4 Carbon Nanomaterials for Electrochemiluminescence-Based Immunosensors: Recent Advances and Applications

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Abstract

Electrochemiluminescence (ECL) technique is defined as luminescence emitted as a result from the occurrence of chemical reaction on the electrode's surface between luminophore (the light-emitting chemical species) and other species present in the same system when a small potential is applied to the electrode. ECL technique is oftentimes adopted for devising biosensors for the detection of various kinds of proteins by manipulating the interactions between antibody (Ab) and antigen (Ag) – these biosensors are also known as immunosensors. This technique is advantageous for immunosensors as it offers numerous benefits including straightforward operation and low background signal. Furthermore, the performance of these immunosensors can be elevated by integrating carbon nanomaterials (CNMs) into the biosensors and exploiting their excellent electrocatalytic properties for improving the sensitivity and specificity of the biosensors. This chapter comprises of an overview of ECL-based immunosensors integrated with CNMs, accentuating their recent developments and applications.

Keywords

Carbon nanomaterials · Electrochemiluminescence · Immunosensor · Biosensor

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4.1 Introduction

Early diagnosis of diseases, particularly of life-threatening nature, is crucial because treatment given at a curable stage will provide a significant impact on the quality of patients' life. A strategy that has a high potential to be employed as a preventive measure is by designing and developing point-of-care (POC) devices since these devices allow fast detection and continuous monitoring of diseases through instant data acquisition. Other advantages for utilisation of the instruments are that these can be used directly without any prior training (Lee et al. 2018) and they are portable and low cost, thus extremely useful in outlying areas and developing countries (Ge et al. 2014; Ahmed et al. 2014). In addition, POC devices allow users to operate the devices using a small amount of samples with reliable and precise results (Ahmed et al. 2016). Thereafter, these merits of POC devices could improve the efficiency of healthcare services where time and effort should be invested for further development as to make these devices to be wearable and also embeddable in vivo, allowing real-time observation of the specified parameters such as change in biomarker concentrations (Siontorou et al. 2017).

Incorporating biosensor in POC diagnostic devices is an attractive prospect in order to meet the demand of providing modern and sophisticated analytical devices for routine detection of biomarker(s). Biomarkers are commonly used in biomedical field to provide essential information that reflects the health status of patients. Biomarkers or biological markers as described by WHO (2001) are "a substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease". Monitoring the concentration of these biomarkers in the patients' serum or saliva can assist in averting the aggravation of diseases as any decrease or upsurge in the biomarkers' level might signify the related disease (Bertoncello et al. 2014).

Immunosensors are widely recognised as the analytical compact type of biosensors that utilised antibodies as bioreceptors, which are immobilised on or within the transducing element (Ju et al. 2017). Meanwhile, electrochemiluminescence (ECL) technique is progressively gaining more attention attributable to its attractive merits which include offering the opportunities for the ECL signal enhancement by modifying the electrode's surface with nanomaterials (Fang et al. 2017). Herewith, this chapter highlights the recent developments and applications of ECL immunosensors that incorporated carbon nanomaterials (CNMs).

4.2 Biosensor

The development of biosensors is instigated by the introduction of glucose detector by Clark and Lyons (1962), and ever since, the interest in inventing biosensors has been flourishing. According to the International Union Pure and Applied Chemistry (IUPAC), a biosensor is a device which comprises of two major modules: a bioreceptor (biological recognition element) and a transducer as means of detecting the target analytes (Farzin and Shamsipur 2017) (Fig. 4.1). This device detects any

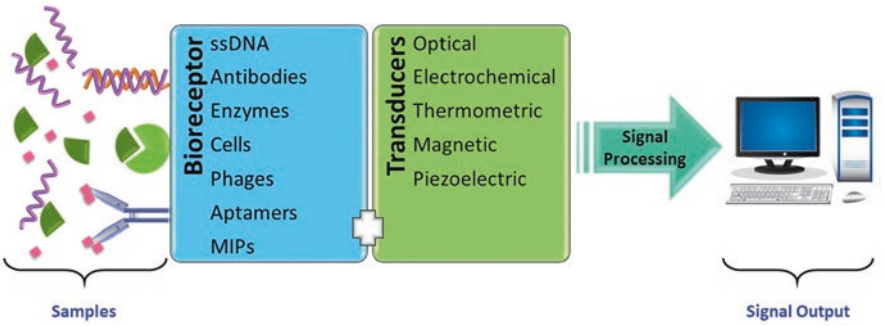

Fig. 4.1 Schematic representation of the basic components of biosensors

biological and/or chemical reactions produced by analytes, and subsequently signals obtained from these biochemical changes are computed and displayed as quantitative and semi-quantitative signals (Bhalla et al. 2016).

Biosensors are able to deliver results accurately and precisely (Ugo and Moretto 2017). Biosensors can be classified as (a) biocatalytic and (b) bioaffinity-based biosensors (Luppa et al. 2001). Biocatalytic-based biosensors mainly rely on enzymes as the biological intermediate that catalyses the generation of the signals from the reactions involved. On the other hand, bioaffinity biosensors involve the direct observation of the binding between the specified bioreceptor and the analyte as a means to generate the signal of the detection. Biosensors that are based on antibodies–antigen interactions are also known as immunosensors. Table 4.1 outlines important aspects of desirable biosensors for commercialisation.

In addition to these features, other preferable characteristics for a biosensor also include its portability and straightforward operation and also should be inexpensive for it to be competently commercialised (da Silva et al. 2017).

4.2.1 Basic Fundamental of ECL Immunosensors

Immunosensors are one of the well-known types of biosensors that employ antibodies (Abs) as the bioreceptors as a means to detect the target analytes. Abs and the corresponding antigens (Ag) interact with each other and form immuno-complexes (Liu and Saltman 2015). The formation of immuno-complexes induces changes in signal responses (e.g. in the form of potential or colour) or in the complexes' attributes (such as change in mass or density). These changes are detected by a specific transducer depending on the nature of the signal generated by the immuno-complexes. Currently, transducers that are widely used are based on optical and electrochemical changes (Moina and Ybarra 2012). Nevertheless, the focus in this chapter is electrochemiluminescence immunosensor that will be concisely defined in the next subsections.

Table 4.1 Characteristics which are preferred to be possessed by biosensor devices (Chakraborty and Hashmi 2017; Thakur and Ragavan 2013)

Aspects/ characteristics	Definition
Specificity	Biosensors are required to be highly selective and specific towards the target analytes with the least or no contaminants
Reproducibility	The device should be able to replicate the identical results of the same concentration of the target analyte
Stability	As biosensors are incorporating biological elements, it is crucial that these elements are able to withstand long-term storage without adversely affecting the device's overall performance
Sensitivity	Biosensors are expected to be able to detect trace amount of analytes without any prerequisite/pretreatment steps for the samples
Linearity	A linear range of concentrations of the target analyte should be detected by the biosensor, providing a quantitative detection
Response and recovery time	Prompt response is always desired especially for POC-based biosensors as to deliver real-time detection, and it is highly beneficial for the biosensor to be effectively reused with quick recovery time

4.2.1.1 Antibodies as the Bioreceptor

An immunosensor is an affinity-based biosensor since antibodies are known to provide high affinity, specificity and sensitivity towards their target proteins (Mathieu 2010). Other advantages for the employment of antibodies used in sensing include their flexibility for modification (e.g. for label-based biosensors) and their commercial obtainability (Rogers 2000). Immunoglobulin (Ig) or Ab is intricately composed of hundreds of separate amino acids, arrayed in the highest-ordered sequences (Vo-Dinh and Cullum 2000). They are formed by B lymphocytes, expressed as a protein and responsible as the antigen (target) receptor in the cell (Donahue and Albitar 2010).

The structure of antibody has a "Y"-like configuration, consisting of two analogous heavy polypeptide chains with the molecular weight of ~50 kDa for each chain and two other analogous light polypeptide chains (~25 kDa each). The respective pair of heavy and light chain is linked to the other pair via a disulphide bridge (Felix and Angnes 2017). Figure 4.2 signifies the structure of an Ab molecule, and Fab is the unit where the antigen binds to the antibody.

Abs can be further classified into monoclonal antibody (MAb) and polyclonal antibody (PAb). MAbs are commonly formed with the hybridoma technology in mice, and they are more responsive towards a single epitome (the binding site whereby Ab interacts with the corresponding antigen or Ag). MAbs possess better affinity and contribute more towards the specificity compared to the PAbs (Omidfar et al. 2013). Meanwhile, PAbs are habitually produced in goats, rabbits or sheep, and they are instinctively, heterogeneously reactive towards several epitomes. This feature jeopardises the overall specificity of the immunosensor and consequently provides less specificity for the detection of the target antigen (Byrne et al. 2009).

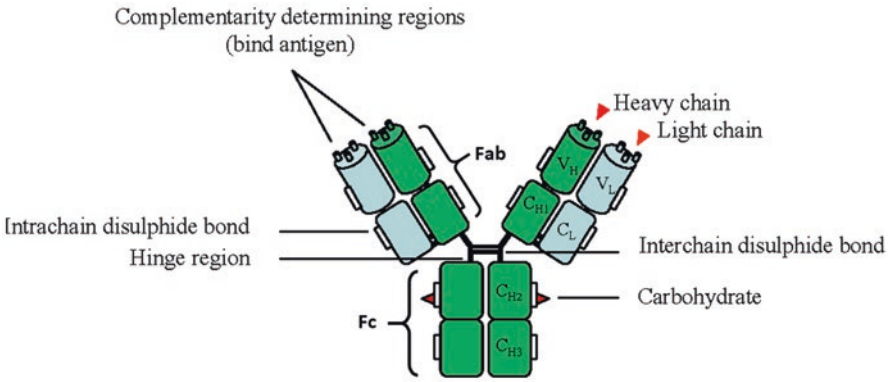

Fig. 4.2 Structure of immunoglobulin. Blue-coloured fragments represent the light chain, whereas the green-coloured fragments denote the heavy chain of the Ab. V_H variable heavy, V_L variable light, C_H constant heavy and C_L constant light. (Reproduced and modified from Byrne et al. 2009)

4.2.1.2 Electrochemiluminescence-Based Transducer

The studies of electrogenerated chemiluminescence, also commonly known as electrochemiluminescence (ECL), were firstly initiated in the 1960s (Hercules 1964; Santhanam and Bard 1965). This technique employs luminophores (molecular species) and fuses electrochemistry with chemiluminescence (CL). When a small amount of potential is applied onto an electrode surface, this will subsequently generate chemical species capable of emitting light without producing heat (Miao 2008).

The basic principle behind electrochemiluminescence-based method for detecting target analytes relies on the occurrence of homogeneous chemical reaction between a minimum of two chemical species in the same system. Both electron acceptor species and an electron donor species are imperatively required for ECL generation. These two species are the products of the chemical reaction that takes place at an electrode's surface and subsequently involved in an electron transfer activity, yielding a species with an excited state (Valenti et al. 2018). Luminol and tris(2,2-bipyridyl)-ruthenium(II) ($[Ru(bpy)_3]^{2+}$) are two of the most prevalent ECL luminophore in formulating POC-based biosensors (Azam et al. 2018; Roy et al. 2016).

There are two principal approaches in ECL technique: ion annihilation and co-reactant-based approach (Kerr et al. 2016). Ion annihilation involves electrochemical production of excited states from the two-step potentials at the electrode's surface, whereas co-reactant approach involves the luminophore and the corresponding co-reactant, which formed a radical species due to the oxidation or reduction of both species on the electrode's surface (Benoit and Choi 2017). With the purpose of elucidating the mechanism behind the two ECL routes, $[Ru(bpy)_3]^{2+}$ is used to exemplify the reactions (Hazelton et al. 2008).

In ion annihilation pathway, reactions are as follows:

$$\left[Ru\left(bpy\right)_3\right]^{2+} \rightarrow \left[Ru\left(bpy\right)_3\right]^{3+} \tag{4.1}$$

$$\left[Ru\left(bpy\right)_3\right]^{2+} + e^- \rightarrow \left[Ru\left(bpy\right)_3\right]^{+} \tag{4.2}$$

$$\left[Ru\left(bpy\right)_3\right]^{3+} + \left[Ru\left(bpy\right)_3\right]^{+} \rightarrow \left[Ru\left(bpy\right)_3\right]^{2+} + \left[Ru\left(bpy\right)_3\right]^{2+*} \tag{4.3}$$

$$\left[Ru\left(bpy\right)_3\right]^{2+*} \rightarrow \left[Ru\left(bpy\right)_3\right]^{2+} + h\nu \tag{4.4}$$

As potential is applied onto the electrode's surface, $[Ru(bpy)_3]^{2+}$ firstly undergoes consecutive reduction and oxidation reactions, generating both $[Ru(bpy)_3]^{3+}$ and $[Ru(bpy)_3]^{+}$ as depicted in Eqs. 4.1 and 4.2. These two resulting species then react with each other, forming an excited state of $[Ru(bpy)_3]^{2+}$ (Eq. 4.3), encouraging the subsequent annihilation process. The excited state will finally decay and return to its ground state and, hence, emit light (Eq. 4.4).

Contrastingly, co-reaction route involves the reactions as stated below:

$$\mathrm{TPrA} \rightarrow \mathrm{TPrA}^{\bullet+} + e^- \tag{4.5}$$

$$\mathrm{TPrA}^{\bullet+} \rightarrow \mathrm{TPrA}^{\bullet} + H^+ \tag{4.6}$$

$$\mathrm{TPrA}^{\bullet} + \left[Ru\left(bpy\right)_3\right]^{2+} \rightarrow \left[Ru\left(bpy\right)_3\right]^{+} + \mathrm{TPrA}^{+} \tag{4.7}$$

$$\left[Ru\left(bpy\right)_3\right]^{+} + \mathrm{TPrA}^{\bullet+} \rightarrow \left[Ru\left(bpy\right)_3\right]^{2+*} + \mathrm{products} \tag{4.8}$$

Oxalate-containing complexes and compounds with a tertiary amine group (e.g. TPrA) are known as the co-reactant for $[Ru(bpy)_3]^{2+}$. As demonstrated through Eqs. 4.5, 4.6, 4.7 and 4.8, the light emanation process was initiated by the formation of the TPrA radicals that react with $[Ru(bpy)_3]^{2+}$. Ultimately, light is emitted when the excited form of $[Ru(bpy)_3]^{2+}$ returns to its ground state (Fig. 4.3).

ECL is highly suitable to be integrated in a biosensor and will complement each other perfectly owing to numerous merits when combined. These merits include low background signal, rapid analysis can be easily achieved and requires less reagents as the reactive intermediates can be electro-regenerated, and better dynamic range can be determined (Sojic et al. 2017; Muzyka 2014). The electrode's surface is usually modified with biomolecules and/or nanomaterial in order to minimise the sample volume, reinforce better specificity, offer better sensitivity and ultimately better limit of detection (LOD) (Rizwan et al. 2018b; Wei et al. 2010). Employment of ECL is beneficial in developing biosensors as parameters can be easily calibrated according to the modification on the electrode's surface (Rizwan et al. 2018b).

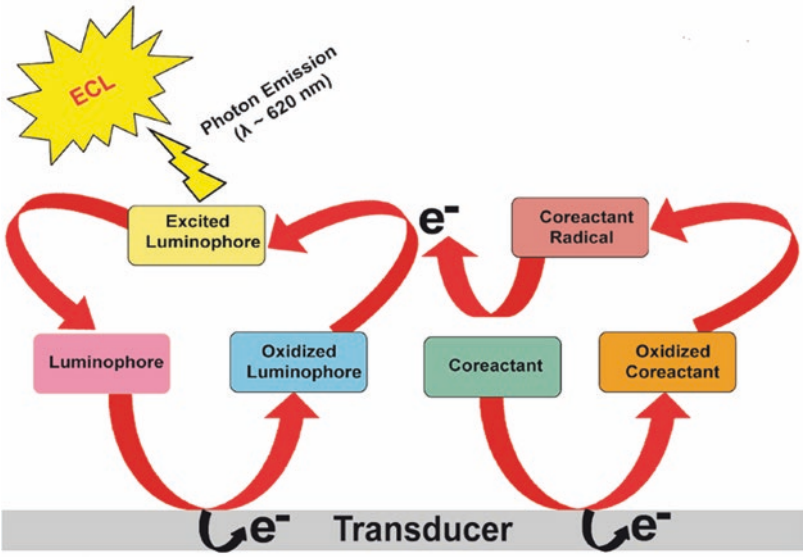

Fig. 4.3 Schematic illustration of the co-reactant-based ECL pathway's mechanism on the electrode's surface. (Adapted from Rizwan et al. 2018b)

4.3 Nanomaterials

Nanotechnology refers to the application of science and technology using materials in nanometre (10^{-9} m) scale in order to exploit their unique properties. Nanotechnology-based biosensor has been increasingly gaining recognition in many different industries such as agriculture (Nair et al. 2011), biomedical applications (Xu et al. 2017), cosmetics industry (Raj et al. 2012) and food industry (Neethirajan et al. 2018; Lim and Ahmed 2016b). It has been widely recognised that there are numerous benefits of using nanomaterials (NMs) in developing biosensors due to their optical, mechanical and electrical properties and also their sizes and shapes. The advantages include providing high biocompatibility in the biosensors and enhancing the electrical signal and rapid detection time.

There are four categories of NMs that are determined by their respective dimensions, which are 0D (zero-dimensional, spherical) NMs; 1D (one-dimensional) NMs such as nanotubes, nanowires and nanofibers; 2D (two-dimensional, e.g. multilayers and film) NMs; and 3D (three-dimensional, for instance, nanoflower and graphite) NMs (Machado et al. 2015; Quesada-González and Merkoçi 2018).

0D nanomaterials are simply delineated as spherical nanostructures, and fullerene (C_{60}), quantum dots (QDs) and metal nanoparticles (e.g. AuNPs and PdNPs) are some of the known 0D NMs. Additional classifications of the 0D NMs are magnetic, metallic and semi-conductor NMs. As for one-dimensional nanomaterials, they have structures with elongated shape with measurement exceeding nanometre range. Gold nanorod (AuNR), carbon nanotube (CNT) and gold nanowire (AuNW)

NMs are a few of the examples of 1D nanostructures. Contrastingly, 2D nanomaterials have layer-like frameworks, and some of these structures include graphene oxide (GO) and graphene nanoplatelets (GNPs). Lastly, 3D nanostructures are the nanomaterials with all of their dimensions transcend nanometre scale such as gold nanoflowers (AuNFs) (Lim and Ahmed 2016a).

Through covalent and non-covalent interactions, various nanocomposite/nanohybrid materials can be synthesised. Modification via covalent interactions engages with different organic functional groups (e.g. –CHO, -NH_2), free radicals, oxygen and dienophiles that cause disorder in the structure of the overall compound. In opposition, non-covalent modification does not perturb the structure of the core nanomaterials involved as they utilise biological moieties such as enzymes and proteins, biomimetic molecules, polymers (e.g. polyethylene glycol and polyvinylpyrrolidone) and other types of NMs (Kuila et al. 2012; Georgakilas et al. 2012).

4.3.1 Advances and Applications of Carbon Nanomaterials in ECL Immunosensors

Carbon nanotubes (CNTs) and graphene-based nanomaterials are two of the most widely used carbon nanomaterials in biosensing research efforts and explicitly for modifying the electrode's surface. Amongst the attractive traits of carbon nanomaterials (CNMs) are their excellent electroconductivity, remarkable compatibility with biological moieties, effortless methods offered for modifications and admirable mechanical strength (da Silva et al. 2017; Lim and Ahmed 2016c; Rizwan et al. 2018a; Zhang and Lieber 2015). On top of these, CNMs aid to elevate the adsorption of bioreceptors/analytes onto the surface of the electrode and, successively, enrich the sensitivity of the biosensor (Baig et al. 2019). Table 4.2 depicts some applications of reported ECL immunosensors that incorporated CNMs in their biosensors.

4.3.1.1 Carbon Nanotubes

Carbon nanotubes are hollow cylindrical tubes that are made up of rolled graphite sheets (sp^2-hybridised carbon units) with thickness in nanoscale range and length that can be within micrometre range. Carbon nanotubes can be rolled either into a single layer, known as single-walled carbon nanotubes (SWCNTs), or multilayers, known as multiwalled carbon nanotubes (MWCNTs). SWCNTs and MWCNTs are the two types of CNTs that are frequently utilised.

The vectors (n, m) of a SWCNT's cylindrical structure portray its electronic characteristic. The integers of the n and m determine the configuration of SWCNTs of being armchair, zigzag or chiral (Gupta et al. 2018). By relying on the chirality and the diameter of the particular SWCNTs, they can be either metallic or semiconductor. They facilitate high heterogeneous electron transfer (HET) with reduced surface obstruction. Functionalised CNTs with –COOH, -COH or –OH groups are more felicitous compared to bare CNTs as they have better affinity towards bio- or chemical receptors (Wohlstadter et al. 2003; Yang et al. 2015). SWCNTs are known

Table 4.2 Some of the reported (2016–2019) ECL immunosensors that employs CNMs in the fabrication process

Developed ECL immunosensor	Target analyte	Detection range	Sensitivity	Specificity	References
GCE/Au-rGO@CB-Ab_1	AFP	0.0001 to 30 ng/mL	33 fg/mL	High	Zhu et al. (2016)
GCE/cit-rGO-$BaYF_5$/PDDA/AuNPs/Ab/BSA/CEA	CEA	0.001 to 80 ng/mL	0.87 pg/mL	High	Zhao et al. (2016)
Magnet/GCE/Magnetic Beads-Ab_1/VV/GO-Ab_2	*Vibrio vulnificus*	$4 \sim 4 \times 10^8$ CFU/mL	1 CFU/mL	High	Guo et al. (2016)
GCE/BGNs/Fe3O4-Au/Ab_1/TTX/luminol-AuNPs/Ab_2	Tetrodotoxin	0.01 to 100 ng/mL	0.01 ng/mL	High	Shang et al. (2017)
GCE/Au-FONDs/Ab_1/BSA/PSA/Ru@FGAPd-Ab_2	PSA	0.0001 to 50 ng/mL	0.056 pg/mL	High	Yang et al. (2017a)
GCE/MWCNTs–Pt–Luminol/Chi/Ab_1/BSA	CA19–9	0.0001 U/mL to 10.0 U/mL	46 μU/mL	High	Zhang et al. (2017)
GCE/anti-CEA/Au-FrGO-CeO_2@TiO_2	CEA	0.01 pg/mL to 10 ng/mL	3.28 fg/mL	High	Yang et al. (2017b)
GCE/erGO/P5Fin/AuNP/Ab_1/CEA/Ab_2-GQDs@AuNP	CEA	0.1 pg/mL to 10 ng/mL	3.78 fg/mL	High	Nie et al. (2018)
GCE/Au/Ab_1/CEA/Ab_2/AuNPs/CQDs-Cu^{2+}-PTCA-graphene	CEA	0.001 fg/mL to 1 ng/mL	0.00026 fg/mL	High	Xu et al. (2018)
GCE/DMSA-CdTe QDs/chitosan/Ab_1/BSA/Ag/Ab_2-SWCNHs-HRP	NSE	1×10^{-9} g/L to 1×10^{-3} g/L	4.4×10^{-10} g/L	High	Ai et al. (2018)
GCE/GO/Ag-AuNRs/Sudan I/BSA/Au CSNs-Ab/CdSe-CdS QDs-PAMAM-Pd	Sudan I	0.001 to 500 ng/mL	0.3 pg/mL	High	Wang et al. (2018)
GCE/Au NPs-Lu/rGO/Ab_1/BSA/insulin/Ab_2-SiO_2@PDA	Insulin	0.0001 to 50 ng/mL	26 fg/mL	High	Xing et al. (2018)
GCE/Luminol-Au@Fe_3O_4-$Cu_3(PO_4)_2$/Ab_1/BSA/NT-proBNP/Ab_2-Au@CuS-rGO	NT-proBNP	0.5 pg/mL to 20 ng/mL	0.12 pg/mL	High	Li et al. (2018b)

(continued)

Table 4.2 (continued)

Developed ECL immunosensor	Target analyte	Detection range	Sensitivity	Specificity	References
GCE/Ce:ZnO/Ag-OVA/Ab/PdNPs/PEI-GO/QDs	DCF	0.001 to 1000 ng/mL	0.3 pg/mL	High	Chen et al. (2018)
GCE-AuNRs-DCF Ag	DCF	0.001 to 800 ng/mL	0.33 pg/mL	High	Wang et al. (2019)
GCE/anti-PSA-Lu-GS@Pt/BSA/PSA	PSA	1 pg/mL to 10 ng/mL	0.3 pg/mL	High	Khan et al. (2019)
GCE/Au NPs-luminol-LDH/Ab_1/PSA/Ab_2-GOx-PGA-Pt NPs	PSA	1.0 pg/mL to 150 ng/mL	0.6 pg/mL	High	Huo et al. (2019)
GCE/CdS/p53-Ab_1/p53/p53-Ab_2-tGO-AuNPs	p53 protein	20 to 1000 fg/ml	4 fg/mL	High	Heidari et al. (2019)

AFP α-fetoprotein, *CA19–9* tumour marker for pancreatic cancer, *CEA* carcinoembryonic antigen, *DCF* diclofenac, *GA* glutaraldehyde, *Gal-3* galectin-3, *NSE* neuron-specific enolase, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *p53* tumour suppressor gene, *PSA* prostate serum antigen, *Sudan I* food colourant

to have better electronic properties in contrast to MWCNTs making them an appealing option in devising biosensors despite its poor dispersal ability especially in polar solvents (Li et al. 2018a). SWCNTs' superb electroconductivity has been substantiated to be facilitating the electron transfer that subsequently improves the sensitivity of the detection. The impediment relating to the dispersal ability of SWCNTs can be resolved by functionalising the SWCNTs chemically with –OH, -COOH, $-NH_2$ or –SH (Zaman et al. 2012). SWCNTs and COOH have been evinced to possess better biocompatibility with the bioreceptors, and also more bioreceptors can be deposited onto the functionalised SWCNTs compared to the bare SWCNTs (Rezaei et al. 2016).

Single-walled carbon nanohorns (SWCNHs) are firstly identified by Iijima et al. (1999) by excising carbon with CO_2 laser at room temperature without requiring any metal catalysts. SWCNHs are also known as nanocones, attributable to their conical structure of sp^2-hybridised carbon atoms with a diameter of 2–5 nm and length of 40–50 nm (Karousis et al. 2016). To date, there are three kinds of SWCNHs discovered: "dahlia-like", "budlike" and "seedlike". Their properties are similar to SWCNTs with the advantage of being less toxic and undemanding to be mass produced compared to SWCNTs (Zhu and Xu 2010). More amount of biomolecules can be immobilised onto SWCNHs on the account of their large surface area when the pores of SWCNHs are opened, in contrast to SWCNTs (Farka et al. 2017).

Electrocatalytic characteristic of SWCNHs was manoeuvred for the construction of an ECL immunosensor for the detection of N-terminal brain-type natriuretic peptide (NT-proBNP), a biomarker for heart failure (Liu et al. 2017). This group immobilised the secondary Abs onto the SWCNHs decorated with PdCu (bimetal) nanocomposites (PdCu@SWCNHs), which have been conjugated with PTC-Lu (3,4,9,10-perylenetetracarboxylic acid-luminol) – the selected luminophore. It was ascertained that by employing PdCu@SWCNHs, the ECL intensity is further enhanced as the nanocomposite facilitates the production of ROS (reactive oxygen species) for luminol-H_2O_2 system. Thereafter, their biosensor can selectively detect NT-proBNP linearly from 0.0001 ng/mL to 25 ng/mL, and the sensitivity is determined to be 0.05 pg/mL. They have also effectually performed the real sample analysis with four different human serums with the reasonable %RSD (% relative standard deviation) of −5.0–6.0%.

MWCNTs are known as lightweight nanomaterials which possess superior tensile strength, excellent electroconductivity and large surface area. Owing to their unique properties, MWCNTs have been progressively amalgamated into biosensors. Zhang et al. (2017) designed an immunosensor for the detection of CA19-9, a tumour marker (pancreatic cancer), by combining MWCNTs, Pt, and luminol (luminophore) as a nanocomposite. They immobilised the nanocomposite on the glassy carbon electrode (GCE) and reinforced the nanocomposite by a layer of chitosan. In their study, they claimed that MWCNT-Pt functions as the catalyst which facilitates the electron transfer as well as a catalyst in the production of reactive oxygen species (ROS) and subsequently enhances the ECL intensity of luminol-H_2O_2 ECL system. H_2O_2 is known to be the oxidising agent for luminol to emit luminescence through the annihilation pathway. The resultant immunosensor is

capable to detect CA19–9 linearly from 0.0001 U mL^{-1} to 10.0 U mL^{-1} with a high sensitivity of 0.000046 U mL^{-1}. They have also successfully applied it for the detection of target in real human serum with good percentage recovery (96.7–105.0%).

Aside from the increasing interest in the development of ECL immunosensors for applications in clinical diagnosis with CNMs, there are also biosensors being devised for applications in other areas. In clinical diagnosis, the growth in the biosensor fabrication is due to the requirement for analyses to be prompt in producing results with accuracy and precision. Therefore, it is crucial for the developed biosensors to explicitly detect the target analytes within the specified range (should include both healthy and unhealthy concentrations). A plethora of researches are being carried out to allow early screening for any anomalies in specified biomarker's concentration that signify the progress of related illness for the prevention of it to be further developed as the consequence might be terminal.

Other recent applications of ECL immunosensors that employed CNTs or CNHs include monitoring environmental situations as it is vital in order to ensure the safety of foods for consumption and as a step for preventing illness in humans, animals and plants. One example of environmental applications is supervising the concentration of pharmaceutical compounds diclofenac in the environment that can cause mortality in aquatic animals (Hu et al. 2018).

4.3.1.2 Graphene-Based Nanomaterials

Per contra, graphene maintains single-layer frameworks with honeycomb-like lattice that are made up of sp^2-hybridised carbon atoms with a plethora of delocalised π electrons within the structure. Graphene nanomaterials appeal researchers for the construction of POC biosensors as they have undeniably marvellous properties that allow rapid, on-site detections. Particularly on the defects of the edges of graphene, the electron transfer is brisker in comparison with that on the plane and, therefore, confirmed to have extraordinary electrocatalytic property. Moreover, graphene has a large surface area of 2630 m^2/g, supplying colossal area for immobilisation of bioreceptors (Adeel et al. 2018).

The oxidised derivatives of graphene – GO and rGO – are two of the most prominent nanomaterials utilised in the fabrication of biosensors. These are due to their exquisite properties as mentioned in the previous paragraph, with additional benefits of possessing exquisite optical transmittance, and excellent mechanical property (Farka et al. 2017). Additionally, the presence of oxygen groups contributes to the hydrophilicity of GO and rGO, and thereupon, they are easier to be dispersed (Erol et al. 2018). Nonetheless, as GO comprises of oxygen-containing functional groups, these groups unfavourably affected the electroconductivity of GO. One of the measures taken to tackle this issue is by loading metal nanoparticles on GO frameworks, as shown by Wang et al. (2018). Their group has reported a competitive type of ECL immunosensor by combining Au nanorods (AuNRs) with GO (AuNRs/GO) as the carrier for the Ab. Employment of AuNRs-GO helps to amplify the ECL signal of the immunosensor as integration of GO allows more AuNRs to be loaded onto the modified detection platform in comparison to the absence of GO.

Moreover, GO can also be converted to its other semi-conductor counterpart via chemical or thermal reactions, known as reduced graphene oxide (rGO). rGO is claimed to possess significantly higher electroconductivity as against to GO but two degree lesser as opposed to graphene (Mao et al. 2012). Therefore, by taking account of this fact, Xing et al. (2018) chose rGO as a scaffold for immobilisation of Abs as rGO has a large surface area. SnO_2 molecules were also decorated onto rGO structure prior to Abs immobilisation as to further improve the overall biosensor's performance. The resulting ECL signal was remarkably intensified as they modified SnO_2/rGO/Au NPs-Lu onto the GCE's surface which subsequently refined the sensitivity of the biosensor to 26 fg/mL with superlative specificity and stability.

GO/rGO-integrated ECL immunosensors have been implemented for various applications such as examining the environmental conditions, for example, detecting the presence of pathogens in water such as *Vibrio vulnificus* (Guo et al. 2016) is important as it is one of the widely utilised raw materials by the living things. On the other hand, the constituents of commercially available food products must be properly analysed, stated and labelled on the packaging for aiding the consumers in selecting the products according to their preferences. Toxins such as tetrodotoxins (one of the types of strong marine neurotoxins) and hazardous food colourant (e.g. Sudan I) might be present in the food products and can be fatal when ingested, and thus, these products should be screened before they are released for commercialisation (Shang et al. 2017; Wang et al. 2018).

Other fascinating nanomaterials that falls under graphene-based CNMs are graphene nanoribbons (GNRs) and graphene oxide nanoribbons (GONRs). The two aforementioned NMs are cognate CNMs that can be procured by unzipping the CNTs, forming stretched monolayer graphene sheets (Georgakilas et al. 2015). Electronic attributes of GNRs/GONRs depend on the width of their respective structures. The difference in the syntheses of GNRs and GONRs is the addition of a strong oxidising agent, causing the presence of oxygen-containing groups in GONRs (Kosynkin et al. 2009). Although GONRs have a large surface area for the immobilisation of bioreceptors, their electrochemical property has attenuated due to the high amount of oxygen functional groups. One of the solutions for this matter is by incorporating metal nanoparticles with GONRs as performed by Ismail et al. (2015). AuNPs were decorated onto the GONRs and facilitated the overall electrocatalytic performance of the ABEI (*N*-(aminobutyl)-*N*-(ethylisoluminol))-functionalised AuNP nanohybrids on the H_2O_2-based ECL system. Other types of carbon nanomaterials that recently gain the attention of the researchers are discussed in the next section.

4.3.1.3 Quantum Dots

Semi-conductor nanocrystals, familiarly known as quantum dots (QDs), are comprised of clusters made of 100–1000 atoms with magnitude ranging from 1 to 10 nm (Alivisatos et al. 1996). These nanocrystals are mostly exploited as both fluorophore and luminophore and, thus, desirable as modules in ECL-based biosensors (Krishna et al. 2018). They were first unearthed in 1983, and ever since then, they are extensively utilised in various fields including in developing electronic and optical

devices (Brus 1984). Furthermore, they acquire attractive optical properties of adjustable emission bands, which vary depending on their size resulting in bandgap energy being inversely related to their size and composition (Chen and Park 2016). As a consequence, multiplex studies are possible as QDs possess broad emission wavelength and absorption spectra. They are also highly resistant towards photobleaching and chemical deterioration and, henceforth, are outstandingly photostable (Chen et al. 2017).

Carbon quantum dots (CQDs) and graphene quantum dots (GQDs) are the two organic nanoparticles composed of carbon atoms that are contemporary alternatives for the traditional QDs (e.g. CdSe and CdS). Contrastingly, these two carbon-based QDs have upper hands in several aspects compared to the conventional QDs that include their better biocompatibility for bioreceptor conjugations, low cytotoxicity and more superiority in photoluminescence property as it is tuneable (Xie et al. 2016; Zheng et al. 2015). CQDs are nanocrystal comprising of sp^2-/sp^3-hybridised carbon atoms with dimension of quasi-spherical, whereas GQDs consist of a single or several layers of sp^2-hybridised carbon atoms which are compressed into a planar form (Sun and Lei 2017; Nie et al. 2018).

Environment-friendly CQDs was opted by Li et al. (2017) as they possess superior photostability and fascinate electroconductivity, as the ECL luminophore in their study. The Ab_2 molecules were immobilised onto the CQD-GO-PEI nanohybrids (Li et al. 2017; Shi et al. 2018). The sandwiched interaction of CEA between Ab_1 and Ab_2 triggered the ECL reaction of CQDs, thereafter producing light as the signal. CQDs' ECL intensity in their work was elevated by the symbiosis performance of PEI-GO, AuNPs, AgNPs and polydopamine. This effect reflected on the immunosensor's accomplishment in sensing CEA dynamically from 5 pg/mL to 500 ng/mL and as low as 1.67 pg/mL with superlative specificity and stability.

Tian et al. (2019) have constructed an immunosensor with the aim of analysing the content of PSA (prostate-specific antigen) in human serum. GQDs fixated on the TiO_2 nanotubes (TiO_2 NTs) were utilised in this research study as an ECL probe as they withhold exceptional ECL characteristic attributable to their ability of catalysing photoluminescence reaction (Gupta et al. 2015). Persulfate ($K_2S_2O_8$) was selected as the co-reactant of the ECL probe. Their immunosensor has triumphantly detected PSA linearly from 1.0 fg/mL to 10 pg/mL with a sensitivity of 1 fg/mL and great specificity. This biosensor has also successfully detected the target analyte in human serum efficiently.

4.4 Conclusion and Future Prospects

ECL technique has gained significant interest from researchers for biosensing applications due to its advantages including simple operation and offer low background signal. Furthermore, an ECL signal can be further refined by incorporating nanomaterials. Unique properties such as large surface area and superb electroconductivity of CNMs contribute to the ability of CNMs in facilitating the operation of a particular immunosensor. Certain types of CNMs exhibit excellent optical property with

notable photostability and thus are employed as the luminophore. Through the application of CNMs, the reported ECL immunosensors have been evinced to be able to detect their respective target with outstanding sensitivity, exceptional specificity and competent stability.

Nevertheless, there are still some areas in the development of these ECL immunosensors that require further studies before they can be applied for practical on-site detection. Limitations that need to be overcome include:

- Lengthy sample pretreatment process, particularly for human serums and food samples. This is due to the presence of complex substances that can impede and intervene with the bioreceptors of the immunosensor and the luminophore (Aydın et al. 2018; Terry et al. 2005).
- Inefficient adsorption of bioreceptors onto the surface of the electrode, compromising the efficiency of transducer's response (Chandra 2016).
- Unsatisfactory stability, reproducibility, response time and robustness of the immunosensors.
- Inadequacy in researches for the applications of ECL immunosensors that are modified with CNMs.

Therefore, to address these issues, better extraction protocols, preferably with only by necessitating one simple step or reagent without jeopardising the purity of the extracted proteins, could be developed as to ameliorate the application for on-site detections. Further studies on the properties of different CNMs whether as a stand-alone nanomaterial or by combining them with other nanomaterials as a nanocomposite (such as gold nanoparticles) can be done to effectively improve the overall performance of a particular immunosensor. This will eventually act as a stepping stone for the development of accurate and reliable POC devices, not only for detecting a single target but also enabling duplex or even multiplex detections.

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