Photoelectrochemical Sensors for the Detection of Disease Biomarkers: Principles and Applications

Jiahui Chi [#,*], Jiaqi Pan [#]

School of Electronic Engineering, Xi'an University of Posts & Telecommunications, Xi'an, China, 710000

* Corresponding Author Email: xygdzycjh@163.com

[#]These authors contributed equally.

Abstract. The rapid and accurate detection of disease biomarkers is crucial for the early diagnosis, prognosis assessment, and therapeutic monitoring of major diseases, including cancer, cardiovascular diseases, inflammatory responses, and infectious diseases. Conventional analytical techniques such as enzyme-linked immunosorbent assay (ELISA), mass spectrometry, and nucleic acid amplification, while reliable, are often constrained by complicated procedures, high cost, and limited applicability in point-of-care settings. In response to the aforementioned challenges, photoelectrochemical (PEC) sensors have garnered significant attention in recent years due to their advantages of low background noise, high sensitivity, and simple instrumentation, emerging as a promising direction in biosensing. This review systematically elucidates the fundamental operating principles of PEC biosensors and summarizes the key functional materials involved in their construction (such as semiconductor optoelectronic materials, photosensitizers, and electron transport aids) and their interfacial regulation strategies. Furthermore, recent progress in the application of PEC sensors for the detection of disease-related biomarkers is critically examined, with representative examples targeting cancer-associated proteins, cardiovascular disease markers, inflammatory mediators, pathogen-derived nucleic acids, and antigens. The performance of different detection strategies is also compared in terms of sensitivity, selectivity, and practical feasibility. Finally, the challenges hindering the broader application of PEC biosensors are discussed. Future perspectives are outlined, highlighting material innovation, interfacial optimization, and device miniaturization as key directions to advance PEC biosensors toward clinical translation and portable diagnostic applications.

Keywords: Photoelectrochemical Biosensors, Disease Biomarkers, Functional Materials, Clinical Diagnostics.

1. Introduction

Abnormal expression of biomarkers is often closely associated with the onset and progression of specific diseases, and their accurate detection plays a crucial role in clinical diagnosis and therapeutic monitoring. For example, procalcitonin (PCT) is widely employed to distinguish between bacterial and viral infections [1–3], while glycated hemoglobin (HbA1c) offers a snapshot of chronic blood glucose management and serves as an essential guidance for the diagnosis, treatment, and management of diabetes [4–6]. However, traditional biomarker detection technologies—such as enzyme-linked immunosorbent assay (ELISA) [7], electrochemiluminescence (ECL) [8], and others—are frequently limited by lengthy detection cycles, cumbersome operations, and reliance on sophisticated instrumentation. These drawbacks hinder their application in primary healthcare and point-of-care testing (POCT). Therefore, there is an urgent demand for novel biomarker detection technologies that integrate high sensitivity, excellent specificity, rapid analysis, and low cost, thereby facilitating early diagnosis, personalized treatment, improved patient outcomes, and advancement of precision medicine.

Photoelectrochemical (PEC) biosensing, which combines optical excitation with electrochemical signal readout, has emerged as a promising solution to these challenges. Light-generated electron-hole pairs (e^- - h^+) drive redox reactions to detect target substances [9]. The separation of "light" and "electricity" significantly reduces background interference, delivering outstanding performance in

complex biological media [10]. The high responsivity of the photocurrent endows the sensor with excellent sensitivity and precision. Combined with advantages of speed, low cost, and ease of miniaturization, PEC biosensing has become a research hotspot in the field of disease biomarker detection.

Recent advances in nanomaterial engineering and system integration technology have greatly accelerated the development of PEC biosensors. Strategies such as surface modification, heterostructure construction, and functional material composites (e.g. Au@Ag[11,12], Fe_3O_4[13,14]) have markedly enhanced photoelectric conversion efficiency and amplified the photocurrent response . Furthermore, the rise of multimodal detection strategies has further improved detection reliability. By integrating methods such as combining photoluminescence emission with photothermal (PT) signals[15] , integrated systems like optical fiber-coupled photoluminescence emission (OF-PEC)[16–18] have been developed. These systems enable simultaneous detection of multiple signals, playing a crucial role in reducing errors while improving detection throughput and flexibility.

Given the aforementioned background, the objective of this review is to furnish the reader with a comprehensive overview of PEC sensors for disease biomarker detection. Specifically, it begins by introducing the fundamental principles and the signal transduction mechanisms of PEC sensors. It then summarizes recent progress in material design and device construction, with an emphasis on their role in improving detection performance. Subsequent section highlights representative advances in PEC biosensors in detecting biomarkers associated with typical diseases Finally, current limitations and future research directions are discussed, offering theoretical insights and practical guidance for advancing PEC biosensors toward clinical application and translation in disease diagnostics (Figure 1).

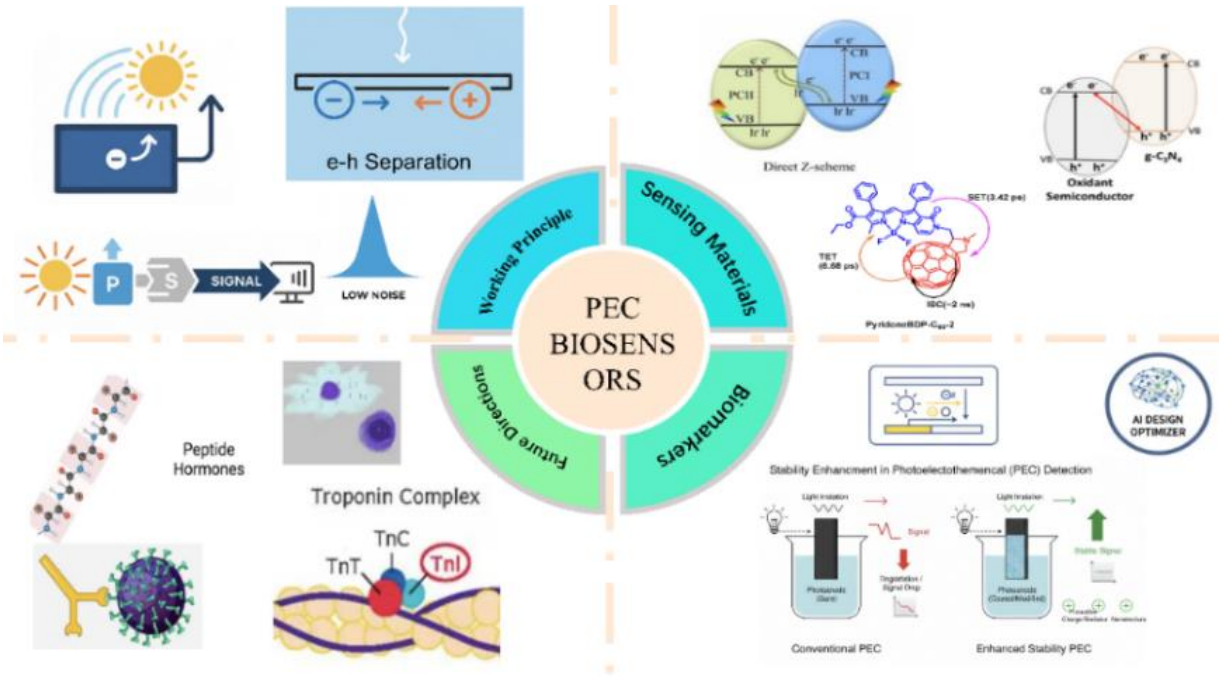

Figure 1. Schematic Diagram of Core Mechanisms and Application Directions of PEC Biosensors

2. The fundamental principle of PEC sensor

2.1. Signal generation mechanism

PEC sensors integrate optical excitation with electrochemical transduction to achieve sensitive detection of biomolecules. The illumination triggers the absorption of photons by photoactive semiconductors, with the energies of these photons equaling or exceeding the bandgap of the semiconductors.

Electrons located within the valence band (VB) have been shown to be capable of transitioning to the conduction band (CB), forming e^- - h^+ pairs. Driven by an applied bias or interfacial field, these carriers separate and migrate to the electrode–solution interface, where they participate in redox reactions, converting light energy into electrical signals (Figure 2).

Photocurrent generation in PEC systems typically follows two modes: (i) cyclic electron transfer, where photoexcited materials continuously donate and regain electrons through redox cycling, and (ii) electron donor/acceptor transfer, in which excited carriers react with species in the electrolyte to complete charge exchange. Depending on the dominant carrier type, anodic or cathodic photocurrents may be observed (Figure 3). Engineering heterojunctions or introducing surface states can effectively enhance charge separation and suppress recombination, thereby improving photocurrent intensity.

Unlike traditional electrochemical analysis, PEC sensors are based on the utilization of light as the excitation source and current as the detection signal, avoiding spectral overlap and background noise. Biorecognition events such as antigen–antibody or aptamer–target interactions, as well as enzyme-catalyzed reactions, can further regulate interfacial charge transfer, enabling quantitative correlation between analyte concentration and photocurrent output.

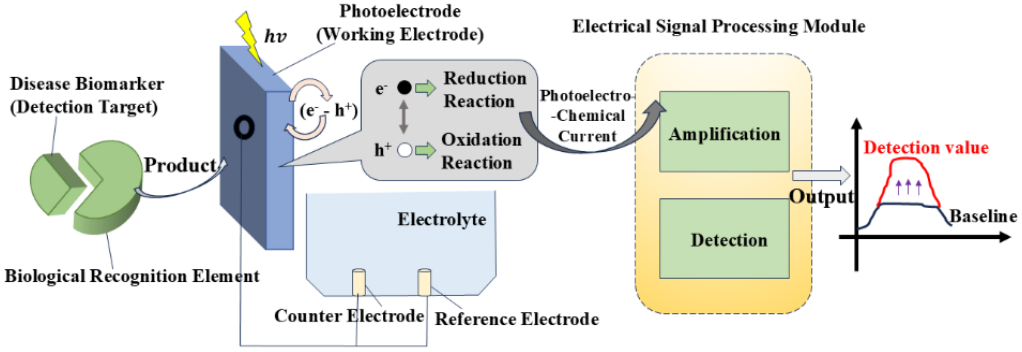

Figure 2. Schematic Diagram of the PEC Biosensor

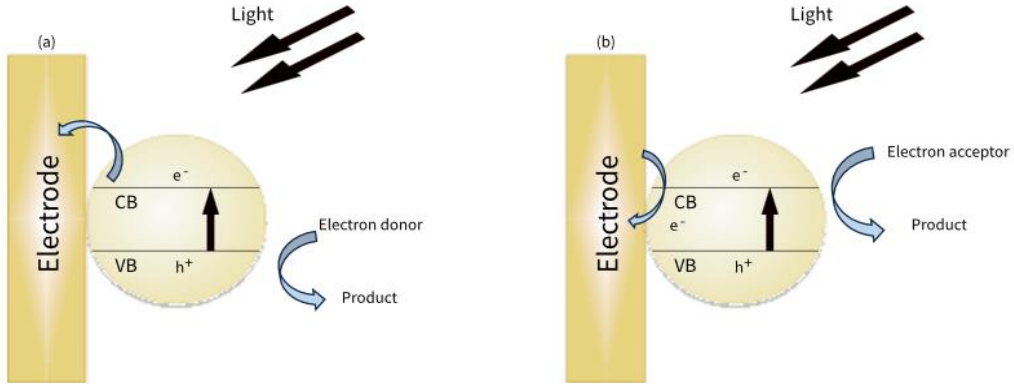

Figure 3. Schematic Diagram of the Generation and Separation Mechanism of Photocurrent

2.2. Advantages over conventional sensing methods

Compared with fluorescence, colorimetry, and electrochemistry, PEC sensing offers superior sensitivity, reduced background interference, and simplified operation. Optical excitation and electrical readout are physically separated, minimizing signal noise and enhancing detection accuracy. Without the need for fluorescent or enzymatic labeling, PEC systems allow straightforward and multiplexed assays. In addition, portable electrochemical modules and compact light sources enable cost-effective and field-deployable devices [19].

The unique dual-layer configuration comprising a photoexcitation layer for photon absorption and an electrochemical transduction layer—further improves charge transport. Bandgap engineering (such as constructing CdS/TiO_2 heterojunctions) [20] enhances charge separation, while surface modifications with antibodies, enzymes, or aptamers provides molecular selectivity [21].

Representative studies demonstrate that PEC sensors outperform traditional methods. Nasrin et al. synthesized TC-GQD with superior dopamine (DA) detection limits compared to electrochemical assays [22]. Fei et al. summarized quantum dot (QDs)-based PEC platforms for DNA and carcinoembryonic antigen (CEA) detection, showing broader linear ranges and higher sensitivities than fluorescence assays [23]. Similarly, PEC sensors have also achieved femtomolar sensitivity for human telomerase RNA (hTR) [24–26] and accurate, rapid detection of SARS-CoV-2 biomarkers, underscoring their potential in early diagnosis and real-time monitoring (Table 1) [27–41].

Table 1. Summary of Disease Biomarker Sensor Performance Comparison

Target Analyte	Sensor Type	Key Materials	Limit of Detection	Detection Range	Ref
DA	EC	TC-GQD/GCE	0.22 μM	1-500 μM	22
	PEC	TC-GQD/GCE	22 nM	0.3-750 μM	22
DNA	Fluorescence	CdTe	4.5 nM	10-200 nM	23
	PEC	CdTe	0.93 fM	10 fM-10 pM	23
	PEC	CdTe	27 aM	50 aM-50 pM	23
CEA	Fluorescence	CdTe/CdSe	6.7 pg/mL	0.05-20 ng/mL	23
	PEC	CdS	0.47 pg/mL	0.001-2 ng/mL	23
hTR	Colorimetric	CHA-MB	41 pM	/	24
	Fluorescence	GO	90 pmol/L	0.2-50 nmol/L	26
	PEC	CHA/HB-HCR	17 fM	200 fM-20 nM	25
SARS-CoV-2-N protein	ELISA-ToAD	/	0.1 ng/mL	10 ng /mL	34
	BioFET	EDL	0.34 ng/mL 0.14 ng/mL	/	39
	NLICS	/	0.026 ng/mL	0.05-1.6 ng/mL	28
	PEC	FSTCA/Ab1 SiO_2@Au-Ab2	2.9 pg/mL	10 pg/mL-100 ng/mL	30
	PEC	CdS:Mn-Bi_2MoO_6/In_2S_3	3.9 fg/mL	10 fg/mL-1 μg/mL	31
SARS-CoV-2-S protein	EC-colorimetric	PtNCs	0.36 pg/mL 0.57 pg/mL	1 pg/mL-1 μg/mL	27
	EC	MIP	15 fM 64 fM	/	36
Sars-CoV-2 RBD	EC	Pt-black	0.23 ng/mL	100-1 μg/mL	33
	PEC	Chitosan/ CdS-gC_3N_4	0.12 nM	0.5-32 nM	29
SARS-CoV-2	SPR	$BaTiO_3$-WS_2	3.5 degrees (FWHM) 128.57 /RIU (FoM)	/	41
	MMRI Optical	SRR	45 /RIU(FoM)	800 nM-1400 nM	35
SARS-CoV-2 and HAdV	fluorescent-colorimetric	PDQB	/	/	38
SARS-CoV-2-N gene	optical fiber	AuNRs-ASO_2-N	1 pM	/	37
SARS-CoV-2 RdRp gene	fluorescent	/	30 fM	/	32
SARS-CoV-2 cpDNA1A cpDNA3A	PEC	GSH-AuNPs	2.2 fmol/L(1A) 3.4 fmol/L(3A)	1-10^4 fM	40

3. PEC photosensitive material

Photosensitive materials constitute the core functional units of PEC biosensors, as their physicochemical properties directly determine sensitivity, detection limit, and selectivity. Photosensitive units not only Beyond serving as the primary photoactive layer in photoelectrodes or composite, photosensitive components are frequently employed to synergize with signal-amplification elements and biorecognition units. Therefore, rational design and optimization of photosensitive materials represent one of the most effective strategies for advancing PEC sensor performance [42]. This section summarizes recent progress from five perspectives: (a) semiconductor photoactive materials; (b) heterojunctions and composite materials; (c) photosensitizers and enhancement strategies; (d) electrode modification and interface engineering; (e) integration strategies for biometric components.

3.1. PEC semiconductor photoelectrically active material

Semiconductor are the most extensively studied photosensitive materials in PEC systems., In recent years, researchers have extensively explored semiconductors such as γ-C_3N_4, ZnO, CdS, and their composites to enhance the lifetime of photogenerated carriers and the efficiency of interfacial charge transfer. For example, Li et al. constructed a g-C_3N_4@CdS heterostructure using carbon nitride graphite g-C_3N_4 and quantum dots CdS QD, achieving sensitive detection of Hg^{2+} with a detection limit of 12 nM [43] (Figure 4). Zhao et al. employed ZnO/polypyrene (PPy) composites as photoactive probes in a sensor for acrylamide based on a molecularly imprinted polymer (MIP), achieving high sensitivity via a signal-quenching mechanism [44]. Dashtian et al. reported an n-n type VO_2–$CuWO_4$ heterostructure deposited on a Ti substrate, modified with photoactive molecularly imprinted poly(2,5-benzimidazole), which enabled DA detection at 0.15 nM [45]. Although semiconductor optoelectronic materials demonstrate excellent photoelectric conversion capabilities in PEC sensors, they commonly suffer from high photogenerated carrier recombination rates and insufficient stability. These inherent limitations constrain their further application in high-sensitivity detection.

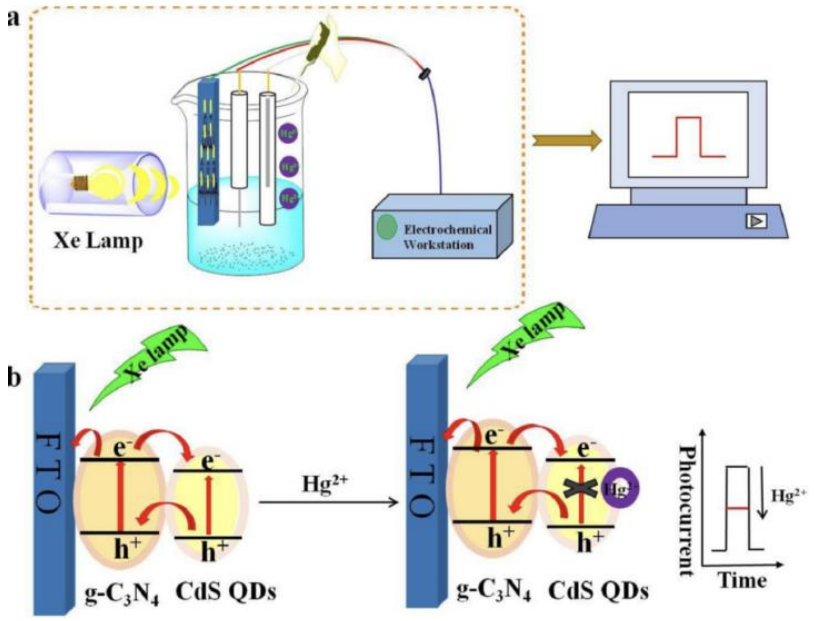

Figure 4. Schematic Diagram of the g-C_3N_4@CdS Photoelectrochemical Sensor Principle for Detecting Hg^{2+}. [43].

3.2. Construction of heterojunctions and composite materials

To address the limitations of single-component semiconductor performance, constructing heterojunctions and composites has emerged as a highly effective approach. By leveraging bandgap

alignment and synergistic interfacial interactions, these structures facilitate efficient charge separation and transport.

p-n heterojunction: The internal electric field enables spatial separation of charge carriers. Liu et al. developed a CuS/CdS nanohybrid-based PEC sensor for Cu^{2+}, demonstrating high sensitivity in both aqueous samples and Cu^{2+} released from senescent HeLa cells [46]. Jian et al. prepared a NiO_x-decorated Cu_2O/ZnO p–n heterojunction, which achieved a Faradaic efficiency of 95 ± 4% for H_2 evolution, highlighting its potential in precious-metal-free photocathodes [47] (Figure 5).

Z-type heterojunction: Unlike conventional p-n junctions, Z-type heterojunctions preserve strong redox potentials while improving charge separation. Feng et al. developed a novel PEC sensor based on a double-Z-type α-Fe_2O_3/MoS_2/Bi_2S_3 ternary heterojunction for circulating tumor cells (CTCs) detection, which delivered excellent sensitivity and specificity [48].

Schottky heterojunction: By exploiting the potential barrier at the metal–semiconductor interface, Schottky junctions regulate electron injection and migration. Dong et al. synthesized a ternary gold nanoparticles (AuNPs)/CdS-QDs/CeO_2 nanocomposite, where a Type II CdS/CeO_2 heterojunction was combined with a Schottky interface between CeO_2 and AuNPs, achieving ultra-sensitive prostate-specific antigen (PSA) detection with a detection limit as low as 31 aM [49].

In summary, heterojunctions and composites substantially enhance photoelectric conversion and material stability. Nonetheless, structural optimization alone is insufficient for signal amplification, making the incorporation of photosensitizers a critical complementary strategy.

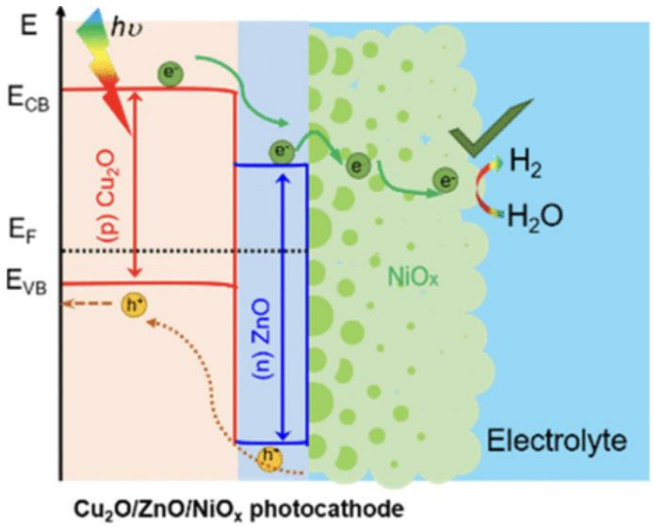

Figure 5. Schematic diagram of the band structure and charge transfer mechanism of the Cu_2O/ZnO/NiO_x p-n junction for water splitting. [47].

3.3. Photosensitizer and enhancement part

Photosensitizers amplify photocurrent responses by extending light-harvesting ranges and accelerating charge transfer. They are widely applied in PEC "signal-on" or "signal-off" sensing platforms.

By constructing signal-off-type PEC sensors using specific photosensitizers, the PEC signal decreases as the target concentration increases while achieving significant signal enhancement. Ma et al. utilized ZnP (zinc meso-tetra(4-carboxyphenyl)porphine) as a photosensitizer, combined with AuNPs embedded in N-doped porous carbon, to construct a "signal-off" PEC sensor for Protein Tyrosine Kinase 7 (PTK-7), achieving a detection limit of 1.42 pg/mL [50]. Meng et al. employed Bi_2S_3 and toluidine blue O (TBO) as co-sensitizers for ZnS, achieving a 136-fold amplification for microRNA-21 detection with an ultralow LOD of 3.3×10^{-18} M [51]. Huang et al. designed an In_2O_3/$CdIn_2S_4$ heterojunction photosensitizer for CEA detection, reaching 2.8 pg/mL via a biocatalytic precipitation (BCP)-based immunoassay [52] (Figure 6). Similarly, Cao et al. constructed

CdS@Au–g-C_3N_4 heterojunctions, where AuNPs functioned simultaneously as plasmonic enhancers and electron mediators, enabling PSA detection at 0.6 pg/mL [53].

Additionally, Hu et al. stabilized the protoporphyrin IX (PPIX) photosensitizer using ionic liquids, thereby resolving the issue of organic photosensitizers readily aggregating and quenching in aqueous media [54]. Despite these advances, the effectiveness of photosensitizers is highly dependent on efficient charge transport at electrode interfaces, necessitating careful electrode engineering.

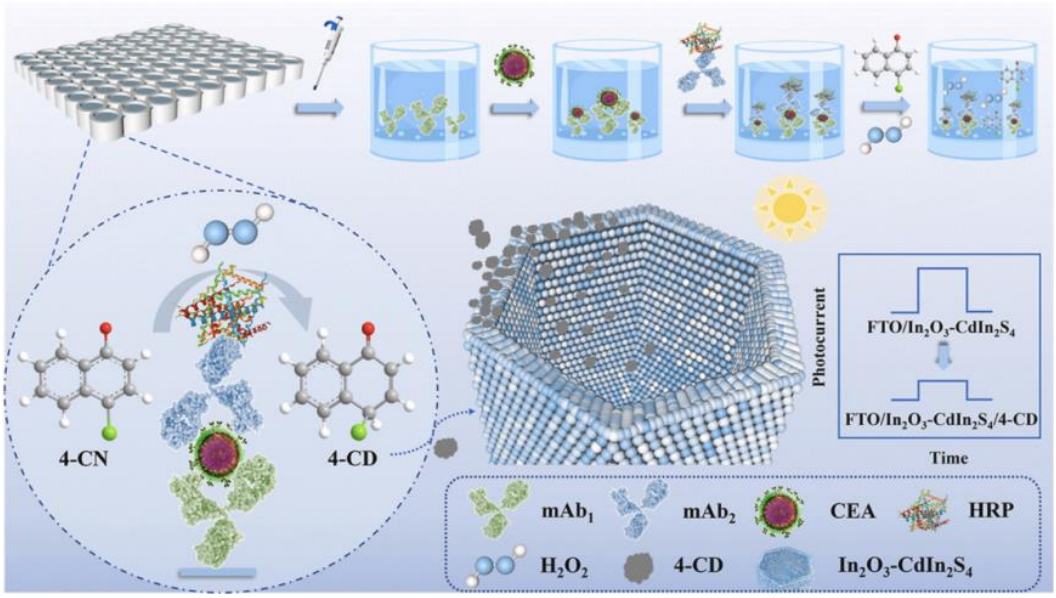

Figure 6. Schematic Diagram of the Working Principle for Separate-Type PEC Sensor Determination of CEA Based on $In_2O_3/CdIn_2S_4$ Photosensitizer. [52].

3.4. Electrode modification and interface engineering

The electrode and interface structure directly determine the charge transport efficiency during photoelectric conversion and the stability of biometric responses. Constructing a stable, efficient interface structure is crucial for achieving low-resistance transport pathways and high biometric recognition efficiency in photoelectric conversion processes. Commonly used conductive substrates include:

Traditional substrates: Transparent conductive oxides such as FTO and ITO remain widely used. Kim et al. achieved a maximum IPCE of 75% in photovoltaic efficiency by regulating the surface of FTO electrodes through a Ti intermediate layer [55]. Tay et al. enhanced the stability of Copper Zinc Tin Sulfide (CZTS)/CdS/Pt photocathodes by utilizing an ITO layer [56].

Novel Substrate Materials: Traditional rigid substrates (such as FTO and ITO) are costly and unsuitable for wearable platforms. To achieve lightweight materials, novel substrate materials are required. Ng et al. incorporated organic PEDOT: PSS films and n-type MoS_2 flakes as underlying and surface co-catalysts, respectively, onto a CuO photocathode, a rational design for a novel PEDOT is: PSS/CuO/MoS_2 integrated structure. This configuration provides additional reaction sites for the hydrogen evolution reaction and demonstrates potential for wearable applications [57].

Functionalization of Substrates: Functionalization of electrode surfaces is a key strategy for enhancing interfacial performance. Primary approaches include self-assembled monolayers (SAMs) [58], crosslinked polymer layers [59–61] (Figure 7), and silane coupling agent modifications [62–65]. These modification techniques not only enhance the loading efficiency and stability of the material but also improve its charge transfer properties, suppress non-specific adsorption, and optimize overall sensing performance. To achieve genuine biomedical applications, PEC sensors must rely on highly selective bio-recognition elements in addition to a stable optoelectronic conversion foundation. Therefore, effectively coupling antibodies, aptamers, or bionic recognition components with the optoelectronic system represents the final critical step in enhancing specific detection capabilities.

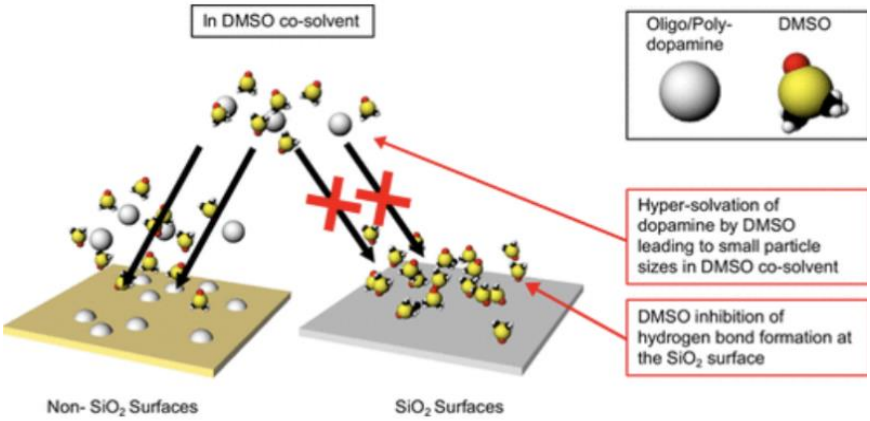

Figure 7. Schematic illustration of the mechanism for novel polydopamine coating in dimethyl sulfoxide (DMSO) co-solvent. [60].

3.5. Integration strategy of biometric components

The ultimate determinant of sensor selectivity lies in biorecognition components, which couple biological interactions with optoelectronic transduction.

Antibodies: Lu et al. prepared a carbon nanotubes (CNT)/Pt cathode substrate by modifying CNTs with platinum NPs, achieving highly selective detection of human chorionic gonadotropin (HCG) with excellent interference resistance and high specificity [66].

Aptamers: To detect ampicillin (AMP), Yan et al. immobilized an amino-functionalized AMP aptamer as a biosensor on a working electrode, enabling specific recognition and capture of AMP. The detection limit reached as low as 0.06 pg/mL, demonstrating excellent stability and selectivity [67]. Deng et al. constructed a PEC sensor for detecting DEHP using DEHP-specific aptamers as the biosensor element. They employed a cross-linking coupling method to immobilize the anti-DEHP aptamer molecules onto GQDs-modified TiO_2 nanotubes, achieving a detection limit of 0.1 ng/L [68].

Biometric elements: In research on detecting CEA, Wang et al. synthesized the ionic liquid BCCPEimBr (3- {[{4-N, N-Bis[(carbamoyl)ethyl methacrylate] butyl} ((carbamoyl)amino) ethyl methacrylate] -propyl}-1-ethenyl-1H-imidazol-3-ium bromide) as the recognition element. A molecularly imprinted hydrogel film was prepared on the surface of a hollow gold nanosphere/$MoSe_2$ electrode, thereby constructing a CEA-imprinted PEC sensor with a detection limit of 11.2 pg/mL and excellent selectivity [69]. The incorporation of such biorecognition components bridges the gap between material optimization and practical biological sensing, propelling PEC biosensors from fundamental design toward clinical and environmental applications.

4. Application of PEC biosensor

PEC sensors integrate electrochemical and spectroscopic principles, providing a versatile platform for clinical diagnostics. They are a key contributor to early detection, classification diagnosis, and therapeutic efficacy assessment of prevalent diseases such as cancer, cardiovascular diseases, inflammatory responses, and infectious diseases. substantial progress has been achieved in leveraging PEC biosensors for biomarker detection, highlighting their potential in point-of-care and precision medicine applications. This section will review recent research advances in the detection of relevant biomarkers using PEC sensors across the aforementioned disease categories, analyzing and comparing representative studies.

4.1. Cancer related marker detection

Cancer is among the foremost etiologies of mortality on an international basis. Expeditious detection is of paramount importance in optimizing survival rates. PEC sensors, with their high sensitivity and selectivity, serve as an ideal tool for early cancer detection. By detecting biomarkers

associated with cancer, precise diagnosis can be achieved and personalized treatment can be supported.

Alpha-fetoprotein (AFP), primarily synthesized by fetal hepatocytes and the yolk sac, is a widely recognized tumor marker. Alpha-fetoprotein exhibits high concentrations in fetal circulation but declines after birth. By 2 to 3 months postnatal, it is largely replaced by albumin and becomes difficult to detect in blood, resulting in extremely low levels in adult serum. Idris et al. found that immunosensors based on gold dendrimer nanoparticle composites prepared under optimized conditions exhibited excellent sensitivity toward AFP, with a linear range of 0.005–500 ng/ml. The detection limits for SWV and EIS were 0.0022 ng/mL and 0.00185 ng/mL, respectively, playing a crucial role in tumor screening [70].

Lung cancer is defined as a malignant tumor originates from the mucosa or glands of the pulmonary bronchi, and it has the highest mortality rate among all cancers. Mao et al. proposed a PEC biosensor utilizing Bi-Metal-Organic Framework (Bi-MOF)/CdS-QDs as the photoactive material for detecting CYFRA21-1, a cytokeratin fragment widely used as a clinical biomarker. The sensor demonstrated outstanding detection performance with a LOD of 30 ng/mL for CYFRA21-1. This method provides a viable platform for the sensitive detection of CYFRA21-1[71]. Beyond cancer, cardiovascular disease—another category of conditions with high global mortality rates—is also increasingly reliant on precise biomarker detection. PEC sensors demonstrate significant potential for application in this field as well.

4.2. Detection of cardiovascular disease markers

Cardiovascular diseases represent a significant proportion of global mortality and disability rates, highlighting the necessity for early screening and continuous monitoring. PEC biosensors, with their rapid response and adaptability to on-site analysis, provide a valuable strategy for detecting cardiac biomarkers.

Cardiac troponin (cTn), a specific protein localized in myocardial cells, is the gold-standard biomarker for diagnosing acute coronary syndrome. Xu et al. developed an immunosensor based on gold nanoparticle-anchored BiOI/Bi_2S_3 nanosheet arrays (BiOI/Bi_2S_3/Au) for the sensitive detection of cTnI. Within the linear range of 500 fg/mL to 50 ng/mL, the detection limit for the target analyte is 32 fg/mL, demonstrating excellent stability and selectivity [72] (Figure 8). Beyond cardiovascular diseases, the early diagnosis of inflammatory responses is also crucial for preventing and treating major illnesses. PEC sensors also demonstrate significant potential in detecting inflammatory markers, particularly for precise early warning in the initial stages of disease.

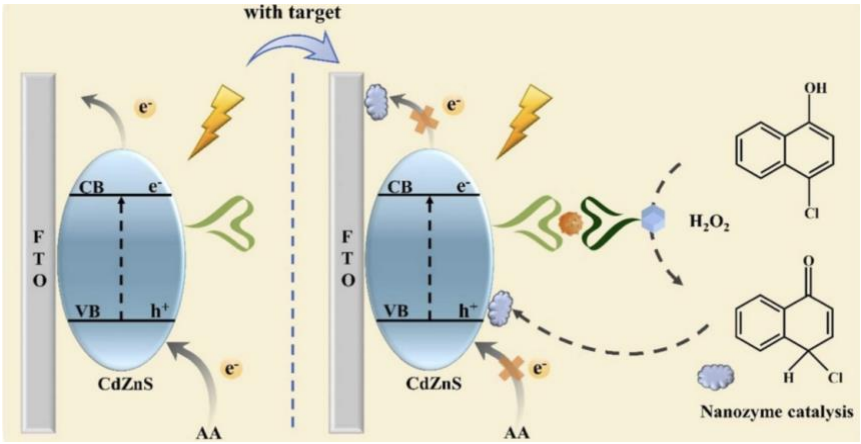

Figure 8. Schematic diagram of the signal shutdown mechanism in a nanozyme-mediated PEC immunoassay for detecting cardiac troponin I. [72].

4.3. Detection of inflammatory response related markers

Chronic or uncontrolled inflammation underlies the pathophysiology of numerous diseases, including cancer, cardiovascular disorders, and diabetes. Consequently, early and precise detection

of inflammatory biomarkers is essential for timely intervention. PEC biosensors have demonstrated remarkable capability in detecting inflammation-related targets at ultralow concentrations. Hepatitis is caused by multiple factors, and its mortality rate has been rising year by year. Chen et al. developed a photoelectrochemical-fluorescence (PEC-FL) dual-mode microsensor for H_2S detection, a critical inflammatory mediator in hepatitis. On one hand, H_2S reacts chemically with the recognition element Cyanine-Dipicolylamine-Copper (Cy-DPA-Cu) to form CuS. The excited CuS generates a photocurrent for quantitative H_2S detection. On the other hand, Cy-DPA-Cu releases Cu^{2+}, prompting Cy-DPA to immediately exhibit a fluorescent response. The dual-mode sensor operates linearly within the ranges of 0.1–200 μmol/L (PEC) and 0–350 μmol/L (FL), with detection limits of 0.0269 μmol/L and 0.0384 μmol/L, respectively [73].

Crohn's disease (CD) and ulcerative colitis (UC) are the two principal forms of inflammatory bowel disease (IBD), a chronic disorder with an unknown origin. Liu et al. constructed a photoelectrochemical-surface-enhanced Raman scattering (PEC-SERS) dual-mode sensing platform for detecting IBD-associated biomarkers: matrix metalloproteinase-9 (MMP-9) and intestinal alkaline phosphatase (IAP). First, MMP-9 is detected through an aptamer-based amplification strategy. The presence of IAP subsequently triggers the trans-cleavage activity of CRISPR-Cas12a (Clustered Regularly Interspaced Short Palindromic Repeats - CRISPR Associated Protein 12a) is activated. The resulting Cas12a specifically cleaves electrode-immobilized single-stranded DNA (ssDNA), triggering signal release and enabling simultaneous detection of both targets. The detection limits for MMP-9 were 0.074 pg/mL (PEC) and 0.016 pg/mL (SERS), respectively, while those for IAP were 0.38 pg/mL (PEC) and 0.16 pg/mL (SERS), respectively. Both demonstrated broad linear ranges [74] (Figure 9).

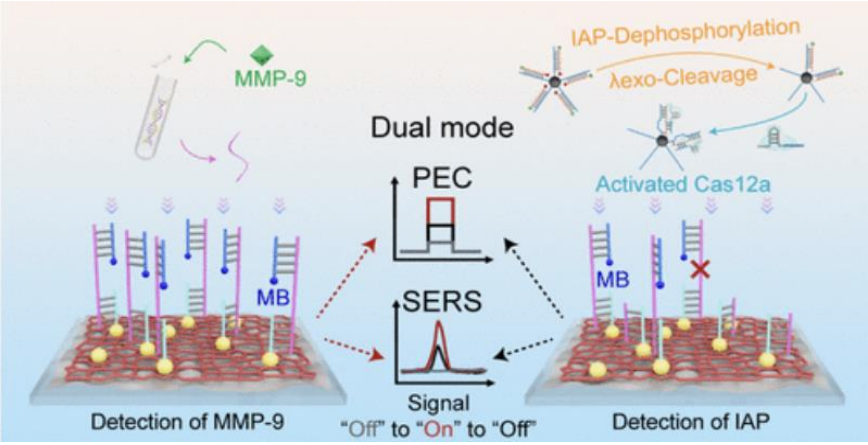

Figure 9. Schematic diagram illustrating the working principle of a dual-mode (PEC-SERS) biosensor for simultaneous detection of IBD biomarkers MMP-9 and IAP. [74].

4.4. Detection of pathogens and antigens of infectious diseases

Infectious diseases are a continual source of risk for the global community due to their high transmission rates, morbidity, and potential for widespread outbreaks. Rapid and accurate diagnosis is thus essential. PEC biosensors offer a reliable approach for detecting pathogens and their associated antigens with high sensitivity and specificity.

During the COVID-19 pandemic, detection of SARS-CoV-2 antigens became a priority. Key antigens of SARS-CoV-2 include the nucleocapsid protein (N protein) and the spike protein (S protein). Jiang et al. developed a two-dimensional MOF-based PEC sensor for the detection of the S protein. The plasmon-enhanced system exhibited high electron–hole separation efficiency, and specific DNA aptamers ensured strong binding affinity. Upon binding to the S protein, the photocurrent decreases due to high steric hindrance and low electrical conductivity. The linear range spans 0.5–8 μg/mL, with a detection limit of 72 ng/mL, demonstrating high sensitivity [75].

Acquired Immunodeficiency Syndrome (AIDS) is a life-threatening condition resulting from infection with the Human Immunodeficiency Virus (HIV). HIV attacks and destroys the human

immune system, leading to death from infections or malignant tumors. Xu et al. synthesized a Cu-MOF@CuPc-TA-COF (Copper Phthalocyanine - Terephthalaldehyde - Covalent Organic Framework) heterostructure via Schiff base condensation reactions. The heterostructure provided large surface area, abundant amino groups, and superior photoactivity, enabling efficient immobilization of HIV-1 DNA probes. Consequently, it provides a sensitive interface for the stable attachment of HIV-1 DNA probes and acts as a signal transducer between PEC and EC sensors. The probe exhibits highly selective hybridization with target DNA, with a detection range spanning 1 fM to 1 nM. The detection limits are 0.07 fM (PEC) and 0.18 fM (EC), respectively, the system demonstrated excellent reproducibility and reusability [76].

5. Conclusion and Outlook

PEC sensing has emerged as a promising platform that integrates optical excitation, electrochemical transduction, and biomolecular recognition for highly sensitive disease biomarker detection. Advances in photoactive material design—particularly narrow-bandgap semiconductors and heterostructure engineering—along with improved signal amplification and device integration, have greatly enhanced detection performance. These developments have enabled PEC biosensors to play an increasingly important role in cancer diagnosis, cardiovascular monitoring, inflammatory analysis, and infectious disease detection, highlighting their potential for precision medicine and early clinical screening.

Despite remarkable progress, several challenges still impede practical translation. The instability of photoactive materials under ambient conditions, non-specific adsorption in complex biological matrices, and signal interference during multiplexed analysis remain key limitations. Moreover, variations in nanomaterial synthesis and device fabrication often lead to poor reproducibility and restrict large-scale manufacturing.

Future efforts should focus on developing more stable and efficient photoactive systems—such as Z-scheme or type-II heterojunctions with optimized band alignment—to improve charge separation and long-term performance. Surface engineering strategies that minimize non-specific interactions, combined with artificial intelligence–assisted data processing, will enhance analytical accuracy and robustness. Integrating PEC with complementary techniques such as fluorescence or Raman spectroscopy can enable multimodal analysis, further reducing false responses. Meanwhile, miniaturization, wearable integration, and self-powered operation will accelerate the implementation of POCT and remote health monitoring.

In summary, PEC biosensors hold great promise as next-generation diagnostic tools. Continued innovation in material design, signal processing, and device engineering—together with progress in standardization and mass production—will bridge the gap between their experimental research and practical clinical use, ultimately advancing precision diagnostics and personalized healthcare.

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