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Leveraging Electrochemical Sensors to Improve Efficiency of Cancer Detection

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Abstract

Electrochemical biosensors have emerged as a promising technology for cancer detection due to their high sensitivity, rapid response, low cost, and capability for non-invasive detection. Recent advances in nanomaterials like nanoparticles, graphene, and nanowires have enhanced sensor performance to allow detection of cancer biomarkers like circulating tumor cells, nucleic acids, proteins and metabolites at ultra-low concentrations. However, several challenges need to be addressed before electrochemical biosensors can be clinically implemented. These include improving sensor selectivity in complex biological media, device miniaturization for implantable applications, integration with data analytics, handling biomarker variability, and navigating regulatory approval. This editorial critically examines the prospects of electrochemical biosensors for efficient, low-cost and minimally invasive cancer screening. We discuss recent developments in nanotechnology, microfabrication, electronics integration, multiplexing, and machine learning that can help realize the potential of these sensors. But significant interdisciplinary efforts among researchers, clinicians, regulators and the healthcare industry are still needed to tackle limitations in selectivity, size constraints, data interpretation, biomarker validation, toxicity and commercial translation. With committed resources and pragmatic strategies, electrochemical biosensors could enable routine early cancer detection and dramatically reduce the global cancer burden.

Key words: Electrochemical sensors; Cancer biomarkers; Nanomaterials; Point-of-care diagnostics; Microfabrication; Machine learning

Core tip: Electrochemical biosensors represent a promising technology for efficient, minimally invasive, and low-cost cancer screening. Recent advances in nanomaterials, microfabrication, and analytics have enhanced sensor capabilities for detecting cancer biomarkers at ultra-low concentrations. However, challenges remain including improving selectivity in complex fluids, device miniaturization, seamless data integration, handling biomarker variability, nanotoxicity, and navigating regulatory approval. Significant interdisciplinary efforts are needed to address these limitations and facilitate clinical translation of electrochemical biosensors for transformative point-of-care cancer diagnostics. Managing expectations and developing pragmatic translational strategies will be imperative to unlock the potential of these sensors for early cancer detection and timely intervention.

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INTRODUCTION

Cancer remains one of the leading causes of death worldwide, with approximately 10 million deaths attributed to various forms of cancer in 2020 alone[1]. While cancer research has made tremendous strides over the past several decades in understanding the molecular basis of cancer and developing targeted therapies, early detection and diagnosis continues to play a pivotal role in patient survival and recovery. The stark reality is that many cancers exhibit no overt symptoms until they have progressed to late stages, severely limiting treatment options and prognosis. There is an urgent need for efficient, affordable and accessible cancer screening techniques that would allow early detection and immediate treatment[2].

In this context, electrochemical biosensors have emerged as a promising platform technology that could potentially enable low-cost, point-of-care diagnostic tests for cancer[3–5]. Electrochemical biosensors utilize electrode interfaces to transduce molecular recognition events into readable electrical signals. They offer a number of advantageous features including rapid response times, high sensitivity, low sample volume requirements, and low cost. In recent years, there has been burgeoning interest in leveraging electrochemical biosensors for detecting cancer biomarkers - signature biomolecules that can indicate the presence of cancerous cells and tissues. Cancer biomarkers such as circulating tumor cells[6], cell-free nucleic acids[7], exosomes[8], proteins[9] and metabolites[10] can act as analyte targets for electrochemical biosensors.

A wide array of electrochemical transduction platforms have been explored for cancer biosensing, including amperometry, potentiometry, voltammetry and impedimetry[11]. Nanotechnology has unlocked further improvements in sensor performance by allowing nanoscale tailoring of electrode interfaces. For instance, nanomaterials like graphene[12,13], carbon nanotubes[14] and metal nanoparticles[15] can facilitate enhanced electron transfer kinetics and provide larger surface area for capture molecule immobilization. Electrochemical sensors have been designed to detect general cancer biomarkers such as prostate specific antigens[16] as well as biomarkers specific to cancers such as lung[17], breast[18], ovarian[19] and colon[20].

While electrochemical biosensors represent a disruptive approach for cancer screening, several challenges need to be addressed before they can be clinically implemented. These include improving sensor selectivity in complex biological media, device miniaturization for possible implantable applications, seamless integration with data analytics, handling inter- and intra-tumor biomarker expression variability, and navigating regulatory approval pathways. That said, the field has been buoyed by exciting developments on multiple fronts – new nanomaterials to improve sensor performance, microfabrication techniques to enable miniaturization, multiplexing and array capabilities, machine learning for robust data analysis, and public-private efforts to facilitate technology translation.

In this editorial, we critically examine the prospects of electrochemical biosensors as a transformative platform for efficient, low-cost and minimally invasive cancer detection. We discuss recent technology advancements that poise these sensors on the cusp of making a tangible clinical impact. However, we also highlight lingering challenges that need to be addressed through committed interdisciplinary efforts among researchers, clinicians, regulators and the healthcare industry. Wider deployment of electrochemical biosensors could allow routine screening for early cancer detection, provide diagnostic decision support to physicians, enable therapeutic drug monitoring, and reduce the global cancer burden through timely intervention. Realizing this potential would require sustained investments, managing expectations, and pragmatic translational strategies.

ELECTROCHEMICAL SENSORS OFFER ADVANTAGES FOR CANCER DETECTION

Electrochemical sensors offer a number of compelling advantages that make them well-suited for cancer detection applications. First and foremost is their ability to provide sensitive and quantitative detection of cancer biomarkers, even at extremely low concentrations[21]. The fundamental principle behind electrochemical biosensing is the specific binding of target analytes to receptor molecules immobilized on the sensor surface, which generates detectable electrical signals. Carefully tailored electrode interfaces allow achieving detection limits as low as femto- or picomolar levels for cancer biomarkers. This is particularly important for early detection since cancer markers are typically present at very low abundances during initial stages.

Recent research has leveraged novel nanomaterials to further improve sensor performance. Nanoparticles[22], nanotubes[14], nanowires[23], graphene[12] and other nanostructures can be integrated with sensor electrodes to enhance electron transfer, provide higher surface area, and incorporate catalytic properties. For instance, gold nanoparticles have been functionalized with aptamers for electrochemical detection of exosomes[24], which are emerging biomarkers for non-invasive cancer diagnosis. The high surface area of nanoparticles increases aptamer loading, allowing ultrasensitive exosome detection down to a few hundred particles per micro liter. Creative combinations of nanomaterials have enabled detection limits that surpass conventional diagnostic modalities for cancer biomarkers by several orders of magnitude.

Apart from high sensitivity, electrochemical sensors also offer rapid response times[25]. Electron transfer reactions occur over milliseconds or shorter timescales. This allows real-time monitoring of interactions enabling quick measurements. For cancer screening applications, rapid results are indispensable to facilitate prompt confirmatory tests and immediate treatment. Lengthy assay times are unsuitable for point-of-care testing scenarios. The fast response kinetics of electrochemical sensors align well with the need for rapid cancer detection. Miniaturized designs also enable multiplexing capabilities for parallel detection of different cancer biomarkers[26].

Low cost and portability represent other major attractions of electrochemical sensors. The electrodes and measurement systems are based on relatively inexpensive materials and fabrication methods, especially compared to advanced imaging modalities used clinically for cancer detection[27]. This becomes particularly important for resource-limited settings and underserved communities. The sensing devices can be designed as portable, handheld gadgets operated with smartphones or miniaturized electronics. Such point-of-care analyzers can perform testing at the convenience of the patient’s home or physician’s office without needing dedicated laboratory infrastructure.

Importantly, electrochemical techniques allow non-invasive detection using easily accessible body fluids like blood, urine or saliva[28]. Cancer biomarkers shed by tumor cells circulate through the body and can be measured in these biofluids. Blood draws or urine samples present a far less invasive approach compared to tissue biopsies which are painful and have potential complications. Patient compliance is also improved with non-invasive tests. Furthermore, longitudinal monitoring can be easily carried out to track biomarker trends or response to therapy.

However, realizing these advantages would require thoughtful sensor engineering and data interpretation. A persistent challenge is the variability in expression levels of cancer biomarkers between not only different malignancies but also across patients with the same type of cancer. This necessitates measuring biomarker panels rather than individual markers[29]. But multiplexing capabilities of electrochemical sensors are still limited and need enhancement. The relevance of circulating biomarkers to primary tumors also remains unclear[30]. Meticulous clinical studies are therefore needed to correlate measurements with cancer onset and progression.

Preventing sensor fouling and degradation during use remains an engineering challenge. Electrochemical measurements in complex media like blood is fraught with artifacts. Sophisticated surface chemistries are necessary to impart specificity and prevent non-specific fouling[31]. The receptor molecules also need optimal orientation and retention of bioactivity upon immobilization. Furthermore, minimizing electrical noise, drift, and variability across fabrication batches is critical for reliable quantification[32]. There are open questions on device packaging for real-world point-of-care applications.

While nanomaterials boost sensor performance, their biocompatibility, toxicity and stability need deliberation[33]. Range of motion limitations and sizing constraints for implantable sensors also exist. Additionally, the lack of established regulatory guidelines is an impediment for commercial translation. Companies need to navigate approval pathways for screening non-FDA approved cancer biomarkers. Reimbursement mechanisms for new diagnostic technologies are uncertain. Hence, despite strong enthusiasm around electrochemical sensors, the path to actual clinical adoption remains strewn with major challenges.

CHALLENGES AND LIMITATIONS MUST BE ADDRESSED

While electrochemical biosensors hold promise for advancing cancer diagnostics, there are salient challenges and limitations that still need to be tackled before effective translation can occur.

One of the most pressing issues is enhancing the selectivity of electrochemical sensors. Biological fluids contain a multitude of components including proteins, metabolites, salts and cells[34]. Distinguishing the targeted cancer biomarkers from this complex milieu is extremely difficult. Non-specific adsorption and matrix effects often produce false signals leading to inaccurate results[35]. Novel surface chemistries, nanostructured coatings and creative receptor scaffolds are being explored to impart sensor selectivity[36]. But extensive optimization across diverse cancer biomarker panels would be needed. Lack of adequate selectivity can preclude regulatory approval and clinical adoption due to concerns over false positives.

Sensor miniaturization is another aspect requiring innovation. Microfabrication and nanotechnology can enable miniaturization but biocompatibility, calibration and wireless communication become challenges at smaller dimensions[37]. Implantable sensors also require optimization of sensor surface area to avoid biofouling from nonspecific protein adsorption and immune reactions[38].

A major limitation is the disconnect between cancer detection and data interpretation for decision making. Sensor development has outpaced diagnostics with most reports demonstrating cancer biomarker detection as a proof-of-concept. The next imperative step is rigorous analytical and clinical validation to generate actionable information. Large-scale studies are needed to understand intra- and inter-patient biomarker variability, correlate this variability with cancer risk, and set appropriate thresholds for screening. User-friendly data analytics need integration within point-of-care devices. Until statistical validation and clinical translation occurs, the true diagnostic utility of electrochemical sensors will remain uncertain regardless of their technical capabilities.

There are inherent biological complexities that electrochemical sensors need to address. Cancers are highly heterogeneous, even within the same organ. Relying on single biomarkers is unlikely to be sufficient, necessitating multiplexing capabilities. Furthermore, the relevance of circulating biomarkers versus primary tumor characteristics remains ambiguous. Differences between early stage, metastasized and treated cancers also need elucidation. Soluble biomarkers being shed into fluids may not comprehensively capture the tumor microenvironment. Implantable or minimally invasive sensors allowing in situ tumor analyses could be impactful.

In summary, while electrochemical biosensors enjoy tremendous advantages over conventional cancer diagnostics, their clinical translation and impact face multiple barriers. Key challenges remain in enhancing sensor specificity, enabling multiplexing, facilitating data interpretation, validating real-world performance, and easing product development. Addressing these limitations will require extensive interdisciplinary collaboration engaging scientists, engineers, clinicians, regulators, and the healthcare industry. With commitment and resources, the field can aspire to reach the lofty goal of deploying electrochemical devices for routine, non-invasive cancer screening. But expectations need calibration and timelines should factor the arduous process of analytical validation, statistical correlation studies, and clinical trials prior to market approval.

THE PATH FORWARD

Despite existing challenges, there are promising developments across academic labs and startups to unlock the true potential of electrochemical sensors for efficient, low-cost cancer detection.

Novel nanomaterials are emerging as a tool to enhance the selectivity of electrochemical cancer biosensing. Two-dimensional nanosheets, nanoparticles, nanocomposites and other nanostructures can provide higher surface area for capture molecule loading while controlling orientation and spacing to minimize non-specific binding[8,18,20,30,39,40]. Combining synthetic receptors like aptamers with nanomaterials can further boost selectivity. Additionally, nanostructured coatings and membranes on sensor surfaces allow selectivity based on analyte size. Advancements in nanotechnology will be crucial to impart the requisite specificity.

Another area gaining traction is micro- and nanofabrication for sensor miniaturization. Techniques like micromachining, photolithography, 3D printing and etching can craft sensor components at the microscale[41–44]. Further miniaturization to the nanoscale may be possible with technologies like two-photon polymerization. Microfluidic integration would enable analysis from miniscule sample volumes. Miniaturized sensors could pave the way for implantable or ingestible devices for surgical and gastrointestinal applications.

Given the complexity of cancer, measuring panels of biomarkers rather than individual markers is imperative. Multiplexing and arrayed platforms allow concurrent analysis of different analytes using several individually addressable electrodes on the same chip. Companies are developing high-density sensor arrays with thousands of electrodes for massively parallel measurements[45]. Multiplexed data provides better predictive power but also necessitates advanced analytics. Towards this, data science approaches like machine learning and artificial intelligence are gaining importance to make sense of multifaceted sensor data[46–48]. Pattern recognition and multivariate models that can assimilate diverse datasets would aid in identifying correlations. Cloud analytics can enable decentralized testing at point-of-care with centralized data storage and analysis. Wider data sharing and open-access data repositories will facilitate large-scale validation studies.

CONCLUSION

In conclusion, the exploration of electrochemical biosensors in the field of cancer screening presents a pathway filled with both promise and challenges. These sensors, characterized by their high sensitivity, cost-effectiveness, and non-invasive nature, hold the potential to revolutionize early cancer detection. However, the journey from laboratory innovation to clinical application is not without obstacles. Critical areas requiring attention include enhancing the selectivity of sensors amidst complex biological fluids, developing multiplexed systems for comprehensive biomarker analysis, miniaturizing devices for wider applicability, and ensuring the safe integration of nanomaterials. Moreover, the interpretation of data generated by these sensors necessitates advanced analytical tools, and the entire process must navigate through the intricate labyrinth of regulatory approvals.

The future of electrochemical biosensors in cancer diagnostics hinges on the successful amalgamation of advancements in nanotechnology, microfabrication, and data science. This will demand sustained collaborative efforts across various domains of science and medicine. Investments in translational research and the formulation of pragmatic strategies are essential for transforming these innovative concepts into viable clinical tools. As we move forward, it is crucial to manage expectations realistically and acknowledge the timelines necessary for rigorous validation and clinical trials. With a balanced approach and dedicated resources, electrochemical biosensors could significantly impact cancer care, facilitating early detection and potentially reducing the global burden of this disease.

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