IJBPAS, July, 2025, 14(7): 3771-3791

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DETECTION OF LUNGS CANCER BIOMARK THROUGH BIOSENSOR TECHNOLOGY

PATIL V[1], MAHAJAN N[2], DUDHE S[3*] AND BORSE L[4]

1: Department of Pharmaceutics, Sandip Foundation, Nashik, Maharashtra, 422213

2: Department of Pharmaceutics, Sandip Foundation, Nashik, Maharashtra, 422213

3: Professor, Sandip Foundation Nashik, Maharashtra, 422213

4: Principal, Sandip Foundation Nashik, Maharashtra, 422213

***Corresponding Author: Mrs. Sujata Dudhe: E Mail: sujata.dudhe@sandippharmacy.org**

Received 20th March 2024; Revised 24th April 2024; Accepted 16th Aug. 2024; Available online 1st July 2025

https://doi.org/10.31032/IJBPAS/2025/14.7.9190

ABSTRACT

Lung cancer is a most prevalent form of cancer, causing numerous fatalities across the globe among both male and females. Timely diagnosis plays a crucial role in increasing the chances of successful cancer treatment. Recently, there was a remarkable interest in utilizing biosensor-based diagnosis techniques for the early detection of various cancer types. These techniques present several advantages over existing diagnostic methods, including but not limited to their ability to process large volumes of samples, non-invasiveness, cost-effectiveness, provision of easily interpretable data, and multiplexing capability. One of the key components in accurately detecting biomarkers is the utilization of biosensors. Biomarkers refer to biological molecules that are generated by the human body or a tumor, while biosensors are devices designed to identify cancer biomarkers. The article provides a quick summary of traditional lung screening methods. It discusses lung cancer biomarkers, summarizes the functioning of biosensors, and explores various biosensor technologies (including electrochemical, optical, and piezoelectric biosensors).

Keywords: Lungs cancer, biomarkers, biosensor technology, electrochemical biosensors, detection, biosensors

1. INTRODUCTION

1.1 Lungs cancer

Lung cancer is a kind of cancer which begins when peculiar cells within the lungs proliferate uncontrollably. It is a primary health hassle that may bring about extreme harm or demise. Cancer is the leading motive of demise worldwide, accounting for 10 million people to expire in 2020. The most commonplace cancer the various human beings is breast cancer (2.26 millions people are affected), lungs cancer (2.21 millions people), rectum and colon (1.93 million people), prostate (1.41 million people), non-melanoma skin cancer (1.20 million people), and stomach (1.09 million people) **[1]**. The American Cancer Society's evaluate on lung cancer in the United state for 2023 are: About 238,340 newer case of lung cancer (117,550 in male and 120,790 in female), About 127,070 people pass their life due to lung cancer (67,160 in male and 59,910 in female **[2]**. This is explained in the below graph **Figure 1**.

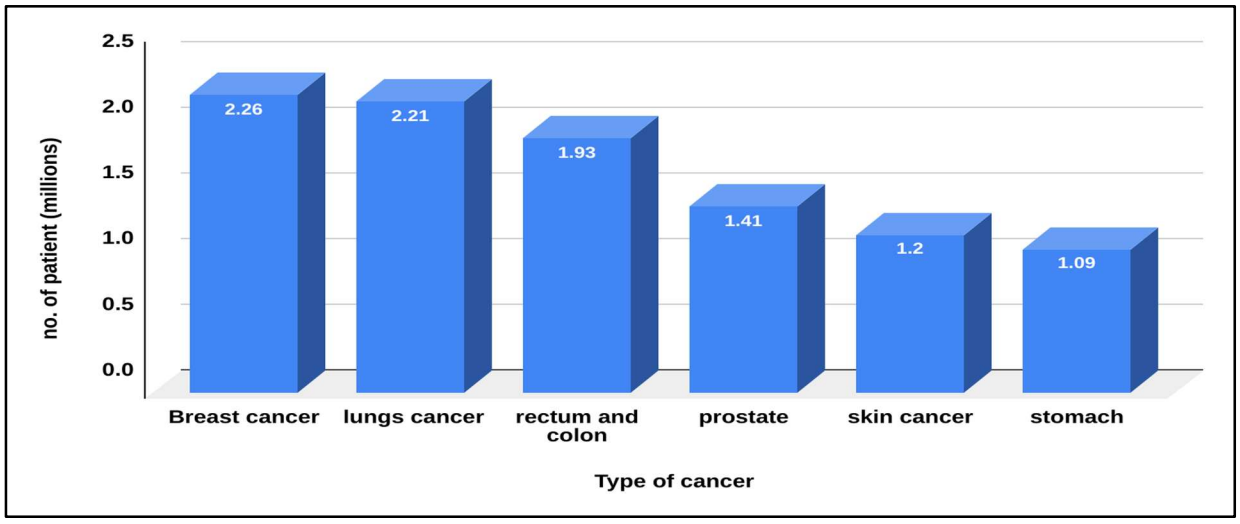

Figure 1: Evaluation on cancer in the United state for 2023

Lung cancers are broadly classified into two main categories: small-cell cancer and non-small-cell cancer. Non-small cell cancer are parted into three types: squamous-cell cancer, adenocarcinomas, and large-cell cancer. Each subtype has distinct characteristics and requires different approaches for diagnosis and treatment. squamous-cell carcinomas make up around 30% of all lung cancers and originate in the squamous cells lining the airways of the lungs. Adenocarcinoma is the most popular type of non-small-cell carcinoma, tends to develop in the outer regions of the lung and affects both smokers and non-smokers, making up around 30-40% of all lung cancers. Large-cell carcinomas,

comprising roughly 10-15 % of all lung cancers, are less common and are characterized by the presence of large, abnormal cells. They tend to develop, spread fast and can appear in any area of the lung **[3]**. Unfortunately, the survival rate for lung cancer patients is low due to late diagnosis and a poor prognosis.

1.2 Causes and some typical technique for identifying lung cancer

Carcinogen exposure is a popular cause for lung cancer. Lung cancer is mostly caused by tobacco use, although other factors including indirect exposure to smoke, arsenic, asbestos, and radon in the environment can also play a role in lung cancer development **[4]**. Its risk is influenced by hereditary variables, according to epidemiological research. An increased risk is associated with those who have a Familial past of lung cancer, indicating a genetic susceptibility **[5]**. There are various difficult challenges related with lung cancer therapy and care, such as persons with this life threatening disease get wrongly diagnosed as pulmonary TB As a result, misdiagnosis not only causes unnecessary delay in initiating the correct medical detection, but it also exposes the patient to improper, not required, or even hazardous treatment, worsening the health outcome and also In the beginning stages of lung cancer, individuals might not have any symptoms, and it may even go unnoticed. Shortness of breath, chronic coughing, and unexplained weight loss might occur as the cancer progresses. Unfortunately, these symptoms are shared by a variety of respiratory and non-cancerous illnesses, making them nonspecific **[6]**.

Abnormal chest imaging plays a crucial role in the conventional Diagnosis method for lung cancer detection. Different imaging techniques offer valuable insights into the structure and function of the lungs and surrounding tissues. Conventional diagnostic methods are ineffective for the early identification of cancer because these mechanisms are based on the phenotypic characteristics of the tumor **[7]**. Here are Some of the most often used screening techniques for imaging of lungs are included in **Table 1**.

Table 1: Conventional method to detect the lung cancer

Type	Advantage	Disadvantage	Time
Chest X-ray	**Trustworthy**	**Generate radiations, less sensitivity, low specificity.**	**Couple of seconds**
CT	**Trustworthy**	**Costly, high false-positive rate, less sensitivity.**	**300 sec**
MRI	**Trustworthy**	**Costly, unsuitable for all cancer**	**40 min-1hr.**
PET	**Reliable**	**Costly, radioactive substance and sophisticated instrument are required, unsuitable for patients with other complications**	**1hr 30min-4hr**

CT (Computed Tomography) scan is valuable in detecting and characterizing lung nodules, providing crucial information about size and tumor growth **[8]**. low-dose computed tomography (LDCT) exposes patients to lower radiation doses compared to conventional CT while LDCT is effective in detecting more initial-stage lung nodules and cancer cells than chest radiography (CRG) **[9]**. MRI (Magnetic Resonance Imaging is less commonly used than CT scans for lung cancer, MRI may be employed in specific cases to obtain detailed photos of soft tissues and blood vessels in the chest **[10]**. Positron emission tomography (PET) is a very effective method for detecting lung nodules and metastases from malignant tissues. Comparing with computed tomography (CT) **[11]**.

Biochemical screening has also been used to screen for lung cancer. For example, the enzyme cathepsin D found in bronchial lavage fluid can be a good marker for screening bronchogenic carcinoma, a subtype of lung cancer. Its increased activity in bronchial lavage fluid might be a sign that lung cancer is present. Thus, it may be possible to detect bronchogenic cancer early by evaluating the activity of cathepsin D in bronchial lavage fluid using biochemical screening **[12]**.

2. LUNGS CANCER BIOMARKERS

As tumors grow, they release various substances such as proteins, Deoxyribonucleic acid and metabolites into the bloodstream. These substances can function as biomarkers in cancer screening. and clinical diagnosis because their levels are associated with different stages of malignancies **[13]**. There are two main types of biomarkers: genetic and proteomics-based. Genetic biomarkers involve identifying specific DNA or RNA modifications in tumor cells or body fluids, offering insights into the genetic makeup of the cancer. Proteomics-based biomarkers focus on analyzing proteins present in tumor cells or body fluids like urine, sputum, blood, providing information about protein expression and modifications. Both types of biomarkers, derived from diverse bodily sources, contribute crucial information for cancer detection, diagnosis, and treatment decisions **Table 2**. Contain the list of biomark use in lung cancer.

Table 2: Lung cancer biomarkers

Category	Biomarker
epigenetics and Genetics and biomarker	• **SHOX2, Epidermal growth factor receptors (c-ErbB-1, c-ErbB-2), CDKN2A, K-ras and p53 mutant, RASSF1A, FHIT, APC, COX2, RASSFIA, MET, APC ESR1, Her2, HOXA9, BRAF, CDH13, PIK3CA, PTEN, IL-8 mRNA, RET.** • **miR-210, miR-200b, miR-708, miR-21, miR-375, miR-137, miR-205, miR-486,**
Protein biomarker	**APOA1, BB isoenzyme of creatine kinase (CK-BB), bombesin-like gastrin-releasing peptide,) plasma kallikrein B1, cytokeratin-7, CEA, carbohydrate antigen 125, chromogranin A, carbohydrate antigen 19-9 (CA 19-9), CYFRA 21-1, TPA, cytokeratin fragment 21-1,vascular endothelial growth factor(VEGF), tumor M2-pyruvate**

	kinase,Ig-free light chain, haptoglobin-R 2, nitrated ceruloplasmin, KLKB1, ProGRP, Annexin II, α-enolase (ENO1, also called neuron-specific enolase (NSE)), α-1-acid glycoprotein, CD59 glycoprotein, GM2 activator protein (GM2AP), transthyretin (TTR).

2.1 Genetics and epigenetic biomarkers

Genetic biomark are categorized into two parts: gene and chromosomal based abnormalities. Genetic materials in both groups suffer deletions, amplifications, rearrangements, and other modifications. Other identified genetic variants in lung cancer that might be used as biomarkers include loss of heterozygosity (LOH), microsatellite instability (MSI) and genetic hypermethylations are the Other identified genetic variants in lung cancer can serve as biomarkers **[14, 15]**. Genetic biomarkers involve variations in the DNA sequence, while epigenetic biomarkers involve modifications to the structure of DNA or its associated proteins **[16]**. Histone and DNA methylation alterations are key epigenetic indicators in cancer, which influence gene expression. Another significant mechanism is microRNAs (miRNAs). These short, non-coding RNAs may specifically target and block certain gene expressions, selectively disrupting protein creation **[17]**. From all these mechanisms, DNA methylation is widely explored as a biomarker for malignancies. The hyper-methylation of particular promoter sites, recognized as CpG islands, has the potential to modify gene expression or result in gene suppression. This phenomenon is frequently observed in various cancer cells, making it a promising option for early cancer detection **[18]**. Some of the genetic based biomarker is explain as follow

2.1.1 P53

The p53 protein regulates cell growth and prevents tumors. However, in the case of lung cancer, the p53 gene may be mutated. These mutations can lead to the production of abnormal p53 proteins that do not function properly. As a result, mutated p53 proteins fail to regulate cell growth properly, resulting in uncontrolled cell division and tumor formation **[19]**.

2.1.2 EGFR

It is a protein that resides on the cell membrane, involved in regulating cell growth and division. When an extracellular ligand binds to EGFR it triggers the formation of homo/heterodimers, initiating signaling cascades that promote cell growth and metastasis. In cases of lung cancer, there may be mutations in the EGFR gene, causing the EGFR signaling pathway to overwork. This can result in uncontrolled cell growth and the development of tumors in the lungs **[20]**.

2.1.3 Ras genes

The Ras gene has three members: H-ras, K-ras, and N-ras. These genes encode proteins which have a role in transmitting signals from the cell surface to the cell nucleus, regulating processes such as cell growth, division, and differentiation. Alteration in Ras gene, particularly in the K-Ras variant, are commonly found in lung cancer patients. These Mutated forms of Ras genes can disrupt the normal regulation of signal transmission from the cell membrane to the nucleus. This erroneous signaling results in the unregulated activation of pathways that promote cell growth and proliferation, which contributes to the development of cancer **[21]**. Roughly 30% of instances of NSCLC and roughly 25% of all cancers have alteration in the Ras gene **[22]**.

2.1.4 Micro RNAs

It is a small RNA molecules about 19 to 25 nucleotides long, play a crucial role in controlling gene activity. In simpler terms, they Serve as small switches that can turn off or decrease the production of proteins from certain genes **[23]**. Surveys have demonstrated that specific microRNAs, like miR-21, are more abundant in certain cases. For example, in NSCLC. The detection of these tiny molecules in fluids like blood or saliva could indicate the presence of cancer, making them valuable for early diagnosis **[24]**.

2.2 Protein based biomarkers

Changes in proteins regulating the cell cycle can negatively impact normal physiological processes, potentially leading to cancer. These alterations result from variations in gene expression, alternative splicing, genetic mutations, gene duplications, and post-translational modifications like phosphorylation, glycosylation, and methylation. Proteins exhibiting significant changes in concentration or function during cancer can be valuable biomarkers for detecting and monitoring the disease **[25]**. A few of the protein biomarkers that have already been used to create cancer biosensors include APOA1, BB isoenzyme of creatine kinase (CK-BB), bombesin-like gastrin-releasing peptide,) plasma kallikrein B1, cytokeratin-7, CEA, CA 125, chromogranin A, carbohydrate antigen 19-9 (CA 19-9), CYFRA 21-1, TPA, cytokeratin fragment 21-1,vascular endothelial growth factor(VEGF), tumor M2-pyruvate kinase,Ig-free light chain, haptoglobin-R 2, nitrated ceruloplasmin, KLKB1, ProGRP, Annexin II, α-enolase (ENO1, also called neuron-specific enolase (NSE)), α-1-acid glycoprotein, CD59 glycoprotein, GM2 activator protein (GM2AP), transthyretin (TTR)

2.2.1 Carcinoembryonic antigen (CEA)

It is a glycoprotein typically found in healthy individuals at concentrations of 2.5 to 5 ng/ml-1, has been identified as a valuable indicator for lung cancer, with elevated levels associated with the disease. Particularly, heavy smokers tend to exhibit higher CEA levels **[26]**. Further research has shown a substantial relationship between CEA levels and survival duration in NSCLC. To enhance predictive accuracy, current approaches involve assessing CEA levels in conjunction with other markers like AFP CA 15-3, and CCAT2 **[27]**.

2.2.2 Neuron-specific enolase (NSE)

NSE is a glycolytic enzyme found mainly in neural cells. Elevated quantity of NSE in the serum have been observed in individuals with small-cell lung cancer (SCLC). This enzyme's presence in the bloodstream is associated with disorders involving neuronal destruction, as increased serum levels may reflect damage or breakdown of neurons so It is better to consider other markers, including CEA and CYFRA 21-1, in addition to this enzyme. NSE is a highly accurate Biomarker used to identify small-cell lung cancer patients **[28]**.

2.2.3 CYFRA 21-1 (Cytokeratin 19)

Cytokeratin 19, a 40 kDa human cytokeratin found in epithelial tissues, is considered an excellent candidate for carcinoma detection. It exhibits high sensitivity and specificity, particularly in adenocarcinomas **[29]**. Recent experiments have highlighted its role as a valuable marker for diagnosing NSCLC. In lung cancer diagnosis, assessing cytokeratin 19 levels (typically around 3.3 ng/ml-1 in normal serum) is often done in conjunction with other biomarkers **[30]**.

2.2.4 Annexin A2 (ANXA2)

Annexin A2, a 36 kDa protein primarily expressed in macrophages and endothelial cells, has emerged as a promising biomarker for lung cancer. This protein plays a role in controlling membrane trafficking and endocytosis. Overexpression of Annexin A2, particularly observed in Primary stages of lung cancer **[31]**. In a complementary approach, combining the detection of ANXA2 with another biomarker, heat shock protein 60 (HSP60), has shown a significant improvement in the earlier diagnosis of lung cancer. This suggests that a multi-marker strategy, involving ANXA2 and HSP60, enhances the effectiveness of earlier lung cancer detection **[32]**.

2.2.5 Serum amyloid A1

Serum Amyloid A1 (SAA1), an acute phase protein whose expression significantly increases during injuries, infections, and other stressful conditions. Various experiments, including one involving 350 samples from

healthy individuals and those with lung cancer, revealed SAA1 levels to be 14 times higher in lung cancer patients **[33]**. Elevated SAA1 levels have also been observed in other cancers such as breast, endometrial, prostate, and uterine serous papillary cancers, highlighting its potential for earlier detection of these disorders **[34]**.

3. BIOSENSORS FOR LUNG CANCER BIOMARKER DETECTION

Biosensor-based diagnostic techniques for earlier identification of many types of cancer have recently attracted significant attention, biosensor is nothing but the device which is designed to detect the cancer biomark A biosensor consists of three components: Recognition Element, Signal Transducer, and Signal Processor. Recognition element detects specific molecules, Signal transducer Converts the detection into an electrical signal, Signal Processor Interprets the electrical signal and displays the results **[35]**. **Figure 2** Describe the fundamental design and operation of a biosensor. Biomarks are biological substances generated by the tumor or body. that can be found in blood, other body fluids or tissues. Biomarkers can come from different types of molecules in the body. These include: DNA (involving specific genetic changes), RNA (related to gene expression), or proteins (such as hormones, antibodies, oncogenes, or tumor suppressors) **[36]**.

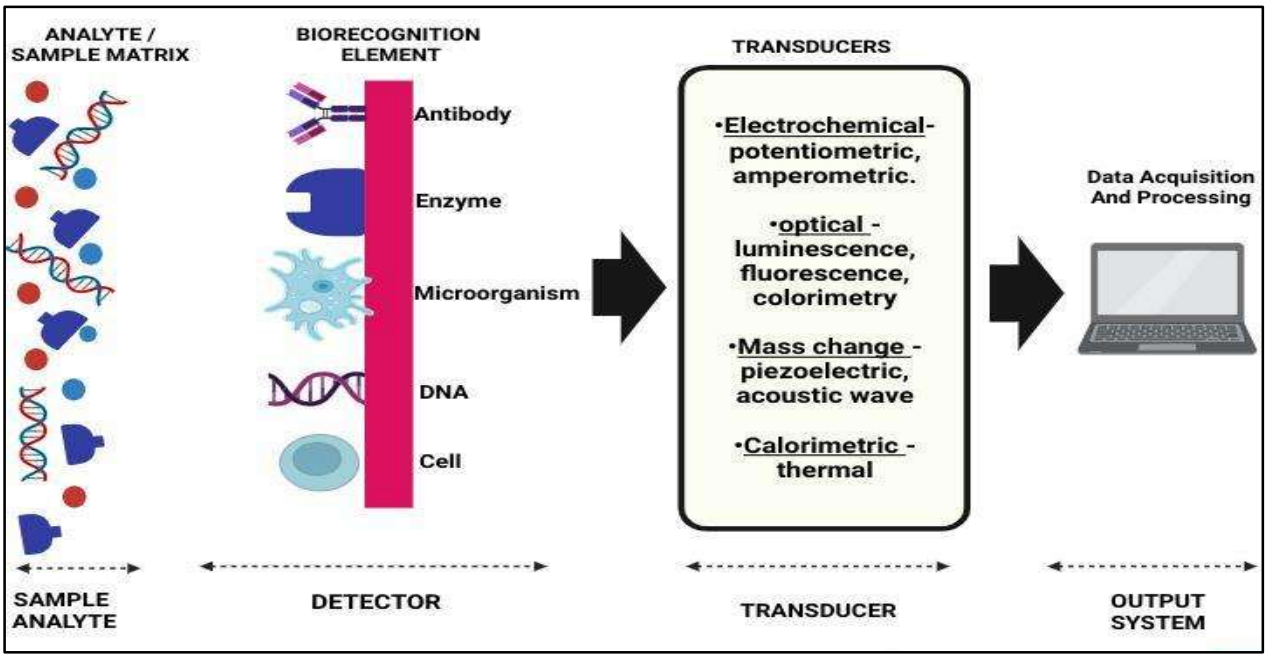

Figure 2: The process by which biosensors function

3.1 Electrochemical Biosensors

In these biosensors, the identification principle relies on electrochemical reactions occurring at the electrode surface when the sensor interacts with the target molecules. This interaction induces changes in the electrical signal, which are then monitored to quantify the presence or concentration of the target **[37]**. Electrochemical immunosensors use antibodies to recognize and bind certain antigens. In an electrochemical immunoassay, a specific antibody is attached to the electrode surface and then interacts with the antigen for an electrochemical reaction Electrochemical immunosensors are constructed using two different methods: a) standard antibody-antigen interaction and b) sandwich-type antibody antigen communication **[38]**.

Y.Park *et al*. Create an aptasensor, in that they detect a VEGF165 biomarker by using PANI/CNT nanocomposite modified electrode functionalized with an anti-VEGF165 RNA aptamer. Here is a summary of the detection process: The Screen-Printed Carbon Electrode (SPCE) is modified with a nanocomposite material consisting of polyaniline (PANI) and carbon nanotubes (CNTs). This modification provides a stable and sensitive platform for detecting a VEGF165 tumor biomarker. The electrode surface is further functionalized with an anti-VEGF165 RNA aptamer. The aptamer specifically binds to a VEGF165 tumor biomarker with high affinity and selectivity. When a VEGF165 tumor biomarker is present in the sample then it binds to the immobilized anti-VEGF165 RNA aptamer over a electrode surface. This binding event causes alteration in the electrochemical properties of the sensor, which can be measured and quantified **(Figure 3) [39]**. In a separate investigation to identify VEGF165 in lung cancer specimens, researchers designed an aptasensor with a gold-modified electrode and mesoporous nanoparticles. The approach involved detecting changes in the electrode's interfacial properties when the immobile anti-VEGF165 aptamer interacted with VEGF165 in samples. This aptasensor was highly effective in detecting ultra-trace amounts of VEGF in lung cancer blood sample **[40]**.

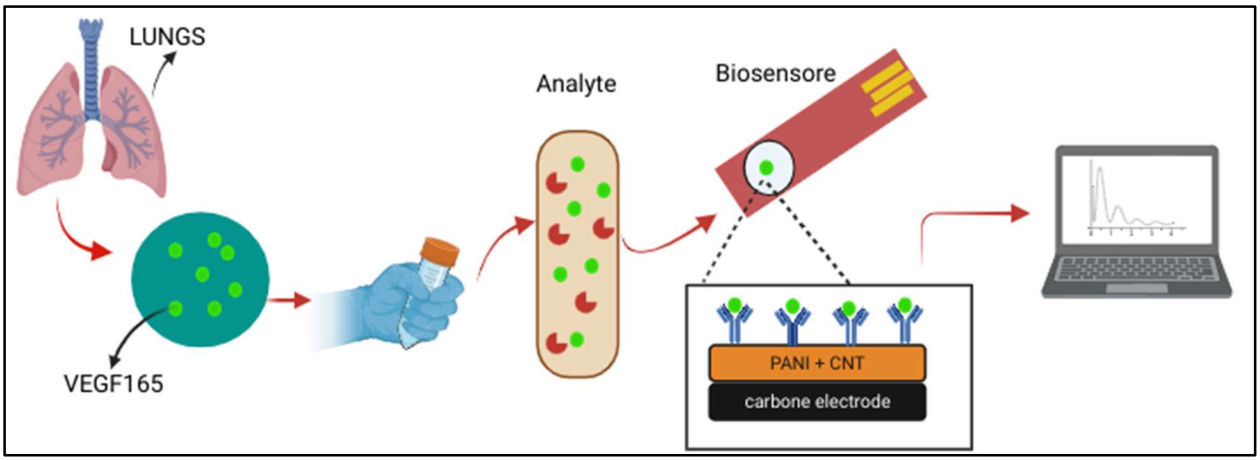

Figure 3: Detection of VEGF165 using a Electrochemical aptasensor with PANI/CNT Nanocomposites

Jou *et al*. identified microRNA (miR) biomarkers using an AuNPs alter screen-printed carbon electrode involving a sophisticated electrochemical sensing approach. SPCE is modified with AuNPs to enhance the sensitivity and efficiency of the electrode. A methylene blue-labeled hairpin structure is immobilized over the electrode surface and the recognition of the target miR is made. When the target miR binds to the hairpin structure, it induces a conformational change, displacing the methylene blue from the electrode surface This conformational change reduces the electrochemical signal, allowing the detection of the miR. The sensor system detect a very small quantity of miRs, with accurate quantification of miR **[41]**. Liu *et al*. used 3D DNA origami to create an electrochemical biosensor that recognizes mir-21 in lung cancer specimens. The biosensor consisted of two parts: a top containing ferrocene-tagged DNA with a stem-loop structure for hybridization with target microRNA and a bottom with thiolated tetrahedral DNA integrated on a gold-modified electroprod and exhibited a low detection limit (10). pM), highlighting its potential clinical application for cancer diagnosis **[42]**.

Yu Li *et al*. recently created a biosensor in which electrode surface is alter to immobilize CEA monoclonal antibody (anti-CEA) by gold-thiol chemistry, additionally, a water-dispersible graphene or amphiphilic pyrene derivative nanocomposite was introduced to improve the immobilization of capture antibodies and enhance detectability **[43]**. When the CEA tumor marker is present in the sample then it binds to anti-CEA on the electrode surface. Such binding event cause impedance changes which can be monitored by electrochemical impedance spectroscopy (EIS) **[44]**.

A sandwich-type electrochemical biosensor is designed for detecting mutations in the EGFR gene. DNA probes, designed around the exon 19 deletion parts in the EGFR gene, served as the bio-recognition elements. λ exonuclease was utilized to convert double-stranded DNA (dsDNA) to single-stranded DNA (ssDNA) molecules in real NSCLC samples. Compared to other denaturation methods like high temperature or urea, the use of λ exonuclease was more efficient. The developed biosensor, assisted by λ exonuclease, successfully detected and differentiated EGFR mutations in PCR-amplified samples **[45]**.

3.2 Optical Biosensors

The most popular form of biosensor is optical biosensors. Optical transducers are devices that use various optical phenomena such as total internal reflection, surface plasmon resonance (SPR), luminescence, light absorption, and fluorescence to detect specific targets. In these effect there is a interactions between materials and light, allowing for sensitive and selective detection of substances through changes in optical properties **[46]**.

3.2.1 SPR based detection techniques

The primary attention is on surface plasmon resonance (SPR)-based biosensors, including localized SPR and SPR imaging, which are the most widely used optical biosensors. The first commercially SPR-based biosensor device is launch by Pharmacia Biosensor AB, thereafter known as Biacore. When polarized light is directed at a certain angle at the interface of two media (usually glass and liquid) over a surface of a metal (or other conducting materials), the SPR phenomenon takes place. This leads to the generation of surface plasmons, causing the intensity of reflected light to decrease at a particular angle referred to as the resonance angle. The surface material has immediate effects on this impact. A sensorgram, depicting the shift of wavelength or reflectivity angle over time, can be obtained through measurements. How SPR works is explained in **Figure 4 [47]**.

By focusing on a particular point that is K-ras gene mutation, Sato *et al*. developed a biosensor for early cancer detection using surface plasmon resonance (SPR). Peptide nucleic acid is mounted on the surface which is used by the biosensor as biorecognition molecules. Furthermore, an SPR-based A biosensor was created to use a molecular inversion probe to detect DNA methylation. Having two inverted recognition ends, offering methylated DNA with great specificity **[48]**.

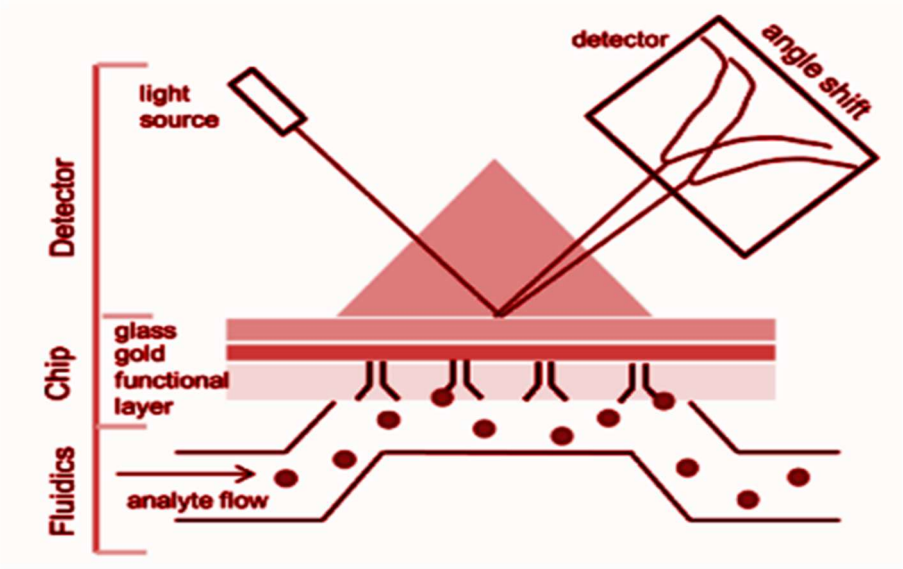

Figure 4: The principle of SPR instrument

To identify the cytokeratin 17 protein (CK17) in lung cancer biopsy samples, an SPR-based biosensor was created. A biocompatible polymer optical fiber was used to immobilize anti-CK17 antibody molecules. Using a gel matrix containing CK17 as a soft tissue mimic, the biosensor's penetration capabilities into soft matter was verified, indicating effective detection within the matrix. The biosensor's capacity to detect CK17 ex vivo in real tissue samples was further confirmed by using real lung cancer biopsy samples. The creation of biocompatible biosensors for the non-invasive in vivo detection of cancer biomarkers is made possible by this exciting strategy **[49]**.

LSPR (Localized surface plasmon resonance) was employed by a few nucleic acid-based cancer biosensors. LSPR is caused by the stimulation of surface plasmons in metallic nanoparticles, such as AuNPs, or nanostructures. This produces characteristic scattering peaks and spectrum absorption. An LSPR-based biosensor was created by Nguyen and Sim to detect methylation and certain tumor alterations (E545K and E542K) in circulating tumor DNA (ctDNA) of the PIK3CA gene simultaneously. Their approach involved PNA (Peptide nucleic acid) probes conjugated to gold nanoparticles (AuNPs) for detecting ctDNA mutations and immunogold colloids for identifying methylation. This biosensor provides a versatile tool for the parallel detection of epigenetic and genetic alterations associated with cancer in the PIK3CA gene **[50]**.

A nanoporous AAO (anodic aluminium oxide) chip is used by Lee *et al*. to create a

biosensor that can identify the lung cancer biomarker serum amyloid A1 (SAA1). The sensing platform was the AAO chip, which was selected due to its biosafety, stability, chemical resistance, and wide surface area. The sensor chip measured variations in the refractive index of the surroundings as antigens entered the chip pores and reacted with immobilized antibodies. The biosensor demonstrated a identification limit of 100 eg/mL, demonstrating the clinical potential of AAO chips for the very sensitive detection of SAA1 in samples **[51]**.

By focusing on the cytokeratin 19 (CK19) biomarker in increasing human plasma, Chiu *et al*. introduced a carboxyl-functionalized graphene oxide-based SPR sensor device for label-free lung cancer (NSCLC) detection. A little quantity of CK19 specific antibody that had been bound on the sensing chip was used by the immunosensor. The described sensor found the CK19 biomarker with both excellent sensitivity and specificity **[52]**.

3.2.2 Fluorescence Based Detection Techniques

A very sensitive biosensor based on FRET (Fluorescence Resonance Energy Transfer) was developed to identify CEA in serum samples from lung cancer patients. It made use of PdNPs (palladium nanoparticles) and upconverting nanoparticles (UCPs). Modified UCPs were connected to CTA aptamer molecules, bringing PdNPs and UCPs close together through interactions with nitrogen groups in molecules of aptamers. Aptamer-PdNPs interactions were disrupted by the presence of CEA. causing concentration-dependent UCP fluorescence recovery, allowing for extremely delicate CEA detection **[53]**.

3.2.3 Chemiluminescence based detection techniques

Another optical method utilized in sensor design is chemiluminescence. When a biomarker attaches to the recognition element in this case, a photochemical emission happens. Chemiluminescence-based biosensors have the benefit of requiring relatively little in the way of measuring apparatus **[54]**. Hao and Ma developed a flow injection chemiluminescent immunoassay-based biosensor for the identification of CEA (Carcinoembryonic Antigen). The technique used goat-anti-mouse IgG tagged with gold nanoparticles (AuNPs) and anti-CEA antibodies in a sandwich assay arrangement to detect CEA. A seed-mediated gold enlargement phase is added to the procedure to improve sensitivity. This biosensor offers a precise and sensitive method for CEA detection, which is important for cancer monitoring and diagnosis **[55]**.

3.3 Mass-based (Piezoelectric biosensors)

Mass-based biosensors measure variations within the mass of a piezoelectric crystal, usually quartz, that oscillates in an applied electric field at a certain frequency. The mass and oscillation frequency of the crystal alter in response to interactions between the target analyte and an immobilized biorecognition molecule on the crystal. To precisely ascertain the analyte concentration in samples, this modification is quantified. A sensitive biosensing technique called (QCM) quartz crystal microbalance enables the identification of even single point mutations in a given gene. Because of their great sensitivity, quartz crystals are frequently employed in the creation of mass-based biosensors **[56]**.

A QCM-based immunosensor was created by Chen *et al*. to help in the quick identification of early-stage lung cancer. Serum samples from vaccinated rabbits were put to the quartz crystal surface, which had lung cancer cells fixed on it. Antibody content may be quickly and accurately detected at nanogram levels thanks to the measurement of the mass and resonant frequency changes brought on by cell-antibody interactions **[57]**. Using certain DNA molecules, the study built SPR and QCM biosensors to find single nucleotide polymorphisms (SNP) in the TP53 gene of lung cancer samples. Both biosensors exhibited highly sensitive hybridization reactions within the range of 0.03–2 μM **[56]**. Similar QCM immunosensors demonstrated their effectiveness in this application. Mass-based biosensors have been widely reported for detecting various cancer biomarkers, including HER-2 **[58]**, BRCA-1 gene mutant **[59]**, PSA **[60]**, hormone-related peptide (PTHrP) **[61]**.

4. CONCLUSION

In conclusion, lung cancer has the highest fatality rate of any cancer due to its short survival time. Biosensor technologies are the most trustworthy and likely to give alternative techniques for early stage lung cancer detection, resulting in a reduction in mortality rates. The significance of disease biomarkers, particularly in the case of lung cancer carcinomas. It emphasizes their crucial role in prognosis, diagnosis, and understanding cancer origins. Early detection of biomarkers is essential for a comprehensive understanding of pulmonary malignancies and efficient patient care. The review discusses various lung cancer biomarkers and summarizes the functioning of biosensors and different biosensor technologies for their detection. The hope is that these techniques will contribute to the simultaneous measurement of new and more specific lung

cancer biomarkers, ultimately improving clinical outcomes for patients.

5. REFERENCES

[1] https://www.who.int/news-room/fact-sheets/detail/cancer#:~:text=The%20problem,lung%20(2.21%20million%20cases)%3B

[2] https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html

[3] Cersosimo, R. J. (2002). Lung cancer: a review. American Journal of Health-System Pharmacy, 59(7), 611-642.

[4] Chang, A. E., Ganz, P. A., Hayes, D. F., Kinsella, T., Pass, H. I., Schiller, J. H., ... & Strecher, V. O. (2007). *An Evidence-Based Approach* (Vol. 34). Springer Science & Business Media.

[5] Bharti, A., Ma, P. C., & Salgia, R. (2007). Biomarker discovery in lung cancer—promises and challenges of clinical proteomics. *Mass spectrometry reviews*, *26*(3), 451-466.

[6] Sutedja, T. G., Venmans, B. J., Smit, E. F., & Postmus, P. E. (2001). Fluorescence bronchoscopy for early detection of lung cancer: a clinical perspective. *Lung Cancer*, *34*(2), 157-168.

[7] Ghosal, R., Kloer, P., & Lewis, K. E. (2009). A review of novel biological tools used in screening for the early detection of lung cancer. *Postgraduate medical journal*, *85*(1005), 358-363.

[8] Latifi, K., Dilling, T. J., Feygelman, V., Moros, E. G., Stevens, C. W., Montilla-Soler, J. L., & Zhang, G. G. (2015). Impact of dose on lung ventilation change calculated from 4D-CT using deformable image registration in lung cancer patients treated with SBRT. *Journal of Radiation Oncology*, *4*, 265-270.

[9] Saghir, Z., Dirksen, A., Ashraf, H., Bach, K. S., Brodersen, J., Clementsen, P. F., ... & Pedersen, J. H. (2012). CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax*, *67*(4), 296-301.

[10] Zurek, M., Bessaad, A., Cieslar, K., & Crémillieux, Y. (2010). Validation of simple and robust protocols for high-resolution lung proton MRI in mice. *Magnetic Resonance in Medicine*, *64*(2), 401-407.

[11] Al-Sarraf, N., Gately, K., Lucey, J., Wilson, L., McGovern, E., & Young, V. (2008). Lymph node staging by means of positron emission tomography is less accurate in non-

small cell lung cancer patients with enlarged lymph nodes: Analysis of 1145 lymph nodes. *Lung Cancer*, *60*(1), 62-68.

[12] Kühn, S. H., de Kock, M. A., & Gevers, W. (1978). The diagnostic value of lysosomal enzyme patterns in bronchial aspirates of patients with suspected bronchial carcinoma. *Chest*, *74*(2), 150-156.

[13] Chanin, T. D., Merrick, D. T., Franklin, W. A., & Hirsch, F. R. (2004). Recent developments in biomarkers for the early detection of lung cancer: perspectives based on publications 2003 to present. *Current opinion in pulmonary medicine*, *10*(4), 242-247.

[14] Hsu, H. S., Chen, T. P., Wen, C. K., Hung, C. H., Chen, C. Y., Chen, J. T., & Wang, Y. C. (2007). Multiple genetic and epigenetic biomarkers for lung cancer detection in cytologically negative sputum and a nested case–control study for risk assessment. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, *213*(4), 412-419.

[15] WANG, Y. C., HSU, H. S., CHEN, T. P., & CHEN, J. T. (2006). Molecular diagnostic markers for lung cancer in sputum and plasma. *Annals of the New York Academy of Sciences*, *1075*(1), 179-184.

[16] Holliday, R. (2006). Epigenetics: a historical overview. *Epigenetics*, *1*(2), 76-80.

[17] Memari, F., Joneidi, Z., Taheri, B., Aval, S. F., Roointan, A., & Zarghami, N. (2018). Epigenetics and Epi-miRNAs: Potential markers/therapeutics in leukemia. *Biomedicine & Pharmacotherapy*, *106*, 1668-1677.

[18] Belinsky, S. A. (2004). Gene-promoter hypermethylation as a biomarker in lung cancer. *Nature Reviews Cancer*, *4*(9), 707-717.

[19] Lutz, W., & Nowakowska-Swirta, E. (2002). Gene p53 mutations, protein p53, and anti-p53 antibodies as biomarkers of cancer process. *International journal of occupational medicine and environmental health*, *15*(3), 209-218.

[20] Khalil, F. K., & Altiok, S. (2015). Advances in EGFR as a predictive marker in lung adenocarcinoma. *Cancer Control*, *22*(2), 193-199.

[21] Vakiani, E., & Solit, D. B. (2011). KRAS and BRAF: drug targets and predictive biomarkers. *The Journal of pathology*, *223*(2), 220-230.

[22] Dearden, S., Stevens, J., Wu, Y. L., & Blowers, D. (2013). Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Annals of oncology*, *24*(9), 2371-2376.

[23] Bartel, D. P. (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. *cell*, *116*(2), 281-297.

[24] Xie, Y., Todd, N. W., Liu, Z., Zhan, M., Fang, H., Peng, H., ... & Jiang, F. (2010). Altered miRNA expression in sputum for diagnosis of non-small cell lung cancer. *Lung cancer*, *67*(2), 170-176.

[25] Bhatt, A. N., Mathur, R., Farooque, A., Verma, A., & Dwarakanath, B. S. (2010). Cancer biomarkers-current perspectives. *Indian Journal of Medical Research*, *132*(2), 129-149.

[26] Dai, H., Liu, J., Liang, L., Ban, C., Jiang, J., Liu, Y., ... & Wang, C. (2014). Increased lung cancer risk in patients with interstitial lung disease and elevated CEA and CA 125 serum tumour markers. *Respirology*, *19*(5), 707-713.

[27] Qiu, M., Xu, Y., Yang, X., Wang, J., Hu, J., Xu, L., & Yin, R. (2014). CCAT2 is a lung adenocarcinoma-specific long non-coding RNA and promotes invasion of non-small cell lung cancer. *Tumor Biology*, *35*(6), 5375-5380.

[28] Isgrò, M. A., Bottoni, P., & Scatena, R. (2015). Neuron-specific enolase as a biomarker: biochemical and clinical aspects. *Advances in cancer biomarkers: from biochemistry to clinic for a critical revision*, 125-143.

[29] Mizuguchi, S., Nishiyama, N., Iwata, T., Nishida, T., Izumi, N., Tsukioka, T., ... & Suehiro, S. (2007). Serum Sialyl Lewisx and cytokeratin 19 fragment as predictive factors for recurrence in patients with stage I non-small cell lung cancer. *Lung cancer*, *58*(3), 369-375.

[30] Zissimopoulos, A., Stellos, K., Permenopoulou, V., Petrakis, G., Theodorakopoulos, P., Baziotis, N., & Thalassinos, N. (2007). The importance of the tumor marker CYFRA 21-1 in patients with lung cancer after surgery or

chemotherapy. *Hellenic journal of nuclear medicine*, *10*(1), 62-66.

[31] Yang, J., Yang, F., Nie, J., Zou, X., Tian, H., Qin, Y. E., & Liu, C. (2015). Evaluation of Annexin A2 as a novel diagnostic serum biomarker for lung cancer. *Cancer Biomarkers*, *15*(2), 205-211.

[32] Mittal, S., & Rajala, M. S. (2020). Heat shock proteins as biomarkers of lung cancer. *Cancer biology & therapy*, *21*(6), 477-485.

[33] Sung, H. J., Ahn, J. M., Yoon, Y. H., Rhim, T. Y., Park, C. S., Park, J. Y., ... & Cho, J. Y. (2011). Identification and validation of SAA as a potential lung cancer biomarker and its involvement in metastatic pathogenesis of lung cancer. *Journal of proteome research*, *10*(3), 1383-1395.

[34] Cocco, E., Bellone, S., El-Sahwi, K., Cargnelutti, M., Buza, N., Tavassoli, F. A., ... & Santin, A. D. (2010). Serum amyloid A: a novel biomarker for endometrial cancer. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *116*(4), 843-851.

[35] Chaplin M. What are biosensors? 2004. Available from: http://www.lsbu.ac.uk/biology/enztech/biosensors.html. Accessed Sep 24 2010.

[36] Bohunicky, B., & Mousa, S. A. (2010). Biosensors: the new wave in cancer diagnosis. *Nanotechnology, science and applications*, 1-10.

[37] Ranjan, R., Esimbekova, E. N., & Kratasyuk, V. A. (2017). Rapid biosensing tools for cancer biomarkers. *Biosensors and Bioelectronics*, *87*, 918-930.

[38] Shan, J., & Ma, Z. (2017). A review on amperometric immunoassays for tumor markers based on the use of hybrid materials consisting of conducting polymers and noble metal nanomaterials. *Microchimica Acta*, *184*, 969-979.

[39] Park, Y., Hong, M. S., Lee, W. H., Kim, J. G., & Kim, K. (2021). Highly sensitive electrochemical aptasensor for detecting the VEGF165 tumor marker with PANI/CNT nanocomposites. *Biosensors*, *11*(4), 114.

[40] Tabrizi, M. A., Shamsipur, M., & Farzin, L. (2015). A high sensitive electrochemical aptasensor for the determination of VEGF165 in serum of lung cancer patient. *Biosensors and Bioelectronics*, *74*, 764-769.

[41] Jou, A. F. J., Chen, Y. J., Li, Y., Chang, Y. F., Lee, J. J., Liao, A. T., & Ho, J. A. A. (2017). Target-triggered, dual amplification strategy for sensitive electrochemical detection of a lymphoma-associated MicroRNA. *Electrochimica Acta*, *236*, 190-197.

[42] Liu, S., Su, W., Li, Z., & Ding, X. (2015). Electrochemical detection of lung cancer specific microRNAs using 3D DNA origami nanostructures. *Biosensors and Bioelectronics*, *71*, 57-61.

[43] Li, Y., Chen, Y., Deng, D., Luo, L., He, H., & Wang, Z. (2017). Water-dispersible graphene/amphiphilic pyrene derivative nanocomposite: High AuNPs loading capacity for CEA electrochemical immunosensing. *Sensors and Actuators B: Chemical*, *248*, 966-972.

[44] Grunnet, M., & Sorensen, J. B. (2012). Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. *Lung cancer*, *76*(2), 138-143.

[45] Xu, X. W., Weng, X. H., Wang, C. L., Lin, W. W., Liu, A. L., Chen, W., & Lin, X. H. (2016). Detection EGFR exon 19 status of lung cancer patients by DNA electrochemical biosensor. *Biosensors and Bioelectronics*, *80*, 411-417.

[46] Jerónimo, P. C., Araújo, A. N., & Montenegro, M. C. B. (2007). Optical sensors and biosensors based on sol–gel films. *Talanta*, *72*(1), 13-27.

[47] Damborský, P., Švitel, J., & Katrlík, J. (2016). Optical biosensors. *Essays in biochemistry*, *60*(1), 91-100.

[48] Carrascosa, L. G., Sina, A. A. I., Palanisamy, R., Sepulveda, B., Otte, M. A., Rauf, S., ... & Trau, M. (2014). Molecular inversion probe-based SPR biosensing for specific, label-free and real-time detection of regional DNA methylation. *Chemical communications*, *50*(27), 3585-3588.

[49] Ribaut, C., Loyez, M., Larrieu, J. C., Chevineau, S., Lambert, P., Remmelink, M., ... & Caucheteur, C. (2017). Cancer biomarker sensing using packaged plasmonic optical fiber gratings: Towards in vivo diagnosis. *Biosensors and Bioelectronics*, *92*, 449-456.

[50] Ma, X., Truong, P. L., Anh, N. H., & Sim, S. J. (2015). Single gold nanoplasmonic sensor for clinical

cancer diagnosis based on specific interaction between nucleic acids and protein. *Biosensors and Bioelectronics*, *67*, 59-65.

[51] Lee, J. S., Kim, S. W., Jang, E. Y., Kang, B. H., Lee, S. W., Sai-Anand, G., ... & Kang, S. W. (2015). Rapid and sensitive detection of lung cancer biomarker using nanoporous biosensor based on localized surface plasmon resonance coupled with interferometry. *Journal of Nanomaterials*, *2015*, 1-1.

[52] Chiu, N. F., Lin, T. L., & Kuo, C. T. (2018). Highly sensitive carboxyl-graphene oxide-based surface plasmon resonance immunosensor for the detection of lung cancer for cytokeratin 19 biomarker in human plasma. *Sensors and Actuators B: Chemical*, *265*, 264-272.

[53] Li, H., Shi, L., Sun, D. E., Li, P., & Liu, Z. (2016). Fluorescence resonance energy transfer biosensor between upconverting nanoparticles and palladium nanoparticles for ultrasensitive CEA detection. *Biosensors and Bioelectronics*, *86*, 791-798.

[54] Al-Ogaidi, I., Gou, H., Aguilar, Z. P., Guo, S., Melconian, A. K., Al-Kazaz, A. K. A., ... & Wu, N. (2014). Detection of the ovarian cancer biomarker CA-125 using chemiluminescence resonance energy transfer to graphene quantum dots. *Chemical Communications*, *50*(11), 1344-1346.

[55] Hao, M., & Ma, Z. (2012). An ultrasensitive chemiluminescence biosensor for carcinoembryonic antigen based on autocatalytic enlargement of immunogold nanoprobes. *Sensors*, *12*(12), 17320-17329.

[56] Altintas, Z., & Tothill, I. E. (2012). DNA-based biosensor platforms for the detection of TP53 mutation. *Sensors and Actuators B: Chemical*, *169*, 188-194.

[57] Chen, Y., Huang, X., Shi, H., & Mu, B. (2011). A novel and cost-effective method for early lung cancer detection in immunized serum. *Asian Pac J Cancer Prev*, *12*, 3009-12.

[58] Loo, L., Capobianco, J. A., Wu, W., Gao, X., Shih, W. Y., Shih, W. H., ... & Adams, G. P. (2011). Highly sensitive detection of HER2 extracellular domain in the serum of breast cancer patients by piezoelectric microcantilevers.

Analytical chemistry, *83*(9), 3392-3397.

[59] Rasheed, P. A., & Sandhyarani, N. (2016). Quartz crystal microbalance genosensor for sequence specific detection of attomolar DNA targets. *Analytica Chimica Acta*, *905*, 134-139.

[60] Su, L., Zou, L., Fong, C. C., Wong, W. L., Wei, F., Wong, K. Y., & Yang, M. (2013). Detection of cancer biomarkers by piezoelectric biosensor using PZT ceramic resonator as the transducer. *Biosensors and Bioelectronics*, *46*, 155-161.

[61] Crivianu-Gaita, V., Aamer, M., Posaratnanathan, R. T., Romaschin, A., & Thompson, M. (2016). Acoustic wave biosensor for the detection of the breast and prostate cancer metastasis biomarker protein PTHrP. *Biosensors and Bioelectronics*, *78*, 92-99.