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Mini review

Electrochemical, Electrochemiluminescent and Photoelectrochemical Immunosensors for Procalcitonin Detection: A review

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Procalcitonin (PCT) is a promising biomarker for identification of the origin and severity of sepsis, which is a deadly body infection. With the aim of early diagnostics of PCT, various PCT analytical technologies have been designed and applied all over the world. Electrochemistry-based immunosensors have attracted wide attention due to their low-cost, simplicity, sensitivity and simultaneous sensing performance, which can transduce the immunoreaction into detectable signal on functionalized solid surface. This review summarizes the development of electrochemistry-based immunosensors for PCT. More importantly, we also highlight nanomaterials-based signal amplification strategies that can remarkably improve the sensitivity of immunosensors. This work will be beneficial for the development of novel electrochemistry-based immunosensors for the detection of PCT and other important biomarkers.

Keywords: procalcitonin; electrochemistry; electrochemiluminescence; photoelectrochemistry; signal amplification

1. INTRODUCTION

Procalcitonin (PCT), as a precursor of the active hormone calcitonin, is an aninflammatory marker for early clinical diagnosis of severe infectious diseases, multiple organ failure and septicemia [1]. The level of PCT increases rapidly after bacterial invasion. Normally, the level of serum PCT in the healthy state is maintained below 0.1 ng/mL by intracellular calcitonin cleavage [2]. It has been documented that it can increase rapidly over 100 ng/mL in case of severe bacterial infections and sepsis, which depends on the severity of infection [3]. Therefore, accurate and specific determination of PCT in serum is of great significance for the timely and appropriate treatment of infectious diseases

and septicemia, and for the evaluation of therapeutic effect.

So far, a variety of analytical approaches have been proposed to detect PCT concentrations, including enzyme-linked immunosorbent assays (ELISA), colloidal gold immunochromatography, surface plasmon resonance, chemiluminescence and fluorescence [4-9]. However, these methods still encounter some challenges in complicated instruments, sensitivity and time consuming. Among these methods, electrochemistry-based immunosensors, including electrochemical (EC), electrochemiluminescent (ECL) and photoelectrochemical (PEC) immunosensors, have recently become burgeoning and powerful analytical methods in virtue of high sensitivity, simplified equipment and operational convenience, based on the coupling of immunochemical reactions to appropriate signal transducers. An enormous research has been focused on the construction of immunosensors for PCT detection, but there are no published reviews on the development of EC, ECL and PEC immunosensors towards PCT detection. Therefore, we summarize the development of EC, ECL and PEC immunosensors for PCT and highlight nanomaterials-based signal amplification strategies for improving the sensitivity of immunosensors.

2. EC IMMUNOSENSORS

EC immunosensors have aroused more and more interest because of their high sensitivity, simple pretreatment, low cost, and fast response time. Nowadays, various proven electrochemical techniques integrated with different types of nanomaterials have opened the door to substantial improvement of the sensitivity of EC immunosensors, including chrono-amperometry, anodic stripping voltammetry (ASV), linear sweep voltammetry (LSV), cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square wave voltammetry (SWV). Generally, there are two key components in bioaffinity-based electrochemical immunoassays, the substrate for the immobilization of capture antibody (Ab_1) and the labels on detection antibody (Ab_2), which generate detectable electrochemical signals under certain conditions [4,5,10,11]. The key to improve the detection sensitivity is to build a powerful and effective signal strategy. For the former, nanostructured electrode surface is popular, because of a larger specific surface area to load a mass of capture antibody. For the latter, various biomolecules, enzymes and nanomaterials with different shapes and compositions have been widely studied and used to label detection antibody for signal amplification.

2.1 Nanomaterials as electrode materials

Steric hindrance produced from the formation of immunocomplexes can inhibit the diffusion of electroactive species in solution to the electrode surface. As the simplest approach for EC immunosensors, electrochemical impedance spectroscopy (EIS) was frequently used to monitor the change of electron transfer resistance with using a redox probe couple such as $[Fe(CN)_6]^{3-/4-}$, which has been widely used in a variety of biosensing applications [12]. Due to the lack of labels for signal amplification, the nanostructured electrode surface is of great importance for label-free EC immunosensors. In situ electrodeposition and electropolymerization are two classical electrode processing technologies. A growing number of nanomaterials have been utilized as electrode modifiers

to enhance the antibody loading and improve the electrode conductivity, including metal, carbon, metal oxide/sulfide nanomaterials (e.g. nanoparticles, nanowires and nanoflowers), metal organic frameworks and polymers. For example, Pu's group used single-walled carbon nanohorns–hollow Pt nanospheres/PAMAM to load capture antibody and horseradish peroxidase (HRP) and further modified the electrodeposited Au electrode for PCT detection [13]. Toluidine blue functionalized NiFe prussian-blue analog nanotubes (NiFe PBA nanotubes@TB) was used as the signal amplifier by Li's group [14]. Besides acting as the carriers, NiFe PBA nanotubes could produce an excellent signal without adding extra reaction reagent. Moreover, Ghrera's group reported the detection of PCT by using the conjugate of zinc sulfide capped cadmium selenide quantum dots and capture antibody to deposit on the indium-tin-oxide (ITO) coated glass substrate [15].

2.2 Sandwich-type biosensors

In contrast to label-free EC immunosensors, sandwich-type immunosensors with the use of signal-generating or amplifying labels have higher sensitivity and wider application [16]. Normally, the sandwich-type structure consists of capture antibody immobilized on the substrate electrode, signal label-conjugated detection antibody and antigen stucked in the middle. In this section, we mainly introduced the application of various signal amplification strategies based on enzymes and nanomaterials and the electrode substrates as well as analytical performances of sandwich-type immunosensors are briefly displayed in Table 1.

Enzyme-based EC immunosensors have attracted intensive attention because of the high sensitivity based on its catalytic amplification property. Furthermore, various nanomaterials are used to carry enzyme and detection antibody at a high ratio, thus further improving the sensitivity of immunosensors. For example, single-walled carbon nanohorns (SWCNHs)/hollow Pt chains (HPtCs) nanocomposites were used to load HRP and detection antibody [17], and Au nanoparticles (NPs)-coated mesoporous silica NPs (MCM-41) were employed to carry high-content HRP-labeled detection antibody [18]. Shen's group further integrated HRP-based signal amplification with Au NPs-enhanced tyramide signal amplification to sensitively determine PCT [19]. Liu's group also used the strategy of glucose oxidase (GOx)-catalyzed Au deposition on GOx for PCT detection [20]. In clinical applications, the measurement of a single biomarker is always not enough to diagnose diseases because of the limited specificity. Moreover, cumbersome process, long time for detection and relatively large volumes of sample also limited the further practical application of many biosensors. To solve these problems, Escarpa's proposed a dual magnetoimmunosensor for simultaneous evaluation of PCT and C-reactive protein (CRP) (Figure 1) [21]. In this report, biotinylated capture antibody against PCT and CRP was immobilized on the streptavidin (SA)-modified magnetic beads (MBs) and detection antibody was labeled with HRP. After the immunoreaction and magnetic separation, two samples were transferred to a dual working electrode on the surface of a screen-printed carbon electrodes (SPCE) for the simultaneous electrochemical transduction. This magnetoimmunosensor achieved a working range of 0.25 to 100.0 ng/mL for PCT and 0.01 to 5.0 μg/mL for CRP with the detection limits of 0.09 ng/mL and 0.008 μg/mL, respectively. However, enzyme-based immunosensors always suffer from

several disadvantages including complex immobilization, poor stability, and high sensitivity to temperature and pH.

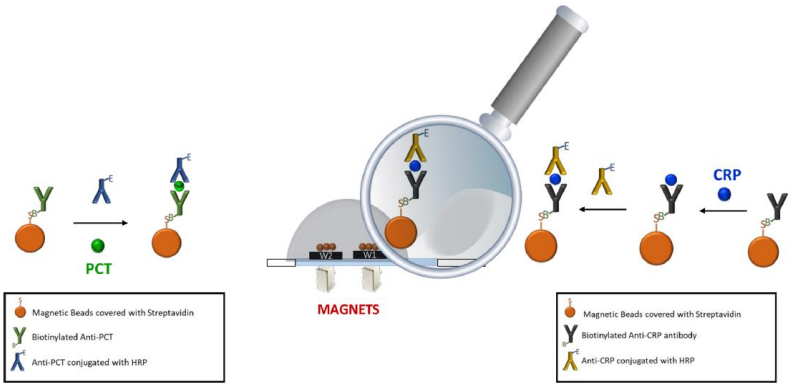

Figure 1. Schematic representation of the electrochemical magnetoimmunoassay strategy for the simultaneous detection of PCT and CRP. Reprinted with permission from reference [21]. Copyright 2019 American Chemical Society.

Alternatively, to overcome the shortages, enzyme-free EC immunosensors based on nanomaterials have attracted much interest recently [22-25]. Yuan's group reported an enzyme-free EC immunosensor for PCT detection based on the host−guest nanonets of N,N-bis(ferrocenoyl)-diaminoethane/β-cyclodextrins/poly(amidoamine) dendrimer-encapsulated Au NPs (Fc-Fc/β-CD/PAMAM-Au) (Figure 2) [26]. In this study, PAMAM, a highly branched three-dimensional macromolecules, was utilized as the template to prepare Au NPs (PAMAM-Au) with precisely controllable size and good morphological homogeneity. Next, PAMAM-Au was cross-linked by Fc-Fc into netlike nanostructure and further modified with detection antibody. Both PAMAM-Au and Fc-Fc catalyzed the oxidation of ascorbic acid (AA) for signal amplification.

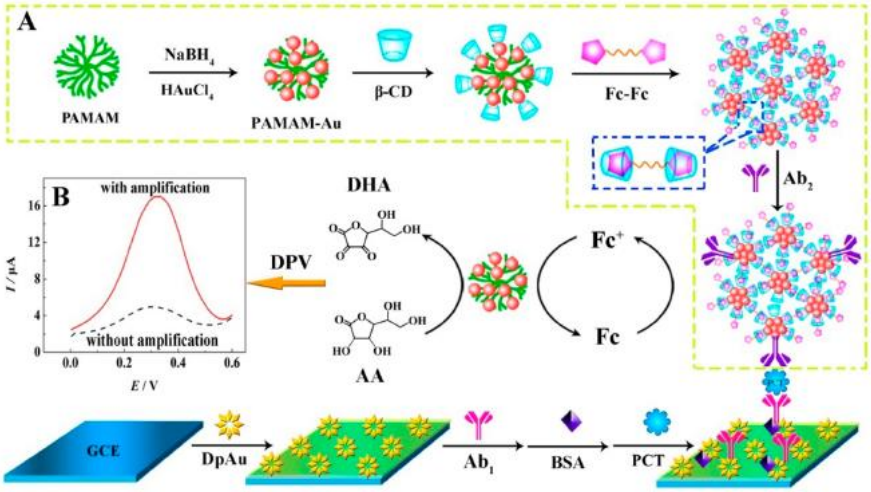

Figure 2. Schematic diagram of fabrication of electrochemical immunosensor based on host−guest nanonets catalyzing amplification for PCT detection. Reprinted with permission from reference [26]. Copyright 2019 American Chemical Society.

Moreover, Fc-Fc provided more eletroactive groups for sensitive electrochemical response. Finally, based on the synergetic catalysis toward AA oxidation, the fabricated immunosensor for PCT detection showed a wide linear range of 1.80 pg/mL to 500 ng/mL and a low detection limit of 0.36

pg/mL. Additionally, Wang's group reported on the determination of PCT by taking the advantage of the synergistic electrocatalytic activity of MoO_3/ Au@rGO nanocomposites towards H_2O_2 reduction [27]. Labeling of detection antibody with a nanoparticle which is electroactive or loaded electroactive molecules is beneficial to obtain better sensitivity of immunosensor because of the huge surface area and hundreds of thousands of atoms. For example, Wu's group used Au@Ag heterojunction nanorods to load electroactive thionine as signal labels and employed CeO_2-CuO nanorods as enhancers for PCT detection [28]. Amino group functionalized C_{60} NPs loaded with ferrocene carboxylic acid (Fc) and modified with Pt NPs were employed to develop EC immunosensor for PCT detection [29]. It has been reported that some electroactive metal-containing NPs could be directly detected without metal preconcentration and complicated acid dissolution step, including silver NPs [30], Cu-based metal organic framework [31], and Ag/CdO NPs [32]. Fang's group reported the detection of PCT with zinc NPs-modified ordered mesoporous carbon-silica nano-composites (OMCSi-Zn) as signal amplifiers [33]. Yuan's group synthesized electroactive cobalt phthalocyanine NPs functionalized with multi-wall carbon nanotubes (nanoCoPc-MWCNTs) as labels for sensitive detection of PCT [34]. NanoCoPc-MWCNTs could directly produce electrochemical signal without the addition or labeling of other redox mediators. For further electrochemical signal amplification, choline oxidase (ChOx) was integrated into the labels, in which H_2O_2 produced from the oxidation of choline catalyzed by ChOx was oxidized by nanoCoPc-MWCNT and thus improved the electron transfer from Co (II) to Co (I).

Although various NPs possessing enzyme-like catalytic ability or electroactive property, few NPs with excellent catalytic activity can be directly used as redox probe to construct EC biosensor. Yuan's group also synthesized Cu/Mn double-doped CeO_2 nanocomposite (CuMn-CeO_2) as both the signal tags and amplifiers for sensitive detection of PCT [35]. As shown in Figure 3, CuMn-CeO_2 has high catalytic activity toward H_2O_2 for signal amplification and can be directly used as the redox probe for electrochemical signal readout in neutral mild buffer solution at low positive potential. Moreover, doping Cu, Mn into the lattice structure of CeO_2 could generate extra oxygen vacancies and result in a higher catalytic activity than pure CeO_2. The designed method exhibited a linear detection range of 0.1 pg/mL to 36.0 ng/mL and the detection limit was calculated to be 0.03 pg/mL, which is superior or comparable compared with other biosensors with nanomaterials as catalysts.

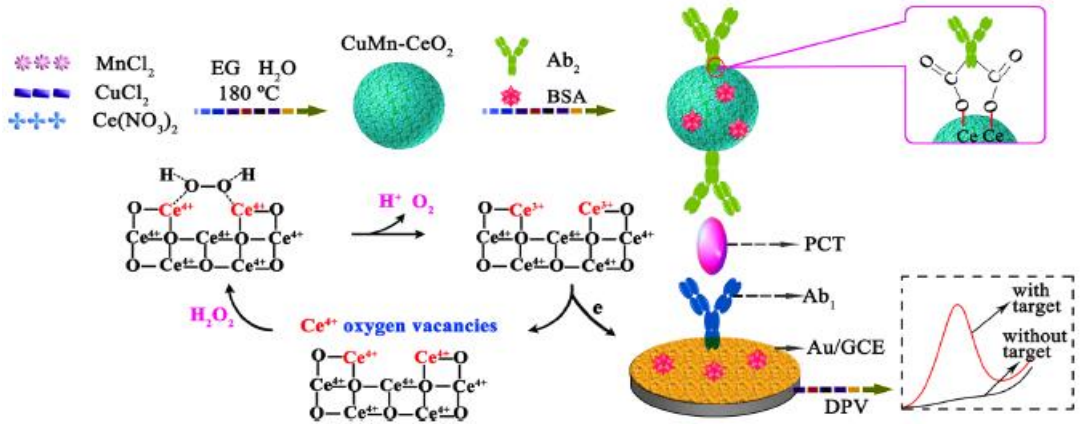

Figure 3. Schematic illustration of the electrochemical immunosensor using Cu/Mn double-doped CeO_2 nanocomposites as signal tags and signal amplifiers. Reprinted with permission from reference [35]. Copyright 2017 American Chemical Society.

Table 1 Sandwich-like electrochemical immunosensors for PCT determination.

Electrode materials	Signal labels	Linear range (ng/mL)	Detection limit (pg/mL)	Ref.
Graphene/CNT	AuNPs-MCM-41/HRP-Ab_2	0.01 to 350	0.5	[18]
Au NFs	Fc-Fc-β-CD-PAMAM-Au/Ab_2	0.0018 to 500	0.36	[26]
MWCNTs-Au NPs	Fc-C_{60}-Pt NPs/GOx-Ab_2	0.01 to 10	6	[28]
Graphene-chitosan	OMCSi-Zn/Ab_2	5×10^{-5} to 80	0.0013	[33]
Au NPs	nanoCoPc-MWCNTs-ChOx/Ab_2	0.01 to 100	1.23	[34]
AuNPs/GCE	CuMn-CeO_2/Ab_2	1×10^{-4} to 36	0.03	[36]
DOPA	GOx-Au NPs	5×10^{-8} to 500	0.00004	[20]
rGO-Au NPs	SWCNHs- HPtCs/Ab_2	0.001 to 2	0.43	[17]
CeO_2-CuO-Au NPs	Au@Ag-Th/Ab_2	5×10^{-4} to 50	0.17	[28]
Au NPs/GCE	MoO_3-Au-rGO/Ab_2	1×10^{-5} to 10	0.002	[27]
rGO-Au NPs	Au NPs-HRP-tyramine/Ab_2	0.05 to 100	0.1	[19]
Magnetic electrode	HRP-Ab_2	0.25 to 100	0.09	[21]

3. ECL IMMUNOSENSORS

Compared with photoluminescence, ECL methods by combining electrochemistry and chemiluminescence gradually attracted widespread focus because of wide linear range and convenient operation [37,38]. Moreover, the methods are free of auto-fluorescence resulting from the interaction of samples with the incident light in the photoluminescence methods. Upon the development of ECL systems, multifarious fascinating ECL emitters and co-reactants have been designed and applied in bioanalysis.

As an analogue of luminol, N-(aminobutyl)-N-(ethylisoluminol) (ABEI) with higher and more stable ECL efficiency can generate ECL signals with hydrogen peroxide (H_2O_2) as co-reactant in alkaline solutions because the primary amine group in ABEI is far away from benzene ring [39]. Wei' group constructed a donor-acceptor nanostructure by using ferritin (Ft) as nanocarrier to load ABEI molecules (ECL donor) via glutaraldehyde interaction and single Au NPs (ECL acceptor) via in-situ reduction of $AuCl^{4-}$ ions (ABEI-Ft@Au) (Figure 4) [36]. Besides, ferric nanocore within Ft possessing enzyme-mimic activity could efficiently catalyze the oxidation of ABEI in the presence of H_2O_2, boosting the ECL emission. Au NPs quenched the ECL of ABEI-Ft with the energy transfer efficiency was 56% through nanosurface energy transfer (NSET). To improve sensitivity and save time, heptapeptide HWRGWVC (HWR) was used as specific antibody immobilizer for site-oriented fixation for maintaining the bioactivity of antibody. Finally, the proposed biosensor achieved a linear detection range of 100 fg/mL to 50 ng/mL and a detection limit of 41 fg/mL. Meanwhile, Wei's group

synthesized hybrid nanocomposite of polyaniline nanorod arrays grafted reduced graphene oxide and Au NPs as sensing substrate and designed an ECL biosensor for PCT analysis on the basis of using ABEI-Ft as signal indicator [40]. 3,4,9,10-Perylenetetracarboxylic acid (PTCA), a perylene derivative, has a five-ring aromatic hydrocarbon with four carboxyl groups and generates stable ECL emission in $S_2O_8^{2-}$ solution so that it has extensive applications in ECL research [41,42].

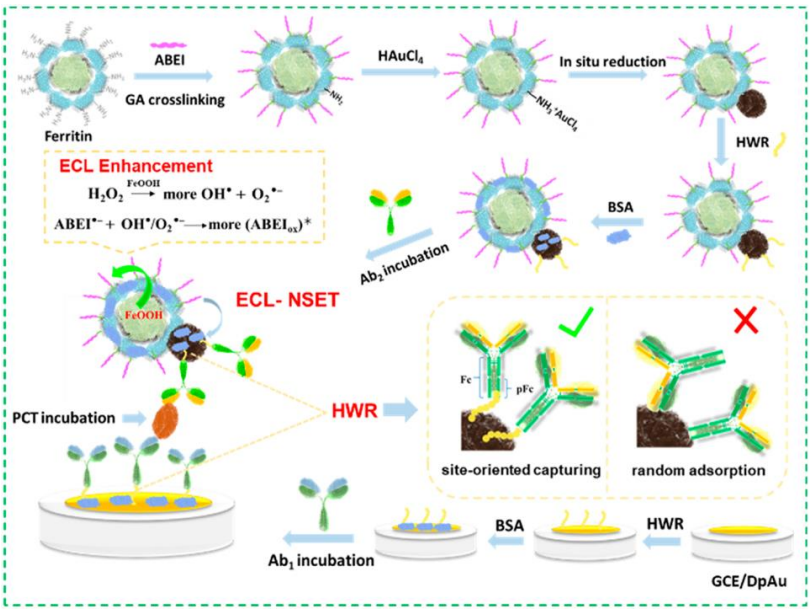

Figure 4. Schematic representation of fabrication process of ferritin-based ECL nanosurface energy transfer system for PCT detection. Reprinted with permission from reference [36]. Copyright 2019 American Chemical Society.

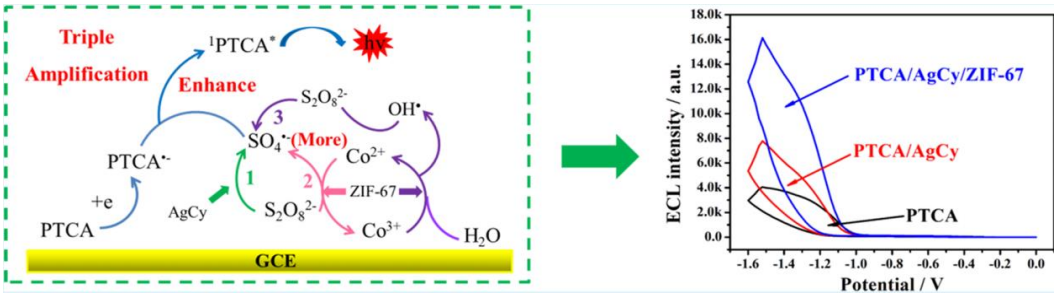

Figure 5. Schematic representation of a possible ECL mechanism in PTCA−$S_2O_8^{2-}$ system with AgCys/ZIF-67. Reprinted with permission from reference [43]. Copyright 2020 American Chemical Society.

Wei's group employed Co^{2+}-based metal−organic frameworks (ZIF-67) to load PTCA and silver-cysteine (AgCys) as the electrode substrate to detect PCT [43]. In this method, ZIF-67 accelerated the reduction of $S_2O_8^{2-}$ to produce abundant Co^{3+} and sulfate radical anions ($SO4^{\bullet-}$). Then, a triple signal amplification was initiated and the detailed reaction mechanism was displayed in the Figure 5. Moreover, perylene-3,4,9,10-tetracarboxylic acid-N,N-diisopropylethylenediamine (PTC-DEPA) exhibited higher ECL intensity compared with PTCA since N,N-diisopropylethylenediamine (DPEA) could donate electron to PTCA. Zhou's group used mesoporous fibrous silica particle (KCC-

1) to carry PTC-DEPA as luminophore for dual-signals response detection of PCT [44].

Graphitic carbon nitride (g-C_3N_4) has attracted broad attentions due to its properties of well chemical stability, and excellent optical and electrical properties. However, the poor conductivity resulted in an unstable and weak ECL signal. To further improve the ECL performance, Wei's group used CNTs and Au NPs to functionalize g-C_3N_4 and applied the composite to construct a quench-type ECL immunosensor for PCT [45]. As illustrated in Figure 6, CNTs enhanced the electrical conductivity and AuNPs increased the loading amount of capture antibody, thus further enhancing the ECL performance. CuO NPs were covered with polydopamine (PDA) layer (CuO@PDA) through self-assembly of dopamine and were first utilized to quench the ECL signal of g-C_3N_4–CNT@Au due to the overlap of the ultraviolet adsorption spectrum of the prepared CuO NPs and the ECL emission spectrum. Under the optimized experimental conditions, this method showed the detection range within 0.0001−10 ng/mL with a detection limit of 25.7 fg/mL.

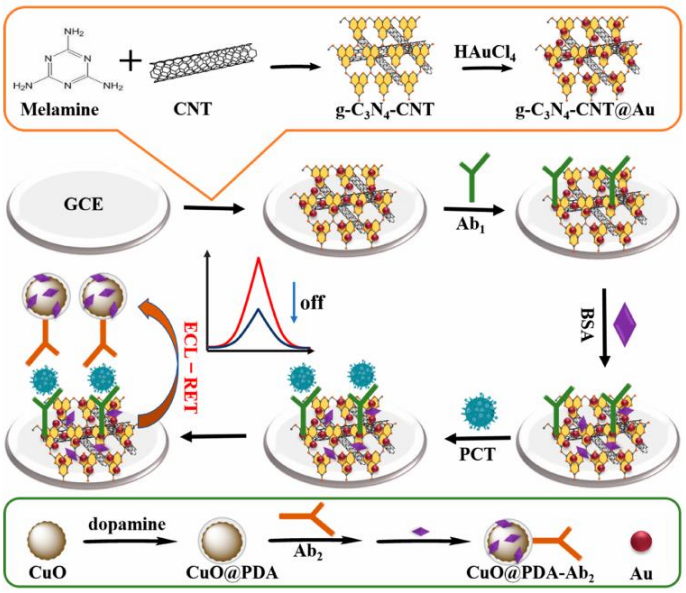

Figure 6. Schematic representation of fabrication process of bioactivity-protected ECL biosensor based on BSA-Au NCs and Cu_2S snowflakes. Reprinted with permission from reference [45]. Copyright 2020 American Chemical Society.

Most of ECL-based biosensors are faced with the inactivation of immune molecules due to the irreversible oxidization of the deoxynucleotide sequences of an antigen or antibody by excessive cyclic potential and superoxide radicals in co-reactant. Thus, the exploration of ECL luminophore which can meet the demands for low excited potential and ultrahigh ECL efficiency has drawn wide attention in recent years. Bovine serum albumin (BSA)-templated Au nanoclusters (Au NCs) also produces an anodic or cathodic ECL signal in various co-reactive systems besides its excellent fluorescent properties [46,47]. Chen's group reported that when BSA-Au NCs coexisted with triethylamine (TEA), a distinct ECL signal was observed under a lower potential [48]. Recently, Wei's group developed a bioactivity-protected ECL biosensor for PCT analysis by using BSA-Au NCs as the luminophore and Cu_2S snowflakes co-reaction accelerator [49]. As shown in Figure 7, Cu_2S snowflake was employed to

modify the electrode for connecting immune molecules and further acted as co-reaction accelerator to produce more cationic radicals $TEA^{\bullet+}$, improving the ECL intensity. After the immunoreaction, a strong low-potential anodic ECL signal in TEA solution at 0.87 V was recorded. The detection limit of this method was as low as an unprecedented value of 2.36 fg/mL. At the same time, Ma's group proposed a BSA-Au NCs-based ECL immunosensor for the detection of PCT by using highly-branched Cu_2O as well-ordered co-reaction accelerator and $K_2S_2O_8$ as non-toxic co-reactant, respectively [50]. Europium-doped phosphoric acid gadolinium ($GdPO_4$:Eu) was also first used by Ma's group as novel low-potential luminophore to develop an ECL double quenching system for PCT detection [51]. In the presence of $K_2S_2O_8$ and cathode, a strong ECL signal was observed at a low potential of −1.15 V (vs. Ag/AgCl). Electrical pair Eu^{3+}/Eu^{2+} generated by potential excitation acted as the novel co-reactant promoter to cyclically produce more $SO_4^{\bullet-}$, which in turn accelerated the oxidation process of $GdPO_4$:Eu. Meanwhile, Core−shell Pd@Cu_2O was chosen as a dual-quencher to modulate the intensity of the ECL system. Thus, the bioactivity-protected ECL "signal on-off" system achieved a detection limit of 0.402 fg/mL toward PCT detection.

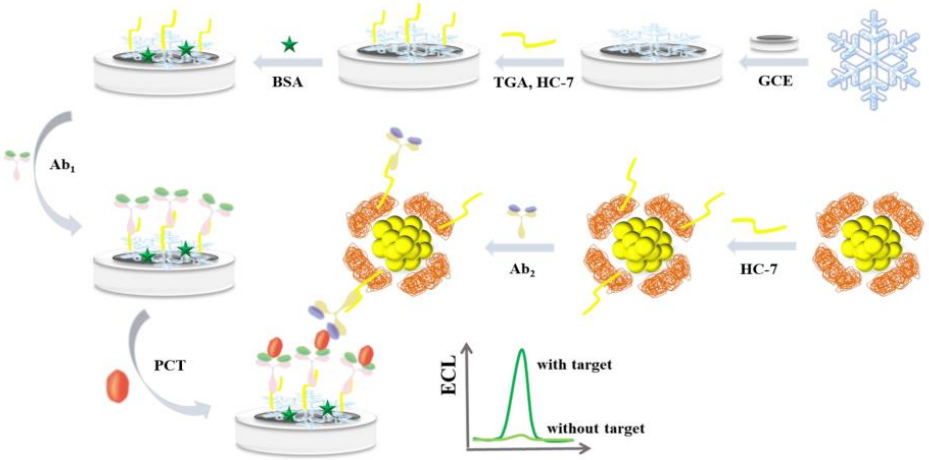

Figure 7. Schematic representation of fabrication process of bioactivity-protected ECL biosensor based on BSA-Au NCs and Cu_2S snowflakes. Reprinted with permission from reference [49]. Copyright 2019 American Chemical Society.

4. PEC IMMUNOSENSORS

PEC bioanalysis are increasingly attracted worldly interests in the past decades owing to their merits of high stability and great sensitivity [52]. Moreover, the difference between excitation (light) and detection (electric current) forms contributes for low background signal. Furthermore, PEC immunoassays perfectly combine the inherent advantages of the PEC bioanalysis and the specific bioaffinity properties of the immunochemical reactions. Signal-off PEC immunosensor is one of classic models whose initial signal decreased due to the introduction of insulated immune complex and signal labels. Signal amplification on basis of steric-hindrance effect caused by the antigen or labeled NPs is frequently used [53]. For example, Wei's group synthesized $Zn_xBi_2S_{3+x}$ sensitized $NiTiO_3$ nanorods ($Zn_xBi_2S_{3+x}$/$NiTiO_3$) and found that the nanocomposites have the GOx-like catalytic function

for oxidation of glucose to generate H_2O_2 as the hole scavenger, which promoted the photo electrons transfer and increased the PEC signal [54]. Additionally, certain NPs or hybrid of different NPs have the steric impedance effect on ECL system and the ability for competitive absorption of light and consumption of electron donor. Wei's group also proposed a "signal-off" PEC immunosensor for the detection of PCT by using $Ru(bpy)_3^{2+}$ and Bi_2S_3 co-sensitized $ZnTiO_3/TiO_2$ polyhedra as matrix and SiO_2/PDA-Au as dual quencher. SiO_2 with the large steric hindrance and poor conductivity hindered the electron transfer and reduced the PEC activity of immunosensor and Au NPs competitively absorbed the visible light.[44] Meanwhile, Wei's group also reported the detection of PTC by using PbS/Co_3O_4 as an effective dual suppression signal quencher [55].

Interference between immune recognition system and PEC analysis system may destroy the structure of biological molecules. Moreover, the modification of biomolecules on the photoelectrode is time-consuming and painstaking. To solve this problem, Xu and co-workers designed a controlled-release split-type PEC immunosensor for PCT detection (Figure 8) [56]. In this work, the PEC electron donor, AA was encapsulated into the functional mesoporous silica nanospheres (MSNs) and CdS QDs loaded on MSNs by the responsive disulfide bonds were used as the caps. Then, the performed nanocomplexes (CdS@MSN-AA) were utilized as the signal amplifiers to label the detection antibody. After the traditional immunoreaction in a 96-well microplate, dithiothreitol (DTT) was introduced to break the disulfide bond, resulting in the disintegration of the nanocomplexes of CdS@MSN-AA and the subsequent release of AA. Then, the solution containing the released AA was transferred to the PEC detection system with the Bi_2S_3 nanorod-sensitized porous In_2O_3 (In_2O_3/Bi_2S_3) as the photosensitive substrate. The linear range of this method was 0.001~200 ng/mL and the detection limit was calculated to be 0.31 pg/mL.

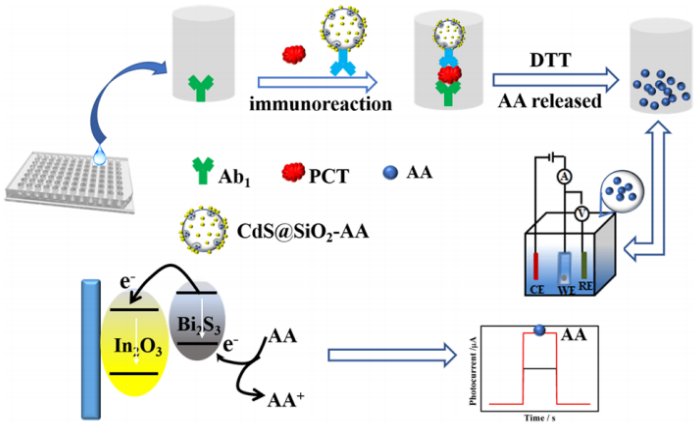

Figure 8. Fabrication process of the split-type PEC immunosensor for PCT detection based on the novel electron donor encapsulation strategy. Reprinted with permission from reference [56]. Copyright 2020 American Chemical Society.

5. CONCLUSION

Integration of novel functional nanomaterials and analytical technologies endow an opportunity for the development of immunosensors with better performance. In this work, we reviewed the progress in the electrochemistry-based detection of PCT by using enzymes or nanomaterials (such as

metal, carbon and metal oxide nanomaterials) as signal amplifiers. Detailed immune-sensing strategies are described as unique and amplified functionality. Although there are still some limits in the practical applications, we believe that the advanced nanotechnology and biotechnology will promise a better future for designing of PCT immunosensors.

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