

Review

## Recent progress in cerium-based nanomaterials for electrochemical biosensors

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Cerium (Ce) is a rare earth element widely used for its excellent physical and chemical properties. Ce-based nanomaterials have become highly relevant for electrochemical biosensors due to their attractive catalytic activities and electrical conductivity properties. Importantly, Ce-based nanomaterial preparation significantly affects their properties for electrochemical applications. This review summarizes some common methods for Ce-based nanomaterial synthesis, including sol-gel, co-precipitation and micro-emulsion approaches, and their applications in electrochemical biosensors, such as DNA sensors, immunosensors and enzyme sensors. Also, we summarize by discussing some defects and complementary methods of Ce-based nanomaterials.

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**Keyword:** CeO<sub>2</sub>; Ce-based materials; electrochemical biosensor; preparation method

### 1. Introduction

With the rapid progress of science and technology, rare earth materials, commonly known as “industrial vitamins” are indispensable materials for high-tech products, across several technological fields [1]. Rare earth elements are comprised of 17 elements, including lanthanum (La), neodymium (Nd), cerium (Ce) and so on. Several classifications exist for these elements, however, two are popular. The first is Ce rare earth, also known as light rare earth (LREE), and Yttrium rare earth, also known as rare earth (HREE). The second is the triad method, including light rare earth (La~ Nd), medium rare earth (promethium (Pm) ~holmium (Ho)) and heavy rare earth (erbium (Er) ~lutecium (Lu) and Yttrium (Y)). Of these elements, Ce belongs to the lanthanide family and is one of the most abundant rare earth elements, and is widely used in many applications. Ce and other similar elements are also known as 4f block elements and lanthanides [2]. Ce physical properties include metal gray coloring, a high boiling point and good ductility, whereas chemically, Ce is easily oxidized in oxygen. Apart from Europium,

Ce is the most active rare earth element. The outermost layer of Ce electronic arrangement is  $4f^1 5d^1 6s^2$ , therefore, the Ce valance state has trivalent and tetravalent ions  $Ce^{3+}$  and  $Ce^{4+}$  and two main types of oxides  $Ce_2O_3$  and  $CeO_2$  [3]. Because of its active chemical properties, metal Ce can be prepared by reducing  $Ce_2O_3$  or Ce (III) chloride ( $CeCl_3$ ).

Ce has many biological applications, for example, Ce (III) nitrate ( $Ce(NO_3)_3$ ) has good antibacterial properties as  $Ce^{3+}$  enhances fibroblast and osteoblast proliferation and differentiation [4]. Additionally,  $Ce^{3+}$  can enter the cytoplasm of declining cells, and Ce solubility has been implicated in heart disease pathogenesis [5]. Also, the rare earth elements can interact with calcium-mediated systems and inhibit some substances in cells [6]. Ce oxides mainly exist as  $CeO_2$  with a face-centered cubic structure [7].

Recently,  $CeO_2$  nanomaterials have attracted considerable attention due to their special physicochemical properties, distinct from other bulk materials [4, 5]. Ce oxide nanoparticles ( $CeO_2$ -NPs) have hexagonal fluorite structures, where  $Ce^{3+}$  and  $Ce^{4+}$  can coexist on surfaces [8].  $CeO_2$  nanomaterials are one of the most important metal oxide nanomaterials in nanotechnology research due to their special physical and chemical properties, particularly the electronical conductivity as n-type semiconductor [3].  $CeO_2$  is mixed with nickel oxide and manganese oxide to form nanosheet arrays for enhanced electrochemical storage performance [9]. Ce oxides can produce catalytically active redox pairs [10], leading to increased catalytic and enzyme simulation performances [11]. Equally,  $CeO_2$  nanomaterials are not cytotoxic, thus, they can be applied to the field of cell and molecular biology [12].  $CeO_2$  are inorganic oxide nanomaterials, and are thus, advantageous for low dimensional and possible quantum confinement effects [13]. In addition, Ce-based materials are cheap, with higher surface reaction rates and high isoelectric points (IEP) [14, 15, 16]. Therefore, Ce-based materials are widely used as catalysts [17, 18], super capacitors [19, 20], biomedicines [21, 22], catalytic oxidants [23, 24], oxygen carriers [25] and three-way catalysts [26], among others [27, 28]. For example, porous silica layers can be adhered to Ni/ $CeO_2$ - $ZrO_2$  particles to expand metal-oxide interfaces for use as highly active catalysts [17].  $CeO_2$ -NPs act as super capacitors by forming composites with multi-walled carbon nanotubes (MWCNTs) [20]. In 2017, Zhou and his colleagues synthesized  $CeO_2$  quaternary ammonium salt solid solutions as three-way catalysts to purify exhausts from gasoline engines [29]. The preparation of cerium-based nanomaterials played a key role for their applications since cerium-based nanomaterials produced in different methods may exhibit quite different properties. Several methods have been used to prepare nanomaterials, such as the sol-gel method [30], co-precipitation [31], the solvothermal method [32], the hydrothermal method [33] and the microemulsion method [34]. Of these, the sol-gel, co-precipitation and microemulsion methods are commonly used to prepare Ce-based nanomaterials. In recent years, green synthesis methods have also been explored to prepare Ce-based nanomaterials, incorporating *gloriosa superba* leaf extract, honey, egg white, and others [35, 36]. This green synthesis method is fast, cheap and has many advantages for biosensor applications [35].

Research on electrochemical biosensors has been extensively carried out with the current realities of the need for years, which is advantageous of low cost, fast detection, high sensitivity, simple operation, and good selectivity. Electrochemical biosensors detect trace amounts of biomolecules, with increased advantages over other classical analytical methods, such as high

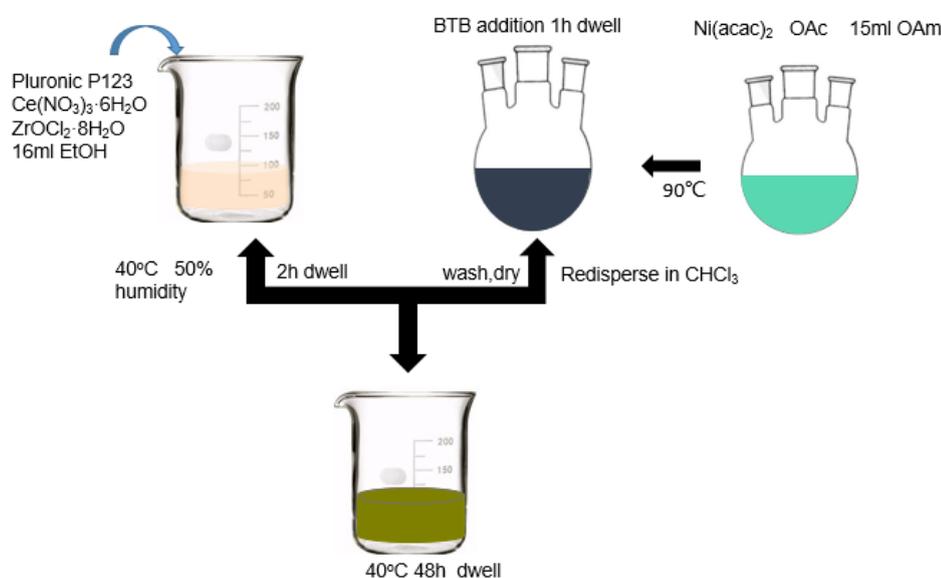
performance liquid chromatography [37, 38], gas chromatography [39] and enzyme-linked immunosorbent assay [40]. Thanks to their excellent electrical conductivity and catalytic effects, Ce-based nanomaterials are not only widely used for DNA sensors [13] and immunosensors [41], but they also have implications in enzymatic mimic sensors [11]. Therefore, in this review, we summarize preparatory methods for Ce-based nanomaterials, and explore their applications in electrochemical biosensors.

## 2. SYNTHESIS METHODS OF CE-BASED MATERIALS

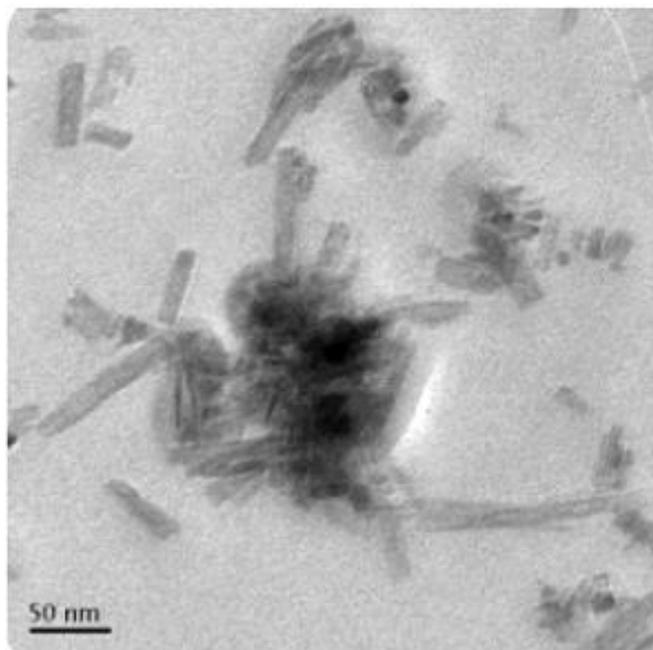
As described, several methods are used to prepare Ce-based nanomaterials, including sol-gel, co-precipitation and microemulsions.

### 2.1 Sol-gel method

The sol-gel approach prepares metal organic or inorganic compounds by curing sol and gel solutions and using heat treatments. During the process, a hydrolyzable metal compound reacts with water in the solvent to form a uniform sol through a hydrolysis and polycondensation process, and is then dehydrated to a gel. After heat treatment, nanomaterials are obtained. Nanometer powders and fibers can be produced to form film and composite materials with several advantages, including high purity, uniform NPs and so on [42, 43]. For example, Wang and colleagues prepared ceria nanopowders using the sol-gel method and mechanical solid-phase reactions [44]. Ce (III) nitrate hexahydrate ( $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ) was put in agate jar with oxalic acid dihydrate ( $\text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ ) and ammonium fluoride ( $\text{NH}_4\text{F}$ ), followed by grinding. After calcination, a  $\text{CeO}_2$  nanopowder was obtained with good dispersity [44]. Figure 1 shows the synthesis of ceria-zirconia using the sol-gel method, by encapsulating nickel (Ni) nanoparticles for  $\text{CO}_2$  methanation [45]. Similarly, the sol-gel method has been used to prepare cerium phosphate particles with relatively small size (Figure 2) [46].



**Figure 1.** Schematic synthesis of Ni encapsulated ceria-zirconia with sol-gel method.

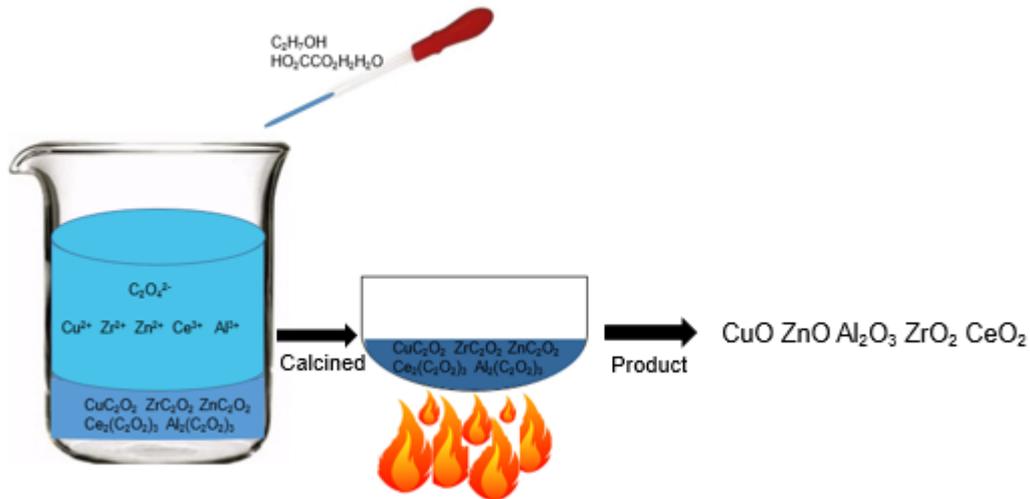


**Figure 2.** TEM of cerium phosphate precursor gel at 400 °C. Reprinted with permission from reference [46]. Copyright 2004 American Chemical Society.

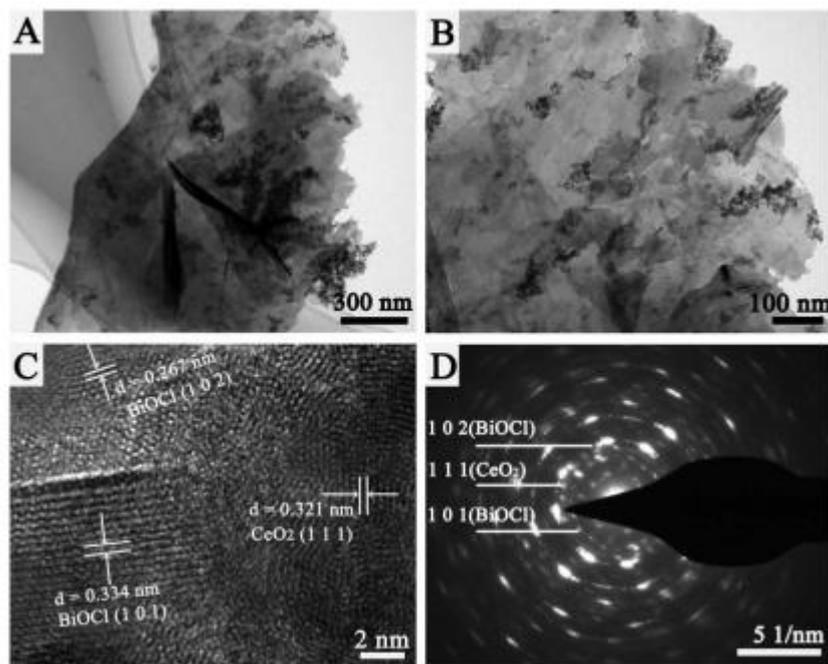
## 2.2 Co-precipitation

The co-precipitation method refers to the addition of a precipitating agent to a solution containing a variety of cations to completely precipitate all ions. The process can be divided into single-phase co-precipitation and mixture co-precipitation. Single-phase co-precipitation usually produces a precipitate of a single compound or single-phase solid solution, whereas mixture co-precipitation produces a mixture of the precipitated product.

Due to the advantages of preparation with co-precipitation method like uniform chemical composition, simplicity and uniform distribution [47, 48], it has attracted numerous attentions of researchers to prepare Ce-based nanomaterials for various applications. For instance, oxalic acid was used to precipitate cations to obtain a gel-like  $\text{CuO-ZnO-Al}_2\text{O}_3\text{-ZrO}_2\text{-CeO}_2$  nanocatalyst with increased uniform catalysis (Figure 3) [49]. Furthermore, co-precipitation has also been used to prepare a new kind of nanocomposite, for instance, carbonate was used to precipitate three metal cations to generate a complex of three metal oxides of  $\text{CeO}_2\text{-CuO-ZnO}$  [50]. Also, a nanocomposite of the metal oxide,  $\text{CeO}_2\text{-CuAlO}_2$  was synthesized by adding sodium carbonate to solutions of  $\text{Cu}(\text{NO}_3)_3\cdot 6\text{H}_2\text{O}$ ,  $\text{Al}(\text{NO}_3)_3\cdot 9\text{H}_2\text{O}$  and  $\text{Ce}(\text{NO}_3)_3\cdot 4\text{H}_2\text{O}$  [51]. Figure 4 is the bimetallic Bi/Ce nanocomposite prepared using the precipitation method, where a polycrystalline structure in sheet shape was obtained [52].



**Figure 3.** Reaction mechanism of the nanocatalyst  $CuO-ZnO-Al_2O_3-ZrO_2-CeO_2$  prepared by oxalate gel co-precipitation.



**Figure 4.** TEM images (A and B), HRTEM image (C) and the electron diffraction image of the selected area of  $Bi/Ce = 4 : 1$  (D). Reprinted with permission from reference [52]. Copyright 2020 Royal Society of Chemistry.

### 2.3 The microemulsion method

Surfactants are important in the microemulsion method, since microemulsions are thermodynamically stable systems composed of surfactants, oils and water [53]. The oil-in-water (O/W) type microemulsion, known as reverse microemulsion is a commonly used method to prepared

nanomaterials [54, 55]. Because of controllable particle size, good mono-dispersity and interfacial properties, the microemulsion method is widely used for nanomaterial synthesis [56, 57], including Ce-based nanomaterials. For example,  $\text{Al}_2\text{O}_3$ - $\text{CeO}_2$  nanomaterials of uniform size were synthesized by placing metal alkoxide solutions of aluminum (Al) and Ce into a cyclohexane/surfactant/n-butanol mixture [53]. Through micro-emulsion method, a thin  $\text{CeO}_2$  layer was embedded with Pt nanoparticles to obtain Pt doped  $\text{CeO}_2$  nanospheres in a diameter of  $\sim 4$  nm (Figure 5) with good catalytic performance [58]. Using the microemulsion method, spherical  $\text{CeO}_2@$  $\text{SiO}_2$  core-shell (CS) nanoparticles and CS-manganese (II) 5-(4-carboxyphenyl)-10, 15, 20-triphenyl porphyrin with uniform particle sizes of 35 nm were prepared for the immobilization of metalloporphyrins [59]. In addition,  $\text{Cu}^{2+}$  was incorporated into the  $\text{CeO}_2$  lattice to generate nanomaterials with good dispersibility [60].

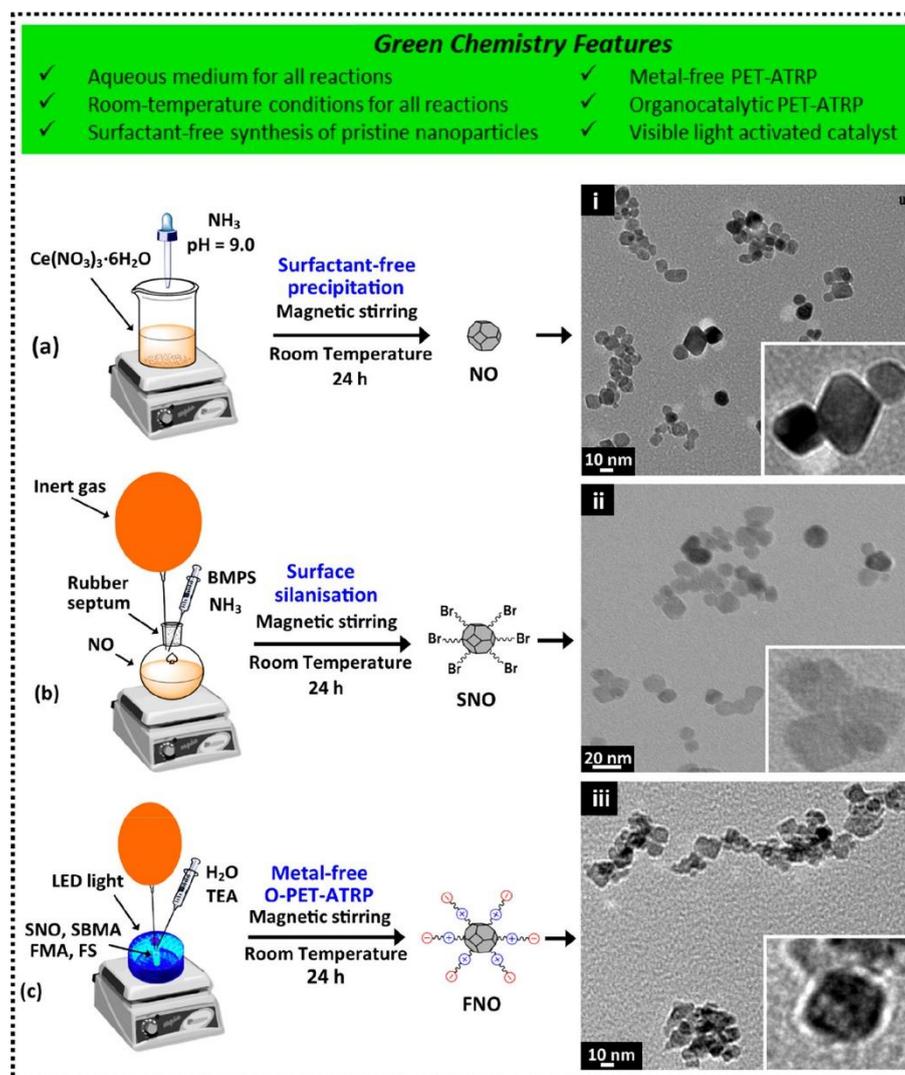


**Figure 5.** TEM of spherical  $\text{CeO}_2$  nanospheres doped with 5wt% Pt. Reprinted with permission from reference [58]. Copyright 2009 American Chemical Society.

#### 2.4 Green synthesis

When compared with the sol-gel method, co-precipitation and other methods, green synthesis is more environmentally friendly, simpler, cheaper and the generated materials usually have smaller particle sizes and increased biocompatibility [61, 62]. These traits promote green synthesis the current research hotspot for preparing nanomaterials. At present, several studies have reportedly used green plant extracts, eggs and other non-pollutants to prepare Ce-based nanomaterials, for instance, Sharmila *et al.* used *Gloriosa superba* leaf extract to prepare nano-cerias of smaller and uniform particle size and distribution, respectively [36]. Also, The size of  $\text{CeO}_2$  synthesized by green chemistry method is relatively small ( $<15\text{nm}$ ) (Figure 6) [63]. Not only is the green synthesis method straightforward, but

the plant extracts/proteins used are biological macromolecules with good biocompatibility, increased biomolecule binding and reduced cytotoxicity.



**Figure 6.** Schematic diagram and TEM of the synthesis of  $\text{CeO}_2$  octahedral particles from materials in aqueous media under various conditions at room temperature. Reprinted with permission from reference [63]. Copyright 2019 American Chemical Society.

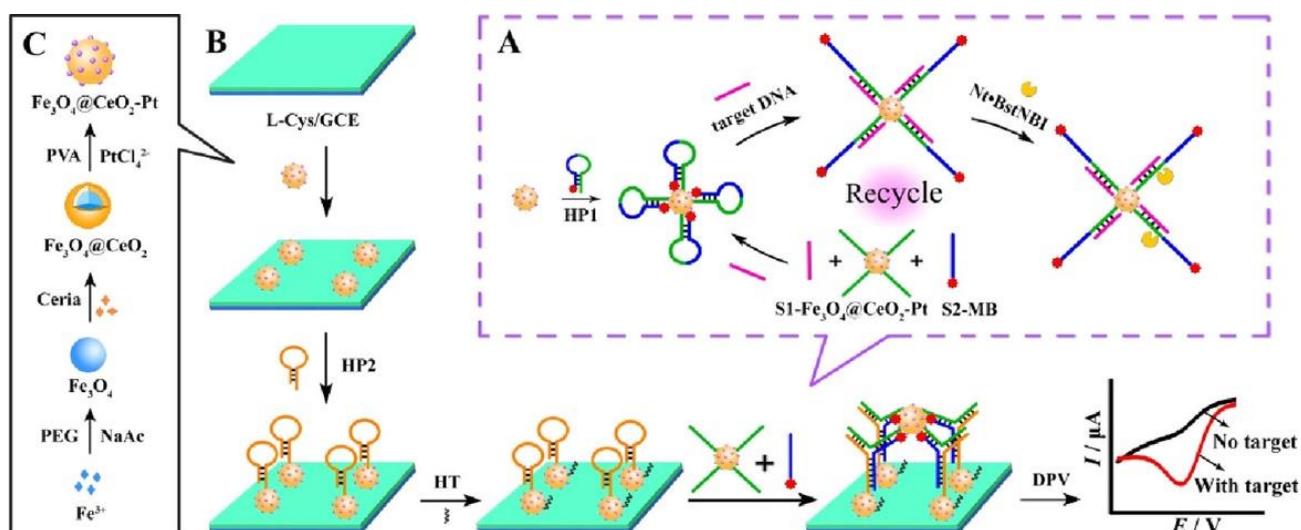
### 3. APPLICATIONS OF CE-BASED NANOMATERIALS IN ELECTROCHEMICAL BIOSENSORS

#### 3.1. DNA Sensors

DNA sensors are analytical devices composed of a transducer and a sequence-specific DNA probe, which use nucleic acids as molecular recognition elements [64]. DNA sensors are widely used in clinical settings, food inspection and environmental areas [65], due to their high sensitivity, specificity, low cost and simple operation [66]. When compared with label-free DNA biosensors,

unlabeled DNA biosensors are more popular due to the simple and effective modification of the interface. Electrochemical DNA sensors are more widely used DNA biosensors where electrical signals produced by probe hybridization with DNA are quantitatively and qualitatively detected. According to the type of hybridization, electrochemical DNA sensors are divided into homogeneous and heterogeneous hybridization techniques.

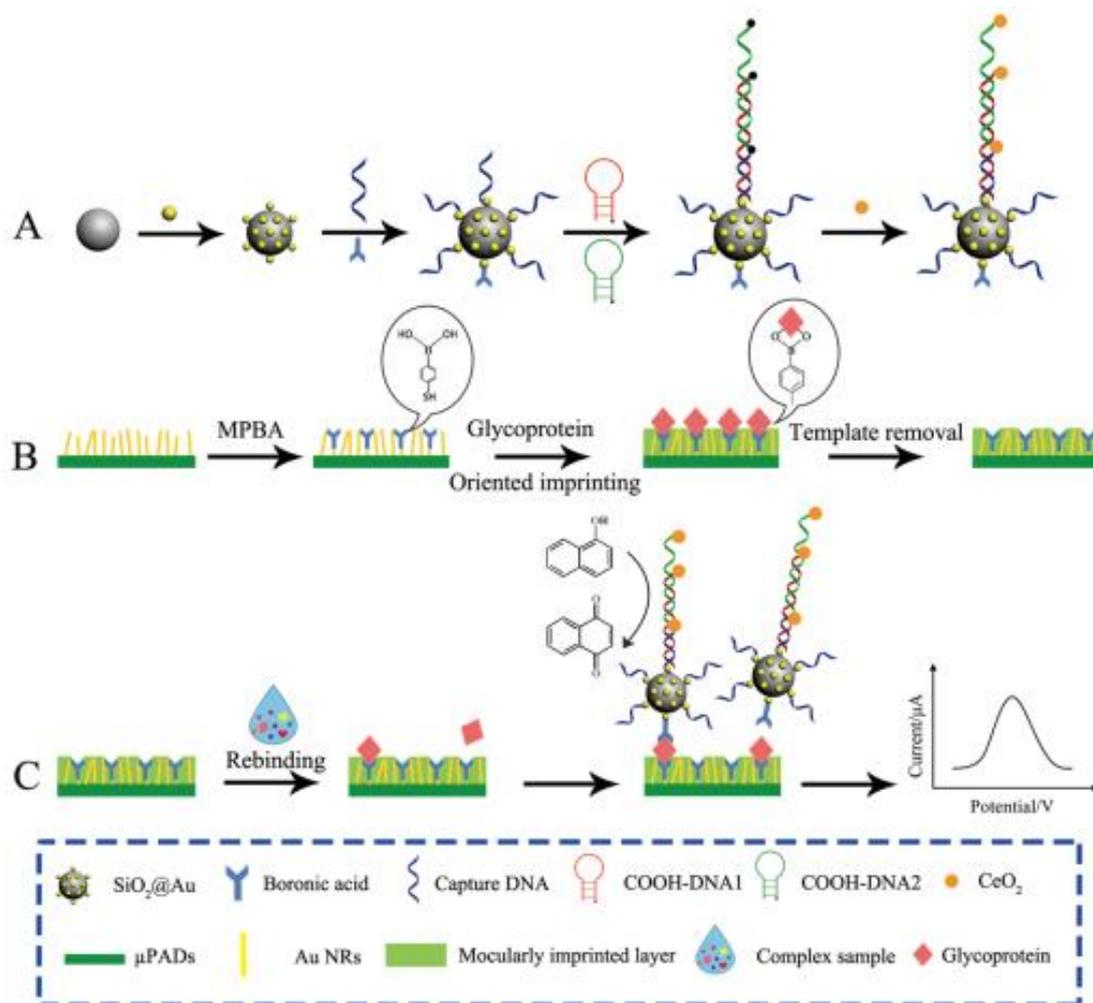
Electrochemical DNA sensors formulated on Ce-based materials have attracted considerable attention, and it is critical to design and prepare Ce-based materials to immobilize DNA probe. Ce-based materials, such as CeO<sub>2</sub> NPs, play key roles in the development of electrochemical DNA sensors because of their non-toxicity to cells and good catalytic effects on hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) [67, 68]. Moreover, CeO<sub>2</sub> NPs combined with other materials can make up for the shortcomings of Ce materials. For example, graphene oxide (GO) was used to increase the stability of CeO<sub>2</sub> NPs by forming a composite with CeO<sub>2</sub> [69]. Equally, the Fe<sub>3</sub>O<sub>4</sub>@CeO<sub>2</sub>-Pt NPs were prepared to fabricate an electrochemical DNA sensor (Figure 7), proposing the Y-DNA formation of efficient target recycling [70].



**Figure 7.** Schematic diagram of biosensor preparation: fixation of target DNA (A), assembly of DNA sensor (B) and synthesis of Fe<sub>3</sub>O<sub>4</sub>@CeO<sub>2</sub>-Pt NPs (C). Reprinted with permission from reference [70]. Copyright 2018 American Chemical Society.

Zhang and his colleagues combined carboxyl fullerene (c-C<sub>60</sub>) and platinum with CeO<sub>2</sub>-NPs to form a composite as a signal material for the electrochemical detection of the CYP2C19\*2 allele [71]. The signal probe and sensor assembly process are shown (Figure 12). When compared with other analytical technologies such as DNA sequencing and restriction fragment length polymorphism (RFLP) analysis, CYP2C19\*2 detection using this electrochemical DNA sensor was more efficient and sensitive due to the increased stability of CeO<sub>2</sub> in combination with c-C<sub>60</sub>. Similarly, Ce-based hybrid nanomaterials have also been used to fabricate electrochemical DNA biosensors. For example, the Ce-based nanocomposites SiO<sub>2</sub>@Au/dsDNA/CeO<sub>2</sub> were used to modify the nicked DNA double-strand

polymers for DNA detection under 1-naphthol conditions (Figure 8) [72]. Wang and his co-workers used  $\text{CeO}_2\text{-ZrO}_2$  hybrid nanospheres to detect target oligonucleotides related to phosphinothricin acetyltransferase (PAT) [13]. Electrochemical DNA biosensor sensitivity was increased in the presence of the  $\text{CeO}_2\text{-ZrO}_2$  nano hybrid thanks to low dimensional and possible quantum confinement effects of  $\text{CeO}_2\text{-ZrO}_2$  nanospheres [13]. In addition to  $\text{CeO}_2\text{-NPs}$ , other Ce-based materials have shown potential applications as electrochemical DNA sensors. Therefore, Ce-based composite materials may have significant applications in genetic testing.



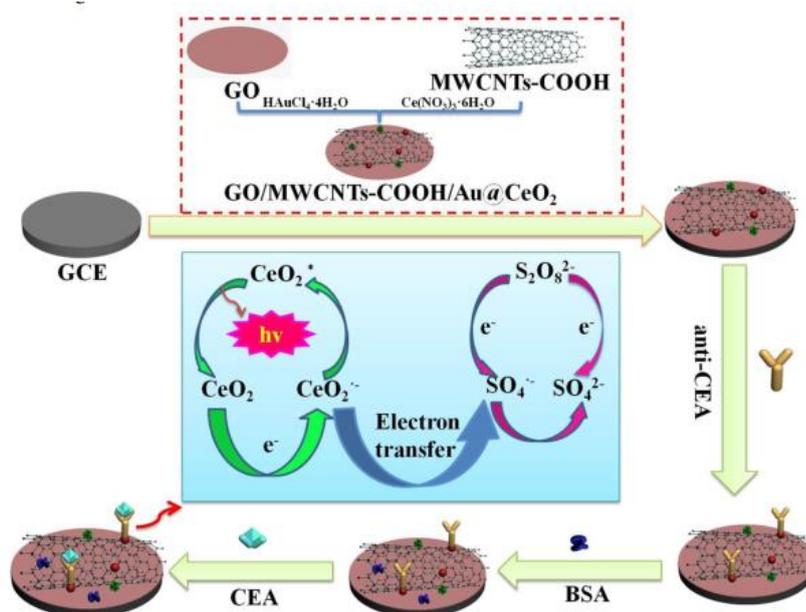
**Figure 8.** Schematic preparation of  $\text{SiO}_2\text{@Au/dsDNA/CeO}_2$  (A), synthesis process of Western blotting membrane (B) and DNA sensor (C). Reprinted with permission from reference [72]. Copyright 2019 American Chemical Society.

### 3.2 Immunosensors

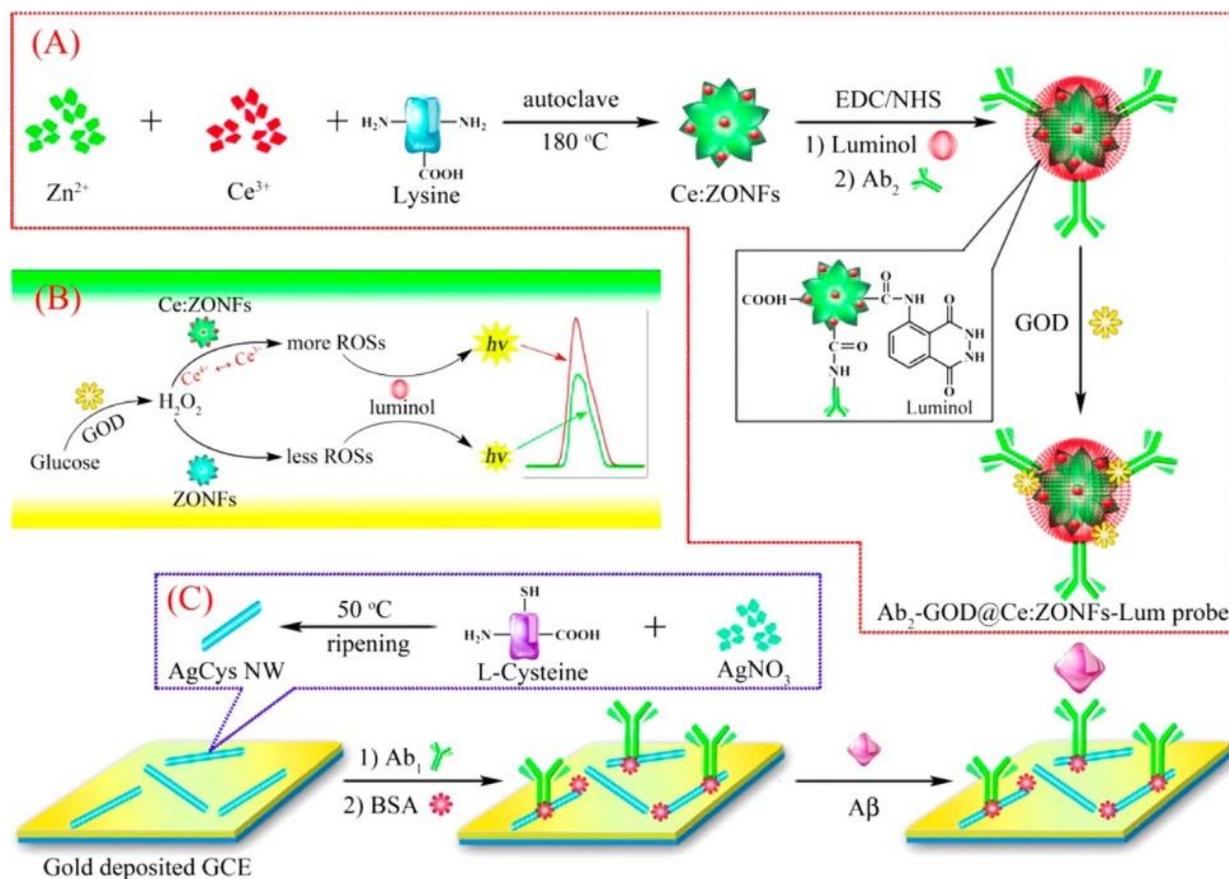
For immunosensors, electrical signals generated between an antibody and an antigen are measured and are usually assigned as labeled [73] and non-labeled [74] immunosensors. Labeled immunosensors are typically prepared using enzyme-labeled specific antibodies or antigens, while

these reagents without immobilized enzymes typically describe non-labeled immunosensors combining with the specific substance to be tested. Electrochemical immunosensors are widely used in clinical medicine and biological monitoring, food testing, environmental monitoring and other fields owing to their high sensitivity, specificity, ease of operation and low costs [75, 76].

Recently, promising developments have been made in electrochemical immunosensors based on Ce materials with low toxicity, good biocompatibility, and so on [77]. As an important rare material, Ce-based materials, especially  $\text{CeO}_2$  nanocomposites, play important roles in electrochemical immunosensors. For example, silver (Ag) was used to prepare  $\text{Ag@CeO}_2$ -based electrochemical immunosensors to detect a tumor specific growth factor [12]. The  $\text{CeO}_2$  NPs loaded GO/MWCNTs-COOH/Au was used as carrier to capture Ab for preparing a high-sensitivity electrochemiluminescence (ECL) sensor toward CEA, as shown in Figure 9, which owned a wider linear range (0.05-100 ng/mL) and a low detection limit (0.02 ng/mL) [78]. Li and his co-workers successfully used a bimetallic doped  $\text{CeO}_2$  composite of  $\text{CeO}_2$ - $\text{MoS}_2$ - $\text{Pb}^{2+}$  as a tag to detect carcinoembryonic antigen (CEA) [76]. Improved linear relationships with lower detection limits were generated thanks to  $\text{CeO}_2$  redox properties,  $\text{MoS}_2$  conductivity and good composite biocompatibility. A luminol-based ECL immunosensor was constructed with the flower-like  $\text{CeO}_2$  doped ZnO nanomaterials (Ce:ZONFs) to detect amyloid- $\beta$  protein (Figure 10), which shows a ultralow detection limit of 52 fg/mL [79].

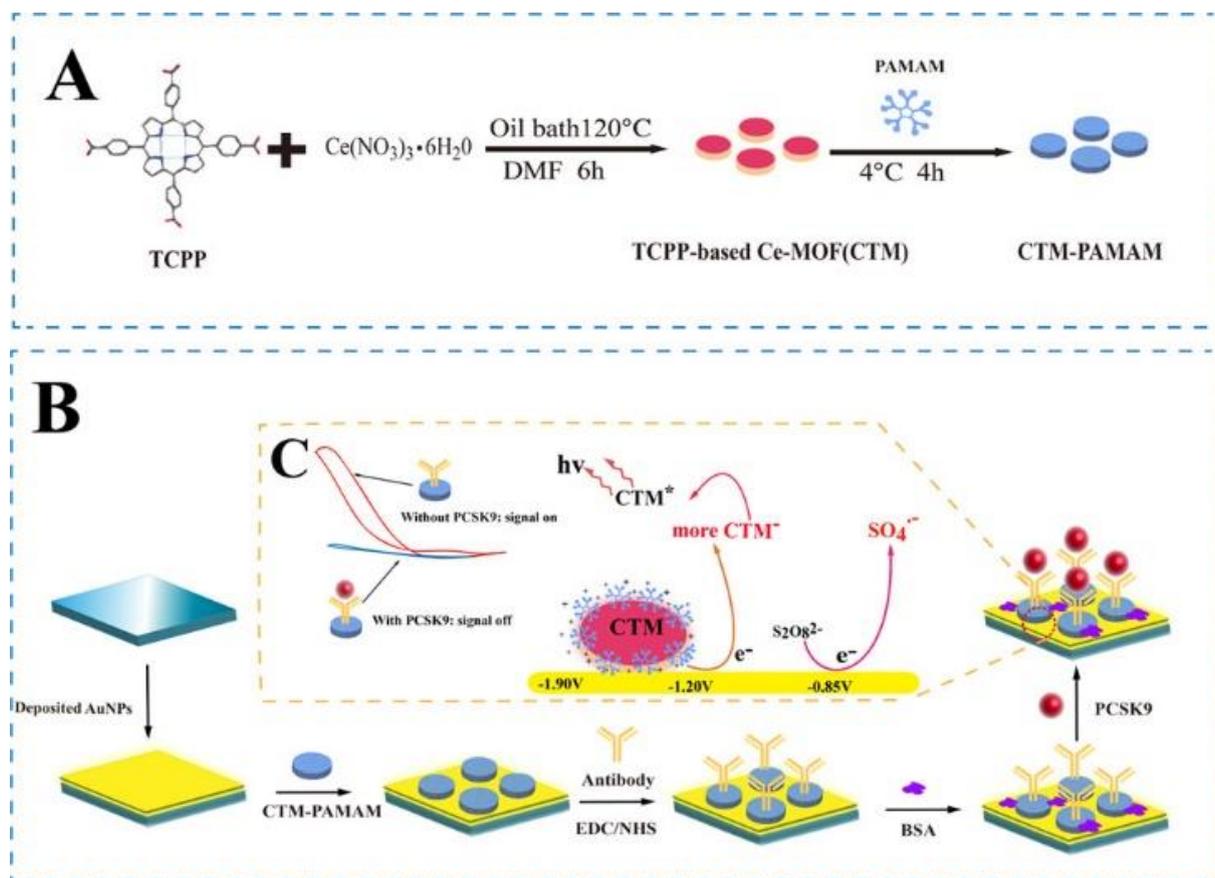


**Figure 9.** Schematic preparation of GO/MWCNTs-COOH/Au@CeO<sub>2</sub> immunosensor. Reprinted with permission from reference [78]. Copyright 2015 American Chemical Society.



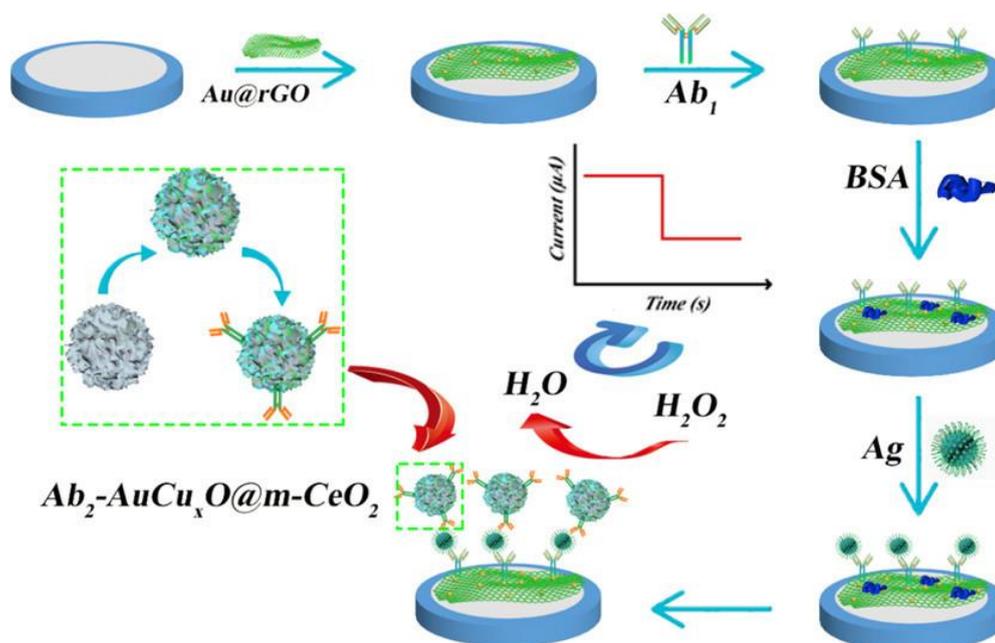
**Figure 10.** The preparation of Ab<sub>2</sub>-GOD@Ce:ZONFs-Lum (A). Schematic preparation of the GOD@Ce:ZONFs-Lum based immunosensor (B) and AgCys nanowires (C). Reprinted with permission from reference [79]. Copyright 2016 American Chemical Society.

The high sensitive detection of the proprotein convertase subtilisin/kexin type 9, a biomarker related to cardiovascular diseases, was achieved using a novel ECL immunosensor fabricated with the luminescent metal-organic framework (MOF) named Ce-TCPP-LMOF (Figure 11) [80]. Also, by using aminopropyltriethox functionalized CeO<sub>2</sub> mesoporous nanoparticles (NH<sub>2</sub>-M-CeO<sub>2</sub>) for supporting toluidine blue (TB) as the electron transfer mediator and anti-PSA as the signal response, Wei developed an amplified sandwich-type electrochemical immunosensor for ultrasensitive detection of prostate specific antigen (PSA), demonstrating remarkable analytical performance of a linear range from 0.5 pg/mL to 50 ng/mL with a detection limit as low as 0.16 pg/mL (S/N=3) [81]. The authors further established a sandwich-type electrochemical immunosensor, based on composites of 3-aminopropyltriethox-silane (APTES), functionalized GO and M-CeO<sub>2</sub> (APTES-M-CeO<sub>2</sub>-GS) loaded with palladium (Pd), octahedral as labels to detect alpha fetoprotein (AFP) [82], displaying increased sensitivity and stability. Equally, CeO<sub>2</sub>-nanowires (NWs) have also been used to prepare free label electrochemical immunosensors to detect *vibrio cholerae* [41].



**Figure 11.** Schematic of CTM and CTM-PAMAM preparation (A) and immunosensor fabrication (B), possible mechanism of CTM-PAMAM/S<sub>2</sub>O<sub>8</sub><sup>2-</sup>/AuNP-GCE(C). Reprinted with permission from reference [80]. Copyright 2020 American Chemical Society.

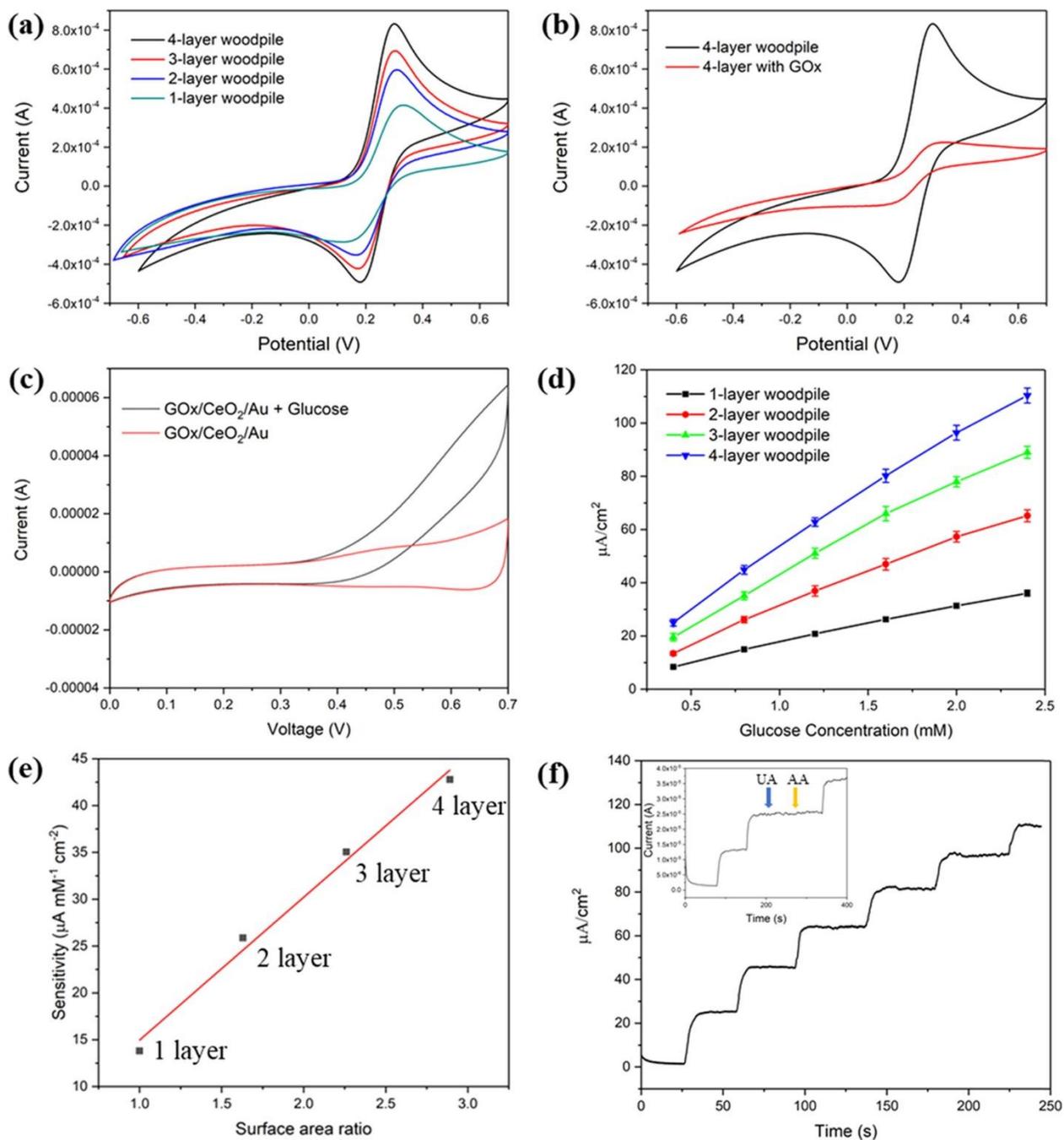
Currently, several other strategies have been explored to produce Ce-based electrochemical immunosensors. For example, using Au @ rGO as the platform and AuCu<sub>x</sub>O@m-CeO<sub>2</sub> to immobilize Ab<sub>2</sub>, a sandwich-type immunosensor was developed to detect amyloid-beta protein (Figure 12) [83]. In this immunosensor, the secondary antibody was no longer required, facilitating easier sensor construction. Because of the unique characteristics of Ce-based materials, there will be increased opportunities to explore and develop more electrochemical immunosensors based on Ce nanomaterials.



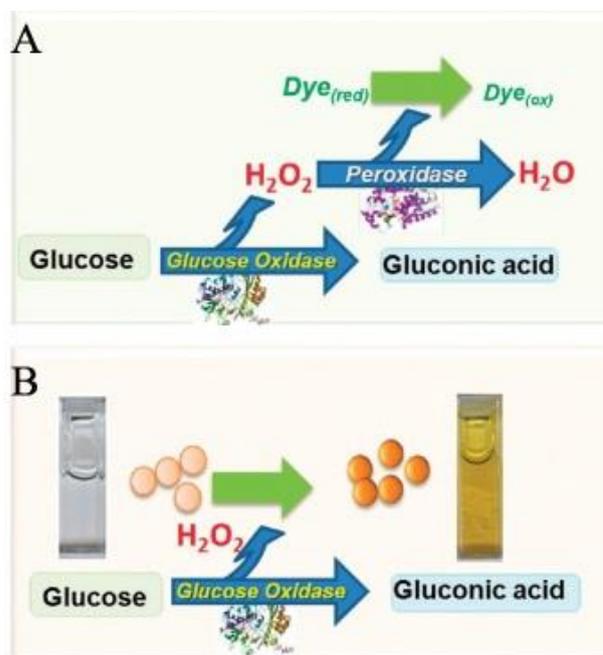
**Figure 12.** Schematic preparation of the  $\text{AuCu}_x\text{O@m-CeO}_2$  based immunosensor for the detection of amyloid-beta protein Reprinted with permission from reference [83]. Copyright 2019 American Chemical Society.

### 3.3 Enzyme and enzyme-mimic sensors

Enzyme sensors transform chemical signals when enzymatic reactions occur. The electro-active analyte penetrates the enzyme layer and participates in the reaction, with a signal detected according to the potential or current signal. Electrochemical enzyme sensors are advantageous because they show efficient catalytic activity, good stability, highly selectivity, less dosage and ease of operation. Common enzyme sensors include glucose and lactic acid sensors, where glucose oxidase and lactate dehydrogenase are used to detect glucose and lactic acid [15, 84]. For example, a novel nanostructured  $\text{CeO}_2/\text{C}$  NW was synthesized to increase the catalytic activity of glucose oxidase for glucose detection [85]. Using a direct patterning technique, three-dimensional  $\text{CeO}_2$  nanoelectrode arrays were reported for glucose biosensor application over relatively large areas. Based on a “stacked-up” architecture with the convenience of sequential imprinting, the four-layer woodpile  $\text{CeO}_2$  nanostructure increased the sensitivity of the glucose sensors to  $42.8 \mu\text{A}/(\text{mM cm}^2)$  and significantly enhanced the selectivity, as shown in Figure 13 [84]. Also  $\text{CeO}_2$  NPs were used together with glucose oxidase to detect glucose based on visual color changes on bioactive sensing paper (Figure 14) [86].



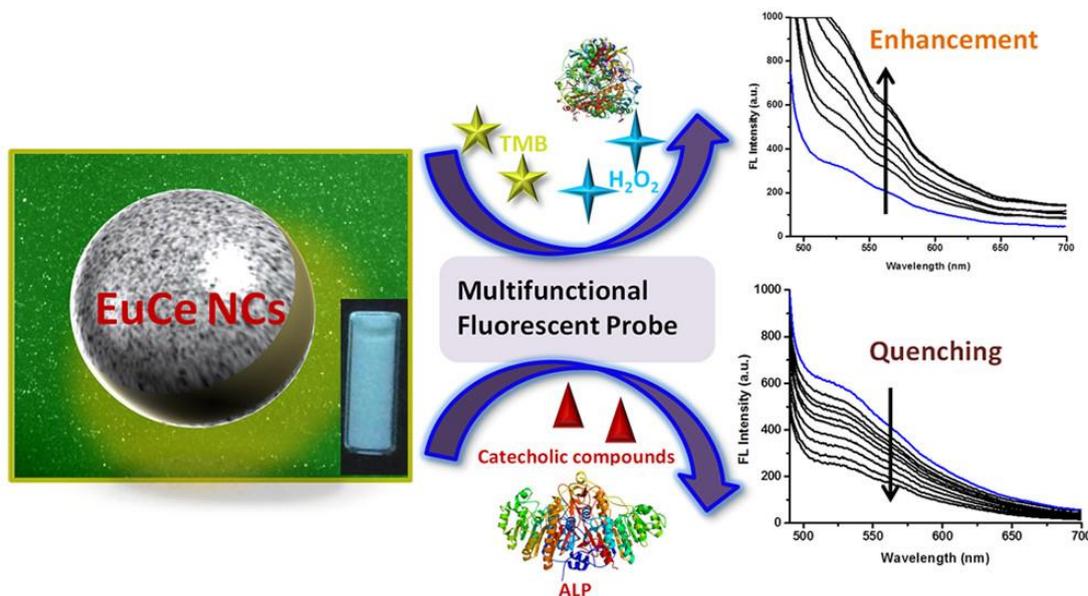
**Figure 13.** CV charts of different layers (a), before and after modification of GOx (b) and with or without glucose (c); Calibration curve of each layer of glucose (d); Relationship between the sensitivity of CeO<sub>2</sub> layers and the ratio of total surface area (e); Current response of the CeO<sub>2</sub> based sensor prepared by four layers of CeO<sub>2</sub> under continuous injection of glucose (f). Reprinted with permission from reference [84]. Copyright 2019 American Chemical Society.



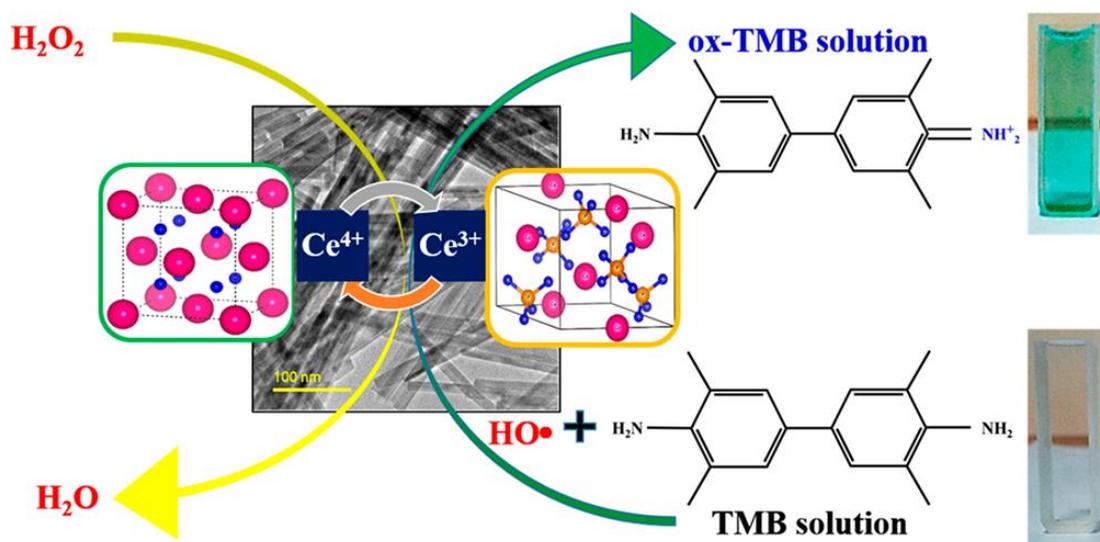
**Figure 14.** Schematic working principle of colorimetric determination. Routine detection of glucose using HRP and organic dyes (A). Detection of glucose based on  $CeO_2$  (B). Reprinted with permission from reference [86]. Copyright 2011 American Chemical Society.

Enzyme mimics are topical in detecting glucose,  $H_2O_2$  and other biological molecules.  $CeO_2$ -based nanomaterials, particularly  $CeO_2$  composites containing noble metals or non-metal materials have attracted considerable attention because of their increased conductivities and high IEFs. A simple and sensitive sensing system was developed by using a porous CoFe-LDH (layered double hydroxides)/ $CeO_2$  hybrid as a peroxidase mimic to detect  $H_2O_2$  and glucose [87]. The NiO and  $CeO_2$  composites were prepared to detect  $H_2O_2$  based on an electrochemical enzyme-mimic sensor [88]. Novel and well-dispersed europium-doped  $CeO_2$  nanocrystals (EuCe NCs) with self-integrated catalytic and fluorescence sensing functions were synthesized with an average size of  $\sim 5$  nm, which not only exhibit high enzyme-mimetic activity but also possess direct fluorescence sensing ability enabling all-in-one recognition, catalytic amplification, and detection of biomolecular targets such as  $H_2O_2$ , glucose/glucose oxidase, lactate/lactate oxidase, and phosphatase. Such EuCe nanoenzyme provides a stable alternative to the more complex systems based on the synergistic effect of natural enzymes and fluorescent dyes (Figure 15) [11]. The  $CePO_4$ - $CeO_2$  composite nanorods with peroxidase mimetic activity were explored for the sensitive detection of  $H_2O_2$  and glucose and their superior peroxidase activity as nanozymes could result from the improved redox switching between  $Ce^{3+} \leftrightarrow Ce^{4+}$  sites from the lattice of  $CePO_4$  and  $CeO_2$ , respectively. Figure 16 shows the schematic mimic of the  $CePO_4$ - $CeO_2$  peroxide enzymes [89].  $CePO_4$ - $CeO_2$  nanoparticles exhibit better catalytic activity of peroxide bionic enzymes because of the enhanced charge transfer interaction between  $Ce^{3+}$  and  $Ce^{4+}$  [89]. In some instances, enzyme, immuno- and DNA sensors can be interrelated. For example, Li *et al.* used a mimic enzyme  $Co_3O_4@CeO_2$ -Au@Pt nanocomposite as a label to prepare an

ultrasensitive electrochemical immunosensor for the detection of squamous cell carcinoma antigen (SCCA) [77].



**Figure 15.** Scheme of the direct fluorescence sensing of EuCe NCs as nano-enzyme probes toward biomolecular targets. Reprinted with permission from reference [11]. Copyright 2018 American Chemical Society.



**Figure 16.** Schematic diagram of the catalytic activity of the CePO<sub>4</sub>-CeO<sub>2</sub> composite nanozymes. Reprinted with permission from reference [89]. Copyright 2019 American Chemical Society.

#### 4. CONCLUSIONS AND PERSPECTIVES

In this review, we summarized methods to prepare Ce-based nanomaterials and their applications for electrochemical biosensors. In considering the poor biocompatibility and limited surface area of CeO<sub>2</sub>, Ce-based nanomaterials have greatly compensated for these disadvantages by

combining with other materials. The doping with precious metals e.g., Au, Pt increases CeO<sub>2</sub> conductivity and biocompatibility, and its combination with carbon-based materials e.g., MWCNTs and GO, increases its specific surface area. Therefore, increased study on the formation of composite materials of CeO<sub>2</sub> and other materials is key for future research. Currently, electrochemical sensors based on Ce-related nanomaterials are primarily used for single molecule detection. Thus, research on how to use Ce-based nanomaterials to design electrochemical sensors for the simultaneous detection of multiple biomolecules will be a major breakthrough.

A short summarization is provided here to help readers to quickly and accurately understand the role of Ce-based nanomaterials in electrochemical biosensors like DNA sensors, immunosensors, and enzyme sensors.

#### CONFLICTS OF INTEREST

There are no conflicts to declare.

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