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Innovative Graphene-Based Electrochemical Biosensors: Advancing Precision in Cancer Diagnostics

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Abstract. Cancer is caused by malignant cell proliferation, invasive and metastatic, which is a serious threat to human health, while early diagnosis and treatment of cancer is the key to reduce the mortality rate. In recent years, research on cancer biomarkers such as DNA, RNA, and protein has gradually attracted more and more scientists' attention, and these markers have specificity and can be specifically recognized to achieve early detection and diagnosis of cancer. Therefore, bio electrochemical sensors targeting different cancer biomarkers have been developed, which have a potential value in facilitating the diagnosis, treatment and prognosis assessment of cancer due to their advantages of high sensitivity, high selectivity, low cost, ease of manipulation and short response time. Graphene and its derivatives possess unique physicochemical properties based on their two-dimensional structure, which include thin thickness, high electrical conductivity and high thermal conductivity, good hydrophilicity, excellent biocompatibility and low toxicity, and thus graphene-based nanomaterials have been widely used in the development of such electrochemical biosensors. In this review, we summarize the properties of graphene and a series of its derivatives also including their preparation methods, introduce the types and principle of electrochemical biosensors, and outlines the value of electrochemical sensors based on graphene and its derivatives in the clinical treatment of lung cancer, hematologic malignancies, and pancreatic cancer.

Keywords: Biosensor, Electrochemical, Graphene, Nanoparticles, Cancer diagnosis

1. Introduction

In recent years, graphene-based electrochemical biosensors have attracted much attention due to their great potential for early diagnosis of cancer. As a two-dimensional material, graphene has a large specific surface area, excellent electrical conductivity and mechanical properties, making it an ideal material for electrochemical biosensors. Graphene and its derivatives, such as reduced graphene oxide (rGO) and graphene oxide (GO), exhibit unique advantages over traditional materials in applications. For example, GO has greater hydrophilicity and good processability due to the oxygen functional groups it contains, while rGO improves dispersibility in solvents by reducing

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the oxygen content while maintaining high electrical conductivity [1,2]. These properties make graphene widely used for cancer biomarker detection. To more nearly improve the sensitivity and specificity of biosensors, graphene-based nanoparticle materials are also used to modify electrodes.

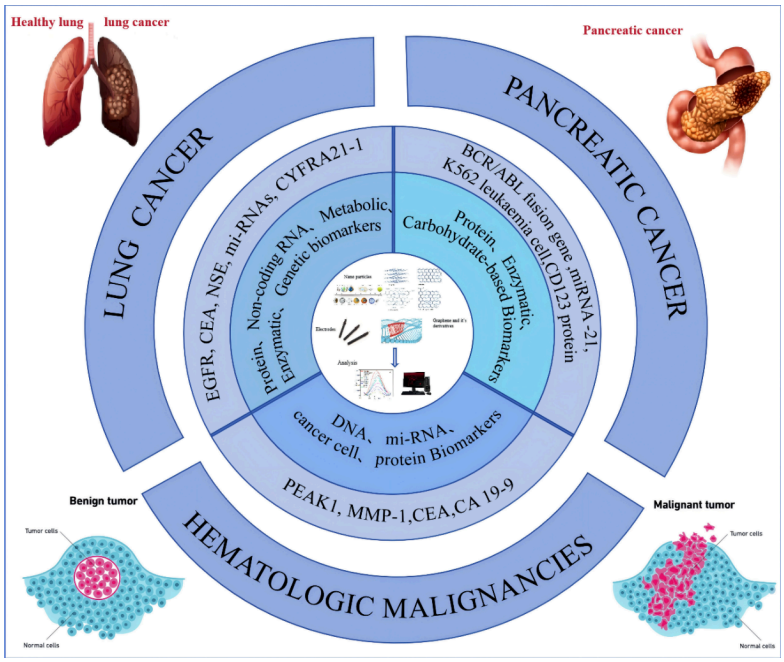


Figure 1. The biomarkers of lung cancer, hematologic malignancies and pancreatic cancer

In the detection of markers of cancer, electrochemical biosensors achieve highly sensitive detection of specific cancer biomarkers by immobilising biorecognition elements (e.g., antibodies, DNA, or aptamers) on the graphene surface. These biomarkers include proteins, DNA, RNA, etc. associated with lung cancer, malignant blood cancers and pancreatic cancers in Figure 1. Taking lung cancer as an example, non-small cell lung cancer (NSCLC) represents the most common form of lung cancer, comprising nearly 85% of all cases, and its early diagnosis is crucial for improving patient survival [1]. Malignant haematological tumours such as acute lymphoblastic leukaemia (ALL) have a high incidence in children and early diagnosis can be aided by testing biomarkers such as the BCR/ABL fusion gene [3]. Pancreatic cancer has a low survival rate, but by detecting specific protein biomarkers such as CA19-9, it can help to improve the efficiency of early screening [4].

For the selection of biosensors, compared to other types of detection methods, such as optical, electrochemical biosensors have the benefits of simple operation, low cost, and environmental adaptability. These types of sensors can provide an effective means for early diagnosis of cancer based on real-time monitoring of biomarker concentration changes. In addition, graphene was chosen because, possessing excellent electrochemical properties and a large specific surface area gives it a unique advantage in improving sensor sensitivity and selectivity.

The highlight of this work is the systematic summary of the synthesis methods of graphene and its derivatives, which covers almost all known top-down and bottom-up. Particularly the electrochemical synthesis analysis, namely the electrochemical exfoliation approach and the arc discharge method, is analyzed. In addition, most of the different types of electrochemical sensors included in the detection methods, amperometry, voltammetry and impedance spectroscopy, etc. On this basis, this paper also provides a detailed classification and overview of the application of graphene-based electrochemical biosensors in the detection of cancer biomarkers, involving the

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detection methods of various biomarkers such as lung cancer, hematologic malignancies and pancreatic cancer. Compared with other related reviews, this review is more comprehensive, especially covering the application of graphene-based materials in different types of cancer biomarkers, such as protein markers and genetic markers. A wider range of detection methods and practical application cases are provided. In contrast, existing literature usually focuses on specific synthesis techniques or detection of specific cancer types, while this review provides a more systematic analysis in terms of both breadth and depth. Therefore, this review provides important reference materials and comprehensive insights for future research.

2. Graphene and its derivatives, and their synthesis

Graphene, also known as monolayer graphene, consists of a network of planar structures in the form of a honeycomb layer of carbon atoms, with three neighboring carbon atoms sharing sp^2 electrons [5]. It is one of the thinnest materials in the world, with a thickness of only 0.334 nanometers [6]. Graphene offers many advantages, such as high electrical and thermal conductivity, oxidation resistance, high sensitivity, and a large surface area. These properties make graphene widely used in healthcare sensors, particularly for detecting early-stage cancer, as well as in electrochemical biosensors, coatings, and more.

To overcome the challenges of producing low-cost and high-quality graphene, several derivatives, such as reduced graphene oxide (rGO) and graphene oxide (GO) have been developed. Graphene oxide retains graphene's hexagonal carbon arrangement but included oxygen-containing functional groups, such as carbonyl groups and hydroxyl, attached to the edges and substrate planes [1]. GO dissolves well in water and polar solvents, forming negatively charged surfaces that are stable in these solutions due to the presence of carboxylic acid groups. However, hydroxyl and epoxy groups contribute weaker interactions with other functional groups [5]. Reduced graphene oxide (rGO) has fewer oxygen-containing groups than GO [1]. The transformation from GO to rGO involves removing oxygen atoms, which restores its electrical conductivity while maintaining biocompatibility due to the formation of a more intact graphite network [5]. This derivative is widely used in biomedicine, cell culture, and biosensors.

Graphene quantum dots (GQDs) consist of tiny fragments of graphene, typically less than 20 nm in size [7]. GQDs offer improved biocompatibility and reduced toxicity because they do not contain heavy metals typically used in conventional quantum dot synthesis. Additionally, their photoluminescence properties can be tuned based on their size, shape, and defects, which makes them idea for use in cell imaging and drug delivery [5].

Graphene and its derivatives are synthesized through two major approaches: top-down and bottom-up. The top-down method involves breaking down graphite into smaller structures and the bottom-up method builds graphene from smaller hydrocarbons using techniques like organic synthesis and chemical vapor deposition (CVD) (figure 2). Both approaches are key to tailoring graphene properties for various applications, particularly in the fields of electronics, biomedicine, and sensing technologies.

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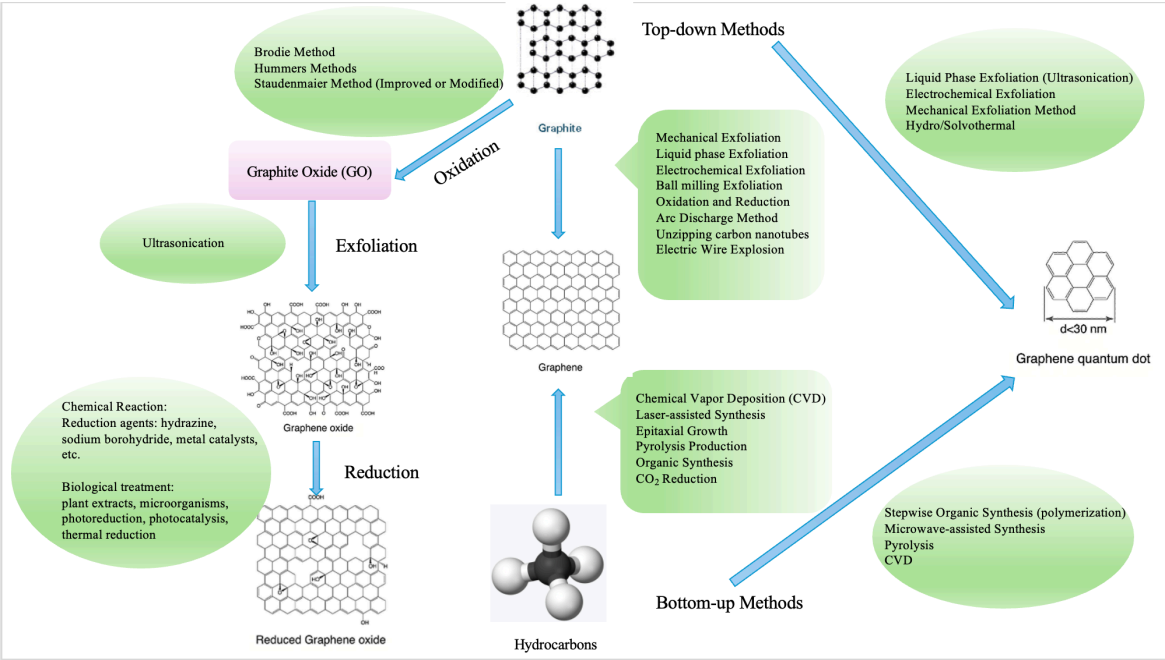


Figure 2. Summary of the synthesis of graphene and its derivatives (structural images of derivatives from [5])

2.1. Top-down approach

In the top-down preparation method, graphite is used as the starting material, and there are eight commonly used preparation techniques, including liquid phase exfoliation, mechanical exfoliation, electrochemical exfoliation, arc discharge, oxidation and reduction, unzipping carbon nanotube, electric wire explosion and ball milling exfoliation [8]. Of these, the same applies to obtaining the product graphene quantum dot by liquid phase exfoliation and electrochemical exfoliation (GQD). In addition, graphene oxide was used as a pristine material to produce GQDs by hydro/solvothermal with KOH at 200 degrees Celsius [9]. The following section focuses on the top-down synthetic approach with respect to electrochemical aspects. Two electrochemical top-down methods, namely electrochemical exfoliation and arc discharge method will be mentioned for the preparation of graphene in the following.

2.1.1. Electrochemical exfoliation approach

Electrolysis is required to prepare a monolayer of graphene, consisting of a counter electrode made of platinum or graphene material, a power supply, an electrolyte and a graphite electrode. The two electrodes are immersed in the electrolyte, and a voltage is applied to the electrodes to cause expansion. The graphene layer floats to the surface of the electrolyte. By applying a voltage, ions in the electrolyte enter the layered structure of the graphite, separating the layers. The electrolysis process is the flow of current through the electrodes of an appropriate electrolyte, thereby producing few-layer or single-layer graphene. Conductive materials, carbon sticks or tungsten are attached to the electrodes to make them more conductive. Typically, graphite electrodes are used, which are made from highly ordered graphite material [10]. In addition, graphene derivatives such as GQDs or graphene oxide can be obtained by using different electrolyte types, intercalation ion sizes and degrees of intercalation [11]. There are two electrochemical exfoliation methods. One of these, the

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anodic exfoliation method, works on the principle that with the aid of ultrasound and by means of a water bath, an oxidation reaction occurs at the graphite electrode (anode), and water and sulfate ions from the electrolyte intercalate into the graphite layer. Voltage causes the intercalated ions to penetrate between the graphite layers, producing bubbles with Sulphur dioxide and oxygen. The whole setup is outside the ultrasonic waves, inside a borosilicate beaker, consisting of a pure graphite anode, a titanium electrode, i.e. the cathode, clad in platinum, and an electrolyte consisting of sulphuric acid and distilled water. The two electrodes, anode and cathode, are placed vertically in the electrolyte, 5 cm apart in figure 3 [12]. Another cathodic stripping electrochemical method can produce high-quality few-layer graphene sheets.

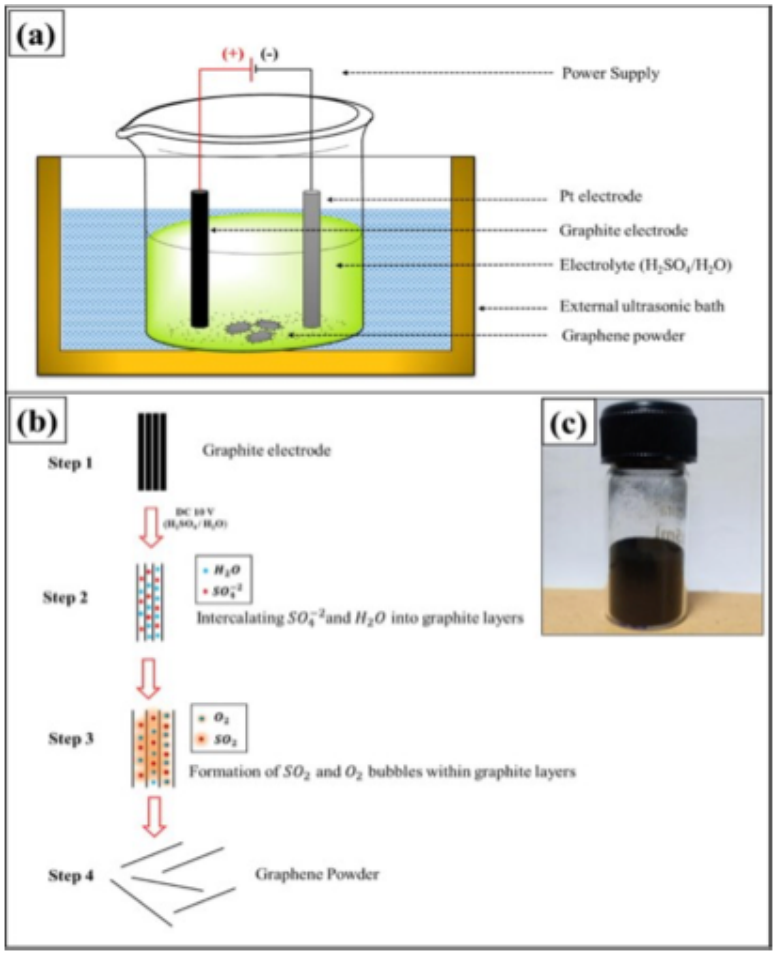


Figure 3. Electrochemical exfoliation device (a) with ultrasonic technology. Schematic of the electrochemical exfoliation process (b) Graphene powder produced by exfoliation (c) [12]

2.1.2. Arc discharge method

In the arc discharge method, a graphite rod is used as the cathode and a carbon precursor as the anode. Graphene is synthesized by means of an electric arc between the two electrodes. This method also has the advantage of reducing the production costs of graphene. In the reaction vessel, the carbon precursor and graphite rod are usually immersed in a liquid medium and, in some cases, in a gas. When the plasma reaches a high enough temperature, an electric current is generated, which is the arc discharge method in figure 4 [13]. The arc discharge method has important research progress

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in the efficient preparation of high-quality graphene. By adjusting the parameters such as current, gas environment (such as He, H-He, O-He, etc.) and arc discharge power, the number of graphene layers, lateral dimensions and quality can be controlled. Studies have shown that reactive gases are critical to the growth mechanism of graphene, which may involve graphite evaporation and carbon cluster crystallization. Different conditions can be used to prepare graphene from few-layer graphene (SLG) with micron-scale to highly crystalline graphene flakes (FLG) with 100 nm scale. The vacuum arc discharge approach has the good points of low cost and non-toxicity. However, the quality of the product is highly dependent on the temperature distribution and gradient within the arc plasma region. Optimizing arc parameters and the type of buffer gas is the key to improving the efficiency of graphene preparation [6].

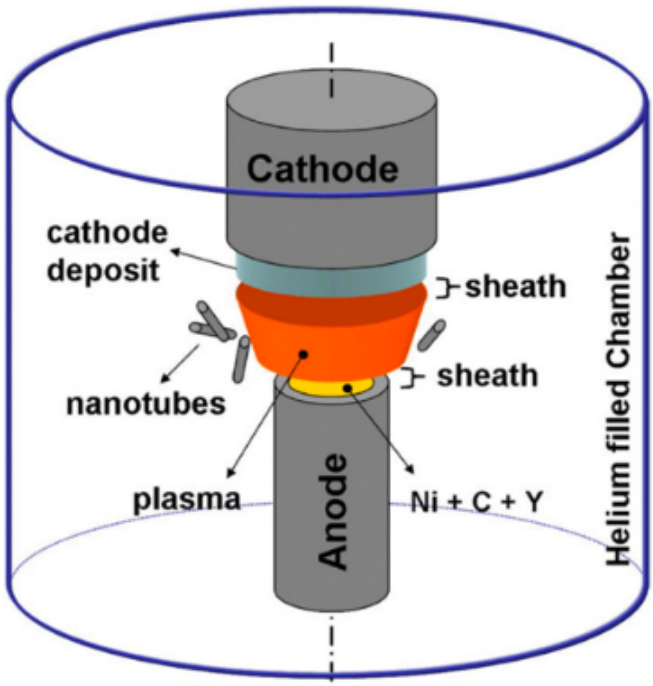


Figure 4. Arc light discharge (ALD) method devices [14]

From the above two electrochemical synthesis methods, when preparing graphene, the electrochemical exfoliation method can produce high-quality single or few-layer graphene through the principles of the two syntheses. It has the advantages of low production cost, simple process, and environmental friendliness. In addition, the thickness and number of graphene layers can be controlled by adjusting the type of electrolyte and voltage, thereby meeting the needs of different applications malignancies encompass a wide variety of severe diseases that pose a serious threat to human health. Given the fact that hematological malignancies are difficult to treat due to their unpredictable and rapid deterioration and high rates of recurrence, growing attention has been paid to their early screening and diagnosis. However, developing a rapid and effective diagnostic tool featuring a noninvasive sampling technique is still extremely challenging. In recent years, novel nanomaterials-based electrochemical biosensors have attracted great interest because of such advantages as simple operation, low cost, fast response, etc. As a kind of rising nanomaterials, two-dimensional materials have excellent electronic and chemical properties, which have been proven to improve the performance of electrochemical biosensors. This review summarizes the applications of

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different types of electrochemical biosensors (nucleic acid sensors, immunosensors, aptamer biosensors, and cytosensors) based on two-dimensional materials in the detection of biological molecules related to hematological malignancies. Two-dimensional materials-based electrochemical biosensors designed for the diagnosis of leukemia could rapidly detect the target biomolecules at a trace level and show great merits such as wide linear range, low detection limit, high sensitivity, excellent selectivity, and cost-effectiveness. In addition, these biosensors have also achieved satisfactory results in the diagnosis of lymphoma and multiple myeloma. Thus, two-dimensional materials-based electrochemical biosensors are attractive for the early diagnosis of hematological malignancies in clinical practice. Nevertheless, more efforts are still required to further improve the performance of electrochemical biosensors. In this review, we propose the possible main concerns in the design of future two-dimensional materials-based electrochemical biosensors, involving the development of sensors for synchronous detection of diverse target biomolecules, the exploration of other superior two-dimensional materials, the simplification of the sensors fabrication process, the construction of new hybrid structures and how to avoid possible environmental [12]. The arc discharge method can prepare large-area, highly crystalline graphene in a relatively short period of time. By adjusting the current, gas environment and discharge power, the number of graphene layers and lateral dimensions can be precisely controlled to obtain graphene sheets of different specifications. The significant advantages of this method are its high efficiency and low cost, and it can prepare graphene from single to multiple layers by changing the reaction conditions, making it particularly suitable for large-scale production. Compared with the arc discharge method, the electrochemical stripping method is more suitable for the preparation of high-purity, few-layer graphene, while the arc discharge method is more suitable for the mass production of highly crystalline graphene [14]. Therefore, selecting the appropriate preparation method according to the specific needs of the sensor is crucial for optimizing the performance of graphene-based electrochemical biosensors.

2.2. Bottom-up approach

The bottom-up approach starts with hydrocarbons, which are also prepared by six methods: epitaxial growth, chemical vapor deposition (CVD), organic synthesis, laser-assisted synthesis, pyrolysis production and carbon monoxide reduction [14]. In addition, other derivatives are synthesized, oxidizing graphite, using the Staudenmaier Method, Hofmann method, Brodie Method and the Hummers method (including sulphuric acid and potassium permanganate [14]) to produce graphite oxide (GO). Next, to obtain graphene oxide, defoliation with ultrasonication is required [15]. Finally, the reduction reaction produces reduced graphene oxide (rGO) by a variety of methods. This reduction method can be divided into two major types; firstly, chemical reactions are carried out, hydrazine, sodium borohydride, hydroquinone and ascorbic acid [4] and even metal catalysts, hydriodic acid and solvents such as various DMFs [1] are used as reducing agents. Secondly, biological treatment, plant extracts help in achieving environmentally friendly development. Proteins like dopamine, glucose, etc., reduce GO with low efficiency than glucose, however ammonia or iron to raise pH improves efficiency. The low cost and industrial utility advantages of microorganisms are also used as one of the reducing agents. Photoreduction methods contain picosecond lasers respectively; in contrast to high wavelength lasers, scanning atmospheres or hydrogen plasmas are more suitable due to not inducing any defects, and UV (photocatalysis), activated promoters and photoactivated nanoparticles as the main two materials. Finally, there is heat reduction, using thermofluidic (autoclaves) and microbe-assisted reduction [1]. For GQD there are three other methods of synthesis, one using nitrilotriacetic acid with polymerization method at

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200 degrees Celsius with trisodium citrate pyrolysis or by microwave irradiation with glucosamine and thiourea as reactants [9].

3. Types and principle of electrochemical biosensors

A biosensor is an analytical device that consists of a living organism, modified materials and biologically derived or biomimetic and is coupled to a physical sensor [16]. It is classified into different categories which can be classified into optical biosensors, optical biosensors and electrochemical biosensors due to the advantages of electrochemical biosensors which are more prominent and have numerous advantages due to the simplicity of their design. The main benefits are the relatively low cost of electrodes, rapid detection due to integration into electronic devices easy to get started. Unaffected by the environment, they can detect the environment in real time and are not susceptible to contamination [17]. Others include high specificity, versatility, shorter recovery time, etc [16]. The detection limit (concentration unit) is used by biosensors to measure the sensitivity of the sensor and the lowest concentration of the target analyte that can be detected. In this paper, we will focus on the principles as well as the different types of electrochemical biosensors. In addition, to further increase the sensitivity, reliability and flexibility to achieve the goal of screening for early-stage cancers, other nanocomposites based on graphene will be introduced, such as metal or metal oxide materials, which can distribute the electrochemical uniformly on the surface and provide a higher surface-to-volume ratio. The exponential distance between the electrochemical activities of the bioreceptors is directly related to the electrode surface and the rate of electron transfer, in order to minimize the distance and the better exchange of electrons, graphene-based modifications This phenomenon occurs at defects present at the edges of graphene sheets, and by constructing a nanoscale channel between the active electrochemical sites and the electrode surface, the direct transfer of electrons is realized, which enhances the performance and sensitivity of the sensor [14]. Early detection of symptoms is obtained, which improves the survival rate and efficacy. On the other hand, based on the biomarkers, different nanomaterials are used to modify the electrodes to achieve repeatability and stability. Based on the above description, electrochemical sensors will be looked at and discussed as the more appropriate choice at this time.

3.1. Principle of electrochemical biosensor

A biosensor consists of four parts: the sample (blood, urine, etc., as mentioned in the application part), the biological receptor (DNA and RNA, etc.), especially cancer biological receptors or antibodies of the immune system, and the transducer, i.e. the sensor or electrode, which is responsible for transmitting the signal detected from the chemical reaction between the biological recognition element and the analyte. Among these, the biosensors mentioned in this article use electrochemical signal detection. Finally, there are the displays and electronics, which have complex circuits that amplify the signal and mainly prepare the conductive signal for display. 9 For detailed electrochemical sensors, as an advanced technology for most biological diagnostics, they are very suitable for point-of-care testing (POCT). They can also be divided into aptamer, immune, cell and accounting sensors according to the different recognition units. For example, cell sensors use proteins, receptors and glycans on the cell surface or cells as the original recognition elements, and the change in the electrochemical signal is caused by the binding of the accounting sequence or ligand to the receptor. There are also aptamer biosensors, where the recognition unit is aptamer, which is functional DNA or RNA with affinity or high specificity for proteins and small molecules.

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The specific interaction between the target molecule and aptamer determines [12]. This electrochemical sensor can interact with chemical solvents to produce an electrical signal that is directly proportional to the concentration of the target analyte, which directly affects the sensor response to changes in the analyte. This mechanism allows the precise detection of the target analyte concentration by converting the biometric event into a measurable electrical signal and using electron-active substances to further quantify the target analyte. The basic components include an operating electrode (redox or sensing electrode), a reference electrode and an auxiliary electrode in between, with an electrolyte solution underneath [17] (Figure 5). The working electrode conducts electricity; the counter electrode is made from silver chloride/silver, carbide or normal hydrogen electrode, and is used to maintain a constant potential and a defined reaction field for the current flow from the counter electrode to the working electrode through the electrolyte solution. Electrochemical biosensors can be used to detect using different techniques: potentiometric, impedimetric, amperometric and conductometric.

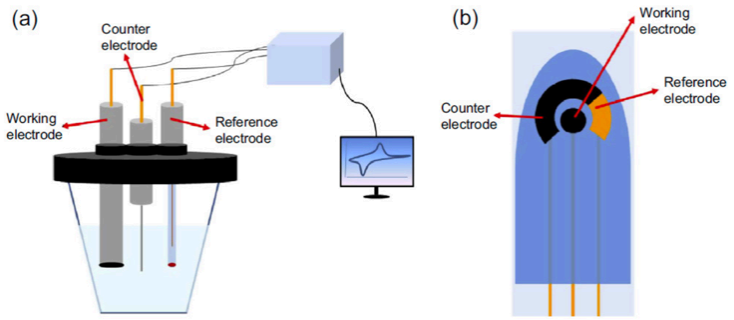


Figure 5. The component of electrochemical biosensor [17]

3.2. Types of electrochemical biosensor

3.2.1. Amperometry

Amperometric biosensors are the most frequently utilized biosensors globally for the detection of cancer biomarkers and cancer cells. [13]. The working principle of the sensor is based on the detection of oxidation or reduction of compounds through enzyme-catalyzed biochemical reactions, generating a measurable electric current, and the core component, mentioned above in the description of the components of electrochemical sensors, is a potentiated, which regulates the voltage and measures the current generated during the reaction. A potentiostat regulates the voltage and measures the change in current generated during the reaction. Data on the potential range as a function of the data on the graph, the reference potential and detection of the applied potential of the working electrode used constant potentiostat. Electrode materials commonly used are glassy carbon and platinum, and the electrolyte is a highly soluble solvent salt. To generate an electric current, the change in enzyme impulse activity of the working electrode is measured by applying a potential. One of the advantages of these sensors is that they are particularly sensitive and suitable for mass production, in comparison with potentiometric electrochemical biosensors [16] and the ability to continuously measure the current generated by the redox of electronic species in biochemical reactions.

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3.2.2. Voltammetry

Electrical analyses of currents are obtained by analyzing changes in potential using voltammetry, which is also divided into many different types, depending on the method of measurement of the different potential changes. For example, Differential Pulse Voltammetry (DPV), where periodic pulses can be superimposed on the current potential sweep to improve the close spacing and signal-to-noise ratio of the redox species resolution. Measurements are made when the Faraday current is at its highest value and the capacitance current is at its minimum, and the data for the difference in current before and after each applied pulse will be plotted as a function of the increase in the potential line. The peak height is proportional to the measured concentration when the differential curve is peaked. Cyclic voltammetry (CV) i.e. cyclic changes in potential between electrodes, specifically, the potential applied to the working electrode is measured as the current changes, scanning back and forth between the initial and termination potentials. The data from CV can be known as redox potentials, nanomaterials modified for use on the surface of the electrodes and peak heights are used to study the kinetics of redox reactions. Electron transfer kinetics and mass transport to the electrode surface occur between the electrode and solution interface [7] and are also used in diffusion processes and electrochemical mechanisms. Finally, there are methods such as square wave voltammetry (SWV), which is a very fast and sensitive method, and averaging multiple measurements improves accuracy. To obtain a square wave voltammogram, one needs to obtain the net current (the difference between the two measurements of the current at the end of the forward and reverse pulses in each cycle) and the applied potential (applied to the working electrode as a symmetrical square wave) to plot the function Fig. 6. Among these, the pulsed methods due to the high sensitivity and analytical power of SWV and DPV are often used. Improved performance, signal clarity and resolution as well as reduction of background noise are necessary in order for the assay to be unaffected by complex environments [18].

3.2.3. Other types of electrochemical biosensor

One is the Impedimetric technique which investigates the behavior of electrochemical systems by applying small amplitude sinusoidal voltages or currents over a range of frequencies and measuring the complex impedance of the system. The advantage of EIS is that it is able to differentiate between the contribution of Faraday and non-Faraday processes in the system, and the complex impedance can be visualized in the form of a Nyquist plot and a Bode plot, reflecting the relationship between the real and imaginary parts of the impedance, or between impedance amplitude and phase angle as a function of frequency. A distinctive feature of the EIS technique is that the total impedance can be decomposed into multiple circuit elements by modelling equivalent circuits, including the charge transfer resistance of the Faraday process, the double-decker capacitance, and the Warburg impedance, which is related to the mass transport or diffusion process. By modelling these circuit elements and fitting EIS data, researchers have been able to gain an in-depth understanding of the various properties of electrochemical systems and develop a variety of applications, including the analysis of in vitro detection and the response mechanisms of anticancer drugs and antibiotics [18]. The Potentiometry technique for detecting changes in potentials generated by the interaction between a bioreceptor and an analyte [17] relies on the sensor's ability to detect potential changes through the recognition of the distinction by recognition of ion-selective materials that act as a barrier between two solutions and do not generate a current. Such sensors are mass-produced thanks to thick film or silicon technology [16]. The final method, Chronoamperometry, differs slightly from SWV in that both use square wave potentials to correlate with currents or potential changes, but

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SWV focuses on current changes, whereas Chronoamperometry applies a square wave potential to a working electrode and measures the time and stabilization of the current relationship. Potential difference relies on the Nernst equation, the relationship between potential and concentration to measure potential, so focuses on changes in potential over time rather than directly measuring the difference in current [13].

4. Applications of cancer diagnosis

4.1. Lung cancer

Lung cancer grows because of unregulated cells growing in the lungs, which is one type of cancer that leads to the deaths of many people globally [19]. NSCLCs are seen more and grow not as fast, while SCLCs seen less but grow faster more often. Leading cause remains smoking, it accounts more of lung cancer cases almost 85%. But nonsmoking peoples also affected. Different risks like inhaling secondhand smoke, workplace exposures like asbestos, radon gas, certain chemicals, air pollutants, some genetic cancers, also chronic lung diseases existent.

Proteins signaling in cells, mutations of genes bringing cancer, also many different enzymes or signs of metabolism are crucial biomarkers for seeing lung cancer [8]. Now, most research groups work on using methods of detecting chemicals in biosensors to find these biomarkers in many lung cancer phases for better outcome and treating disease. The biomarkers discussed in this review are categorized into five main groups: proteins, metabolites, enzymes, genes, and non-coding RNA, each playing a distinct role in lung cancer detection and prognosis. Compared to previous reviews that focus primarily on a single type of lung cancer biomarker, this paper provides a more comprehensive analysis, including various biomarkers such as proteins, metabolites, and non-coding RNA, thereby offering a broader understanding of electrochemical biosensors' potential in early lung cancer diagnosis.

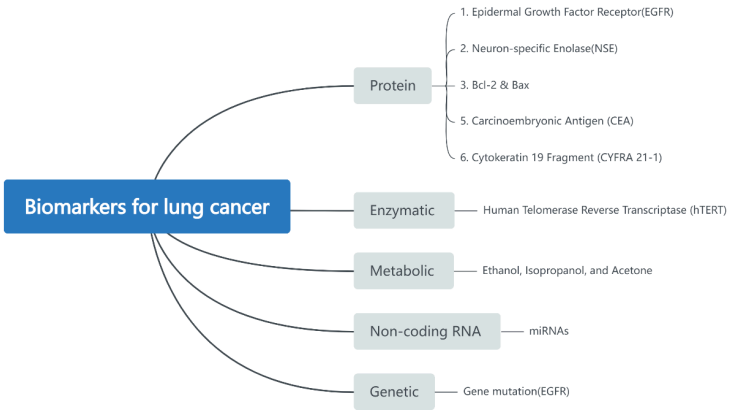


Figure 6. The types of lung cancer biomarkers

4.1.1. Protein biomarkers

EGFR

In an earlier study it was found that mutations in epidermal growth factor receptor's (EGFR's) tyrosine kinase domain affect its normal function, and these changes are directly linked to the development and progression of lung cancer. As a result, EGFR mutations can serve as a biomarker

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in the detection and treatment of lung cancer [20]. In 2020, study on biosensor for detecting epidermal growth factor receptor (EGFR) which is a transmembrane glycoprotein, using paper-based microfluidics and electrochemical measurements principles, was done [21]. Coupled with ligand, genes activated by it drive cell division, proliferation. Normal EGFR levels are from 1 to 25 ng/mL in human. Thus, EGFR levels could be used for lung cancer diagnosis biomarker. This sensor constructed with Screen Printed Electrode (SPE), which is sensor's basic platform. SPE surface changed with aminated graphene, might increase conductivity, biocompatibility of electrode. Then sulphur cordial added, might improve electroactivity stability. After, sulphur cordial-modified electrode got gold nanoparticles. Due to high affinity, gold nanoparticles work as electron acceptors increasing anodic peak current. Anti-EGFR aptamer immobilized through self-assembly between gold nanoparticles and aptamer's sulfhydryl groups, ensuring aptamer bind to EGFR protein. Development of aptamer-antigen immune complex limits electron flow during construction, resulting in low electrochemical signal, useful to identify EGFR presence. Finally, electrochemical methods like cyclic voltammetry (CV) and differential pulse voltammetry (DPV) characterize biosensor's EGFR detection capacity. This approach makes device more user-friendly, simplifying sample insertion, detection. Nanocomposites modifying working electrode improve environment for aptamer immobilization. According to test results, the device detects EFGR effectively and sensitively in range of 0.05-200 ng/mL, with detection line of 5 pg/mL. No cross-reactivity found and high specificity for potential interferences confirmed.

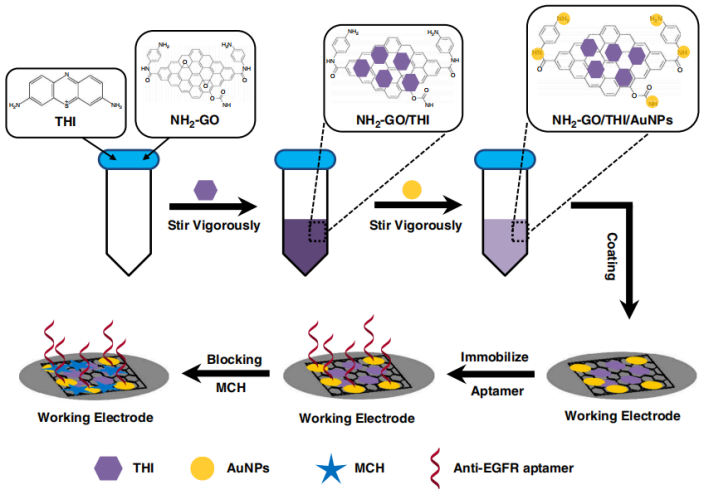


Figure 7. Procedure for modifying the EGFR aptasensor based on origami paper [21]

NSE

Neuron-specific enolase (NSE) is a biomarker found at higher levels in the serum of patients with small-cell lung cancer. Detecting NSE levels can help with the early diagnosis and surveillance of lung cancer. In a 2022 paper [22], researchers presented an electrochemical biosensor that used electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) to detect NSE. Using the synergistic effect of rGO and r-MoS_2, a sensor is created by altering rGO on multilayer r-MoS_2 nanosheets, yielding a large electroactive surface area and heterogeneous transfer constants. rGO (reduced graphene oxide) and r-MoS_2 (reduced molybdenum disulfide) are two forms of two-dimensional nanomaterials with large specific surface areas, which can provide more binding sites for biomolecules and hence increase sensitivity. The experimental results show that using electrochemical impedance spectroscopy (EIS) technology, the sensor has a detection limit of 1

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ng/mL and a linear detection range of 1 ng/mL to 200 ng/mL. The sensor has a detection limit of 0.1 ng/mL using the cyclic voltammetry (CV) technique and a linear detection range of 0.1 ng/mL to 100 ng/mL. The sensor has good sensitivity, a large linear detection range, a short incubation time, and great reproducibility. The sensor has a wide linear detection range and can detect NSE concentrations ranging from 0.01 ng/mL to 200 ng/mL, making it ideal for early identification and therapy monitoring. The sensor is highly selective for NSE, with no reaction to other endogenous interfering molecules, such as other proteins in human serum.

Another research in 2019 [23] discovered the creation of mesoporous carbon-silicon-gold composites (OMCSi-Au) through the 3D-GNS synthesis process. Materials complying with graphene gold nano-example were used to prepare electrochemical DNA biosensor. Testing indicated immunosensor had decent linearity for NSE from 0.02 pg/mL to 35 ng/mL, with detection limit of 0.008 pg/mL. 3D-GNS shown porous structure which speeds up electron transport and captures more protein molecules, bettering sensor performance. Porous shape of 3D-GNS quickens electron transit and catches more protein molecules, making sensor more sensitive. Also, the 3D-GNS-doped chitosan (CS)-modified electrode showed lower electron transfer resistance than CS/GCE, proving antibody modification on electrode's surface successful. 3D graphene has a larger specific surface area than normal graphene, likely boosting biosensor effectiveness. OMCSi as well has notable pore volume, high mechanical stability, larger specific surface area, all improving catalytic activity, stability, and dispersion of gold nanoparticles.

Bcl-2 & Bax Antigen

Bcl-2 and Bax are essential apoptotic proteins that regulate cell survival and death. Changes in Bcl-2 and Bax expression levels in lung cancer may be connected with tumor growth, progression, and therapy response, making them potential biomarkers for the disease. By measuring the expression of these proteins, we can gain a better understanding of lung cancer's molecular pathways and perhaps predict disease progression and therapy efficacy [24]. A 2016 article described an electrochemical biosensor developed with dual-signal labelling technique of sandwich style [25]. With Hummers method graphene oxide (GO) was created and reduced to RGO, which was used as base to immobilize Bcl-2 and Bax antibodies, catching target antigens. The electrode was altered with antibody I (for Bcl-2 and Bax), and active sites sealed using bovine serum albumin (BSA). Electrodes were modified with antibody Π against NCs (QDs), which served as signal probes proportional to antigens amount, also proportional to Bcl-2 and Bax antigens number. Finally, by measuring oxidation peak currents of Cd and Ag using anodic stripping voltammetry (ASV), indirect measurement of Bcl-2 and Bax proteins was done. Bcl-2 and Bax proteins amount was indirectly measured by recording oxidation peak currents of Cd and Ag. Sensor showed strong linearity in protein concentration range from 1 ng/mL to 250 ng/mL, with detection limit close to 0.5 fmol, thus very sensitive to minute protein levels. Additionally, it can be used to check medication impact on cancer cell apoptosis, so a valuable tool for clinical detection and therapy effect evaluation. CdSeTe@CdS quantum dots (QDs) and Ag nanoclusters (NCs) were chosen due to ease in making, uniformity, many functional groups for antibody changes, and good dispersion. Selecting and designing these materials enhance the sensor’s performance, making it apt for clinical detection.

CEA

CEA is a glycoprotein found in the gastrointestinal tract, pancreas, and liver. CEA is commonly used as a tumor marker for colorectal cancer. At the same time, multiple studies have revealed that elevated baseline CEA levels in individuals with non-small cell lung cancer (NSCLC) are related with a poorer prognosis. This suggests that elevated CEA levels can predict the severity of lung

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cancer and the patient's prognosis. As a result, CEA can also serve as a biomarker for lung cancer [26].

In 2015 [27], examining was a smart conductive paper by researchers, they used polyethylene dioxythiophene composite having polystyrene sulfonate (PEDOT: PSS) and reduced graphene oxide (RGO), then made cancer biosensor. For detecting CEA was this biosensor used. Making of sensor used a dip-coating simple procedure where 1.3 wt% aqueous solution of PEDOT: PSS, along with 3% ethylene glycol (EG), and Whatman filter paper soaked in solution then dried in hot oven at 100°C created conductive paper. High sensitivity was shown by the biosensor in detecting CEA with sensitivity of 25.8 mA/ng mL/cm^2 in physiological range of 1-10 ng/mL. This high sensitivity came from co-formal rearrangement of compounds on conductive paper and non-covalent synergistic interactions among PEDOT and cellulose. Design strength of sensor was its low-cost, flexibility, and environmentally friendly nature, making it a promising alternative against costly electrodes (e.g., ITO, gold, glassy carbon), which had limited use in quick field detection devices (POC).

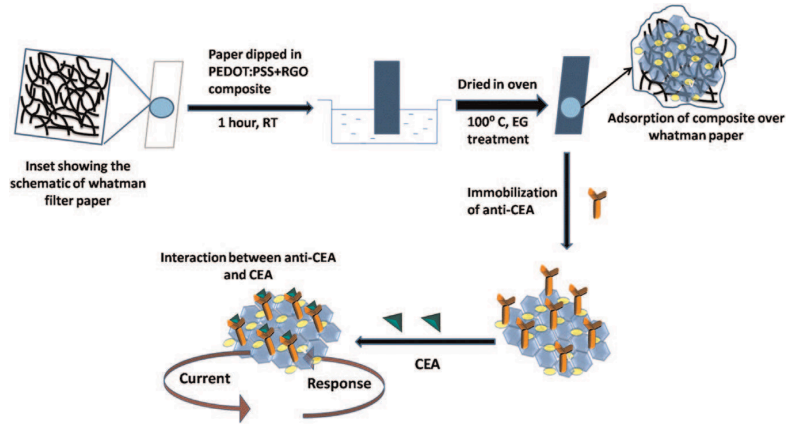


Figure 8. Schematic of proposed electroactive paper sensor [27]

In a 2017 publication [28], biosensor for cancer marker, researchers looked at developing biosensor methods based on making water-friendly graphene/amphiphilic pyrene derivative material that holds high gold nanoparticle (AuNP) content easy. This was used for electrochemical testing of carcinoembryonic antigen (CEA). Graphene mixing with pyrene butyric acid in water got ultrasound treatment. This made graphene sheets separate better. Then they went through chemical changes like using agents EDC and NHS for better reaction and joining polyethylene glycol (PEG), creating PPYGR composites. Using electrochemical impedance spectroscopy (EIS) tech, CEA presence and amount were judged. Results showed the sensor's response to CEA spanned broadly from 0.1 to 1000 ng/mL ideally, with a correlation number 0.9959 and detection threshold as tiny as 0.06 ng/mL. The sensor had AuNPs which bound proteins well, and good AuNPs load and anti-CEA fixed making a good setting for keeping CEA biologically active, boosting sensor’s detection better. PEG on graphene, improved water-friendly nature much while keeping good conductivity.

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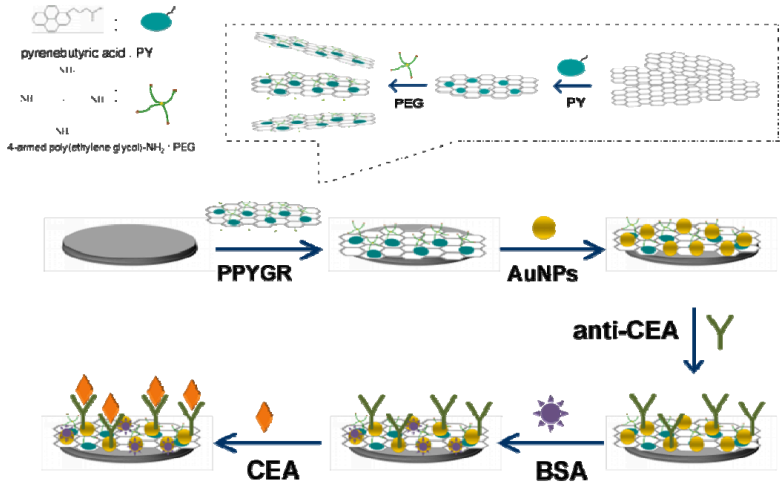


Figure 9. Schematic diagram of electrochemical impedance immunosensor [28]

Also, in same 2017 article [29], researchers saw label-free electrochemical sensor method using silver-platinum rings (AgPt NRs) supported by less graphene oxide (rGO) for spotting cancer marker CEA. This came about through one-pot wet chemical route with 2,4-dihydropyridine (DHP) as new guide. GO dissolved in a solution with DHP, silver nitrate, chloroplatinic acid, and then hydrazine hydrate put in slowly to make AgPt NRs-rGO. CEA tracked by change in reduction peak current before after immune compound formed using specific immune reaction. Results from tests showed CEA was detected using AgPt NRs dopant as redox medium, and cyclic voltammetry (CV) measures in PBS, pH 7.4 noted for CEA tracking. They found sensors showed a big linear range, low limit to detect CEA. The AgPt NRs-rGO-based immunosensor detects CEA with a wide linear range of 5 fg/mL~50 ng/mL and a low detection limit of 1.43 fg mL-1, making it a potential platform for clinical research and diagnostics. DHP as new guide helping forming nanoscale setup with good fit for life and high conduct structure critical for better sensor functioning.

In the year 2019 [30], a study which was conducted by scientists made use of polypropylene imine dendrimers and also nano complexes containing carbon nanodots upon graphite electrodes—those ones that have been extended. Detected by the sensor is something called CEA, utilizing electrochemical basics, especially known as differential pulse voltammetry. In order to reduce non-specific binding areas, the way the sensor was built involved dropping CNDTs by coating, adding G2-PPI via electrodeposit, placing an anti-CEA antibody, and then coating with bovine serum albumin (BSA) by dropping. What was finally determined by monitoring changing currents was the concentration of CEA. Results from the tests said the immunosensor could detect CEA within concentrations from 0.005 until 300 ng/mL, with detecting limits found at 0.00145 ng/mL, showing high sensitivity and wide linear ranges. Additionally, after storage for two weeks, the sensor's signal reduced by less than 4% while detecting the same CEA concentration. Interfering substances in solutions made the sensor show selectivity, with current changes beneath 11% for all of those substances. Furthermore, examining CEA in human serum showed recoveries between 99.96% and 100.03% surrounded by RSDs from 0.0192% to 0.1313%, illustrating the sensor's analytical capability in serum. Due to nanoscale structures, sensor nanocomposites provide larger electrode surface areas, boosting sensitivity. Strong electron transport capabilities are in carbon nanodots, helping fast electron transfers at electrode interfaces.

CYFRA 21-1

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CYFRA 21-1, a circulating cytokeratin-19 fragment, has a high sensitivity for detecting non-small cell lung cancer which means that CYFRA 21-1 has a significant role in lung cancer diagnosis and could be employed as a biomarker [31]. In the publication from 2020 [32], what scientists did was to describe making an electronic biosensor which is portable and fast for detecting CYFRA 21-1—known as a cancer biomarker. Creating a new layer which immobilizes antibodies by using reduced graphene oxide as the primary transfer layer and melamine for immobilizing antibodies. When CYFRA 21-1 present in a sample attaches to the recognition surface on the electrode, it alters the charge on the sensor, creating a signal. Results from tests reported the sensor's reaction rate to CYFRA 21-1 ranged from 6.18% reaching 64% for concentrations between 1 pg/mL till 800 ng/mL, signalling biological sensitivity for this biomarker. Furthermore, having a detection limit at 0.04 pg/mL means the sensor detects quite low biomarker levels. Naturally, the sensor also held stability; after storage for two weeks at 4°C, the response to CYFRA 21-1 was at 28.7%, compared to newly made sensor responses. Experimenting outcomes indicate that this innovative sensor has great promise for early cancer diagnosis in clinical settings.

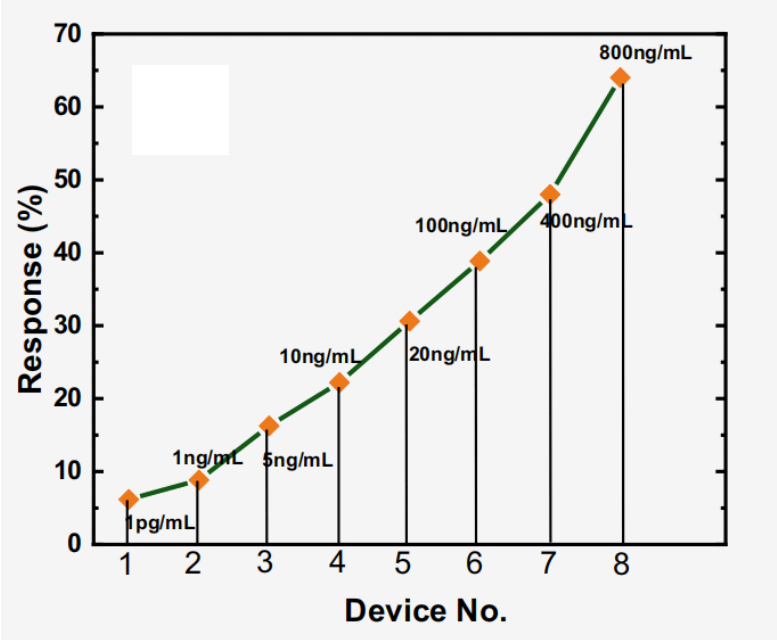


Figure 10. reaction between 1 pg/mL and 800 ng/mL of CEA for reduced graphene oxide (rGO)/ melamine (MEL)/ antibodies/ bovine serum albumin [32]

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Table 1. Published works about electrochemical detection of lung cancer biomarkers

Biomarkers	Detection method and main material	Detection limit	Detection range	References
EGFR	Paper-based microfluidics and electrochemical measurements, SPE, amino graphene, thiovio, gold nanoparticles	5 pg/mL	0.05-200 ng/mL	[21]
NSE	Electrochemical biosensor, rGO, r-MoS2 coating, ITO electrode coating 2D surface	1 ng/mL（EIS） 0.1 ng/mL（CV）	1 ng/mL to 200 ng/mL 0.1 ng/mL to 100 ng/mL	[22]
	Electrochemical DNA Biosensors, 3D-GNS, OMCSi-Au	0.008 pg/mL	0.02 pg mL^-1 to 35 ng mL^-1	[23]
Bcl-2 & Bax	Electrochemical biosensors, RGO, dual-signal labelling technology	0.5 fmol	1 ng/mL to 250 ng/mL	[25]
ANXA2,VEGF,ENO1	Label-free biosensor, suspended single crystal graphene (SCG)	0.1 pg/mL	1 pg/mL to 1 μg/mL	[33]
	Water-dispersible graphene/amphiphilic pyrene derivatives nanocomposites	0.06 ng mL^-1	0.1 to 1000 ng mL^-1	[28]
CEA	Silver-platinum nanorings (AgPt NRs) are supported on reduced graphene oxide (rGO).	1.43 fg mL–1	5 fg mL–1~50 ng mL–1	[29]
	Polypropylimide dendritic molecules and carbon nanodot nanocomposites	0.00145 ng/mL	0.005 to 300 ng/mL	[30]
CYFRA 21-1	Portable electronic biosensor, reduced graphene oxide	0.04 pg/mL	1 pg/mL to 800 ng/mL	[32]

4.1.2. Genetic biomarkers

Graphene oxide and DNA nanohybrids for lung cancer caused by changes in EGFR gene, described in a 2023 article [34]. Graphene oxide synthesized with Hummer's method, confirmed by Fourier transform infrared, ultraviolet-visible, and transmission electron microscopy. EGFR gene deletions marked with FAM probe and checked by fluorescence spectroscopy. DNA probe and targeted DNA hybridized caused fluorescence to go up due to weaker non-covalent bonding with graphene oxide. Mutations in exon 19 EGFR gene found, like codons 746-752. Experiments showed biosensor's differential reaction to healthy versus mutant DNA helps find lung cancer. Fluorescence went up with healthy DNA, no change with mutant because of mismatch. Biosensors are cheaper, simpler, have lower detection limits than others. Technology offers early, quick, cost-effective lung cancer detection.

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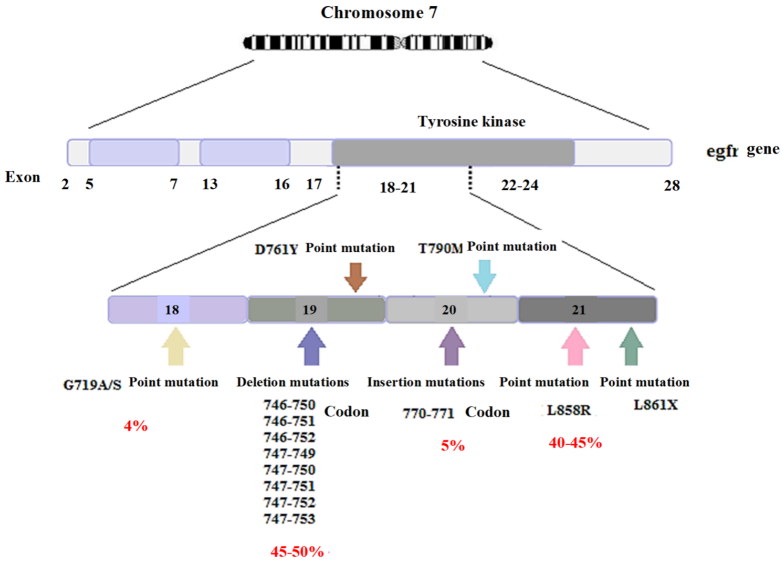


Figure 11. The frequencies of mutations in the EGFR gene [34]

4.1.3. Metabolic biomarkers

A 2019 study [35] described a new approach for detecting ethanol, isopropanol, and propanol using multilayer graphene biosensors. A crucial observation is that lung cancer patients exhale a high concentration of VOCs. The sensor was made via chemical vapor deposition of multilayer graphene, then transferred to a substrate and the Ni catalyst was removed using an iron (III) chloride hexahydrate solution. Flexible electrodes are made through lamination. Molecular and graphene modify electrode conductivity when exposed to biomarkers, which can be identified chemically. The conductivity of the p-MLG electrode increased to around 11 μA with acetone at 1.4 × 105 ppm concentration, while f-MLG at around 10 μA. Ethanol and isopropanol maintained stable conductivity, with f-MLG at 7 μA and p-MLG at 5 μA. Acetone had a more noticeable effect on conductivity. Sensors are sensitive and selective, particularly for propanol and graphene is stable and does not degrade. Consequently, the future usage of MLG sensors has the potential to detect lung cancer biomarkers and other disorders.

4.1.4. Non-coding RNA

Non-coding RNAs, such as long non-coding RNAs and microRNAs, can be used as biomarkers to detect lung cancer because their expression changes in many lung diseases, and their levels in biofluids can reflect changes in the expression of their lung-specific counterparts. This feature makes non-coding RNAs useful as non-invasive lung disease markers, particularly in the diagnosis of lung cancer. Furthermore, the stability and detectability of non-coding RNAs in biofluids give further benefits for their use as biomarkers, making them attractive for key applications in the diagnosis and treatment of lung cancer [36]. In year 2021 [37], a device biosensor made from paper that is electrochemical was designed and evolved over time. Using nitrocellulose membrane, the foundation was laid with fluidic channels and assembly points by click method. Wax printer used to form hydrophobic barrier on membrane. Then, based on carbon working electrode with either reduced graphene oxide or molybdenum disulfide nanosheets, which surface chemically active on RGO paper electrode through EDC/NHS as agents for cross-linking. Using time-dependent current method, AuNPs were deposited on these modified electrodes in solution containing water and

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chloroauric acid. These biosensors detect miRNA-155, also miRNA-21 by differential pulse voltammetry needing just 5.0 μL of material. Results show AuNPs/RGO sensors sensitive to miRNA-21 and miRNA-155 at 12.0 and 25.7 nM concentrations respectively, whereas AuNPs/MoS2 sensors detect at 51.6 and 59.6 nM. These biosensors sufficiently identify target miRNAs, even with one base mismatch or non-matching miRNA sequences. The setup allows for biosensors on paper, cheap and limiting cross-contamination due to disposable use. Plus, gold nanoparticles and nanosheets make sensor more sensitive.

In 2018 paper [38], researchers high-throughput methods revealed to find small compounds modulating miRNA inside living cells and a new type of biosensor involving PNA and NGO. PNA probe includes fluorescence marker, emits signal. When PNA-NGO mix finds target miRNA in cell, PNA attaches to it, detaches from NGO, and gets fluorescent signal back. A modified Hummers method used to create graphene oxide from natural graphite nanofibers. This sensor, detected miRNA with two different fluorescently labelled PNA probes (Cy3 and Cy5), makes it possible to determine exact miR-21 expression levels. By adding PANGO sensor in cell culture, real-time measure of miR-21 expression, also cell phenotype changes tracked by fluorescence signal changes. Researchers concluded, PANGO sensor not only screens small molecules affecting miR-21 effectively, but also evaluates compound effects on cells, including screening conclusion, relationship of cell growth miRNA expression, Z'-factor evaluation, effects of compounds on cell function, and changes to cell shape, providing new method beneficial to cancer study.

4.1.5. Enzymatic biomarkers

Human telomerase reverse transcriptase catalytic subunit (hTERT) can be utilized as a biomarker to diagnose lung cancer because it activates telomerase, which is required for infinite cell proliferation and immortalization. In this study, researchers examined hTERT expression in 153 patients with stage I non-small cell lung cancer and discovered that hTERT mRNA expression was linked to lower overall survival, disease-specific survival, and disease-free survival. A multivariate study revealed the independent prognostic effect of hTERT expression. Thus, hTERT mRNA expression is associated with malignancy progression and a bad prognosis, making it a helpful marker for identifying individuals with a poorer prognosis and choosing patients with early-stage non-small cell lung cancer who may benefit from adjuvant chemotherapy [39]. A paper from 2013 talks about an extremely sensitive immunosensor, designed majorly for detection of hTERT, which is a telomerase linked to lung cancer [40]. It is a significant indicator being examined. The sensor employed graphene oxide (GO) made by using an adjusted Hummer strategy. Covalent immobilization of anti-hTERT antibody was performed upon GO film. Followed by treatment with ethanolamine (0.96 M) for precisely 5 minutes, aimed to block leftover active sites. Non-specific binding was thus prevented. This sensor was built on indium tin oxide (ITO)-coated glass. Surface alterations got confirmed and electrochemical traits checked via cyclic voltammetry (CV) situated in Zobell solution. Outcomes indicated this kind of GO-based sensor had high specificity and minimal detection limits within 10 ag/mL to 50 ng/mL for hTERT. The detection range was from 100 fg/mL to 10 ng/mL within a span of less than half a minute. Highlighted features of this immunosensor include its manufacturing simplicity coupled with cost-effectiveness, facilitating early-stage non-invasive lung cancer detection.

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4.2. Hematologic malignancies

Malignant hematologic malignancies originate from the hematopoietic stem system and commonly include leukaemia, lymphoma, and multiple myeloma. Leukaemia accounts for about 5% of the total number of malignant neoplasms, with the majority of cases occurring in children and adolescents, leukaemia can be classified into acute and chronic leukaemia according to the course of the disease and the maturity of the cells, and into lymphocytic leukaemia and myeloid leukaemia according to the cells involved, of which acute leukaemia is the most common malignancy among young people under 35 years of age. However, the low detection rate in the early detection of malignant hematologic tumours is a major challenge for early treatment and prevention.

Other than that, available detecting methods including flow cytometry (FCM), real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR), chromosome analysis, etc., generally require high cost as well as specialized technicians, and their inconvenience for rapid clinical diagnosis of cancer. In contrast, the application of electrochemical biosensors in cancer detection is highly anticipated because of their sensitivity, ease of operation, and low cost. Electrochemical biosensors targeting different cancer biomarkers have potential applications in early diagnosis, timely treatment, and late prognosis.

4.2.1. DNA

With the recent development of biomedicine, including molecular biology and genetics, people have studied malignant hematologic tumours more deeply and discovered a series of biomarkers related to malignant hematologic tumours, and a series of biosensors targeting the detection of their different biomarkers have been designed and produced. Among them, electrochemical DNA sensors are considered as having potential value in cancer-related DNA biomarkers detecting because of their simplicity, sensitivity, specificity and cost-effectiveness.

Chronic myeloid leukaemia (CML) is a malignancy caused by the expression of the BCR/ABL fusion gene that is due to the Philadelphia chromosome (Ph') translocation. All patients with CML must have either the Ph chromosome or the BCR/ABL fusion gene, and testing for them is mandatory for diagnosis. Most patients with a slow onset of disease are often asymptomatic at the beginning of the disease, and it easily results in missing the optimal time for treatment. Therefore, the development of electrochemical sensors to detect BCR/ABL fusion genes has vital implications in the early detection of the disease and improvement of the prognosis. The team successfully used AuNPs/PANI/CS-GS to research and develop an electrochemical DNA sensor targeting BCR/ABL fusion genes. During the preparation process, the prepared graphene oxide (GS) suspension was immobilized to capture the probe by electropolymerizing polyaniline (PANI) to form a layer, and electrodepositing gold nanoparticles (AuNPs). The use of hairpin-structured capture probes with 5′-SH and 3′-biotin dual labelling improved the selectivity and sensitivity of the assay. In the streptavidin-alkaline phosphatase (SA-AP) covalent binding to the capture probe via the biotin-affin system, high sensitivity (2.11 pM) was achieved using biotin-affin signal amplification and alkaline phosphatase [41]. Whereas, Shamsipur Mojtaba proposed a convenient and low-spending preparation method. They successfully synthesized stabilized graphene nanosheets by sonication of graphite powder using hemoglobin-coated gold nanoclusters (Hb@AuNCs) solution. The application of the "signal off" and "signal on" bimodal strategies enabled the ultra-sensitive detection of BCR/ABL fusion genes with the ability to detect cDNAs as low as 0.037 fM. In addition, this study validated the selectivity of the sensor for the target cDNA, which can effectively discriminate even among DNA sequences with single base mismatches, which can help improve the

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accuracy of cancer detection [5]. Acute lymphoblastic leukaemia (ALL) is a cancer originating from lymphocytes with a high incidence, especially in children, so the selective biosensors are sorely needed. A team developed an electrochemical DNA biosensor based on a novel composite material prepared from graphene sheets, poly catechol and biosynthesized gold nanoparticles. The use of expensive enzymes was discarded in the preparation of the material and instead poly (catechol) was synthesized by an electrochemical method, which is a convenient and inexpensive process. The detection range of the sensor covers DNA levels from high to very low concentrations (100.0 μM-10.0 pM) with very high sensitivity (down to 0.001 pM DNA concentration). It provides a low-cost, highly sensitive and selective assay for the early diagnosis of ALL [5]. Non-Hodgkin's lymphoma (NHL) is a cluster of lymphocytic blood cancers and the lesions of NHL occur mainly in lymphoid organs such as lymph nodes, spleen, and thymus etc. NHL is highly heterogeneous. Electrochemical biosensors provide a minimally invasive, simple, rapid and cost-effective way to diagnose it. Scientists has formed a conductive nanocomposite platform by dispersing MWCNTs on graphene nanosheets. The platform has a high specific surface area and π-π stacking ability to efficiently immobilize lymphoma probe DNA. In a clinical sample application, a synthetic NHL gene target was tested by adding a known concentration to a 10% serum sample, and the recovery values ranged from 93-99%, demonstrating ability of accurately detection in multiple clinical tests. It provides a fast and convenient platform for the early diagnosis of NHL [42].

4.2.2. Mi-RNA

Mi-RNAs take part in a series of important processes of our life, not only including cell proliferation, cell differentiation, cell death, etc., but also are closely related to cancer development. For example, miRNA-21 is expressed in different kind of cancers and is an important biomarker for cancer diagnosis and prognosis assessment. Therefore, developing biosensors detecting such mi-RNA is important in the diagnosis and prevention of some diseases. Scientists developed an electrochemical sensor based on graphene-modified disposable pencil graphite electrode (GME) used for detecting miR-21 in cell lysates. The high conductivity and large surface area of graphene were utilized in the study to improve the sensitivity of the sensor, the detection limit of this is lower than the unmodified pencil graphite electrode (GE) nearly 2.77 times. The sensor has a wide detecting range of miR-21 concentrations with good selectivity and can be applied to different test samples. In addition, the sensor can be used to detect miR-21 directly in samples without the pre-treatment or RNA extraction and purification steps, which can help improve the efficiency of cancer detection [9]. In the Cheng and Fang-Fang‘s study, scientists developed an electrochemical miRNA biosensor based on metal ion functionalized titanium phosphate nanospheres (TiP-Cd2+).During the experiment ,an "electron bridge" formed by using an electron transfer medium made by Ru(NH3)63+and interacting with DNA base pairs, the sensor significantly enhanced the electron transfer efficiency and increased the electrochemical signal (more than 5-fold).In addition, two DNAs were designed as capture probes, which further improved the selectivity and sensitivity of the detection by hybridization with the target miRNAs, and achieved a wide dynamic linear range from 1.0 aM to 10.0 pM, with a detection limit of 0.76 aM. The sensor provide a rapid and efficient way to detect miRNAs directly in human serum without complicated isolation and enrichment steps [43]. MiRNA-155 is an inflammation-associated oncogene that is frequently overexpressed in haematological malignancies and solid tumours, and is a vital indicator for clinical diagnosis, treatment, and late prognosis of cancer. Biosensors targeting it have potential for application in early cancer diagnosis and disease prevention. For the development of biosensors for the detection of MiRNA-155, a team developed an electrochemical nano biosensor using gold nanorods (GNR) and

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graphene oxide (GO) for rapid clinical diagnosis. Among them, GNR was used for electrochemical nano biosensors due to its high surface area, good chemical stability, strong biocompatibility, and fast electron transfer efficiency. Oracet Blue (OB) was used as a signal indicator to amplify the signal, resulting a high sensitivity with a low detection limit of 0.6 Fm [44]. Another team utilized aminated an electrochemical platform made by graphene to provide a new strategy for cancer detection and prevention by simplifying the immobilization process of biomolecules through its amino-functionalized nature, which leads to a high sensitivity and selectivity. The sensor is capable of fast response, which helps in rapid clinical screening. The sensor has good reusability and can be reused by simple regeneration process, which reduces the cost of the assay [45]. miRNA-128 is used for the early diagnosis of acute lymphoblastic leukaemia (ALL), in addition to the differentiation between ALL and acute myeloid leukaemia (AML). Scientists has provided a new low-spending and easy-to-operate strategy for cancer detection. Using a composite of RGO and AuNPs as a sensor platform, the high conductivity and large surface area of RGO and the signal amplification properties of AuNPs were utilized to improve the conductivity of the sensor, and the signal amplification ability to achieve a highly sensitive and selective detection of miRNA-128, and in the label-free assay (using ferricyanide) the detection The detection limit was 0.08761 fM in the unlabelled assay (using ferric hex cyanoacetic acid) and 0.00956 fM in the labelled assay (using methylene blue), showing higher sensitivity than previous studies [46].

4.2.3. Cancer cell

Antibodies to antigens on biosensors can specifically bind to certain groups (proteins etc.) on the cancer cells surface, enabling selective capture of tumour cells. Therefore, different cancer cells are regarded as cancer biomarkers and used for early detection by being specifically recognized by graphene electrochemical sensors. A team successfully developed a novel electrochemical aptamer biosensor based on Graphene-hemin Composite Decorated Au Nanoflower, which has significant advantages in detecting K562 leukaemia cells with enhancing sensitivity and selectivity. This aptamer biosensors with high affinity, good spatial effects and excellent selectivity have great potential for small molecule biomarker detection. The novel sensor utilizes the multi-spine morphology of gold nanoflowers to provide higher catalytic capacity compared to conventional gold nanoparticles, significantly improving its performance as a peroxidase mimic and achieving highly sensitive detection of K562 with a detection line as low as 2 cells, which is important for the early diagnosis of cancer [47]. Another team combined graphene with hyaluronic acid using a chemical reduction method to improve the selective recognition and capture of specific tumour cells (e.g., HCT-116), with a wide detection range (5.0×10^2 - 5.0×10^6 cells-mL-1), and a low detection limit (100 cells-mL-1), which has potentially application value in the early clinical test [47].

4.2.4. Protein

Proteins can also be used as biomarkers for early detection of malignant hematologic tumours. The scientists designed a graphene quantum dots (GQDs)-based cellular sensor for specific capture of CD123 antibody in acute myeloid leukaemia (AML) cells and detection of KG1a cells, which provides a convenient and fast new strategy for AML detection and treatment. The biosensor has a wide detection range (1 cell/mL to 25 cells/mL) and a detection line as low as 1 cell/mL. The specific binding between CD123 antibody and CD123 protein enables the highly specific detection of AML cells. The sensor maintains high specificity and can accurately recognizes targeted cells

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even other types of leukaemia cells mixed in. In addition, the sensor is biocompatible, enabling detection without compromising cellular activity [48].

4.3. Pancreatic cancer

Pancreatic cancer is a deadly disease in which abnormal cells form in the pancreas. It's often diagnosed late because the pancreas is deep inside the human body leading to high mortality rates. Smoking, obesity, and diabetes will increase the risk of pancreatic cancer. Pancreatic adenocarcinoma is the most common type of pancreatic cancer, which takes up 95 percent of it. [49]

Due to the discovery and use of numerous biomarkers, especially those based on proteins, enzymes, and carbohydrates, the early diagnosis and detection of pancreatic cancer have greatly improved in recent years. These biomarkers are essential for helping doctors identify cancers early on, which improves patient outcomes.

4.3.1. Proteins biomarkers

Protein biomarkers, particularly in cancer research, are extremely valuable because of their ability to reflect cancer's complexity and dynamics, deconvolute mixed cancer subtypes, and integrate seamlessly into clinical practice. Although advances in multimers and protein technologies such as mass spectrometry, the discovery, and development of cancer protein biomarkers remain daunting due to the high bar for clinical utility, patient-friendliness, and cost-effectiveness [50]. In the following text, three proteins biomarkers that are in use or in the process of development were discussed, mainly focus on their research progress and results.

Pseudopodium Enriched Atypical Kinase 1 (PEAK1)

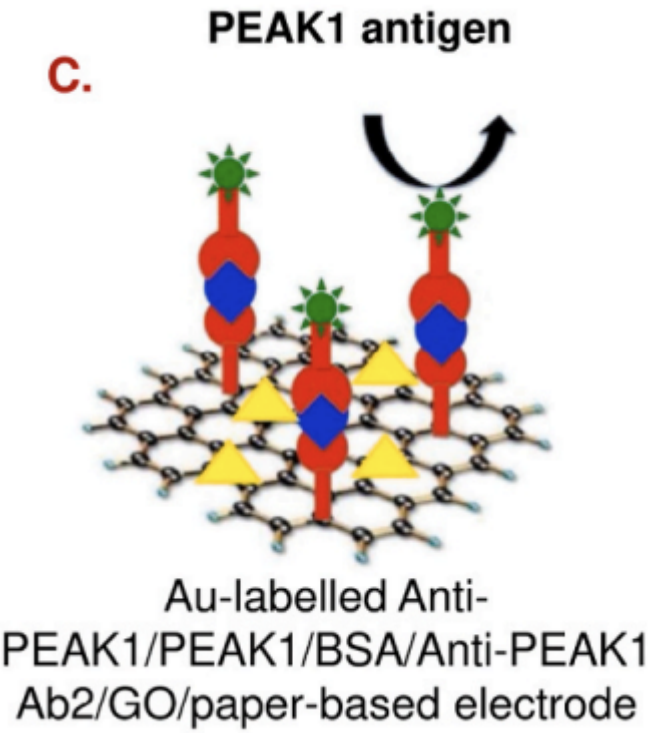


Figure 12. Representation of Au-labelled Anti-PEAK1 electrochemical immunosensor [50]

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In a 2022 study [51], a biosensor for detecting PEAK1, a biomarker linked to certain cancers, was created using paper-based microfluidics and electrochemical measurement principles. PEAK1 levels, which are critical for early cancer detection, vary significantly among patients, necessitating accurate detection. The biosensor was built around a Screen-Printed Electrode (SPE), which serves as its main platform. The SPE surface was functionalized with carbon nanotubes to improve conductivity and biocompatibility. Gold nanoparticles were then added, which improved electron transfer and electrochemical response due to their large surface area and conductivity. PEAK1 detection used a specific antibody immobilized on the SPE through a self-assembly process involving gold nanoparticles.

The above factors combined to produce a potent and specific binding to PEAK1. The electrochemical signal changed noticeably as a result of the antibody-PEAK1 complex formation, and this change could be seen using both differential pulse voltammetry (DPV) and cyclic voltammetry (CV). A detection limit of 10 pg/mL was functioned below, the biosensor was able to detect PEAK1 with efficacy and sensitivity at concentrations ranging from 0.1 to 150 ng/mL. The device's suitability for PEAK1 biomarker detection was confirmed by its high specificity and lack of cross-reactivity with substances that could interfere.

4.3.2. Carcinoembryonic Antigen (CEA)

In a 2010 study [52], the best performance condition for CEA was examined. Researchers used a chitosan-titanium dioxide (CS-Fc + TiO_2) composite film and a gold nanoparticle-graphene nanocomposite (Au-Gra) to create an electrochemical immunosensor for the detection of carcinoembryonic antigen (CEA). The Au-Gra nanocomposite was deposited after the CS-Fc + TiO_2 solution was made and applied to a glassy carbon electrode (GCE). Bovine serum albumin (BSA) was used to block nonspecific sites and immobilize CEA antibodies. The even dispersion of the gold nanoparticles on the graphene film was verified by scanning electron microscopy (SEM).

Cyclic voltammetry (CV) revealed a stable redox peak in the buffer solution, along with a significant decrease in current response in the presence of 60 ng/mL CEA, indicating effective antigen-antibody binding. The sensor performed best at pH 6.86 and a temperature of 35°C.

Mature than other proteins biomarkers, CEA is an important tumor marker for pancreatic cancer detection and monitoring. The immunosensor that appeared above detects CEA in a sensitive and specific manner, utilizing the enhanced conductivity and surface area of the Au-Gra and CS-Fc + TiO_2 composites to improve binding and signal transduction.

4.3.3. Enzymes biomarkers

Matrix Metalloproteinase-7 (MMP-7)

An experiment was set up in a 2021 study to assess the effectiveness of Matrix Metalloproteinase-7 (MMP-7) detection [53]. Researchers exfoliated powdered MoS_2 and mixed it with GO to create a 2D MoS_2/GO nanocomposite. The nanocomposite was applied to screen-printed carbon electrodes (SPCEs), and then methylene blue (MB) and anti-MMP-7 antibodies were added. Nonspecific sites were blocked using bovine serum albumin (BSA). Lastly, different concentrations of MMP-7 were added to the electrodes, and electrochemical measurements were made using methods like electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV).

The surface morphologies of the electrodes were examined using FE-SEM. The bare SPCE showed a rough surface with irregular microparticles, whereas the GO-modified SPCE had a wrinkled GO nanosheet structure. The 2D MoS_2-modified SPCE showed irregular nanosheet

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orientations, while the 2D MoS_2/GO composite revealed MoS_2 nanosheets embedded within GO layers, indicating material compatibility.

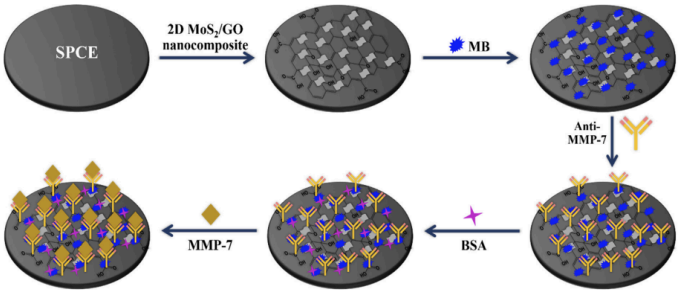


Figure 13. Illustration of the fabrication steps used for the MMP-7 immunosensor [53]

Using CV and EIS, the electrochemical characterization was completed. According to the CV results, the 2D MoS_2/GO-modified SPCE had the best electron transfer kinetics, as evidenced by its highest oxidation peak current (52.8 μA) and lowest peak-to-peak separation (0.190 V). According to the EIS data, the 2D MoS_2/GO-modified SPCE exhibited the lowest charge transfer resistance (2323 Ω) compared to bare, GO, and 2D MoS_2-modified SPCEs, indicating enhanced conductivity and electrochemical reactivity. Moreover, the 2D MoS_2/GO composite demonstrated outstanding repeatability over ten electrodes, with 1.26% as the corresponding standard deviation. [53]

4.3.4. Carbohydrate-based biomarkers

Carbohydrate Antigen 19-9 (CA 19-9) is a carbohydrate-based biomarker that is most frequently used to identify pancreatic cancer. Elevated levels of CA 19-9 are often linked to pancreatic tumors, but they lack full specificity as levels can rise in conditions like bile duct cancer or liver disease. Despite this, it remains valuable for tracking disease progression and assessing treatment efficacy when combined with other diagnostic tools.

The goal of a 2003 study was to determine how to use an electrochemical immunosensor and immobilize antigen in a titania sol-gel matrix to detect CA 19-9 [54]. For the materials and the methods, CA19-9 ELISA kits with various standard solutions and HRP-labeled antibodies were sourced from Diagnostic Products (USA). Bovine serum albumin (BSA) and other reagents were obtained from Sigma and Aldrich. Electrochemical measurements were taken with a CHI 730 analyzer with a three-electrode system, and scanning electron microscopy was done with a Hitachi X-650 microscope. For the immunosensor preparation, a graphite electrode was polished and electrochemically pretreated before immobilizing CA19-9 and forming a titania sol-gel membrane through the adsorption of titanium isopropoxide. The immunosensor was incubated with CA19-9 standards or serum samples, followed by electrochemical analysis using cyclic voltammetry and differential pulse voltammetry in a deaerated solution containing catechol and H_2O_2.

About the results and discussion, the cyclic voltametric behavior of the HRP/CA19-9 mod111ified electrode demonstrated effective electrocatalysis when immersed in 0.1 M PBS (pH 6.6) with catechol and H_2O_2. Initial measurements showed a low background current, but the addition of catechol produced distinct oxidation and reduction peaks. Adding H_2O_2 resulted in increased reduction peak current, reduced oxidation peak current, and a negative shift in the reduction peak potential, suggesting electrocatalytic activity. The titania sol-gel and CA19-9/titania sol-gel films' homogeneous porosity structure and effective immobilization of CA19-9, which enhanced electrode performance, were discovered by scanning electron microscopy. Optimization

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studies found that using a 10 μL CA19-9 solution at 240 U/ml and a deposition temperature of 25°C for 6 hours yielded the best results. The optimal immunoassay conditions included using 50 μL of HRP-labeled CA19-9 antibody, with an incubation pH of 6.6, temperature of 30°C, and time of 120 minutes to ensure maximum electrochemical response. In competitive assays, the electrochemical response decreased with increasing CA19-9 concentrations, with a linear correlation (r = 0.9965) between 3 and 20 U/ml. The detection limit was determined to be 2.68 U/ml, allowing for accurate measurement of CA19-9 levels in serum samples.

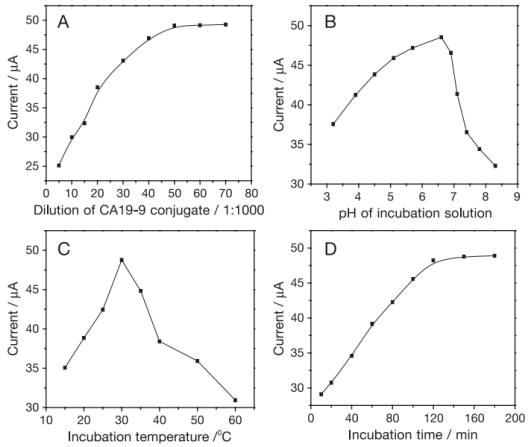


Figure 14. Dilution of HRP-labeled CA19-9 antibody solution (A), pH of incubation solution (B), incubation temperature (C), and incubation time (D) affect DPV peak current of the immunosensor in 0.1 M PBS pH 6.6 containing 0.5 mM catechol and 0.5 mM H_2O_2 [54]

5. Conclusion and future prospects

This paper reviews the application of graphene and its derivatives in electrochemical biosensors for cancer marker detection, with a particular focus on the early diagnosis of biomarkers for lung cancer, pancreatic cancer and malignant hematological tumors. By analyzing the high electrical conductivity and large specific surface area of graphene and the biocompatibility of its derivatives (such as graphene oxide and reduced graphene), the study shows that these materials have unique advantages in improving the sensitivity and selectivity of sensors. Compared with other detection methods, electrochemical sensors are simple to operate, low-cost, suitable for real-time detection and can adapt to complex environmental conditions. Graphene sensors show great potential for the early detection of cancer markers and can provide sensitive and reliable detection methods for early cancer screening. Although graphene electrochemical biosensors show great potential for cancer diagnosis, further research is needed to overcome the current challenges. First, improving the stability and reproducibility of the sensor while ensuring high sensitivity is an important direction for future research. With the discovery of multiple cancer markers, there is great potential for developing a more comprehensive multiplexed detection platform that can simultaneously detect multiple cancer markers, as this could help improve the accuracy and efficiency of early cancer screening. In addition, combining the sensor with wearable devices, the Internet of Things (IoT) and artificial intelligence (AI) could enable instant and intelligent diagnosis and detection, promoting the development of personalized medicine. AI and big data analysis can further enhance the detection capabilities of the sensor and automatically process and analyses complex data through machine learning algorithms to identify potential abnormal patterns. It can also extract useful information from massive amounts of data, automatically identify changes in the concentration of cancer

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markers, and help medical professionals make more timely decisions. Connectivity with the Internet of Things (IoT) enables remote real-time monitoring and data sharing. By connecting sensors to an IoT platform, patients' health data can be transmitted to healthcare providers in real time to improve efficiency, which is particularly suitable for diseases that require continuous monitoring, such as cancer, to get quick feedback. On the other hand, 3D printing technology offers new possibilities for the manufacture of sensors, making their structures more precise and the production process more flexible. This will help to develop customized diagnostic equipment and lay the foundation for mass production and the development of personalized medical devices. In short, graphene sensors have broad application prospects in the early diagnosis of cancer. Combining these sensors with technologies such as artificial intelligence, 3D printing, and the Internet of Things will greatly facilitate the early detection and diagnosis of cancer. This requires more interdisciplinary collaboration and technological innovation to better develop this field.

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