepatitis B virus gene (HBV)	0−0.75−0.017 cps μL−1	Coreactant	0.05 cps μL−1	genome extracted from real samples	[81]

Table 4
Summary of various biosensors for zika virus detection.

Platform	Type of Virus detection	ECL luminophor	ECL pathway	Linear ranges	LOD	Matrix	Ref
polystyrene beads (PSB)	immunosensor	Ru(bpy)$_3^{+2}$	Coreactant	0−104 PFU	1 PFU in 100 μl	human plasma, human urine.	[92]
Fe-MIL-88 MOFs	genosensor	AuNPs&g-C$_3$N$_4$@Zr-MOG	Coreactant	0.3 nM to 3 μM	0.1 nM	Human serum	[93]
SiO$_2$ microspheres	immunosensor	CdS QDs	Coreactant	1.0 fg mL^{-1} to 1.0 ng mL^{-1}	0.3 fg mL^{-1}	Human serum	[94]

Recently, a platform based on the sandwich immunoassay method was reported to detect the Zika virus (Fig. 6B), which was designed based on CdS quantum dots capped with 3-mercaptopropionic acid (MPA@CdS QDs) as ECL labels and silica microspheres as the carrier. One of the advantages of this method is that the generated ECL signals are robust enough that their photos may be captured by smartphone usage. The proposed immunosensor could quantify ZIKV from 1.0 fg mL^{-1} to 1.0 ng mL^{-1}, and the LOD reported was

0.3 fg mL^{-1} [94].

5. Conclusion and future perspective

Currently, the world faces a health crisis caused by the pandemic of SARS-CoV-2. Besides the challenges of diagnosing and treatment of COVID-19, lots of efforts have been put into the prevention of future outbreaks. Despite significant developments in biosensor-
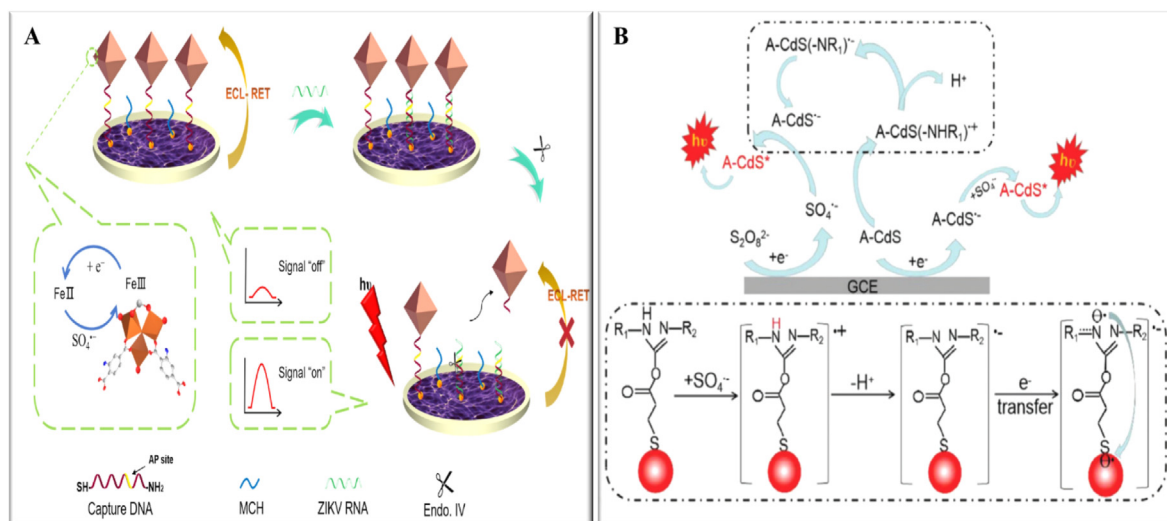

Fig. 6. A. Schematic illustration of the construction process of the proposed ECL sensing platform [88]. B. Preparation of the activation of MPA@CdS QDs (A), the fabrication process of the proposed ECL immunosensor (B) and ECL mechanism of A-CdS QDs (C) [89].

based disease diagnosis through previous years, there is still much room for improvement. In recent years, ECL-based biosensors as sensitive, cost-effective, and easily adaptable techniques have been increasingly employed for clinical diagnosis of viruses and other infectious diseases. ECL biosensors are ideal platforms with many advantages, such as high detection capability, simplicity, stability, reliability, and they can be developed without compromising the sensitivity and reproducibility of standards in clinical analysis.

Although some attempts to design different ECL biosensors for virus detection and especially COVID-19 diagnosis have been made, not many portable ECL biosensors for virus detection were fabricated due to many challenges in their use in point-of-care tests. For example, a large number of interferes (antibodies, proteins, cells, DNA, etc.) in several complex samples, a small volume of the viruses in the whole sample volume, and how to isolate the viruses from the real samples are some of the main challenges in the sample preparation step. Also, the immobilization of the bio-recognition elements, uniform distribution of the receptor on the electrode surface, and the affinity of bio-recognition elements remain unresolved challenges in ECL biosensors. Moreover, the development of the miniaturized, reproducible, stable, environment-friendly, and cost-effective ECL-based biosensors is another challenge for the fabrication of ECL-based point-of-care biosensors. Therefore, more effort shall be put to overhaul the above challenges in the design and fabrication of the portable ECL biosensors. Despite the critical emerging advances that have considerable capability to design ECL devices for virus diagnosis, the effort to develop an integrated smart ECL sensing system, which is also user-friendly, employed biocompatible substances that provide wearable devices, and the use of minimally invasive samples, such as tears, saliva, urine, or breath is needed.

We have generally introduced the different ECL-based biosensors for each virus and reported various bio-recognition elements. Some examples and recent trends in ECL biosensors are described and gathered in tables with their detection limits for each section. This review primarily prepared valuable references for designing platforms for viral diagnosis based on the ECL methods.

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.

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Acknowledgements

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