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Article

Quantum dot-based electrochemical sensors for early detection and monitoring of blood cancer

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Abstract: Recent advancements in quantum dot (QD)-based electrochemical sensors have shown significant promise for the early detection and monitoring of blood cancers, such as leukemia and lymphoma. QDs, with their unique optical properties, high surface area, and tunable fluorescence, offer highly sensitive and specific detection of cancer biomarkers, enabling rapid, real-time diagnostics. These sensors are capable of multiplexed detection, allowing for the simultaneous identification of multiple biomarkers or circulating tumor cells (CTCs), crucial for early diagnosis and monitoring minimal residual disease (MRD). Despite their potential, challenges remain, including concerns over biocompatibility, toxicity, and the need for regulatory approval. Future research is focused on addressing these issues by developing non-toxic, biocompatible QDs, optimizing sensor performance, and integrating these technologies into point-of-care devices. Additionally, the combination of electrochemical and optical sensing techniques, along with advancements in surface modification and signal enhancement, holds promise for further improving the sensitivity, reliability, and clinical applicability of QD-based sensors. As research progresses, QD-based electrochemical sensors are poised to become a powerful tool for non-invasive, early-stage blood cancer detection and personalized treatment monitoring.

Keywords: quantum dots; electrochemical sensors; blood cancer; leukemia; lymphoma; cancer biomarkers; circulating tumor cells (CTCs); minimal residual disease (MRD)

1. Introduction

The early detection and precise monitoring of blood cancers, such as leukemia and lymphoma, are critical for improving patient outcomes and enabling timely interventions. Traditional diagnostic methods, such as biopsies and imaging, often require invasive procedures, lengthy waiting times, and complex interpretation of results. Consequently, there is a growing demand for non-invasive, rapid, and highly sensitive diagnostic tools that can detect blood cancers at their earliest stages and allow for continuous monitoring of disease progression and treatment response. In this context, electrochemical sensors, particularly those incorporating quantum dots (QDs), have emerged as a promising technology for revolutionizing cancer diagnostics [1–3]. Electrochemical methods and detection mechanisms of blood cancer cells using QDs-modified electrodes are explored in **Figure 1**.

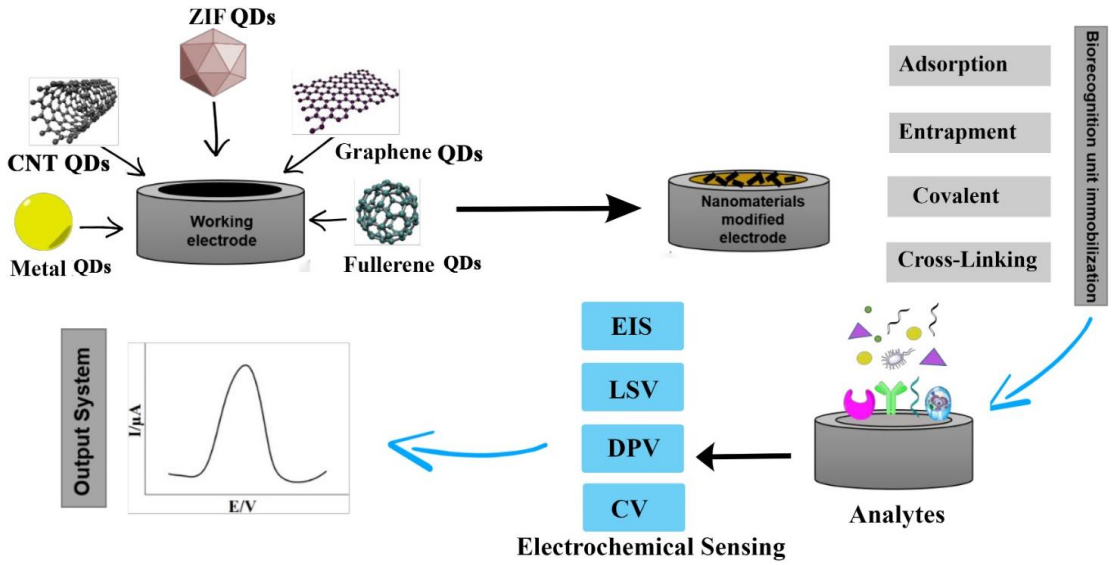

Figure 1. Electrochemical methods and detection mechanism of blood cancer cells using QDs-modified electrodes.

Quantum dots are semiconductor nanoparticles that exhibit unique optical properties due to quantum confinement effects. These properties include size-tunable fluorescence, high surface area, and robust chemical stability, which make them ideal candidates for biosensing applications [4,5]. QDs can be functionalized with a wide variety of biomolecules, such as antibodies, aptamers, or DNA, to enable selective binding to cancer biomarkers or abnormal cells, which is essential for detecting specific diseases like blood cancers. The ability to fine-tune QD fluorescence to different wavelengths also enables multiplexed detection of multiple biomarkers in a single assay, a critical advantage in complex diagnostic applications. Recent advancements have highlighted the potential of QD-based electrochemical sensors for blood cancer detection. Researchers have developed highly sensitive sensors capable of detecting minute quantities of cancer biomarkers, such as cell surface proteins (e.g., CD34, CD45, CD19, CD20) [6] or circulating tumor cells (CTCs) [7–9], that are often present at low concentrations in the bloodstream, even in the earliest stages of cancer. These sensors rely on the electrochemical properties of quantum dots [10,11] and the interactions between functionalized QDs and cancer-related molecules, resulting in detectable changes in current, impedance, or potential. Moreover, the integration of electrochemical detection with QD-based platforms offers several advantages, including rapid results, ease of use, low cost, and potential for point-of-care applications.

However, despite the significant progress made in the field, there are still several challenges that need to be addressed for the widespread adoption of QD-based electrochemical sensors in clinical settings [12,13]. One of the primary concerns is the toxicity and biocompatibility of quantum dots, especially those made from heavy metals such as cadmium [14,15]. Although non-toxic alternatives, such as carbon-based or silica-coated quantum dots [16,17], are being explored, further research is needed to ensure their safety for use in humans. In addition, the regulatory approval of such biosensors remains a critical hurdle, as medical devices must meet rigorous standards for safety and efficacy. Furthermore, optimizing the sensitivity and selectivity of these sensors for complex blood samples and reducing signal

interference from other components of the blood remain significant challenges. The future direction of quantum dot-based electrochemical sensors for blood cancer detection is focused on addressing these challenges while enhancing the overall performance of the sensors. Research efforts are increasingly directed towards developing non-toxic, biocompatible quantum dots that retain the desirable optical and electrochemical properties of their toxic counterparts. This includes the use of biodegradable materials, carbon quantum dots, and silica-based quantum dots, which offer a safer alternative without compromising the sensor's performance. Additionally, the development of more sophisticated surface functionalization strategies will enable more efficient binding to cancer biomarkers and improve the specificity of the sensors. Another promising area of research is the integration of quantum dot-based sensors with other technologies, such as microfluidics, to create portable, lab-on-a-chip devices for point-of-care diagnostics [18,19]. These systems would allow for the real-time detection of cancer biomarkers directly from patient samples, facilitating faster clinical decision-making and personalized treatment. Moreover, the use of artificial intelligence (AI) and machine learning algorithms to analyze sensor data [20,21] could further improve the accuracy of diagnoses and provide actionable insights based on biomarker patterns or minimal residual disease (MRD) levels [22–25].

Therefore, quantum dot-based electrochemical sensors represent a highly promising platform for the early detection and monitoring of blood cancers. As the field progresses, the focus will shift towards improving sensor performance, ensuring biocompatibility [26–29], and integrating these systems into practical, portable diagnostic tools. By overcoming existing challenges, QD-based biosensors have the potential to transform cancer diagnostics, offering non-invasive, rapid, and highly sensitive methods for detecting blood cancer at its earliest stages and monitoring treatment efficacy [30].

Hence, it introduces the unique properties of quantum dots (QDs) that make them ideal for biosensing, particularly in blood cancer detection. It outlines the design and function of QD-based electrochemical sensors, and key challenges such as toxicity, selectivity, and clinical application are also discussed.

2. Recent advancements in quantum dot electrochemical sensors for blood cancer cell detection

Blood cancers, including leukemia, lymphoma, and myeloma, pose significant diagnostic challenges, as they often lack clear, detectable physical signs in early stages. Early detection of blood cancer cells is crucial for effective treatment and improving patient prognosis. **Table 1** emphasizes the critical impact of early diagnosis on patient survival, illustrating improved long-term outcomes when blood cancers are detected at an initial stage versus an advanced stage. Recent advancements in quantum dot (QD)-based electrochemical sensors for blood cancer cell detection have shown great promise in improving the sensitivity, selectivity, and speed of diagnosis [31,32]. By integrating the unique properties of QDs with electrochemical detection techniques, researchers have made significant strides in developing sensitive, rapid, and cost-effective tools for the detection of blood cancer cells and biomarkers [33,34].

Table 1. 5-year survival rate comparison between early and late-stage blood cancer diagnoses.

Cancer Type	Stage 1 Survival Rate	Stage 2 Survival Rate	Stage 3 Survival Rate	Stage 4 Survival Rate	Late-Stage Detection Survival	References
CLL	~95% (Rai Stage 0)	~82% (Rai Stage I–II)	~64% (Rai Stage III–IV)	~64% (Rai Stage III–IV)	~64% (Rai Stage III–IV)	[35]
CML	>90% (Chronic Phase)	>90% (Chronic Phase)	~70% (Accelerated Phase)	~50–70% (Blast Crisis)	~50–70% (Blast Crisis)	[36]
ALL	90–95% (Children, Early)	80–85% (Adults, Early)	~40% (Adults, Late)	~40% (Adults, Late)	~40% (Adults, Late)	[37]
AML	~60–70% (Under 45)	~60–70% (Under 45)	~30–40% (Over 65)	~2–5% (Over 65, Late)	~2–5% (Over 65, Late)	[38]
HL	~95% (Stage I)	~90% (Stage II)	~85% (Stage III)	~85% (Stage IV)	~85% (Stage IV)	[39]
NHL	~82.3% (Localized)	~82.3% (Localized)	~74% (Regional)	~62.7% (Distant)	~62.7% (Distant)	[40]
MM	~76% (Smoldering)	~76% (Smoldering)	~52% (Stage III)	~52% (Stage III)	~52% (Stage III)	[41]

** Chronic Lymphocytic Leukemia (CLL),* * Chronic Myeloid Leukemia (CML), ** Acute Lymphocytic Leukemia (ALL), * Acute Myeloid Leukemia (AML), * Hodgkin Lymphoma (HL), * Non-Hodgkin Lymphoma (NHL), * Multiple Myeloma (MM).*

2.1. Quantum dots and electrochemical sensors for blood cancer detection

Quantum dots are semiconductor nanocrystals with distinctive optical and electrical properties, such as size-tunable fluorescence and high surface area, making them ideal candidates for sensor applications. Their ability to conjugate with various biological molecules, such as antibodies, aptamers, or peptides, enables the development of highly specific and sensitive sensors for detecting blood cancer biomarkers and cells [42–44]. In electrochemical sensors, QDs serve as signal transducers [45,46]. When cancer cells or tumor markers bind to a sensor's surface, the QDs undergo changes that affect the electrochemical response, such as shifts in current, impedance, or voltage [47,48]. This change is directly related to the amount of cancer cells or biomarkers present in the sample, allowing for quantitative analysis.

2.2. Integration of quantum dots with nanomaterials

Nanomaterials, including graphene, gold nanoparticles (AuNPs), and carbon nanotubes (CNTs), are increasingly being incorporated into QD electrochemical sensors to improve their sensitivity, selectivity, and signal amplification. This synergy enhances the electrochemical response, enabling the detection of blood cancer biomarkers or cancer cells at very low concentrations [49,50]. They enable rapid analysis, providing results significantly faster than conventional diagnostic methods. Additionally, these sensors are cost-effective, making them suitable for large-scale cancer screening applications, as shown in **Table 2.**

Table 2. Evaluation of QD electrochemical sensors against established detection techniques.

Detection Method	Sensitivity (%)	Specificity (%)	Test Duration	Approx. Cost	References
QD Electrochemical Sensor	95–99	95–98	30–60 min	$10–$50	[51]
Microarray Analysis	97.47	98.1	1–2 days	$300–$600	[52]

(i) *Gold Nanoparticles (AuNPs)*: When coupled with QDs, gold nanoparticles significantly enhance electron transfer and electrochemical signals, resulting in more sensitive detection of cancer biomarkers [53,54]. Gold nanoparticles also enable direct electron transfer between redox proteins and electrode surfaces, eliminating the need for external mediators in electrochemical sensing. Their properties, such as a large surface-to-volume ratio, elevated surface energy, reduced distance between metal particles and proteins, and their role as conductive bridges between prosthetic groups and the electrode, are key factors that enhance electron transfer efficiency in such systems [55]. The combination of QDs and AuNPs increases the surface area available for functionalization with cancer-specific antibodies or aptamers, improving the sensor's ability to capture circulating tumor cells (CTCs) or blood cancer biomarkers [56,57].

(ii) *Graphene*: The high electrical conductivity and biocompatibility of graphene make it an ideal material to integrate with QDs for electrochemical biosensing [58,59]. Graphene-QD hybrid sensors exhibit improved charge transfer efficiency, resulting in faster and more sensitive detection. These sensors are particularly useful for detecting specific surface markers on blood cancer cells, such as CD19 or CD33, which are associated with leukemia and lymphoma [60,61]. Graphene–quantum dot (QD) hybrid sensors exhibit enhanced charge transfer efficiency due to the synergistic interaction between the excellent electrical conductivity of graphene and the unique optoelectronic properties of QDs. Graphene serves as a highly conductive platform that facilitates rapid electron transport, while QDs generate electron-hole pairs upon stimulation. When QDs are integrated with graphene, the excited electrons from the QDs can quickly transfer to the graphene layer, effectively reducing electron-hole recombination. This efficient charge separation and transfer mechanism leads to faster response times and heightened sensitivity. Additionally, the large surface area of graphene provides ample binding sites for target molecules, further improving detection performance. The improved electron transfer can be explained by electrochemical theories involving energy band alignment, electron tunneling, and Schottky junction formation between the QDs and graphene, which together create favorable conditions for signal enhancement in biosensing applications [62,63].

(iii) *Carbon Nanotubes (CNTs)*: CNTs enhance the electrochemical properties of QD sensors by providing large surface areas and high conductivity. The integration of CNTs with QDs creates highly sensitive sensors for detecting blood cancer biomarkers, improving both signal strength and selectivity. Additionally, CNTs help in the stable immobilization of cancer-related biomarkers on the sensor surface, which is crucial for reliable detection [64,65]. Integrating carbon nanotubes (CNTs) with quantum dots (QDs) creates highly sensitive sensors for blood cancer biomarkers by leveraging the complementary properties of both materials. CNTs offer excellent electrical conductivity and a large surface area, enabling rapid electron transport and high-density loading of sensing molecules. QDs contribute tunable optical and electronic properties, allowing precise detection through fluorescence or electrochemical signals. When combined, QDs can transfer excited electrons to CNTs, enhancing signal strength by minimizing electron–hole recombination. This synergy results in improved sensitivity, while functionalization of CNT surfaces with specific ligands ensures selective detection of biomarkers like CD19 or CD33, enabling

accurate and early diagnosis of blood cancers [66,67]. Various QDs were used to modify the working electrode of the sensor for the detection of blood cancer cells, as shown in **Figure 2**.

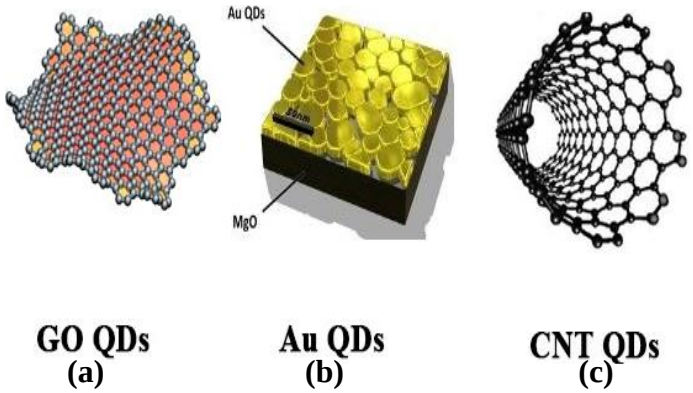

Figure 2. Various QDs used to modify the working electrode of the sensor for the detection of blood cancer cells. Here are **(a)** GO (graphene oxide) QDs, **(b)** Au (gold) QDs, and **(c)** CNT (carbon nanotube) QDs.

2.3. Multiplexed detection of blood cancer biomarkers

The simultaneous detection of multiple biomarkers, also known as multiplexing, is a significant advancement in QD electrochemical sensors. For blood cancers, multiple biomarkers may need to be detected to identify the cancer type, monitor disease progression, or assess therapeutic efficacy. Quantum dots are well-suited for multiplexed biosensing due to their ability to emit at different wavelengths depending on their size, allowing for the detection of several biomarkers in one sample [68,69].

(i) *Quantum Dots with Tunable Emission*: QDs can be synthesized in different sizes to emit at specific wavelengths, making them ideal for detecting multiple cancer biomarkers simultaneously. In the case of blood cancers, sensors can detect a range of biomarkers (e.g., CD19, CD33, CD34, CD45, and CD47) associated with leukemia, lymphoma, or myeloma cells. This enables a comprehensive view of cancer progression or remission, enhancing personalized treatment [70]. In QD-based multiplexed blood cancer detection, signals are distinguished primarily through the size-dependent and narrow emission spectra of quantum dots (QDs). Each QD can be engineered to emit light at a specific wavelength when excited by a common light source, allowing simultaneous detection of multiple biomarkers. For example, QDs linked to different antibodies can target distinct cancer markers like CD19 or CD33, and their emissions can be separated based on wavelength using fluorescence spectroscopy. To further improve resolution and avoid spectral overlap, advanced techniques such as spectral unmixing, time-gated detection, and fluorescence lifetime imaging (FLIM) may be applied. These strategies ensure accurate identification of each target, making QD-based sensors highly effective for multiplexed diagnostics in blood cancers [71,72].

(ii) *Fluorescence and Electrochemical Dual-Mode Detection*: The combination of fluorescence and electrochemical detection methods, often referred to as a dual-mode sensing approach, significantly enhances both the sensitivity and accuracy of blood cancer diagnostics. Fluorescent quantum dots (QDs) play a crucial role by

enabling real-time visualization of molecular interactions, such as the binding of antibodies or aptamers to specific cancer cell surface markers like CD19 or CD33. Due to their high brightness, photostability, and tunable emission spectra, QDs provide clear and multiplexed optical signals that allow for the qualitative or semi-quantitative monitoring of target binding events. Simultaneously, the electrochemical component of the sensor offers precise quantitative analysis by measuring electrical changes such as current, voltage, or impedance that occur upon target recognition. These changes are directly correlated with the concentration of the analyte, enabling accurate quantification of cancer cells or biomarkers present in the sample. By integrating both detection modes into a single platform, the dual-mode sensor compensates for the limitations of each individual method. Fluorescence detection ensures specificity and allows spatial tracking, while electrochemical readouts provide numerical accuracy, low detection limits, and rapid response times. This synergy improves overall diagnostic reliability, reduces false positives or negatives, and supports early detection and monitoring of blood cancers, ultimately enhancing clinical decision-making. Rewrite it shortly [73,74]. **Figure 3** represented a schematic for dual mode detection of cancer biomarkers.

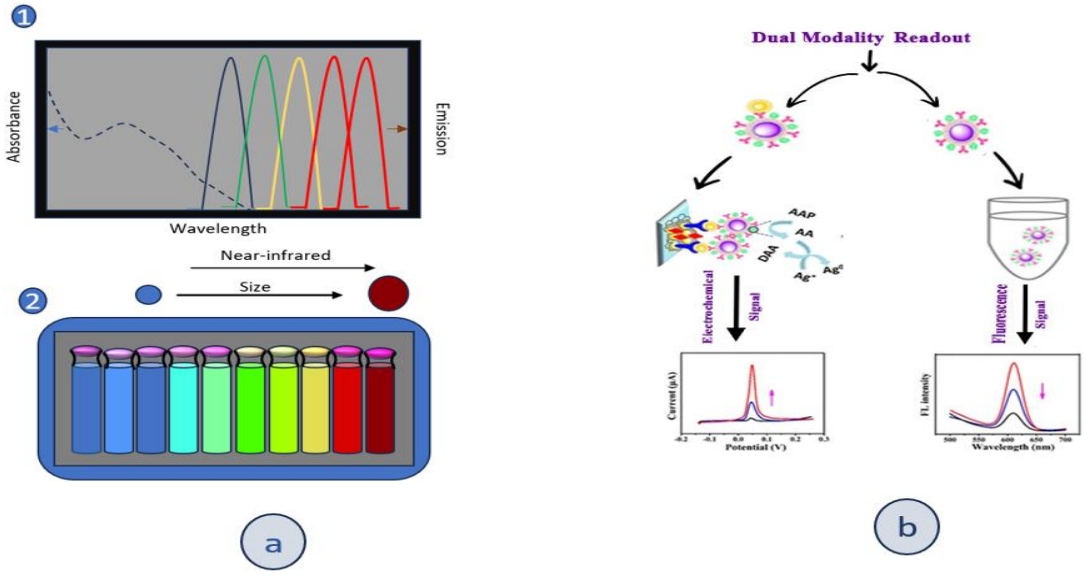

Figure 3. Fluorescence and electrochemical dual-mode detection of cancer cells.

2.4. Signal amplification for low concentration detection

The ability to detect blood cancer cells or biomarkers at extremely low concentrations is one of the most valuable features of quantum dot (QD) electrochemical sensors, making them highly suitable for early diagnosis and monitoring of hematological malignancies. Early-stage cancers often release only minute amounts of biomarkers into the bloodstream, making their detection challenging with conventional techniques. QD electrochemical sensors address this by combining the high surface area and excellent electrical conductivity of nanomaterials with the unique optoelectronic properties of QDs, allowing for enhanced signal generation and sensitivity. Recent research has focused on improving signal amplification strategies to push detection limits even further. These include enzyme-

assisted amplification, where enzymes catalyze reactions that produce electroactive species, and redox cycling, which recycles electrochemical signals to amplify response. Additionally, nanomaterial-based amplification such as incorporating gold nanoparticles, carbon nanotubes, or graphene—further enhances electron transfer and signal strength. Quantum dots themselves can also act as redox-active labels or electron donors/acceptors, increasing the electrochemical signal output upon target binding. Together, these advancements allow QD electrochemical sensors to detect cancer biomarkers like CD19, CD33, or circulating tumor DNA (ctDNA) at trace levels, often in the femtomolar or even attomolar range. This heightened sensitivity enables clinicians to identify malignancies earlier, monitor minimal residual disease, and assess treatment responses with greater precision, ultimately contributing to improved patient outcomes [75,76].

(i) *Enzyme-Mediated Signal Amplification*: Enzymes such as horseradish peroxidase (HRP) and alkaline phosphatase (AP) are commonly employed to enhance the performance of QD-based electrochemical sensors, particularly in the detection of low-abundance cancer biomarkers. These enzymes serve as catalytic labels that amplify the electrochemical signal through specific reactions upon target binding. When a biomarker such as CD19 or CD33 binds to a QD-functionalized electrode surface, the attached enzyme catalyzes a redox reaction involving a suitable substrate. For example, HRP can catalyze the oxidation of hydrogen peroxide in the presence of electron mediators, generating a measurable current that is directly proportional to the concentration of the target molecule. This enzymatic reaction acts as a signal amplification step, converting a single binding event into multiple detectable electrochemical signals. As a result, even trace amounts of cancer cells or biomarkers in blood samples can be identified with high sensitivity. Furthermore, because QDs can be engineered to carry multiple enzyme molecules or bind to multiple targets, they contribute to an even greater amplification effect. This strategy not only lowers the detection limit often reaching the picomolar to femtomolar range but also enhances the signal-to-noise ratio, improving overall diagnostic accuracy. Incorporating enzyme-mediated amplification into QD-based sensors has proven to be a powerful method for enabling early-stage blood cancer detection and monitoring minimal residual disease [77,78].

(ii) *Polymerization Amplification*: Another effective signal amplification strategy in QD-based electrochemical sensors is the use of polymerization of conductive polymers, such as polyaniline (PANI), polypyrrole (PPy), or polythiophene. In this approach, the presence of a target cancer biomarker initiates a catalytic or enzyme-mediated polymerization reaction on the sensor surface. This reaction results in the localized growth of a conductive polymer layer, which significantly increases the electrochemical signal. When a biomarker binds to the QD-functionalized surface, often via a biorecognition element like an antibody or aptamer, it can trigger the release or activation of a polymerization initiator or enzyme (e.g., HRP). This, in turn, catalyzes the in-situ formation of a conductive polymer. The growing polymer network increases the effective surface area and conductivity of the electrode, facilitating greater electron transfer and amplifying the electrochemical response. The magnitude of the current generated is proportional to the amount of polymer formed, which is, in turn, directly linked to the concentration of the target biomarker. This

polymerization-based amplification offers several advantages: it enables ultrasensitive detection, enhances signal stability, and provides a visual cue in some cases due to color changes in the polymer. Moreover, this method can be easily integrated with QDs, which act as both carriers for biorecognition elements and facilitators of electron transfer. Overall, polymerization-based amplification is a powerful technique for improving the sensitivity of electrochemical sensors, making it possible to detect extremely low levels of blood cancer biomarkers with high accuracy [79,80]. The polymerization signal amplification method to detect cancer biomarkers is given in **Figure 4**.

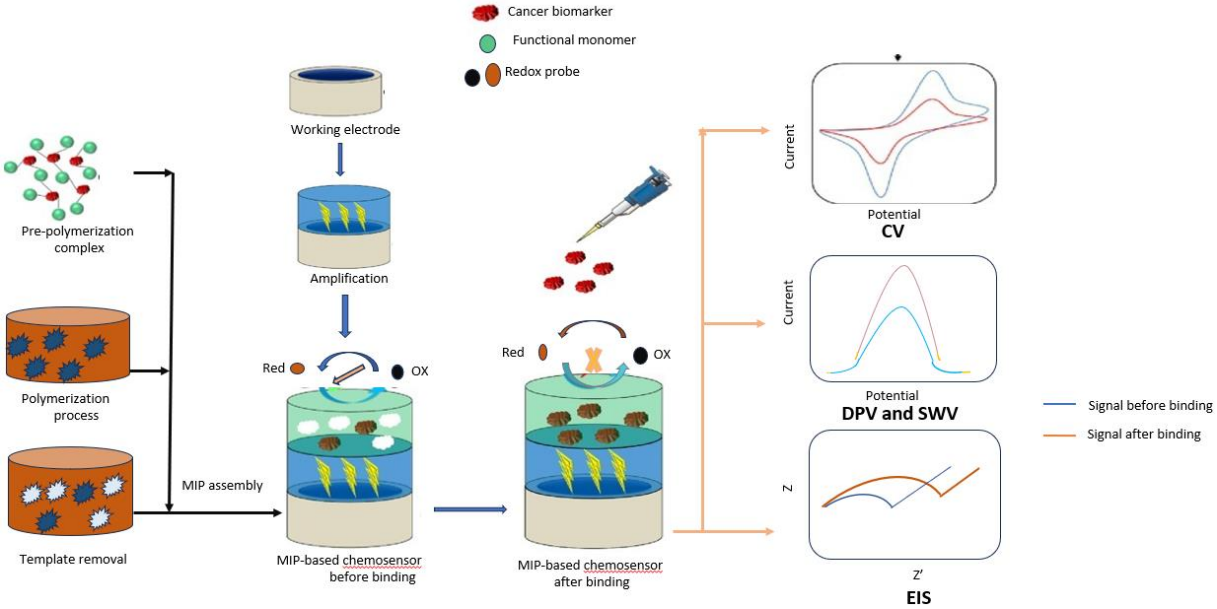

Figure 4. Polymerization signal amplification method to detect cancer biomarker.

(iii) *Magnetic Nanoparticles for Signal Enhancement*: Magnetic nanoparticles are sometimes incorporated into QD electrochemical sensors for enhanced target capture and signal amplification. The magnetic nanoparticles concentrate the target cancer cells at the sensor surface, increasing the efficiency of the sensor and providing a higher signal output. This approach is particularly useful for detecting circulating tumor cells (CTCs) in blood samples, as it allows for the efficient isolation and capture of rare cells from complex biological matrices [81,82].

2.5. Microfluidic integration and point-of-care applications

The integration of QD electrochemical sensors with microfluidics is a significant advancement that facilitates point-of-care (POC) diagnostics. Microfluidic devices allow for the manipulation of small sample volumes and can process samples quickly, making them ideal for on-site cancer diagnostics, especially in resource-limited settings.

(i) *Microfluidic Chips*: QD-based electrochemical sensors integrated with microfluidic chips offer significant improvements in the precision, efficiency, and speed of blood cancer detection. Microfluidic chips allow for precise control over sample volume, flow rate, and reaction time, enabling optimized manipulation of small blood samples. When coupled with QDs, these platforms can efficiently isolate and

concentrate circulating tumor cells (CTCs) from blood, enhancing the sensor's ability to detect low-abundance cancer biomarkers. The microfluidic system's design enables selective isolation of CTCs based on specific properties like size or surface markers, enriching the sample with cancer cells of interest and improving detection sensitivity. The QDs, functionalized with biomarker-specific recognition elements, facilitate real-time detection of these target cells through fluorescence or electrochemical signals, providing fast and accurate results. This integration also supports real-time monitoring of disease progression, as clinicians can track changes in the concentration of CTCs or biomarkers over time. This continuous monitoring allows for more effective disease management, early detection of relapse, and personalized treatment adjustments. Overall, the combination of QD sensors and microfluidic chips represents a powerful tool for fast, sensitive, and reliable blood cancer detection and ongoing monitoring [83,84]. A schematic of a microfluidic biosensor is given in **Figure 5**.

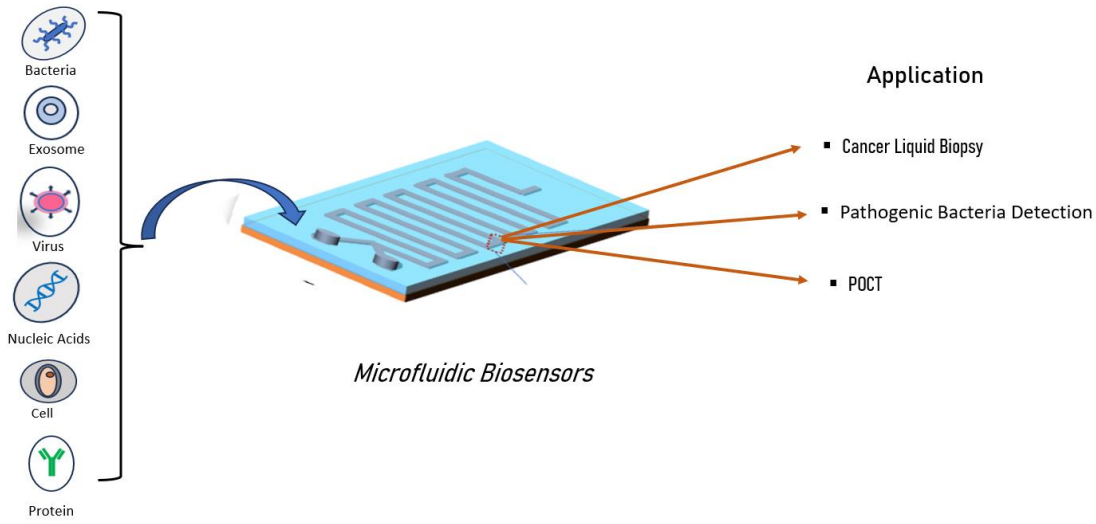

Figure 5. Cancer liquid biopsy using microfluidic chips.

(ii) *Portable Devices*: With the development of portable, handheld devices, QD electrochemical sensors are now enabling cancer detection at the point of care (POC). These compact, easy-to-use devices offer a non-invasive and cost-effective solution for early cancer diagnosis. By detecting specific cancer biomarkers in blood or saliva with high sensitivity, these devices eliminate the need for complex laboratory equipment and specialized staff. This advancement allows for faster cancer detection, crucial for early-stage diagnosis where timely treatment can improve outcomes. Additionally, the affordability and portability of these devices make them ideal for routine screenings, increasing access to early detection, particularly in areas with limited healthcare resources. These devices are also valuable for monitoring cancer patients during chemotherapy. They enable frequent, real-time tracking of biomarker levels, providing immediate feedback on treatment effectiveness and allowing adjustments to therapy as needed. This reduces the need for hospital visits, offering patients a more convenient and less disruptive way to manage their treatment. In summary, integrating QD electrochemical sensors into portable devices makes cancer detection and monitoring more accessible, affordable, and efficient, improving early diagnosis and enhancing ongoing care for cancer patients [85,86].

2.6. Biocompatibility and safety considerations

Given the use of QDs in biological systems, biocompatibility and toxicity remain crucial concerns. Traditional QDs, such as cadmium-based QDs, have raised safety issues due to their potential toxicity. Recent advancements in the development of biocompatible QDs, such as carbon quantum dots (CQDs) and silica-coated QDs, have addressed these concerns by reducing the toxicological risks while retaining the optical and electrochemical properties necessary for biosensing applications.

(i) *Carbon Quantum Dots (CQDs)*: CQDs are carbon-based nanomaterials that are less toxic and more biocompatible than traditional QDs. Their photostability, high surface area, and easy functionalization make them ideal candidates for blood cancer detection [87–89]. They are also more easily biodegradable in vivo, reducing long-term toxicity risks. **Figure 6** illustrates carbon and silica-coated QDs for cancer biomarker detection.

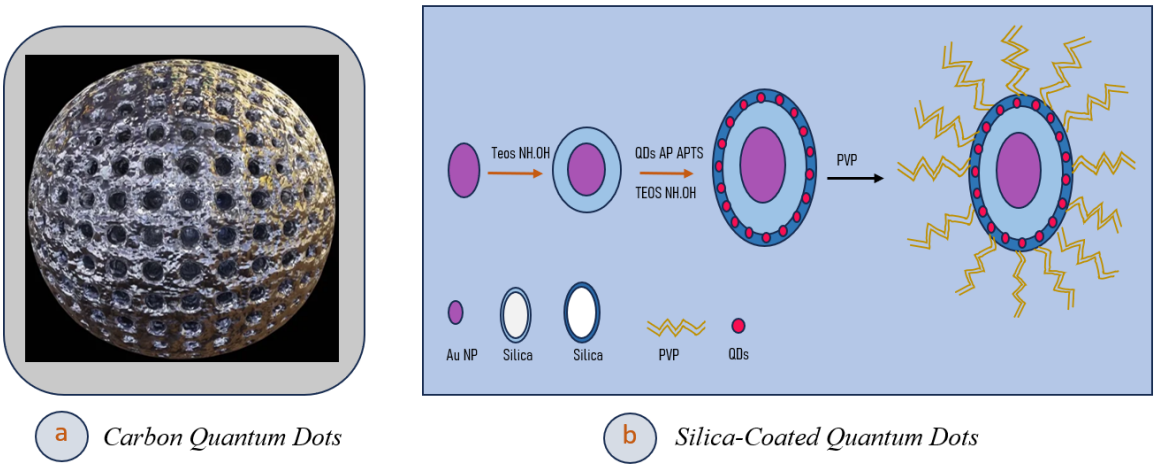

Figure 6. Carbon and silica-coated QDs for cancer biomarker detection.

(ii) *Silica-Coated Quantum Dots*: Silica coatings on traditional QDs help mitigate the release of toxic substances into the body, enhancing the biocompatibility of the sensor. This approach improves the safety profile of QD-based electrochemical sensors, making them more suitable for clinical applications. The type of QDs and corresponding biosensor parameters in terms of limit of detection (LOD) and linear dynamic detection range (LDR) given are given in **Table 3**.

Table 3. Type of QDs and corresponding biosensor parameters.

Type of QDs	LOD	LDR	Reference
CdSe/ZnS QDs	0.1 nM	0.1~100 nM	[90]
GO QDs	5:00 PM	0.005~50 nM	[91]
CQDs	2.3 nM	2.3~150 nM	[92]
InP/ZnS QDs	1.2 nM	1~100 nM	[93]
AgInS2 QDs	10 nM	10~200 nM	[94]
ZnO QDs	0.5 nM	0.5~75 nM	[95]
Perovskit QDs	3 nM	3~120 nM	[96]
Si QDs	8 nM	8~160 nM	[97]

3. Research directions to overcome challenges of quantum dot (QD) electrochemical sensors for cancer cell detection

Quantum dot (QD) electrochemical sensors have demonstrated tremendous potential for cancer cell detection due to their unique optical and electronic properties. However, there are several challenges that need to be overcome to fully realize their potential for clinical applications. These challenges include issues related to biocompatibility, sensitivity, selectivity, signal transduction, stability, and integration into practical, cost-effective devices. Here are key research directions aimed at addressing these challenges:

3.1. Enhancing biocompatibility and reducing toxicity

QD-based sensors often face concerns regarding their potential toxicity and biocompatibility, especially when used in clinical applications such as in vivo cancer detection. The inorganic nature of traditional QDs (such as cadmium-based QDs) can lead to leaching of toxic materials into the body, which could pose health risks.

Research directions:

(i) *Surface passivation*: Surface modification is one of the most effective strategies for reducing the toxicity of quantum dots (QDs), as it involves coating the QD surface with biocompatible materials such as silica, polyethylene glycol (PEG), or polymers to prevent the release of toxic metal ions and enhance stability in biological environments. However, this approach presents several technical challenges. Achieving uniform, stable coatings at the nanoscale is complex, and incomplete coverage can lead to ion leakage and reduced biocompatibility. Additionally, coatings must maintain the QDs' optical and electrochemical properties, as poorly designed layers can quench fluorescence or hinder signal transduction. Functionalization is another challenge, as adding targeting ligands without compromising the coating's integrity requires precise surface chemistry. Scalability and reproducibility remain obstacles as well, with batch-to-batch variation affecting consistency in large-scale production. Furthermore, the long-term biodegradability and clearance of coated QDs are not yet fully understood, raising concerns about potential accumulation in the body. Addressing these challenges is critical for advancing the safe and effective use of QDs in biomedical applications.

(ii) *Environmentally friendly QDs*: The development of "greener" quantum dots (QDs) made from less toxic elements such as copper, zinc, indium, or silicon offers a promising alternative to traditional heavy metal-based QDs. These environmentally friendly QDs aim to retain key advantages such as strong fluorescence and tunable optical properties while significantly reducing the associated health and environmental risks. However, several technical challenges must be addressed to make them viable for practical use. One of the main issues is that greener QDs often have lower quantum yields, broader emission spectra, and reduced photostability compared to cadmium-based QDs, which can limit their sensitivity and reliability in imaging or sensing applications. Additionally, achieving efficient surface passivation is more difficult, leading to more surface defects that degrade optical performance. The synthesis of greener QDs also tends to be more complex and less reproducible, making it harder to control particle size and uniformity. Integration into existing sensor platforms can be

challenging due to differences in surface chemistry, requiring new functionalization strategies. Furthermore, many of these materials are still in the early stages of development, and scalable, cost-effective production methods are not yet fully established. Lastly, although considered safer, the long-term biocompatibility and clearance of these QDs in biological systems remain underexplored. Addressing these challenges is essential for realizing the full potential of greener QDs in biomedical and environmental applications.

3.2. Improving sensitivity and detection limits

While QD-based sensors are highly sensitive, detecting low-abundance cancer cells, particularly in complex biological samples like blood or urine, remains a challenge. Achieving high sensitivity at low concentrations is crucial for early cancer diagnosis.

Research directions:

(i) *Signal amplification*: Signal amplification is a widely used strategy to enhance the sensitivity of QD-based electrochemical sensors, particularly for detecting low concentrations of cancer biomarkers. Enzymatic amplification techniques involve using enzymes like horseradish peroxidase (HRP) or alkaline phosphatase (AP) to catalyze reactions that generate measurable electrochemical signals in response to biomarker binding. Similarly, nanomaterial-based strategies such as incorporating gold nanoparticles, graphene, or carbon nanotubes can boost signal strength by increasing the electrode's surface area, enhancing electron transfer, and facilitating more efficient biomolecular interactions. Despite their advantages, these amplification methods present several technical challenges. Enzymatic systems can suffer from limited stability, as enzymes are sensitive to changes in temperature, pH, and storage conditions, which can impact their catalytic activity. Immobilizing enzymes onto sensor surfaces without compromising their functionality requires precise control over surface chemistry, and any non-specific activity can introduce background noise, affecting signal accuracy. Nanomaterial-based amplification also faces hurdles, including the need for uniform and stable dispersion of nanomaterials on the electrode surface. Poor integration can lead to signal variability and reduced reproducibility. Additionally, interactions between nanomaterials and QDs must be carefully managed to avoid interference with fluorescence or electron transfer properties.

(ii) *Hybrid nanomaterials*: Combining quantum dots (QDs) with nanomaterials such as graphene oxide, carbon nanotubes (CNTs), or metal-organic frameworks (MOFs) is a promising strategy to enhance the performance of electrochemical sensors for cancer detection. These hybrid systems leverage the high surface area and excellent electrical conductivity of the nanomaterials along with the tunable optical and electronic properties of QDs. Together, they improve electron transfer efficiency, provide more binding sites for cancer biomarkers, and significantly boost the overall electrochemical signal. However, several technical challenges must be addressed to fully harness the potential of these hybrid materials. One key issue is achieving stable and uniform integration of QDs with the nanomaterial matrix. Differences in surface chemistry or charge can lead to aggregation or poor dispersion, reducing the effectiveness of the hybrid structure. Ensuring strong interfacial interactions without

compromising the photoluminescence of QDs or the conductivity of the nanomaterial is also a complex task. Another challenge lies in the reproducibility and scalability of the synthesis process. Producing these hybrid materials with consistent quality, morphology, and performance across batches remains difficult, which can impact the reliability of the final sensor. Functionalizing the hybrid surface with biological recognition elements—such as antibodies or aptamers—adds another layer of complexity, as it must be done without interfering with the material's electrochemical or optical behavior. Moreover, while these hybrids may enhance detection performance, their long-term biocompatibility and stability under physiological conditions must be carefully evaluated, especially for clinical applications. Factors such as degradation, potential toxicity, and interaction with biological systems need to be thoroughly understood.

(iii) *Integration with microfluidics*: Integrating quantum dot (QD) sensors with microfluidic devices offers a promising approach to enhance the sensitivity and precision of cancer detection. Microfluidics enables the manipulation of small sample volumes with high accuracy, reducing the need for large amounts of reagents and minimizing background interference. This level of control allows for the efficient handling of complex biological samples, such as blood or serum, and enhances the reliability of the detection process. A significant advantage of combining QD sensors with microfluidic platforms is their ability to isolate and concentrate rare cancer cells, such as circulating tumor cells (CTCs), from complex mixtures. The microfluidic channels can be tailored to selectively capture target cells based on physical properties like size or specific surface markers. By concentrating the analyte in this way, the signal-to-noise ratio is improved, enabling the QD sensors to generate clearer and more robust signals, even when the target is present in very low concentrations. Moreover, microfluidic systems can facilitate automation and multiplexing, allowing for the simultaneous detection of multiple biomarkers in a single sample. This, coupled with the high sensitivity and tunable fluorescence of QDs, enables faster, more accurate diagnostics, making it particularly beneficial for early cancer detection and ongoing monitoring. However, challenges remain, such as ensuring stable QD performance under continuous flow conditions and scaling up these systems for widespread clinical use.

3.3. Achieving high specificity for cancer cell detection

For clinical applications, it is essential that QD sensors specifically detect cancer cells without interference from healthy cells or other biomolecules. Non-specific binding can lead to false positives or false negatives, reducing the reliability of the sensors.

Research directions:

(i) *Surface functionalization*: The functionalization of QDs with specific targeting molecules, such as antibodies, aptamers, or peptides, is key to enhancing selectivity. These ligands should specifically bind to cancer cell surface biomarkers (e.g., HER2, EpCAM, or CD133). Ongoing research is focused on optimizing the functionalization process to ensure that only cancer cells or specific cancer markers are detected, even in complex samples.

(ii) *Multi-target sensing*: To further improve specificity, QD-based sensors can be designed to detect multiple biomarkers simultaneously. This multimodal approach allows for more accurate detection by reducing the likelihood of interference from other cell types. Researchers are exploring multiplexed QD sensors that can target a range of cancer-related biomarkers, improving diagnostic accuracy.

3.4. Enhancing stability and reproducibility

The stability of QDs in real-world biological samples is a critical challenge. QDs can undergo degradation or aggregation, leading to a decrease in sensor performance over time. This affects the long-term usability of QD-based sensors in cancer detection applications.

Research directions:

(i) *Stabilizing QD structures*: Researchers are developing strategies to improve the physical and chemical stability of QDs in biological environments. This includes the use of surface coatings or the development of core-shell QD structures that provide enhanced protection against degradation.

(ii) *Long-term reproducibility*: To ensure consistent performance over time, it is important to develop QD sensors that can withstand repeated use without significant loss of sensitivity. Developing highly reproducible sensor fabrication methods, along with improved calibration protocols, will be essential for maintaining performance across multiple detection cycles.

3.5. Developing cost-effective and scalable manufacturing techniques

Despite their potential, the cost of producing QD-based sensors can be prohibitive, particularly when scaling up for clinical or commercial use. The need for cost-effective and scalable manufacturing methods is crucial to making QD electrochemical sensors accessible and practical for widespread cancer diagnostics.

Research directions:

(i) *Green synthesis methods*: Traditional methods of QD synthesis can be expensive and environmentally damaging. Researchers are working on developing cost-effective, sustainable, and scalable synthesis methods for QDs, such as “green” synthesis techniques that use fewer toxic chemicals and simpler processes.

(ii) *Roll-to-roll fabrication*: For large-scale production, roll-to-roll (R2R) fabrication methods for integrating QDs into sensor platforms are being investigated. This technology would allow for the mass production of sensors with high uniformity and low cost, making it possible to manufacture QD electrochemical sensors on a large scale.

3.6. Integration with wearable and point-of-care devices

For QD-based sensors to be widely adopted in cancer diagnostics, they must be integrated into portable, user-friendly, and cost-effective devices that can be used in point-of-care (POC) settings.

Research directions:

(i) *Wearable platforms*: Researchers are exploring the integration of QD-based sensors with wearable devices that could monitor cancer markers in real time. Such

wearable sensors could continuously track cancer progression or treatment efficacy without the need for regular hospital visits.

(ii) *Portable detection devices*: Miniaturized electrochemical sensors, coupled with QD technology, could be embedded into portable diagnostic tools that enable in-field cancer cell detection. These devices would be particularly useful for low-resource settings, where access to sophisticated diagnostic equipment is limited.

3.7. Real-time monitoring and early detection

Real-time cancer cell detection is crucial for early-stage cancer diagnosis, as early intervention significantly improves treatment outcomes. QD-based electrochemical sensors must be optimized for rapid, real-time detection of cancer cells.

Research directions:

(i) *Real-time sensing systems*: Researchers are working on systems that enable continuous or real-time monitoring of cancer cells, especially using non-invasive methods like blood or saliva samples. These systems would require high-speed signal processing to provide instant results.

(ii) *In vivo sensing*: For more effective early detection, QD-based sensors could be integrated into in vivo sensing platforms that allow for the detection of cancer cells directly in the body. This would require the development of biocompatible, minimally invasive systems that can operate in complex biological environments without affecting the accuracy of detection.

4. Conclusion

In conclusion, quantum dot (QD)-based electrochemical sensors represent a promising frontier in the early detection and diagnosis of blood cancers. Their unique optical properties, high surface area, and versatility in surface functionalization make them highly effective for detecting low concentrations of cancer biomarkers and circulating tumor cells (CTCs). Despite their potential, several challenges remain, including improving sensitivity, enhancing specificity, ensuring biocompatibility, and overcoming issues related to reproducibility and clinical integration. Recent research has made significant strides in addressing these challenges by developing innovative strategies such as signal amplification techniques, the use of biocompatible QDs, and the integration of QDs with nanomaterials and microfluidic platforms. These advancements have improved the performance of QD electrochemical sensors, making them more sensitive, reliable, and applicable for real-world diagnostic use. Looking forward, overcoming the remaining barriers related to clinical translation, cost-effectiveness, and scalability will be key to unlocking the full potential of QD-based electrochemical sensors in cancer detection. With continued innovation in the areas of nanomaterial design, biosensor integration, and regulatory approval processes, QD-based sensors have the potential to revolutionize early cancer detection, offering a fast, non-invasive, and accurate alternative to current diagnostic methods. Ultimately, these advancements could lead to improved patient outcomes through more personalized and timely treatment strategies, ultimately contributing to the fight against blood cancers.

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