Medical Oncology (2024) 41:73
https://doi.org/10.1007/s12032-023-02297-y

REVIEW ARTICLE

Advancements in biosensors for cancer detection: revolutionizing diagnostics

Syed Khalid Mustafa[1] · Mohd. Farhan Khan[2] · Mehak Sagheer[3] · Deepak Kumar[4] · Sadanand Pandey[5]

Received: 28 October 2023 / Accepted: 28 December 2023 / Published online: 19 February 2024

Abstract

Cancer stands as the reigning champion of life-threatening diseases, casting a shadow with the highest global mortality rate. Unleashing the power of early cancer treatment is a vital weapon in the battle for efficient and positive outcomes. Yet, conventional screening procedures wield limitations of exorbitant costs, time-consuming endeavors, and impracticality for repeated testing. Enter bio-marker-based cancer diagnostics, which emerge as a formidable force in the realm of early detection, disease progression assessment, and ultimate cancer therapy. These remarkable devices boast a reputation for their exceptional sensitivity, streamlined setup requirements, and lightning fast response times. In this study, we embark on a captivating exploration of the most recent advancements and enhancements in the field of electrochemical marvels, targeting the detection of numerous cancer biomarkers. With each breakthrough, we inch closer to a future where cancer's grip on humanity weakens, guided by the promise of personalized treatment and improved patient outcomes. Together, we unravel the mysteries that cancer conceals and illuminate a path toward triumph against this daunting adversary. This study celebrates the relentless pursuit of progress, where electrochemical innovations take center stage in the quest for a world free from the clutches of carcinoma.

Keywords Electrochemical biosensors · Cancer · Biomarkers · Diagnostics

Abbreviations

AFP:	alpha-fetoprotein
CA125:	cancer antigen 125
CA15-3:	cancer antigen 15–3
CEA:	carcinoembryonic antigen
PSA:	prostate-specific antigen
WHO:	world health organization
EBs:	electrochemical biosensors
PCR:	polymerase chain reaction
RIA:	radioimmunoassay
ELISA:	enzyme-linked immunosorbent assay
HPLC:	high-performance liquid chromatography
PSA:	prostate-specific antigen
RF:	radio frequency
MW:	microwave
mmW:	millimeter wave
THz:	tetrahertz
EIS:	electrochemical impedance spectroscopy
DDPpy:	DNA dendrimers and polypyrrole
ITO:	indium-tin oxide
DNA:	deoxyribonucleic acid
CV:	cyclic voltammogram
EIS:	electrochemical impedance spectroscopy
GLC:	gas liquid chromatography VI
ROS:	reactive oxygen species
LPO:	lipid per oxidation
H_2O_2:	hydrogen peroxide
dsDNA:	double-strand DNA
ssDNA:	single-strand DNA

✉ Syed Khalid Mustafa
khalid.mustafa938@gmail.com

✉ Sadanand Pandey
sadanand.au@gmail.com; spandey@shooliniuniversity.com

[1] Department of Chemistry, Faculty of Science, University of Tabuk, P.O. Box 741, Zip 71491 Tabuk, Saudi Arabia

[2] Faculty of Science, Gagan College of Management & Technology, Aligarh 202002, India

[3] Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India

[4] Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shoolini University, Solan, Himachal Pradesh 173229, India

[5] Faculty of Applied Sciences and Biotechnology, School of Bioengineering and Food Technology, Shoolini University, Solan, Himachal Pradesh 173229, India

SPGEs: screen-printed gold electrodes
BESs: bio-electrochemical systems
HPLC: high-performance liquid chromatography
GC–MS: gas chromatography–mass spectrometry
LC–MS: liquid chromatography–mass spectrometry
AFM: atomic force microscopy
SEM: scanning electron microscopy
TEM: transmission electron microscopy
US EPA: U.S. environmental protection agency
IARC: international agency for research on cancer
SAW: surface acoustic wave

Introduction

After heart diseases, different cancer diseases come in the second largest position for causing mortality around the globe, as far as non-communicable diseases are concerned [1]. Cancer is difficult to diagnose and treat on time, especially in low-income countries. Only 26% of low-income countries can provide entire pathology administrations to public non-communicable diseases [2, 3]. The Global Burden of Disease 2015 study published that the prevailing categories in males and females are prostate and breast cancer, respectively. However, lung and colorectal cancer prevail in all adult humans. For persons around the age of 15 to 39 years, the most frequent category is cervical as well as breast cancer. The mortality rates are common in leukemia and liver patients of cancer. The situation is more dire in low-income countries [4].

Diagnostic analysis refers to the process of converting diagnostic findings into a structured, categorized prescription of the illnesses given. The prompt and timely identification of many diseases is critical not only for patient life but also for reducing the cost-effectiveness and time in the proper assessment of the diseases. Locating therapeutic neoplastic biomarkers is significant for early cancer detection, tailoring specific therapy, and identifying basic principles implicated in the disease [5]. As a result, detecting cancer indicators is extremely important in clinical management and improves overall patient outcomes in the fight against cancer [6].

The common available approaches for biomarker screening include varied techniques, which have technical constraints, viz. immunohistochemistry usage [7], PCR-based biomarkers [8]; Western-Blot analysis [9]; RIA blood test [10]; HPLC techniques [11]; and ELISA for cancer biomarker detection [12]. The current approaches can be described as difficult, lengthy, and frequently requiring costly equipment and close attention to detail. A more accurate and quick technological system is desperately needed to satisfy the demands of biomarker recognition for fast diagnostics, especially in the initial phases of the disorder [13]. As a result, new, cost-effective techniques for identifying cancer biomarkers are desperately required and various types of biosensors for detecting cancer biomarkers have been described during the last decade [14].

The biosensors hold promise as alternative technologies showcasing the potential to provide rapid, accurate, and sensitive early detection, monitor the progression of carcinogenesis, and evaluate the effectiveness of cytotoxic treatments in a non-invasive manner [15]. Among various biosensor technologies [16, 17], the advantages of electrochemical biosensing tools encompass affordability, ability to miniaturize, and scalability for large-scale production. Moreover, they can be deployed in healthcare facilities and at home as point-of-care (POC) systems. Consequently, the development of extremely specific and targeted electrochemical biosensors for the identification of antigens unique to cancer has therefore received a great deal of interest and effort [18, 19].

Cancer-based biomarker

Cancer biomarkers are quantitatively measurable biological materials or traits used to analyze certain cellular structures or biomacromolecules, defining an organism's healthy or pathological physiological condition. The definitions, status, and uses of biomarker have evolved over time. The World Health Organization (WHO) defines a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" [20, 21]. The Biomarkers Definitions Working Group of the National Institutes of Health defined a biomarker as "a trait that is accurately analyzed and evaluated as an index of normal biochemical functions, pathogenic processes, or pharmacological reactions to a therapeutic strategy" in 1998 [22, 23].

Biomarkers can be obtained from tissues and bodily fluids associated with the progression of hematological malignancies [24, 25]. These materials may be present either within cancer cells or in the extracellular space. When located within the tumor, collecting and concentrating them is necessary, often requiring cell lysis to release the biomarkers for analysis, particularly when their concentration is low. Various forms of cancer biomarkers include protein cancer markers, embryonic/carbohydrate antigens, enzyme-induced tumor-indicators, isozyme-tumor markers, and oncogenic/hormones-concerned cancerous biomarkers [26]. Table 1 lists some of the most important tumor or cancer markers [27–33].

Quantifying specific cancer biomarkers in a patient's bodily fluids may be used to detect malignancy in its initial phase, identify tumor regrowth, determine the risk of developing additional cancers, and track the effectiveness of therapy during treatment. However, obstacles to initial phase

Table 1 List of tumor or cancer markers that oncologists like to keep track of

Cancer markers	Type	Description	Sign	Threshold Level	Reference
Alpha-fetoprotein (AFP)	Liver	Adults typically have an AFP level of less than 10 ng/mL, and a blood level of more than 500 ng/mL is considered abnormally high	Liver tumors	< 20 ng/dL	[26]
Cancer antigen 125 (CA125)	Ovarian	It gauges the blood's concentration of the protein CA 125 The CA 125 test is effective for regulate some cancers prior to and after therapy, as well as to search for early indicators of ovarian cancer	Ovarian cancer	< 35 U/mL	[27]
Cancer antigen 15–3 (CA15-3)	Breast	Assessment is made possible by the release of CA15-3, a protein that is generated by different cells, most notably breast cancer cells, into the bloodstream It is usual for women whose breast cancer has spread to other parts of their body to have elevated CA15-3 levels	Metastatic breast cancer	< 30 U/mL	[28]
Carbohydrate antigen 19–9 (CA19-9)	Gastro-intestine	Patients with gastrointestinal cancers may have higher levels of CA 19–9 It is 0–37 units per milliliter in a healthy individual	Cholangio-carcinoma, Pancreatic cancer, Colon cancer	< 37 U/mL	[29]
Carcinoembryonic antigen (CEA)	Intestine and Rectum	CEA test is used especially for cancers of the large intestine and rectum	Large Intestine and Rectum cancer	< 2.5 ng/mL in nonsmokers; < 5 ng/mL in smokers	[30]
Human chorionic gonadotropin (hCG or beta-hCG)	Testicular, ovarian, liver, stomach, and lung	Pregnancy causes the placenta to produce the hormone known as hCG or b-hCG. Some cancer cells, though, have the ability to survive	Testicular cancer, ovarian cancer, liver cancer, Stomach cancer and Lung cancer	< 5—10 IU/mL in men	[31]
Prostate-specific antigen (PSA)	Prostrate	Both benign and cancerous prostate gland cells can produce the protein PSA. The PSA test determines how much PSA is present in a man's blood. Zero to 2.5 ng/mL is regarded as the safe range. For most males, 2.6 to 4 ng/mL is safe	Enlarged prostate or prostate cancer	Aged based: 40—49 years: < 2.5 ng/mL; 50—59 years: < 3.5 ng/mL; 60—69 years: < 4.5 ng/mL; 70—79 years < 6.5 ng/mL	[32]

cancer diagnosis exist, such as reduced amounts of blood markers in the earliest days of the disorder, patient heterogeneity in the onset plus concentration of such biomarkers, and difficulties in carrying out prospective research [34].

Biosensor

The origin of biosensors dates back to the start of the 1950s [35]. L.C. Clark Jr., the original oxygen electrode innovator and father of biosensors [36], outlined the various parts of a biosensor in his book in 1956. Table 2 depicts the initial breakthroughs of biosensors, and with the start of the twenty-first century, numerous studies have been reported advancements in the field [37–90]. A good biosensor should be extremely specific; sensitive; reproducible; stable; pH and temperature independent; biocompatible; cost-efficient; and precise in addition to being effective [91, 92]. The different types of cancer-related biosensors reported are electrochemical biosensors (EBs); optical biosensors; thermal biosensors; nano-biosensors; piezo-electric biosensors; acoustic biosensors, etc. [93]. However, other types of biosensors viz. radio signal frequencies, RF; microwave radiations, MW; millimeter wave (mmW), and tetrahertz (THz) biosensors are also utilized for the identification of cancerous cells/fibroblast cells/other biomolecules [94].

Biosensors are tools that combine certain molecular reactions with biological elements to detect a target molecule with high sensitivity. Such tiny sensors are capable of measuring biological responses and producing an electrical impulse per the amount of analyte present. Biosensors as shown in Fig. 1 usually comprise.

Analyte: a target molecule which is intended to be detected,
Bio-receptor: a biomolecule that identifies analytes,
Transducer: a device that converts energy into a recognizable output,
Electronic setup: uses a sophisticated network of circuitry to process transduced signals, which are then amplified and converted into digital form,
Display: to offer a picture, chart, or other visual aid.

Typically, biosensors are classified according to the type of transducing signals and the biorecognition components employed. The signal transduction mechanisms include electrochemical, optical, mass detection, and enthalpic principles. Conversely, the categorization of bio-recognition components depends on the utilization of bio-components with catalytic properties, such as enzymes, cells, tissues, or microorganisms, and affinitive properties, such as antibodies, nucleic acids, or aptamers [23, 25]. Regardless of the source of the bioreceptor component and the signaling principle, a desirable biosensor should possess analytical properties such as enhanced sensitiveness and selectiveness, increased precision and accuracy, a broad spectrum of linearity, a rapid reaction time, as well as improved reproducibility and stability [24, 95]. Figure 2 illustrates working procedure of biosensors concerning carcinogenic diagnostics [96].

Electrochemical biosensors for biomarker detection

While various methods exist for biomarker identification, electrochemical approaches are commonly employed in cancer biomarker detection due to their advantageous attributes. These include moderate cost, quick reaction time, user-friendly operation, quantifiability, excellent accuracy and vulnerability, speedy and non-intrusive target identification, and low detection limits (LOD) [97–99]. Furthermore, electrochemical methods offer the possibility of downsizing and constructing portable/disposable biosensors [100]. Electrochemical-based biosensors comprise 3 essential elements: a (bio)-recognition component, a signal-transducing element, and a 3-electrode-based electrochemical system. The working principle is that the recognition components (chemically selective layer) identify and interact with a target biomolecule in a real-time, leading to transducers generating measurable electrochemical signals that are subsequently recorded [101]. The analytical signal can manifest as a change in redox potential, current, conductivities, or resistance of the biosensing surface [24, 95, 102]. In electrochemical sensing, the generated impulse correlates proportionally with the amount of the marker being measured. This relationship allows for a quantitative assessment of the biomarker based on the observed electrochemical impulse.

The critical phase in constructing electrochemical biosensors is the design of (bio)-recognition elements. The effectiveness of the sensing or biosensing strategy relies on achieving a specific interaction between the analyte and the recognition component, while also minimizing non-specific interactions. This precision is crucial for accurate and selective detection, ensuring the distinction of the targeted analytes from the other potential interfering substances. The meticulous design of these layers is fundamental to the overall performance and dependability of the electrochemical sensor or biosensor [23, 103]. The efficacy of these biosensing approaches depends on the inherent nature and distinctive characteristics of the monitored species, as well as the sensitivity/specificity of the chosen biorecognition component. Electrochemical biosensors, categorized as immunosensors and apta-sensors, are distinguished based on the nature and design of these employed (bio)-recognition components.

Table 2 Developmental Timeline of Biosensors: From nothing to something

S. No	Developmental timeline of bio-sensors	Year	Reference
1	*M. Cramer* found an electric potential between fluid parts	1906	[37]
2	*Soren Sorensen* came up with the concept of pH and the pH scale	1909	[38]
3	Griffin and Nelson showed that invertase could be rendered immobile using charcoal as well as aluminum hydroxide	1909–1922	[39, 40]
4	The first glass pH electrode was found by W.S. Hughes	1922	[41, 42]
5	The first O_2 electrode was invented by *Leland C. Clark, Jr*	1956	[43]
6	*Leland C. Clark, Jr.* and colleagues conducted experiments to develop an amperometric enzyme electrode for glucose sensing	1962	[44]
7	Using glucose oxidase coupled to an oxygen sensor, Updike and Hicks were the first to create a functional enzyme electrode	1967	[45]
8	Guilbault and Montalvo demonstrated and published the first potentiometric enzyme electrode-based urea sensor	1969	[46]
9	The ion-sensitive field-effect transistor (ISFET) was discovered by Bergveld	1970	[47]
10	Guilbault and Lubrano described glucose and lactate enzyme sensors based on H_2O_2 detection at a Pt electrode	1973	[48]
11	Enzyme thermistor was improved by K. Mosbach and B. Danielsson	1974	[49]
12	D.W. Lubbers and N. Opitz demonstrated a fiber-optic biosensor for the detection of CO_2 & O_2	1975	[50]
13	The earliest commercialized biosensor for detecting glucose was created by Yellow Springs Instrument Company (YSI)	1975	[51, 52]
14	An immunosensor based on microbes was initially demonstrated by *Suzuki* et al	1975	[53]
15	*Clemens* et al. were the first to demonstrate a bedside artificial pancreas	1976	[54]
16	Peterson demonstrated the initially developed fiber-optic pH sensor for in vivo blood gases	1980	[55]
17	Schultz developed a fiber-optic biosensor for determination of glucose	1982	[56]
18	Liedberg discovered surface plasmon resonance (SPR) immunosensors	1983	[57]
19	The initially developed piezoelectric detection-based immunosensor was created by Roederer and Bastiaans	1983	[58]
20	Ferrocene and a glucose oxidase were employed in the first mediated amperometric biosensor for detecting glucose	1984	[59]
21	Introduction of the disposable MediSense ExacTechTM blood glucose biosensor pen & strips	1987	[55]
22	1990 witnessed the introduction of *Pharmacia Biacore's* SPR-based biosensor technology and its SPR-based biosensor	1990	[60]
23	i-STAT's portable blood biosensor	1992	[60]
24	Introduction of LifeScan FastTake a blood glucose biosensor	1998	[51]
25	The first nanobiosensor was demonstrated by *Poncharal* et al	1999	[61]
26	Quantum dots, nanoparticles, nanowire, nanotube, nanocantilever, and BioNMES	1999 to Till Date	[62–66]
27	Biosensors based on acetylcholinesterase inhibition: Comprehending the effects of pesticides	2012	[67]
28	Quartz crystal biosensor: Toward the development of incredibly sensitive liquid-protein detection	2013	[68]
29	Biosensors built around the nanomaterials: For a variety of uses, such as biomedicine, such as diagnostic instruments	2012–2015	[69]
30	Utilizing uric acid as a biosensor to identify diseases or clinical anomalies	2013–2015	[70]
31	Microfabricated biosensor: For drug development	2013	[71]
32	Hydrogel-based biosensor: biomolecular immobilization utilizing polyacrylamide	2013	[72]
33	Silicon biosensor: Bioimaging, biosensing, and cancer therapy	2014	[73]
34	HbA1c biosensor: Sturdy analytical technique for glycated hemoglobin measurement	2014	[74]
35	Biosensors that are fluorescently tagged or genetically encoded: For comprehending biological processes, including different molecular systems inside the cell	2014–2015	[75–78]
36	Microbial fuel cell-based biosensors: To track environmental toxicity and biochemical oxygen demand, as well as pesticide and heavy metal toxicity	2015	[79]
37	Nerve-on-chip biosensor to evaluate the transmission of nerve impulses	2018	[80]
38	Wearable biosensors in order to monitor health	2019	[81]
39	Biosensors for Virus Detection	2019	[82]
40	Graphene biosensors	2020	[83]

Table 2 (continued)

S. No	Developmental timeline of bio-sensors	Year	Reference
41	Microbes as biosensors	2020	[84]
42	Biosensors for infectious disease point-of-care testing	2021	[85]
43	Biosensors based on potentiometry for the detection of biomarkers	2021	[86]
44	MXenes for sensors and biosensors	2022	[87]
45	Optical biosensors for cancer detection	2022	[88]
46	Metal–organic framework electrochemical biosensors	2023	[89]
47	Immunosensors	2023	[90]

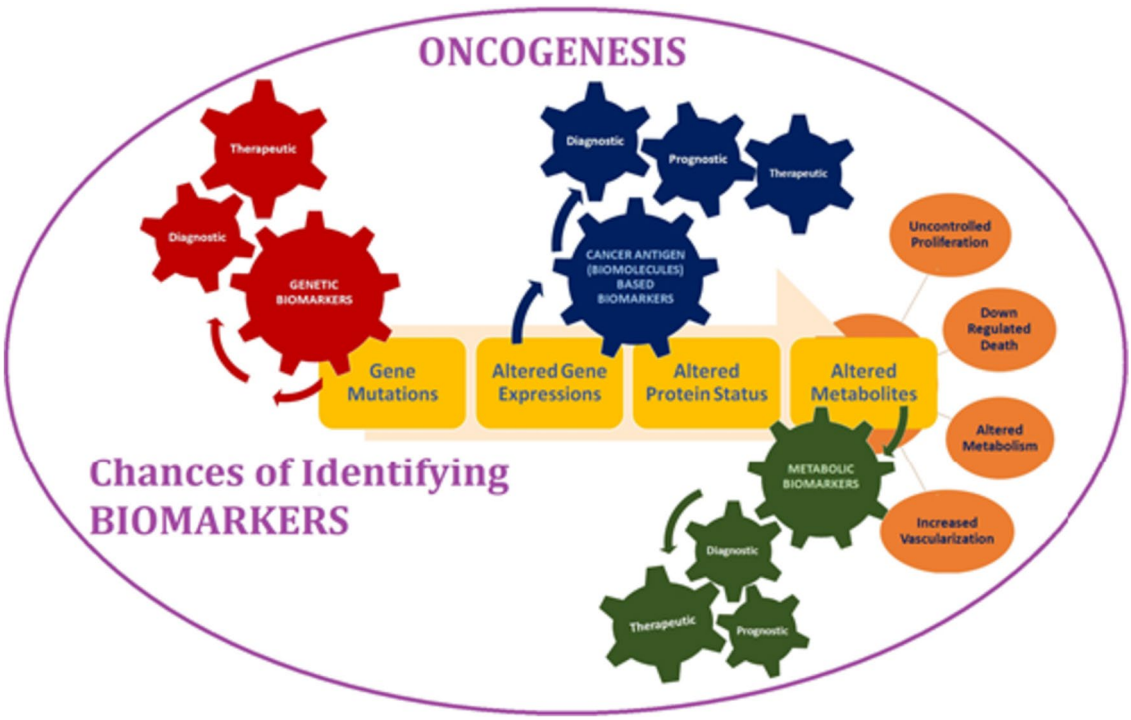

Fig. 1 Oncogenesis depicting chances of identifying the Biomarkers

The categorization of electrochemical devices broadly depends on evaluating transport characteristics in ionized species and exploring electrochemical equilibrium, charge-transfer mechanisms, and interface components [104]. These procedures are also classified as voltammetry, potentiometry, amperometry, and electrochemical impedance spectroscopy (EIS) based on the observed electrical impulses related to potential, impedance, or time, in both static and dynamic situations [24, 104, 105]. Voltammetry and EIS play a significant role among electrochemical assays. The utilization of sophisticated voltammetric techniques has not only enhanced electrochemical signal amplification but has also provided insights into the mechanisms of electrochemical reactions [24]. Table 3 provides a summary of selected electrochemical biosensors and demonstrates their efficacy in identifying malignant biomarkers [99, 100, 106–134].

Voltammetry

Voltammetry, a subset of electrochemical systems, involves deriving statistics about the interaction between a biorecognition element and an analyte by altering the redox potential and calculating the resultant current. Given the various ways to manipulate potential, several forms of voltammetry exist, including cyclic voltammetry, CV; differential pulse voltammetry, DPV; linear sweep voltammetry, LSV; stripping voltammetry, SV; and square wave voltammetry, SWV. Among these, SWV as well as DPV are frequently employed due to their highly sensitive nature, especially in cancer-based biomarker detection across diverse matrices. These voltammetric techniques have proven effective in detecting numerous cancer biomarkers, including miRNAs, PSA, CEA, HER2, OPN,

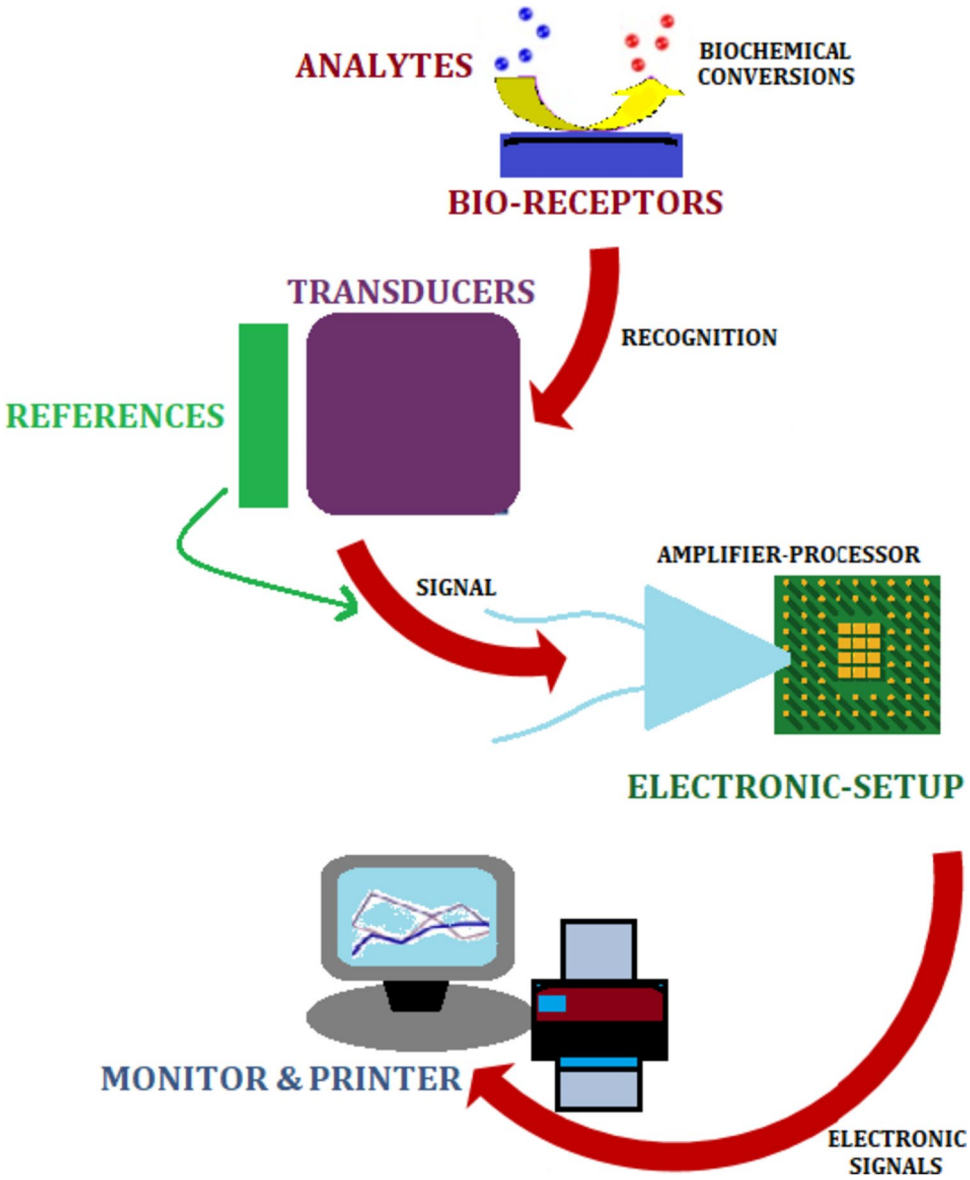

Fig. 2 Conceptual illustration of a characteristic biosensor consisting of bioreceptor, transducers, and an electronic setup with monitor & printer

CA 15–3, HER2-ECD, p53, CYFRA21-1, and more [135, 136].

In their investigations, *Zeng* et al. revealed the efficacy of an electrochemical biosensor that employs a signal-amplification approach in identifying the lung cancer biomarkers CYFRA21-1. A composite of chitosan (CS), 3-D graphene, and glutaraldehyde was used in the created immuno-sensor on a glassy carbon electrode (GCE), guaranteeing a high surface area-to-volume ratio, sa/vol and superior conductivities. Using the $[Fe(CN)_6]^{4-/3-}$ redox technique, cyclic voltammetry, CV was used to measure the electrode response. The sensor's remarkable 43 pg per mL detection threshold was accompanied with a linear range of 0.1 to 150 ng mL^{-1} [137]. Additionally, *Heidari* et al. demonstrated a glassy carbon electrode (GCE)-based graphene sensor for the sensitive identification and measurement of p53 cancerous biomarkers. Square wave voltammetry, SWV as well as differential pulse voltammetry, DPV were used to track the electrode's electrochemical properties. GCE/CdS/p53-Ab1 as well as p53-Ab2-tGO-AuNPs were added in the sandwich assay that was designed, proving its usefulness in the accurate identification of p53 cancerous biomarkers [110]. In a different work, *Freitas* et al. used linear sweep voltammetry, LSV to build an immune sensor that used carboxylic acid-functionalized magnetic beads, COOH-MBs in order to identify HER2 in human serums over a broad concentration ranging from 5 to 100 ng/mL, with a limit of detection, LOD as low as 2.8 ng/mL [138]

An effective sensor for cancerous prevalent exosomal-miRNA-21 detection in sera was developed by Boriachek et al. [139]. The miRNA was isolated utilizing magnetic beads containing functionalized complementary probes,

Table 3 List of some of the reported electrochemical biosensors with their performance to detect cancerous biomarkers

Biomarker Targeted	Details of electrodes	Method	Limit of Detection	Linear Range	Reference
CEA	anti-CEA/PEDOT/Ag@BSA/rGO/CNTs-COOH/Au		1×10^{-4} ng/mL	0.002–50 ng/mL	[99]
	Ab1/rGO-AuNPs/GCE		5.3 pg/mL	50–650 pg/mL	[106]
	Anti-CEA/MWCNTs/GNPs/HNF/CPE	EIS	0.09 ng/mL	0.4–125 ng/mL	[107]
	SPCE/GNP-MnO2/ Fe_3O_4@Au-anti-CEA	LSV EIS	0.10 pg/mL, 0.30 pg/mL	0.001–100 ng/mL	[108]
PSA	Ab_2- QD(CdTe:Ni)/Fe_3O_4@ TMU-10		0.45 pg mL^{-1}	1 pg/mL–100 ng/mL	[109]
	GCE/CdS/p53-Ab1 p53-Ab2-tGO-AuNPs		3 pg/mL	0.005–10 ng/mL	[110]
	Nafion-rGO-CHO-MPGE/$[Fe(CN)_6]^{3-/4-}$	DPV	1.6 pg mL^{-1}	5 pg/mL–90 ng mL	[111]
	Aptamer/IDE/$[Fe(CN)_6]^{3-/4-}$ Label free		0.51 ng mL^{-1}	0.5 ng/mL–5000 ng/mL	[112]
	COOH-AgPtPd-NH_2-rGO/$[Fe(CN)_6]^{3-/4-}$	DPV	4 fg mL^{-1}	4 fg/mL–300 ng/mL	[113]
CYFRA21-1	GCE/rGO/PPy/AgNPs/ssDNA		2.14 fM		[114]
	ssDNA-modified prob		1.0×10^{-14} M	10 fM–100 nM	[115]
	BSA/Ab1/GA/3D-G @Au/GCE	DPV	100 pg/mL	0.25–800 ng/mL	[116]
AFP	Isoorientin/anti-AFP modified GCE	DPV	0.0002 ng/mL	0.001–10 ng/mL	[117]
	Au-APTESMCS/$[Fe(CN)_6]^{3-}$	DPV	0.13 pg mL^{-1}	0.4 pg/mL–100 ng/mL	[118]
	Ab_2 label/AFP/BSA/Ab1/D-Au NPs/GCE	Amperometry	6.7 fg/mL	20 fg/mL–100 ng/mL	[119]
NSE	GCE/Au@MOFs/Ab1/BSA/NSE/MnO_2 UNs/Au@Pd^Pt NCs-Ab_2	DPV	4.7 fg/mL	10 fg/mL–100 ng/mL	[120]
CA15-3	Dye labeled DNA probe		0.0039 U/mL	0.01–1 U/mL	[121]
	CoS_2-GR-AuNPs/Ab/SPE	DPV	0.03 µ/mL	0.1–150 u/mL	[122]
BRCA1	Self-assembled ferrocenecored poly (amidoamine) dendrimers		0.38 nM	1.3–20 nM	[123]
CA 125	Ab/CysA-AuNPs/Ag-DPA-GQDs/GCE	DPV	0.001 U/mL	0.001–400 U/mL	[124]
CD59	Anti-CD59/GrONPs/PG	CV	1 fg/mL	1 fg/mL–10 ng/mL	[125]
EpCAM	Anti-EpCAM/rGO@TiO2/ITO	DPV	0.0065 ng/mL	0.01–60 ng/mL	[126]
MEG3	Primer probes		0.25 fM	1 fM–100 pM	[127]
UBE2C	Ab/GCE-PANI/$[Fe(CN)_6]^{3-/4-}$		7.907 pg mL^{-1}	500 pg/mL –5 mg/mL	[128]
LAG-3	SiO_2-Ab2/LAG-3/BSA/bio-Ab1/streptavidin/rGO-SnO_2/HNMs/AuPt/GCE	Amperometry	1.1 pg/mL	0.01 ng/mL–1 µg/mL	[129]
MUC1 **CA15-3** **HER2**	Screen-printed carbon electrode /PEI-AuNPs		0.21 U mL^{-1} 0.53 ng mL^{-1} 0.50 ng mL^{-1}		[130]
IgG	GCE/G2Fc/Ab		2.0 ng/mL	5.0–50 ng/mL	[100]
EGFR exon 21	ssDNA λ-exo-modified prob		120 nM	0.1 µM–3 µM	[131]
	PPD-GR-AuNPs/Ab/SPE	DPV	0.3 ng/mL	1–1000 ng/mL	[132]
miRNA-141 **miRNA-21**	Dual signal-labeled hairpin-structured DNA (dhDNA)-based probes		0.89 fM 1.24 fM	2.0 to 10^5 fM	[133]
miR-21	FTO/SWCNTs/den-Au/prob		0.01 fM L^{-1}	01 fM/L–1 µM/L	[134]

which were directly immobilized upon elemental gold electrodes. The concentration of deposited miR was measured using the DPV response and $[Fe(CN)_6]^{4-/3-}$ redox techniques, revealing a limit of detection, LOD of 1.0 pmol/L. This sensor offered multiple benefits, including improved capture, inexpensive production, shorter testing durations, and the matrix effect [139]. Similarly, Sabahi and colleagues developed an innovative electrochemical sensor for miR-21 detection seamlessly integrating electrochemical sensors and nanocomposites while harnessing the selective nature of oligo-nucleotides. The fluorine-doped tin oxide (FTO)-based sensor containing probe-functionalized dendritic gold nanostructures (den-Au) immobilized onto a single-wall carbon nanotubes (SWCNTs) by an amide bond. The oxidation potential of Cd^{2+} acted as a quantifiable signal using the DPV technique, demonstrating a reproducibility and linearity ranging from 0.01 fmol. L^{-1} toward 1 µmol.L^{-1} concentration of miR-21 as well as a limit of detection, LOD of 0.01 fmol.L^{-1} [134].

An ultrasensitive platform composed of a nanocomposite containing Ag@BSA nanoflower decorated with SWCNTs and rGO, referring to single-walled carbon nanotubes and reduced graphene oxide, with adsorbed PEDOT, was constructed to detect CEA, where Anti-CEA antibodies were fixed or attached. The electrochemical sensor demonstrated a linearity across concentration range 0.002–50 ng/mL with a limit of detection, LOD of 1×10^{-4} ng/mL. The performance assessment utilizing CV and LSV demonstrated the stability of the sensor, exhibiting good reproducibility, high selectivity, and an additional advantage of real-time measurement of analyte in patient serum specimens [25]. In an alternative approach, Luo et al. introduced an electrochemical sensor utilizing a composite platform of SWCNTs and GQDs, referring to single-walled carbon nanotubes and peroxidase-like graphene quantum dots as SWCNTs@GQDs, adorned alongside rGO-AuNPs, also referring to reduced graphene oxide with Gold nanoparticles, for detection of CEA [106]. With a limit of detection, LOD of 5.3 pg/mL, the voltammetric biosensor demonstrated linearity at analyte concentrations ranging from 50 pg/mL to 650 pg/mL (Fig. 3). In order to diagnose HER2-ECD [140] or CA 15–3 [141] in patient samples, *Pacheco* et al. demonstrated a molecular embossed polymeric institued [140] or screen-printed Au-SPE-instituted [141] biosensor. This biosensor may be detected at low concentrations.

Electrochemical impedance spectroscopy

Impedimetric techniques have emerged as a viable method for the identification of neoplastic marker proteins associated with cancer due to their numerous benefits, including low activation current, quick response, and high sensitivity [142, 143]. Notably, these techniques offer the advantages of prolonged, instant, and on-location detection capabilities [144, 145]. Among impedimetric methods, electrochemical impedance spectroscopy (EIS) stands out as the most frequently employed. In contrast to voltammetric methods that necessitate excitation voltages in the range of − 200 mV to 600 mV, EIS requires only minimal excitation current of 5 or 10 mV. This reduces damage to biological components caused by electrode heating, making it an effective instrument for detecting cancer biomarkers [146–148].

A non-amplification-based biosensor utilizing strand displacement reaction (LSDR) and locked nucleic acid (LNA) assistance was proposed by *Luo* et al. [149]. The sensing mechanism involves building a polylysine layer on the glassy carbon electrode, GCE to generate a PLLy/GCE nanocomposite. Electrochemical impedance spectroscopy (EIS) was utilized for confirmation. When miR-21 is present, the 'Y'-shaped architecture rearranges itself into a hairpin-like loop, making the methylene blue (MB) pulse active while turning off the ferrocene (Fc) indicator (Fig. 4). With a LOD of 2.3 fM, the biosensor displayed excellent repeatability in identifying exosomal miR produced from cancer [149].

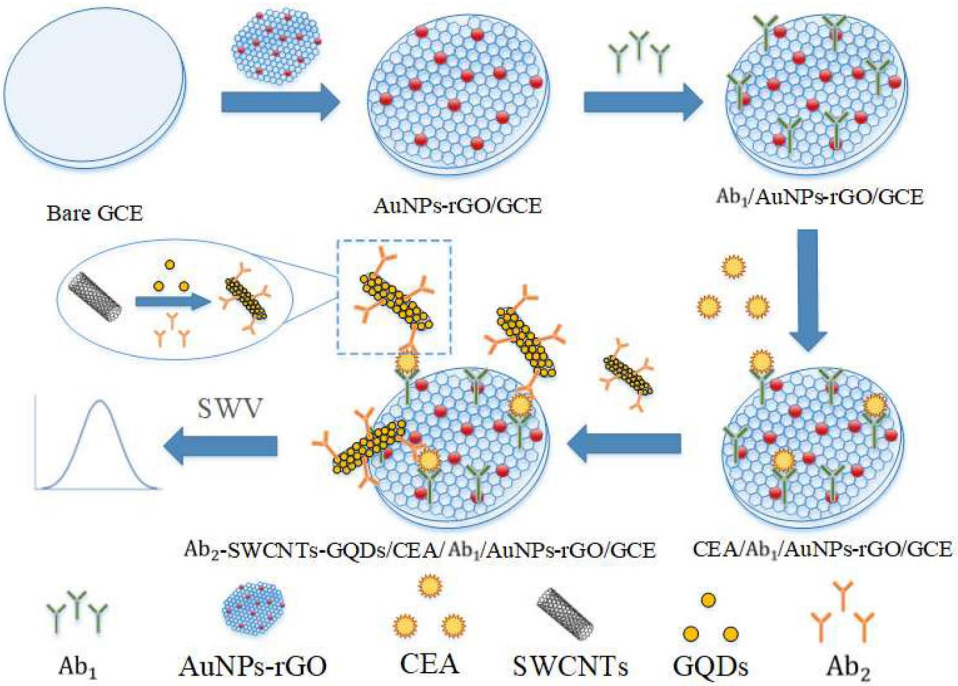

Fig. 3 Diagrammatic representation of the process for fabricating the immunosensor (Produced with permission from *Luo* et al. 2018 [106], https://doi.org/10.1016/j.aca.2018.08.023, © 2018 Elsevier B.V.)

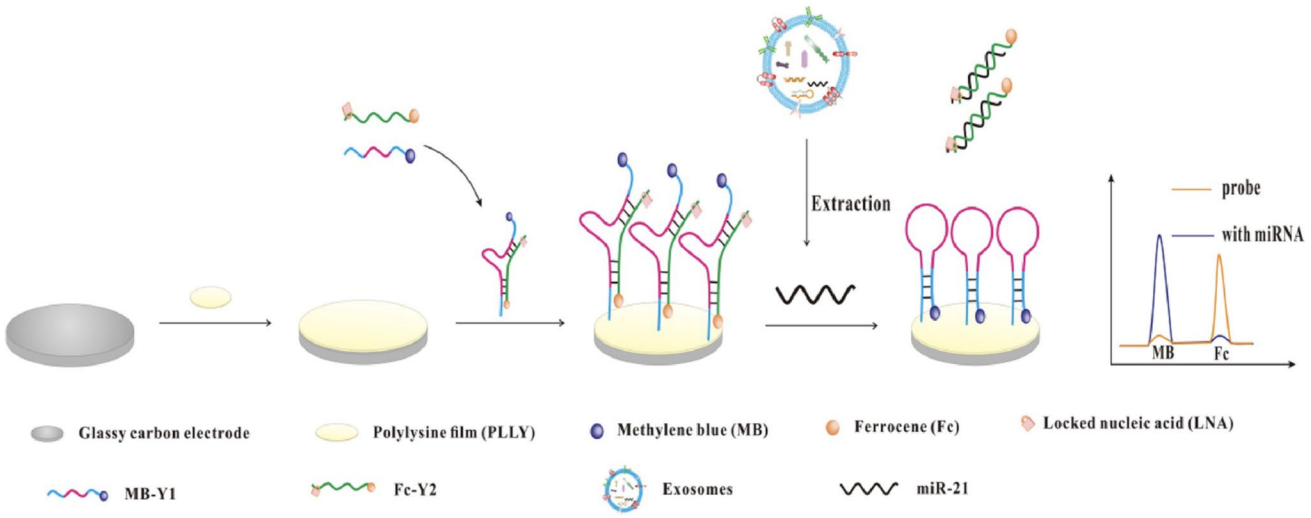

Fig. 4 Diagrammatic representation of the exosomal miR-21 detecting ratiometric electrochemical biosensor (Produced with permission from *Luo* et al. 2020 [149], https://doi.org/10.1016/j.talanta.2019.120298, © 2020 Elsevier B.V.)

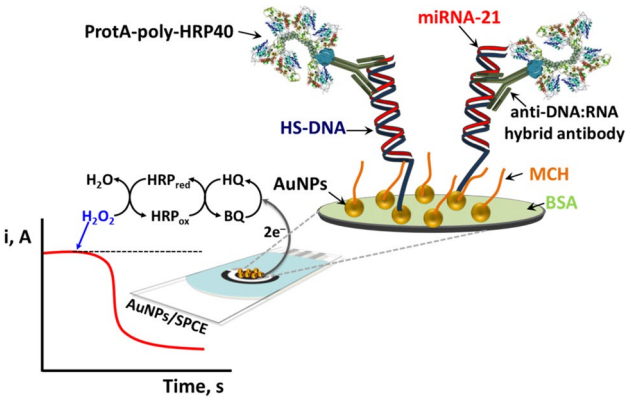

Fig. 5 Schematic Illustration of the biosensor architecture using AuNPs and Screen-Printed Carbon-Based Electrodes (SPCEs) for miRNA-21 amperometric measurement. Utilizing an anti-DNA-RNA antibody as a detection bioreceptor, further tagged with ProtA-PolyHRP40, is one step in the procedure along with direct DNA/miRNA hybridization and a particular HS DNA probe (Adapted from *Zouari* et al. 2018 [150] under an ACS AuthorChoice License. © 2018 American Chemical Society)

Amperometry

For the production of a disposable sensor for the accurate measurement of miRNA-21, a thiolated capture probe was affixed onto an electrode platform treated with gold nanoparticles (AuNPs). A direct hybridization assay that involved a particular antibody's selective and specific identification of the generated DNA–miRNA-21 heteroduplex was made easier by this immobilization. Further binding of horseradish peroxidase (HRP) and Protein A (ProtA) bind this antibody further, resulting in the creation of a strong sensing mechanism (Fig. 5). This biosensor's incorporation of amperometric amplification produced an astounding limit of detection (LOD) of 29 fM within a dynamic detection range of 0.1 to 25 pM [150]. Sarcosine oxidase (SOx) had been covalently immobilized onto a nanocomposite substrate made of chitosan with graphene nanoribbons (GNRs) and afterward electrically deposited atop a gold electrode, in a concurrent method to create second biosensor. With a low LOD of 0.001 µM, this electrochemical system showed a linear association over an effective concentration that ranged from 0.001 to 100 µM [151]. Both biosensors emphasize accuracy, preciseness, and variability in detecting procedures, adding to the growing repertory of electrochemical sensing technologies for various biological molecules.

Challenges

Selective analysis in electrochemical sensors is obtained by means of specific chemical processes occurring on the functionalized sensor interface. Although achieving maximal selectivity is still a difficult task, it is essential for addressing the common problem of random interactions in the majority of sensing technologies. Non-specific interactions may hinder the usefulness of the sensor framework for specific applications by introducing issues, including distorted sensor outputs, inaccurate readings, and challenges to reproducibility.

In order to overcome these challenges, the sensor's chemical barrier needs to be carefully engineered to optimize sensitivities to the intended reaction and reduce intervention from non-specific interactions. This means that in order to achieve the best results in terms of selectivity and sensitivity, the chemical layer's arrangement and composition must be carefully balanced. Thus, developments

leading to absolute selectivity improve the stability and dependability of electrochemical sensors and increase their usefulness in a range of applications.

Conclusion

Cancer is widely recognized as one of the most perilous diseases, resulting in millions of deaths each year. Because of its catastrophic effects on humans, it has become a big concern for academics and experts. Researchers have been attempting to discover the most up-to-date and effective methods for detecting, analyzing, and treating cancer. Cancer therapy has grown in popularity as a means of battling the disease. It is critical to find a way to reliably diagnose cancer in its early stages. Nanoparticles have a significant role in modern approaches due to their widespread application in medicine. The particles can be utilized to diagnose cancer and treat it effectively. This method assesses targets such as bioluminescent enzymes, fluorescent proteins, and numerous nanoparticles to evaluate microRNA function. Nanoparticles have various advantages over conventional probes, including adjustable physical properties, ease of surface modification, and lengthy circulation time. They can also be combined in a variety of ways for multimodal imaging and therapy. Another advantage of employing nanoparticles in imaging technology is that these cancer locating agents can be used to provide precise and accurate medication and treatment of cancer disease as soon as possible. Nanoparticles have multifunctional properties, and scientists will be able to use them to detect tumor subtypes such as heterogeneous and epigynous markings in the near future. Nanomaterials have special properties that make them an excellent fit for our needs. Recent developments in the discipline of diagnosing cancer early through the use of diverse nanostructures as biosensors, which have a broad variety of applications, are revolutionary. All the four major biomarkers like CTCs, CtDNA, Exosome and circulating miRNA, CtDNA, and CTCs are comparatively superior investigated, they have to be identical. Fluid biopsy forecasters such as cell-free microRNA and exosomes should be explored and validated. These topics were not discussed. Finally, fluid biopsy might become a standard medical reimbursement for many cancer patients in the near future.

Acknowledgements The authors would like to thank the Department of Chemistry, Faculty of Science, University of Tabuk, Saudi Arabia, for their ardent encouragement of their current project.

Funding This research received no external funding (self-funded).

Data availability All data is available in the script.

Declarations

Competing interests The authors declares no conflict of interest in this study.

References

1. GBD. 2015 Mortality and causes of death collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global burden of disease study 2015. Lancet. 2016;388:1459–544.
2. Do N, Grossman R, Feldman T, Fillmore N, Elbers D, Tuck D, Dhond R, et al. "The Veterans Precision Oncology Data Commons: transforming VA data into a national resource for research in precision oncology. In Sem Oncol. 2019;46(4–5):314–20.
3. Horton S, Gauvreau CL. Cancer in Low- and Middle Income Countries: an Economic Overview. In: Gelband H, Jha P, Sankaranarayanan R, et al. editors. SourceCancer: Disease Control Priorities, Third Edition (Volume 3). Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2015 Nov. Chapter 16
4. Nagai H, Kim YH. Cancer prevention from the perspective of global cancer burden patterns. J Thorac Dis. 2017;9(3):448.
5. Li J, Li S, Yang CF. Electrochemical biosensors for cancer biomarker detection. Electroanalysis. 2012;24(12):2213–29.
6. Goossens N, Nakagawa S, Sun X, Hoshida Y. Cancer biomarker discovery and validation. Transl Cancer Res. 2015;4(3):256–69.
7. Khoury JD, Wang WL, Prieto VG, Medeiros LJ, Kalhor N, Hameed M, Broaddus R, Hamilton SR. Validation of immunohistochemical assays for integral biomarkers in the NCI-MATCH EAY131 clinical trial validation of IHC integral marker assays. Clin Cancer Res. 2018;24(3):521–31.
8. Ausch C, Kim YH, Tsuchiya KD, Dzieciatkowski S, Washington MK, Paraskeva C, Radich J, Grady WM. Comparative analysis of PCR-based biomarker assay methods for colorectal polyp detection from fecal DNA. Clin Chem. 2009;55(8):1559–63.
9. Geisler C, Gaisa NT, Pfister D, Fuessel S, Kristiansen G, Braunschweig T, Gostek S, Beine B, Diehl HC, Jackson AM, Borchers CH. Identification and validation of potential new biomarkers for prostate cancer diagnosis and prognosis using 2D-DIGE and MS. BioMed Res Int. 2015.
10. Shlyapnikov YM, Malakhova EA, Vinarov AZ, Zamyatnin AA Jr, Shlyapnikova EA. Can new immunoassay techniques improve bladder cancer diagnostics with protein biomarkers? Front Mol Biosci. 2021;7:620687.
11. Al-Wajeeh AS, Salhimi SM, Al-Mansoub MA, Khalid IA, Harvey TM, Latiff A, Ismail MN. Comparative proteomic analysis of different stages of breast cancer tissues using ultra high performance liquid chromatography tandem mass spectrometer. PloS One. 2020;15(1):e0227404.
12. Hu R, Sou K, Takeoka S. A rapid and highly sensitive biomarker detection platform based on a temperature-responsive liposome-linked immunosorbent assay. Sci Rep. 2020;10(1):1–11.
13. Pulumati A, Pulumati A, Dwarakanath BS, Verma A, Papineni RVL. Technological advancements in cancer diagnostics: improvements and limitations. Cancer Rep (Hoboken). 2023;6(2):e1764.
14. Stobiecka M, Ratajczak K, Jakiela S. Toward early cancer detection: focus on biosensing systems and biosensors for an anti-apoptotic protein survivin and survivin mRNA. Biosens Bioelectron. 2019;137:58–71.

15. Bohunicky B, Mousa SA. Biosensors: the new wave in cancer diagnosis. Nanotechnol Sci Appl. 2010;30(4):1–10.
16. Arya S. K. and Estrela P., 2018 Recent advances in enhancement strategies for electrochemical ELISA-based immunoassays for cancer biomarker detection. Sensors (Switzerland), 18
17. Ranjan R, Esimbekova EN, Kratasyuk VA. Rapid biosensing tools for cancer biomarkers. Biosens Bioelectron. 2017;87:918.
18. Mahato K, Kumar A, Maurya PK, Chandra P. Shifting paradigm of cancer diagnoses in clinically relevant samples based on miniaturized electrochemical nanobiosensors and microfluidic devices. Biosens Bioelectron. 2018;100:411.
19. Freitas M, Nouws HPA, Delerue-Matos C. Electrochemical biosensing in cancer diagnostics and follow-up. Electroanalysis. 2018;30:1576.
20. Lassere MN. The biomarker-surrogacy evaluation schema: a review of the biomarker-surrogate literature and a proposal for a criterion-based, quantitative, multidimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. Stat Meth Med Res. 2008;17(3):303–40.
21. WHO. 2001 Biomarkers in risk assessment: Validity and validation. WHO
22. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89–95.
23. Topkaya SN, Azimzadeh M, Ozsoz M. Electrochemical biosensors for cancer biomarkers detection: recent advances and challenges. Electroanalysis. 2016;28(7):1402–19.
24. Cui F, Zhou Z, Zhou HS. Measurement and analysis of cancer biomarkers based on electrochemical biosensors. J Electrochem Soc. 2019;167(3):037525.
25. Varol T. Ö. 2020 Electrochemical Sensors and Biosensors for the Detection of Cancer Biomarkers and Drugs. In: H. S. Tuli (eds) Drug Targets in Cellular Processes of Cancer: From Nonclinical to Preclinical Models. https://doi.org/10.1007/978-981-15-7586-0_2
26. Sarhadi VK, Armengol G. Molecular biomarkers in cancer. Biomolecules. 2022;12(8):1021.
27. Liu H, Xu Y, Xiang J, Long L, Green S, Yang Z, Zimdahl B, Lu J, Cheng N, Horan LH, Liu B. Targeting alpha-fetoprotein (AFP)–MHC complex with CAR T-cell therapy for liver cancer CAR T therapy against AFP for the treatment of liver cancer. Clin Cancer Res. 2017;23(2):478–88.
28. Qin YY, Wu YY, Xian XY, Qin JQ, Lai ZF, Liao L, Lin FQ. Single and combined use of red cell distribution width, mean platelet volume, and cancer antigen 125 for differential diagnosis of ovarian cancer and benign ovarian tumors. J Ovarian Res. 2018;11(1):1–6.
29. Li X, Dai D, Chen B, Tang H, Xie X, Wei W. Clinicopathological and prognostic significance of cancer antigen 15–3 and carcinoembryonic antigen in breast cancer: a meta-analysis including 12,993 patients. Dis Mark. 2018.
30. Sekiguchi M, Matsuda T. Limited usefulness of serum carcinoembryonic antigen and carbohydrate antigen 19–9 levels for gastrointestinal and whole-body cancer screening. Sci Rep. 2020;10(1):1–10.
31. Kelleher M, Singh R, O'Driscoll CM, Melgar S. Carcinoembryonic antigen (CEACAM) family members and inflammatory bowel disease. Cytokine Growth Factor Rev. 2019;47:21–31.
32. Betz, D. and Fane, K., 2018. Human chorionic gonadotropin (HCG). 2023 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023
33. Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostat Diseas. 2018;21(1):57–63.
34. Chinen AB, Guan CM, Ferrer JR, Barnaby SN, Merkel TJ, Mirkin CA. Nanoparticle probes for the detection of cancer biomarkers, cells, and tissues by fluorescence. Chem Rev. 2015;115(19):10530–74.
35. Nikhil B, Pawan J, Nello F, Pedro E. Introduction to biosensors. Essays Biochem. 2016;60(1):1–8.
36. Heineman WR, Jensen WB. Leland C. Clark Jr. (1918–2005). Biosens Bioelectron. 2006;8(21):1403–4.
37. Cremer, M., 1906. Über die Ursache der elektromotorischen Eigenschaften der Gewebe, zugleich ein Beitrag zur Lehre von den polyphasischen Elektrolytketten. R. Oldenbourg.
38. Sörensen, S.P.L., 1909. Uber die Messung und die Bedeutung der Wasserstoffionenkonzentration bei enzymatischen Prozessen.
39. Griffin EG, Nelson JM. The influence of certain substances on the activity of invertase. J Am Chem Soc. 1916;38(3):722–30.
40. Nelson JM, Griffin EG. Adsorption of invertase. J American Chem Soc. 1916;38(5):1109–15.
41. Hughes WS. The potential difference between glass and electrolytes in contact with the glass. J American Chem Soc. 1922;44(12):2860–7.
42. Karunakaran, C., Rajkumar, R. and Bhargava, K., 2015. Introduction to biosensors. In Biosensors and bioelectronics (pp. 1–68). Elsevier.
43. Heineman WR, Jensen WB. Leland c clark jr (1918–2005). Biosens Bioelectron. 2006;8(21):1403–4.
44. Clark LC Jr, Lyons C. Electrode systems for continuous monitoring in cardiovascular surgery. Ann New York Acad Sci. 1962;102(1):29–45.
45. Updike SJ, Hicks GP. The enzyme electrode. Nature. 1967;214:986–8.
46. Guilbault GG, Montalvo JG Jr. Urea-specific enzyme electrode. J American Chem Soc. 1969;91(8):2164–5.
47. Bergveld P. Development of an ion-sensitive solid-state device for neurophysiological measurements. IEEE Trans Biomed Eng. 1970;1:70–1.
48. Guilbault GG, Lubrano GJ. An enzyme electrode for the amperometric determination of glucose. Analytica chimica acta. 1973;64(3):439–55.
49. Mosbach K, Danielsson B. An enzyme thermistor. Biochimica et Biophysica Acta (BBA)-Enzymology. 1974;364(1):140–5.
50. Lübbers DW, Opitz N. The pCO2-/pO2-optode: a new probe for measurement of pCO2 or pO in fluids and gases (authors transl). Zeitschrift fur Naturforschung, Biosci. 1975;30(4):532–3.
51. Newman JD, Turner AP. Home blood glucose biosensors: a commercial perspective. Biosens Bioelectron. 2005;20(12):2435–53.
52. D'Orazio P. Biosensors in clinical chemistry. Clinica chimica acta. 2003;334(1–2):41–69.
53. Suzuki S, Takahashi F, Satoh I, Sonobe N. Ethanol and lactic acid sensors using electrodes coated with dehydrogenase—Collagen membranes. Bullet Chem Soc Japan. 1975;48(11):3246–9.
54. Clemens, A.H., Chang, P.H. and Myers, R.W., 1976. Le développement d'un système automatique d'infusion d'insuline controle par la glycemie, son système de dosage du glucose et ses algorithmes de controle. Journ. Annu. Diabétol. Hotel Dieu, pp.269–278.
55. Yoo EH, Lee SY. Glucose biosensors: an overview of use in clinical practice. Sensors. 2010;10(5):4558–76.
56. Schultz, J.S. 1982 Optical Sensor of Plasma Constituents. U.S. Patent No. 4,344,438A
57. Liedberg B, Nylander C, Lunström I. Surface plasmon resonance for gas detection and biosensing. Sens Actuat. 1983;4:299–304.
58. Roederer JE, Bastiaans GJ. Microgravimetric immunoassay with piezoelectric crystals. Analytic Chem. 1983;55(14):2333–6.
59. Cass AE, Davis G, Francis GD, Hill HAO, Aston WJ, Higgins IJ, Plotkin EV, Scott LD, Turner AP. Ferrocene-mediated

enzyme electrode for amperometric determination of glucose. Analyt Chem. 1984;56(4):667–71.
60. Mun'delanji, C.V.; Tamiya, E. Nanobiosensors and nanobioanalyses: A Review. In Nanobiosensors and Nanobioanalyses, 1st ed.; Mun'delanji, C.V., Kerman, K., Hsing, I.M., Tamiya, E., Eds.; Springer: Tokyo, Japan, 2015; pp. 3–20.
61. Poncharal P, Wang ZL, Ugarte D, De Heer WA. Electrostatic deflections and electromechanical resonances of carbon nanotubes. Science. 1999;283(5407):1513–6.
62. Serra, P.A. 2011. Biosensors for health, environment and biosecurity. BoD–Books on Demand. https://doi.org/10.5772/928
63. Nayak V, Singh KR, Verma R, Pandey MD, Singh J, Singh RP. Recent advancements of biogenic iron nanoparticles in cancer theranostics. Mater Lett. 2022;313:131769.
64. Chaturvedi VK, Sharma B, Tripathi AD, Yadav DP, Singh KR, Singh J, Singh RP. Biosynthesized nanoparticles: a novel approach for cancer therapeutics. Front Med Technol. 2023.
65. Augustine S, Singh J, Srivastava M, Sharma M, Das A, Malhotra BD. Recent advances in carbon based nanosystems for cancer theranostics. Biomater Sci. 2017;5(5):901–52.
66. Nisar S, Chansi Mathur A, Basu T, Singh KR, Singh J. Template free anisotropically grown gold nanocluster based electrochemical immunosensor for ultralow detection of cardiac troponin I. Biosensors. 2022;12(12):1144.
67. Pundir CS, Chauhan N. Acetylcholinesterase inhibition-based biosensors for pesticide determination: a review. Analyt Biochem. 2012;429(1):19–31.
68. Ogi H. Wireless-electrodeless quartz-crystal-microbalance biosensors for studying interactions among biomolecules: a review. Proc Jan Acad Ser B. 2013;89(9):401–17.
69. Ko PJ, Ishikawa R, Sohn H, Sandhu A. Porous silicon platform for optical detection of functionalized magnetic particles biosensing. J Nanosci Nanotechnol. 2013;13(4):2451–60.
70. Vigneshvar S, Senthilkumaran B. Current technological trends in biosensors, nanoparticle devices and biolabels: Hi-tech network sensing applications. Med Dev Sens. 2018;1(2):e10011.
71. Schneider E, Clark DS. Cytochrome P450 (CYP) enzymes and the development of CYP biosensors. Biosens Bioelectron. 2013;39(1):1–13.
72. Khimji I, Kelly EY, Helwa Y, Hoang M, Liu J. Visual optical biosensors based on DNA-functionalized polyacrylamide hydrogels. Methods. 2013;64(3):292–8.
73. Peng F, Su Y, Zhong Y, Fan C, Lee ST, He Y. Silicon nanomaterials platform for bioimaging, biosensing, and cancer therapy. Accounts Chem Res. 2014;47(2):612–23.
74. Wang B, Anzai JI. Recent progress in electrochemical HbA1c sensors: a review. Materials. 2015;8(3):1187–203.
75. Randriamampita C, Lellouch AC. Imaging early signaling events in T lymphocytes with fluorescent biosensors. Biotechnol J. 2014;9(2):203–12.
76. Oldach L, Zhang J. Genetically encoded fluorescent biosensors for live-cell visualization of protein phosphorylation. Chem Biol. 2014;21(2):186–97.
77. Kunzelmann, S., Solscheid, C. and Webb, M.R., 2014. Fluorescent biosensors: design and application to motor proteins. Fluorescent Methods for Molecular Motors. Springer Basel. Basel. pp. 25–47
78. Wang S, Poon GM, Wilson WD. Quantitative investigation of protein-nucleic acid interactions by biosensor surface plasmon resonance. Methods Mol Biol. 2015;1334:313–32.
79. Garcia-Gomez NA, Balderas-Renteria I, Garcia-Gutierrez DI, Mosqueda HA, Sánchez EM. Development of mats composed by TiO2 and carbon dual electrospun nanofibers: a possible anode material in microbial fuel cells. Mater Sci Eng: B. 2015;193:130–6.
80. Gribi S, Bois Du, de Dunilac S, Ghezzi D, Lacour SP. A microfabricated nerve-on-a-chip platform for rapid assessment of neural conduction in explanted peripheral nerve fibers. Nat Communicat. 2018;9(1):1–10.
81. Kim J, Campbell AS, de Ávila BEF, Wang J. Wearable biosensors for healthcare monitoring. Nat Biotechnol. 2019;37(4):389–406.
82. Saylan Y, Erdem Ö, Ünal S, Denizli A. An alternative medical diagnosis method: biosensors for virus detection. Biosensors. 2019;9(2):65.
83. Jiang Z, Feng B, Xu J, Qing T, Zhang P, Qing Z. Graphene biosensors for bacterial and viral pathogens. Biosens Bioelectron. 2020;166:112471.
84. Inda ME, Lu TK. Microbes as biosensors. Annual Rev Microbiol. 2020;74:337–59.
85. Jain S, Nehra M, Kumar R, Dilbaghi N, Hu T, Kumar S, Kaushik A, Li CZ. Internet of medical things (IoMT)-integrated biosensors for point-of-care testing of infectious diseases. Biosens Bioelectron. 2021;179:113074.
86. Karimi-Maleh H, Orooji Y, Karimi F, Alizadeh M, Baghayeri M, Rouhi J, Tajik S, Beitollahi H, Agarwal S, Gupta VK, Rajendran S. A critical review on the use of potentiometric based biosensors for biomarkers detection. Biosens Bioelectron. 2021;184:113252.
87. Alwarappan S, Nesakumar N, Sun D, Hu TY, Li CZ. 2D metal carbides and nitrides (MXenes) for sensors and biosensors. Biosens Bioelectron. 2022.
88. Kaur B, Kumar S, Kaushik BK. Recent advancements in optical biosensors for cancer detection. Biosens Bioelectron. 2022;197:113805.
89. Fu X, Ding B, D'Alessandro D. Fabrication strategies for metal-organic framework electrochemical biosensors and their applications. Coordinat Chem Rev. 2023;475:214814.
90. Galyamin D, Liébana S, Esquivel JP, Sabaté N. Immuno-battery: a single use self-powered immunosensor for reassured diagnostics. Biosens Bioelectron. 2023;220:114868.
91. Naresh V, Lee N. A review on biosensors and recent development of nanostructured materials-enabled biosensors. Sensors. 2021;21(4):1109.
92. Coccia M, Roshani S, Mosleh M. Scientific developments and new technological trajectories in sensor research. Sensors. 2021;21(23):7803.
93. Khan MA, Mujahid M. Recent advances in electrochemical and optical biosensors designed for detection of Interleukin 6. Sensors. 2020;20(3):646.
94. Damborský P, Švitel J, Katrlík J. Optical biosensors. Essays Biochem. 2016;60(1):91–100.
95. Kurbanoglu S, et al. Chemical nanosensors in pharmaceutical analysis. In: New developments in nanosensors for pharmaceutical analysis. Amsterdam: Elsevier; 2019. p. 141–70.
96. Qian L, Li Q, Baryeh K, Qiu W, Li K, Zhang J, Yu Q, Xu D, Liu W, Brand RE, Zhang X. Biosensors for early diagnosis of pancreatic cancer: a review. Trans Res. 2019;213:67–89.
97. Chang J, Wang X, Wang J, Li H, Li F. Nucleic acid-functionalized metal-organic framework-based homogeneous electrochemical biosensor for simultaneous detection of multiple tumor biomarkers. Anal Chem. 2019;91:3604–10.
98. Zhang X, Xie G, Gou D, Luo P, Yao Y, Chen H. A novel enzyme-free electrochemical biosensor for rapid detection of Pseudomonas aeruginosa based on high catalytic Cu-ZrMOF and conductive Super P. Biosens Bioelectron. 2019;142:111486.
99. Zhang X, Yu Y, Shen J, Qi W, Wang H. Design of organic/inorganic nanocomposites for ultrasensitive electrochemical detection of a cancer biomarker protein. Talanta. 2020;212:120794.
100. Khanmohammadi A, Aghaie A, Vahedi E, Qazvini A, Ghanei M, Afkhami A, Hajian A, Bagheri H. Electrochemical biosensors for the detection of lung cancer biomarkers: a review. Talanta. 2020;206:120251.

101. Vijayan VM, Jothi L, Arunagirinathan RS, Nageswaran G. Recent advances in the electrochemical sensing of lung cancer biomarkers. Biosens Bioelectron: X. 2022;12:100235.
102. da Silva ET, Souto DE, Barragan JT, De Giarola J, De Moraes AC, Kubota LT. Electrochemical biosensors in point-of-care devices: recent advances and future trends. Chemelectrochem. 2017;4(4):778–94.
103. Sandhyarani N. Surface modification methods for electrochemical biosensors. In: Electrochemical biosensors. Amsterdam: Elsevier; 2019. p. 45–75.
104. Scholz F. Voltammetric techniques of analysis: the essentials. ChemTexts. 2015;1(4):17.
105. Anik Ü. Electrochemical medical biosensors for POC applications. In: Medical biosensors for point of care (POC) applications. Amsterdam: Elsevier; 2017. p. 275–92.
106. Luo Y, Wang Y, Yan H, Wu Y, Zhu C, Du D, Lin Y. SWCNTs@GQDs composites as nanocarriers for enzyme-free dual-signal amplification electrochemical immunoassay of cancer biomarker. Anal Chim Acta. 2018;1042:44–51.
107. Paimard G, et al. An Impedimetric Immunosensor modified with electrospun core-shell nanofibers for determination of the carcinoma embryonic antigen. Sens Actuat B Chem. 2020;311:127928.
108. Butmee P, et al. An ultrasensitive immunosensor based on manganese dioxide-graphene nanoplatelets and core shell Fe3O4@ Au nanoparticles for label-free detection of carcinoembryonic antigen. Bioelectrochemistry. 2020;132:107452.
109. Ehzari H, Amiri M, Safari M. Enzyme-free sandwich-type electrochemical immunosensor for highly sensitive prostate specific antigen based on conjugation of quantum dots and antibody on surface of modified glassy carbon electrode with core–shell magnetic metal-organic frameworks. Talanta. 2020;210:120641.
110. Heidari R, Rashidiani J, Abkar M, Taheri RA, Moghaddam MM, Mirhosseini SA, Seidmoradi R, Nourani MR, Mahboobi M, Keihan AH, Kooshki H. CdS nanocrystals/graphene oxide-AuNPs based electrochemiluminescence immunosensor in sensitive quantification of a cancer biomarker: p53. Biosens Bioelectron. 2019;126:7–14.
111. Jeong S, Barman SC, Yoon H, Park JY. A Prostate cancer detection immunosensor based on nafion/reduced graphene oxide/aldehyde functionalized methyl pyridine composite electrode. J Electrochem Soc. 2019;166:B920.
112. Ibau C, Arshad MK, Gopinath SCB, Nuzaihan Fathil MMF, Estrela P. Gold interdigitated triple-microelectrodes for label-free prognosticative aptasensing of prostate cancer biomarker in serum. Biosens Bioelectron. 2019;136:118.
113. Sharifuzzaman M, Barman SC, Rahman MT, Zahed MA, Xuan X, Park JY. Green synthesis and layer-by-layer assembly of amino-functionalized graphene oxide/carboxylic surface modified trimetallic nanoparticles nanocomposite for label-free electrochemical biosensing. J Electrochem Soc. 2019;166:B983.
114. Jafari-Kashi A, Rafiee-Pour HA, Shabani-Nooshabadi M. A new strategy to design label-free electrochemical biosensor for ultrasensitive diagnosis of CYFRA 21–1 as a biomarker for detection of non-small cell lung cancer. Chemosphere. 2022;301:134636.
115. Chen M, Wang Y, Su H, Mao L, Jiang X, Zhang T, Dai X. Three-dimensional electrochemical DNA biosensor based on 3D graphene-Ag nanoparticles for sensitive detection of CYFRA21-1 in non-small cell lung cancer. Sens Actuat B: Chem. 2018;255:2910–8.
116. Zeng Y, Bao J, Zhao Y, Huo D, Chen M, Yang M, Fa H, Hou C. A sensitive label-free electrochemical immunosensor for detection of cytokeratin 19 fragment antigen 21–1 based on 3D graphene with gold nanoparticle modified electrode. Talanta. 2018;178:122–8.
117. Shi P, et al. Non-covalent modification of glassy carbon electrode with isoorientin and application to alpha-fetoprotein detection by fabricating an immunosensor. Sens Actuat B Chem. 2020;305:127494.
118. Zhang X, Li Y, Lv H, Gao Z, Zhang C, Zhang S, Wang Y, Xu Z, Zhao Z. Electrochemical immunosensor with enhanced stability for sensitive detection of α-fetoprotein based on Pd@Ag@CeO2 as signal amplification label. J Electrochem Soc. 2018;165:B931.
119. Zhang X, et al. Sandwich-type electrochemical immunosensor based on Au@ Ag supported on functionalized phenolic resin microporous carbon spheres for ultrasensitive analysis of α-fetoprotein. Biosens Bioelectron. 2018;106:142–8.
120. Ma E, et al. Electrochemical immunosensors for sensitive detection of neuron-specific enolase based on small size trimetallic Au@ Pd^Pt nanocubes functionalized on ultrathin MnO2 nanosheets as signal labels. ACS Biomater Sci Eng. 2020;6(3):1418–27.
121. Zhao L, Kong D, Wu Z, Liu G, Gao Y, Yan X, Liu F, Liu X, Wang C, Cui J, Lu G. Interface interaction of MoS_2 nanosheets with DNA based aptameric biosensor for carbohydrate antigen 15–3 detection. Microchem J. 2020;155:104675.
122. Khoshroo A, Mazloum-Ardakani M, Forat-Yazdi M. Enhanced performance of labelfree electrochemical immunosensor for carbohydrate antigen 15–3 based on catalytic activity of cobalt sulfide/graphene nanocomposite. Sens Actuat B Chem. 2018;255:580–7.
123. Senel M, Dervisevic M, Kokkokoğlu F. Electrochemical DNA biosensors for label-free breast cancer gene marker detection. Analyt Bioanalytic Chem. 2019;411(13):2925–35.
124. Saadati A, et al. A novel biosensor for the monitoring of ovarian cancer tumor protein CA 125 in untreated human plasma samples using a novel nano-ink: a new platform for efficient diagnosis of cancer using paper based microfluidic technology. Anal Methods. 2020;12(12):1639–49.
125. Chauhan D, Nohwal B, Pundir C. An electrochemical CD59 targeted noninvasive immunosensor based on graphene oxide nanoparticles embodied pencil graphite for detection of lung cancer. Microchem J. 2020;156:104957.
126. Jalil O, Pandey CM, Kumar D. Electrochemical biosensor for the epithelial cancer biomarker EpCAM based on reduced graphene oxide modified with nanostructured titanium dioxide. Microchim Acta. 2020;187:1–9.
127. Li X, Peng G, Cui F, Qiu Q, Chen X, Huang H. Double determination of long noncoding RNAs from lung cancer via multi-amplified electrochemical genosensor at sub-femtomole level. Biosens Bioelectron. 2018;113:116–23.
128. Jayanthi VSPKSA, Das AB, Saxena U. Fabrication of an immunosensor for quantitative detection of breast cancer biomarker UBE2C. RSC Adv. 2019;9:16738.
129. Xu W, et al. A signal-decreased electrochemical immunosensor for the sensitive detection of LAG-3 protein based on a hollow nanobox-MOFs/AuPt alloy. Biosens Bioelectron. 2018;113:148–56.
130. Kuntamung K, Jakmunee J, Ounnunkad K. A label-free multiplex electrochemical biosensor for the detection of three breast cancer biomarker proteins employing dye/metal ion-loaded and antibody-conjugated polyethyleneimine-gold nanoparticles. J Mater Chem B. 2021;9(33):6576–85.
131. Shoja Y, Kermanpur A, Karimzadeh F. Diagnosis of EGFR exon21 L858R point mutation as lung cancer biomarker by electrochemical DNA biosensor based on reduced graphene oxide/functionalized ordered mesoporous carbon/Ni-oxytetracycline metallopolymer nanoparticles modified pencil graphite electrode. Biosens Bioelectron. 2018;113:108–15.
132. Amani J, et al. An electrochemical immunosensor based on poly p-phenylenediamine and graphene nanocomposite for detection

of neuron-specific enolase via electrochemically amplified detection. Anal Biochem. 2018;548:53–9.
133. Khodadoust A, Nasirizadeh N, Seyfati SM, Taheri RA, Ghanei M, Bagheri H. High-performance strategy for the construction of electrochemical biosensor for simultaneous detection of miRNA-141 and miRNA-21 as lung cancer biomarkers. Talanta. 2023;252:123863.
134. Sabahi A, Salahandish R, Ghaffarinejad A, Omidinia E. Electrochemical nano-genosensor for highly sensitive detection of miR-21 biomarker based on SWCNT-grafted dendritic Au nanostructure for early detection of prostate cancer. Talanta. 2020;209:120595.
135. Hasanzadeh M, Shadjou N, de la Guardia M. Early-stage screening of breast cancer using electrochemical biomarker detection. TrAC - Trends Anal Chem. 2017;91:67.
136. Raji MA, Amoabediny G, Tajik P, Hosseini M, Ghafar-Zadeh E. An aptabiosensor for colon cancer diagnostics. Sensors (Switzerland). 2015;15:22291.
137. Zeng Y, Bao J, Zhao Y, Huo D, Chen M, Qi Y, Yang M, Fa H, Hou C. A sandwich-type electrochemical immunoassay for ultrasensitive detection of non-small cell lung cancer biomarker CYFRA21-1. Bioelectrochemistry. 2018;120:183–9.
138. Freitas M, Nouws HPA, Keating E, Delerue-Matos C. High-performance electrochemical immunomagnetic assay for breast cancer analysis. Sens Actuat B Chem. 2020;308:127667.
139. Boriachek K, Umer M, Islam MN, Gopalan V, Lam AK, Nguyen NT, Shiddiky MJA. An amplification-free electrochemical detection of exosomal miRNA-21 in serum samples. Analyst. 2018;143:1662–9.
140. Pacheco JG, Rebelo P, Freitas M, Nouws HPA, Delerue-Matos C. Breast cancer biomarker (HER2-ECD) detection using a molecularly imprinted electrochemical sensor. Sens Actuat B Chem. 2018;273:1008–14.
141. Pacheco JG, Silva MSV, Freitas M, Nouws HPA, Delerue-Matos C. Molecularly imprinted electrochemical sensor for the point-of-care detection of a breast cancer biomarker (CA 15–3). Sensor Actuator B Chem. 2018;256:905–12.
142. An L, Wang G, Han Y, Li T, Jin P, Liu S. Electrochemical biosensor for cancer cell detection based on a surface 3D micro-array. Lab Chip. 2018;18:335.
143. Zandi A, Gilani A, Abbasvandi F, Katebi P, Tafti SR, Assadi S, Moghtaderi H, Parizi MS, Saghafi M, Khayamian MA, Davarish Z, Hoseinpour P, Gity M, Sanati H, Abdolahad M. Carbon nanotube based dielectric spectroscopy of tumor secretion; electrochemical lipidomics for cancer diagnosis. Biosens Bioelectron. 2019;142:111566.
144. Dowling CM, Herranz Ors C, Kiely PA. Using real-time impedance-based assays to monitor the effects of fibroblast-derived media on the adhesion, proliferation, migration and invasion of colon cancer cells. Biosci Rep. 2014;34:415.
145. Parekh A, Das D, Das S, Dhara S, Biswas K, Mandal M, Das S. Bioimpedimetric analysis in conjunction with growth dynamics to differentiate aggressiveness of cancer cells. Sci Rep. 2018;8:1.
146. Xiao F, Wang L, Duan H. Nanomaterial based electrochemical sensors for in vitro detection of small molecule metabolites. Biotechnol Adv. 2016;34(3):234–49.
147. Cardoso AR, et al. Novel and simple electrochemical biosensor monitoring attomolar levels of miRNA-155 in breast cancer. Biosens Bioelectron. 2016;80:621–30.
148. Nayak V, Patra S, Singh KR, Ganguly B, Kumar DN, Panda D, Maurya GK, Singh J, Majhi S, Sharma R, Pandey SS. Advancement in precision diagnosis and therapeutic for triple-negative breast cancer: Harnessing diagnostic potential of CRISPR-cas & engineered CAR T-cells mediated therapeutics. Environ Res. 2023;235:116573.
149. Luo L, Wang L, Zeng L, Wang Y, Weng Y, Liao Y, Chen T, Xia Y, Zhang J, Chen J. A ratiometric electrochemical DNA biosensor for detection of exosomal MicroRNA. Talanta. 2020;207:120298.
150. Zouari M, Campuzano S, Pingarrón JM, Raouafi N. Amperometric biosensing of miRNA-21 in serum and cancer cells at nanostructured platforms using anti-DNA-RNA hybrid antibodies. ACS Omega. 2018;3(8):8923–31.
151. Deswal R, Narwal V, Kumar P, Verma V, Dang AS, Pundir CS. An improved amperometric sarcosine biosensor based on graphene nanoribbon/chitosan nanocomposite for detection of prostate cancer. Sensors Int. 2022;3:100174.