Analytical Biochemistry xxx (xxxx) xxx

Contents lists available at ScienceDirect

Analytical Biochemistry

journal homepage: www.elsevier.com/locate/yabio

# Optical-based biosensor for detection of oncomarker CA 125, recent progress and current status

Alexei Valerievich Yumashev [a], Mohammad Rudiansyah [b], Supat Chupradit [c], Mustafa M. Kadhim [d,e], Abduladheem Turki Jalil [f], Walid Kamal Abdelbasset [g,h], Wanich Suksatan [i], Rosario Mireya Romero Parra [j], Yasser Fakri Mustafa [k], Bekhzod Abdullaev [l], Ramtin Bidares [m,*]

[a] Department of Prosthetic Dentistry, Sechenov First Moscow State Medical University, Moscow, Russia
[b] Division of Nephrology & Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Lambung Mangkurat / Ulin Hospital, Banjarmasin, Indonesia
[c] Department of Occupational Therapy, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, 50200, Thailand
[d] Department of Medical Laboratory Techniques, Dijlah University College, Baghdad, 10021, Iraq
[e] Techniques Department, Al-Farahidi University, Baghdad, Iraq
[f] Medical Laboratories Techniques Department, Al-Mustaqbal University College, Babylon, Hilla, 51001, Iraq
[g] Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia
[h] Department of Physical Therapy, Kasr Al-Aini Hospital, Cairo University, Giza, Egypt
[i] Faculty of Nursing, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, 10210, Thailand
[j] Department of General Studies, Universidad Continental, Lima, Peru
[k] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, 41001, Iraq
[l] Scientific Department, Akfa University, Tashkent, 111221, Uzbekistan
[m] Department of Anatomy, Histology Forensic Medicine, Sapienza University of Rome, Rome, Italy

ARTICLE INFO

*Keywords:*
Biosensors
SPR
Nanomaterial
Ovarian cancer (OV)
CA 125

ABSTRACT

Ovarian cancer (OV) is the second most mortal gynecological malignancy. The oncomarker CA125 has been used as the main ovarian cancer marker for diagnosing and screening ovarian cancer in stages I and II. Therefore, sensitive and real-time detection of CA 125 is critical in ovarian cancer monitoring. Various tests are used to diagnose the CA 125. In recent years, modern methods such as biosensor technology have replaced the old tests for rapid, sensitive and specific detection of CA 125. Various types of biosensors are being developed, among which Surface Plasmon resonance (SPR) biosensors are one of the most important and remarkable types. Considering the importance of SPR biosensors in the diagnosis of enocomarker CA 125, the main focus of the present study is to consolidate the research work from the past two decade to the present. Also, the advantages and challenges in SPR biosensors development have been considered in the detection of CA 125 oncomarker.

## 1. Introduction

Ovarian cancer (OC) is a group of maladies that originates in the ovaries, or in the associated areas of the fallopian tubes and the peritoneum [1]. OC is a common malignant tumor in gynecology, with the maximum mortality rate and the second highest incidence rate of gynecologic malignancies [2]. There are often no obvious signs of ovarian cancer, however abdominal bloating, back, abdominal or pelvic pain, menstrual irregularities, and unexplained weight loss or weight gain are some important symptoms of OC. Some factors that can increase risk of ovarian cancer include: changes in the genes BRCA1 or BRCA2, early onset of periods (before 12 years) and late menopause, and using oestrogen only hormone replacement therapy or fertility treatment. Early, accurate and rapid detection of ovarian cancer is extremely important. For this purpose, several methods are used, the most important of which are: Physical examination, Blood tests, Pelvic ultrasound, CT scan, PET scan, and Colonoscopy. In the meantime, identifying biomarkers is very important. Some of the most important biomarkers of ovarian cancer are summarized in Table 1.

Human Epididymis Protein 4 (HE4), Osteopontin (OPN), Kallikreins (KLKs), Creatine Kinase B (CKB), Transthyretin (TTR), matrix-assisted laser desorption-ionisation (MALDI), Vascular Endothelial Growth

* Corresponding author.
*E-mail address:* Ramtin.bds@gmail.com (R. Bidares).

https://doi.org/10.1016/j.ab.2022.114750
Received 22 December 2021; Received in revised form 2 May 2022; Accepted 20 May 2022
Available online 25 May 2022

**Table 1**
Summary of ovarian cancer biomarkers.

| Biomarker | Detection methods | Comments and significances | Ref |
|---|---|---|---|
| CA-125 | ELISA | Used for screening of OC; assess the chemotherapy response and monitor disease recurrence | [3] |
| HE4 | ELISA | Sensitivity indicator for detecting stage I OC | [4] |
| OPN | PCR, ELISA | Prognostic indicator of metastasis | [5] |
| KLKs | ELISA | Prognostic indicator of OC | [6] |
| CKB | Microarray technology | Predict survival rate and prognosis of OC | [7] |
| TTR | MALDI | Diagnosis of early stage OC | [8] |
| VEGF | ELISA | Indicator of a shorter survival time in patients with OC | [9] |
| apoA-I | ELISA | Clinically biomarker | [10] |

Factor (VEGF), Apolipoprotein A-I (apoA-I).

As summarized in Table 1, there are several biomarkers associated with ovarian cancer, one of the most widely used and well-known being is carbohydrate antigen-125 (CA-125), which is of great importance in diagnostic tests. For this reason, it will be considered below.

## 2. Carcinoma antigen 125 (CA-125)

Carcinoma Antigen 125 (CA-125), a repeating peptide epitope of the mucin 16 (MUC16), and contains an important O- and N-linked glycosylated portion [11]. CA125 is a heavily glycosylated type I transmembrane protein that is overexpressed in several tumors as well as pancreatic, peritoneal mesotheliomas, colorectal cancer, mesothelial cell interaction and, plays a key role in tumorigenesis [12,13]. CA125 marginally expressed in normal ovarian tissues however, is highly expressed in ovarian carcinomas and used as a biomarker to monitor ovarian cancer disease progression [14]. It has been revealed CA125 to inhibit cytolytic responses of human natural killer (NK) cells in ovarian cancer, so acting as a suppressor of the immune response directed against the ovarian tumors and promote cancer cell proliferation [15,16]. CA 125 test results are measured in units of milliliters (U/mL). Typical values are less than 46U/mL. If CA 125 levels are higher than normal, the patient may have a benign illness. Alternatively, the test results may have cancer of the ovaries, endometrium, peritoneum, or fallopian tubes.

MUC16 has cytoplasmic, transmembrane, and extracellular components that alter O- and N-glycosylation sites. The peptide component of MUC16 is approximately 22,152 amino acids. The N-terminal domain of MUC16 has 12,000 amino acids and hosts only O-glycosylation. Important part its peptide component is composed of a tandem repeat region with more than 60 repeats of 156 amino acids. MUC16 hosts approximately 56 unienterokinase and agrin (SEA) domains. SEA domain A common feature of mucin, this domain is involved in the cleavage and association of MUC16.

Schematic illustration of MUC16 (CA125) structure and its role in ovarian cancer presented in Fig. 1.

Due to the limitations and disadvantages of routine and traditional testers in the diagnosis of CA-125, the development of modern methods is expanding. One of these advanced methods is biosensors, which have a high sensitivity and specificity compared to the old methods. In addition, biosensors have a simple and inexpensive structure that allows them to be developed.

## 3. Biosensor technology

From the past decades until today, many important technological developments have provided us with the tools and materials needed to create biosensor devices [17,18]. Since the discovery of the Clark Oxygen Electrode sensor, there have been various progresses in the multiplexing capacity, sensitivity, selectivity, and of the current biosensor [17,18]. What is the biosensor? Biosensors are widely defined as analyzers that target molecules or macromolecules using biological recognition systems. Biosensors can be combined with physicochemical converters that convert this detection into a detectable output signal [18].

Biosensors typically consist of three components: (A) A detector that identifies stimuli. (B) A transducer that converts the stimulus into a useful output. (C) Signal processing system. This includes amplifying and displaying the output in the proper format [19]. The purpose of this combination is to use the high sensitivity and selectivity of biological sensors for analytical purposes in various areas of research and technology [19].

Biosensor structure represented in Fig. 2.

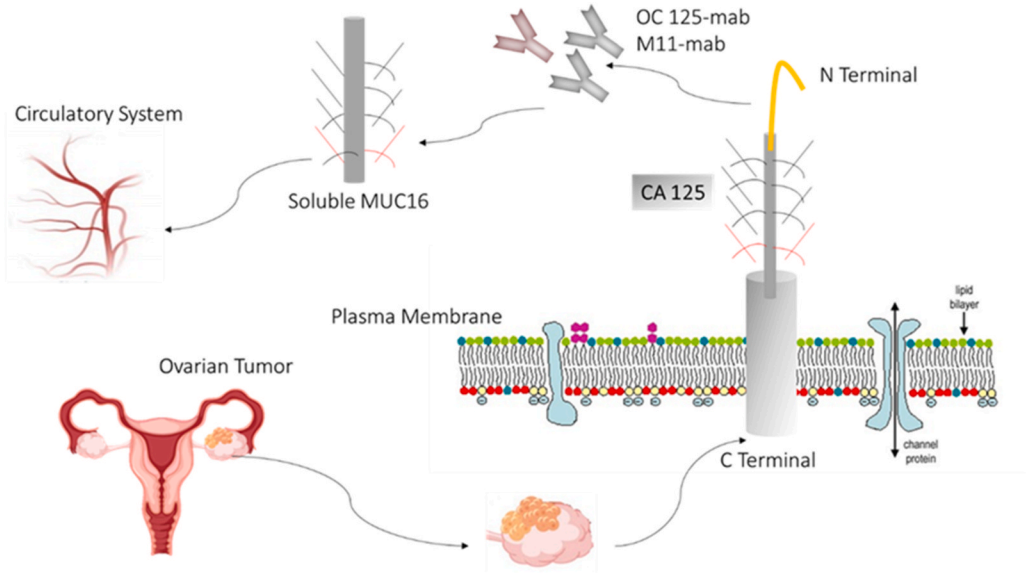


**Fig. 1.** Depiction of MUC16 (CA125) structure and its role in ovarian cancer. The transmembrane domain is followed by a 32-amino acid cytoplasmic tail with a potential phosphorylation site. MUC16 is cleaved from the plasma membrane by the extracellular position of approximately 12 amino acids. The cleavage product is a 17 kDa molecule containing the CA125 repeat epitope in the tandem repeat domain [67,68].

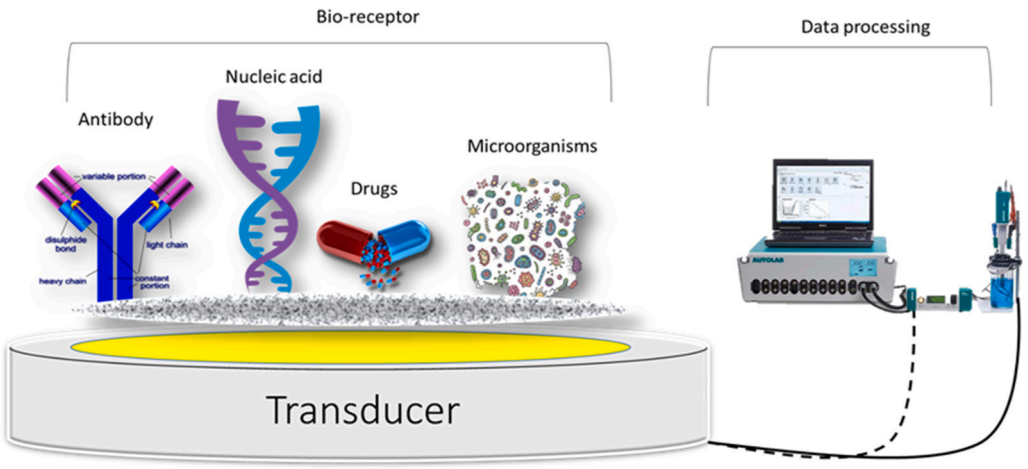


**Fig. 2.** Schematic illustration of biosensor technology. The biomolecule is contained in an analytical solution that binds to an immobilized enzyme or immune agent on the linker. The linker is then attached to the transducer. The transducer then converts the charge of the analyte into an electrical signal, which is sent for data processing. Biosensors can be considered part of a field of study known as "chemical sensors" by using biological mechanisms to detect the analyte in the analyte solution.

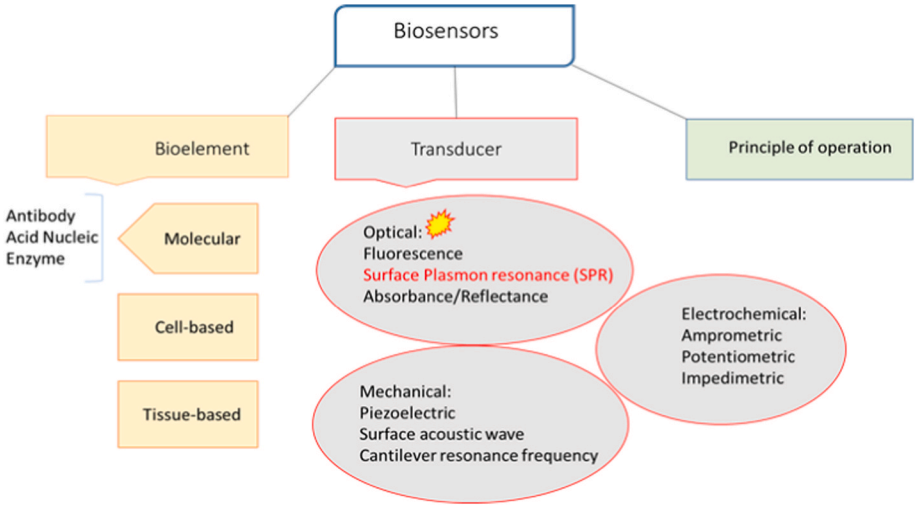


**Fig. 3.** Biosensors classification, as revealed, biosensors can be categorized by type of physicochemical transmission or type of biometric element. Based on transducers, biosensors can be classified into electrochemical, optical, mechanical and electrochemical biosensors.

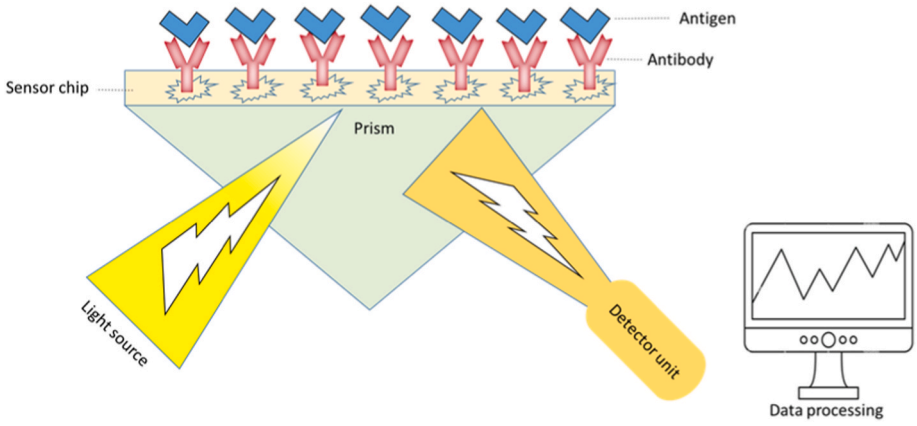


**Fig. 4.** Schematic diagram of an SPR-based biosensor. As the solution of the analyte ("ligand") flows over the surface of the nanocomposite film ("acceptor"), the interaction between the ligand and the acceptor immobilizes an increased amount of material on the surface, which amount becomes the index of refraction. Detection is possible because the resonance angle changes depending on the refractive index. Reflex shadows indicate energy losses that can be detected by SPR-based devices.

### *3.1. Biosensors classification*

Several types of biosensors such as tissue-based thermal and piezoelectric biosensors, enzyme-based, immunosensors, and DNA biosensors, have been developed and applied in numerous fields as well as medical sciences. The main classification of biosensors is based on transducer, which includes: optical, electrochemical and mechanical biosensors (Fig. 3).

## 4. Surface plasmon resonance (SPR) biosensor

Surface plasmon resonance (SPR) is one of the most important and

**Table 2**
Working principles of some important optical biosensors.

| Technique | Working principal | Ref |
|---|---|---|
| ECL | Electrochemical sensors operate on the principle that an electric current generated by an electrochemical reaction generated on the surface of a detection electrode coated with a catalyst such as platinum flows through the detection electrode. | [29] |
| SPR | In SPR biosensors, probe molecules are firstly immobilized on to the sensor surface. When the solution of target molecules is flown into contact with the surface, a probe-target binding via affinity interaction occurs, which consequently induces an increase in the refractive index at the SPR sensor surface. | [30] |
| SPRI | The SPRI system uses a coherent polarized beam instead of multicolored light. This change helps extend the range of light to a larger area of the sensing surface. | [31] |
| CL | Chemoluminescence is the emission of light (luminescence) as the result of a chemical reaction. There may also be limited emission of heat. | [32] |
| FRET | Under optimal conditions FRET occurs between the two probes upon excitation of the donor, which transfers energy also to the acceptor. | [33] |
| NIR | Near infrared (NIR) spectroscopy is based on the absorption of electromagnetic (EM) radiation at wavelengths in the range 780 to 2500 nm. The light interacts with the sample and the detector measures its transmittance and absorbance. | [34] |

**Abbreviations:** Fluorescence resonance energy transfer **(FRET),** Chemiluminescence resonance energy transfer **(CRET),** Electrochemical **(ECL),** Chemoluminescence **(CL),** Near infrared **(NIR)** spectroscopy.

widely used sensing technologies. SPR biosensors are label-free optical tools as worked-based on the interaction between a molecule immobilized on the surface of the sensor and the interacting molecular partner in a solution have made SPR sensors a very powerful tool for biomolecular interaction analysis and biomolecular research in general. In recent years, SPR biosensors have been increasingly used also for the detection of chemical and biological substances related to medical diagnostics, environmental monitoring, food safety and security (Fig. 4).

### 4.1. SPR biosensors types

#### 4.1.1. Localized surface plasmon resonance (LSPR)

LSPR offers a label-free method to detect biomolecule with nanoscale spatial resolution [20]. LSPR procedure has promising applications in the study of proteins, DNA-protein interactions, toxins and vesicles [20]. The small sensor size and portability allows the sensor miniaturization to a scale unapproachable by other planar procedure like SPR [21].

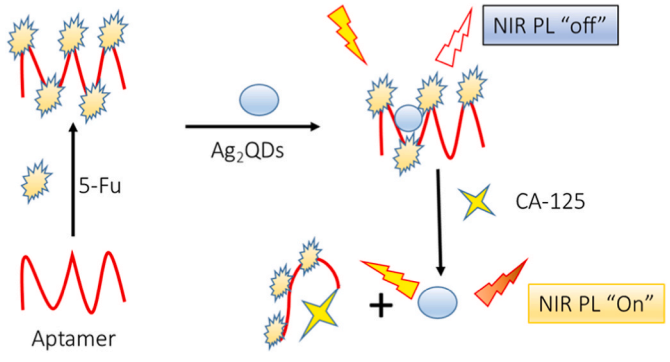


**Fig. 5.** The negatively charged aptamer of CA125 was combined with 5fluorouracil (5Fu) to generate an aptamer/5Fu complex by electrostatic interaction. $Ag_2S$ QD is modified with polyethyleneimine (PEI). Placed on the surface of the QD and combined with the aptamer/5Fu complex, the electrostatic interaction between the aptamer and the QD produces a QD/aptamer/5Fu hybrid. The $Ag_2S$-QD's NIR-PL can be quenched by 5Fu bound to the aptamer. This is due to photoinduced electron transfer (PIET) from $Ag_2S$-QD to 5Fu reproduced from Ref. [51].

Moreover, unique to LSPR is that the nano-plasmonic resonance condition is satisfied in a transmitted light geometry or simple reflected common to equally spectroscopy and microscopy applications, while SPR excitation requires incident light that is entirely inside reflected [20,21]. LSPR-based bio-sensing procedures can be effortlessly fabricated with low-priced sensing platforms. The utility of LSPR based sensing can be improved by integrating it with multiplexed microfluidic tools [20,21]. In a some research studies LSPR biosensors were used for detection of ovarian cancer biomarkers [22,23].

#### 4.1.2. Surface Plasmon Resonance Imaging method

Routine SPR sensors measure the dependence of the reflectance as a function of the incidence angle. SPR Imaging (SPRI) is the important progresses in the field is the SPR [24,25]. The technique of the SPRI version reduces the intricacy of the scan angle [25]. The measurements are made at a particular angle of incidence light. The imitated light is collected using a camera and revealed as an image [26]. The angle at which the measurement is carried out is in the linear area of the reflectance reduction. The light intensity variations are proportional to the consecutive molecules bound to the biosensor surface [26,27]. In SPRI the measurement result is acquired as an image (picture), which is subjected to analysis in order to acquire the value of the SPR signal. Specially prepared chips are used for measurements of many samples simultaneously [27,28]. Working principal of some important optical biosensors were summarized in Table .2.

## 5. Developed SPR biosensor for detection of CA 125

Surface plasmon resonance integrated microfluidic concentration gradient fabricated for real time detection of ovarian cancer biomarker. Developed tool showed acceptable linearity and LOD and applicable for clinical samples [35]. Surface Plasmon Resonance Imaging (SPRI) based bio-sensing device advanced for sensitive determination of CA-125. Designed system showed wide range linearity and acceptable selectivity with simple and cost-effective construction [36]. A simple and sensitive immunosensor platform based on SPR method was planned for detection of CA-125. Developed device revealed satisfactory analytical properties and was faster than conventional method such as ELISA [37]. Gold-silver alloy film based SPR sensor was invented for identification of CA-125 in biological samples. Finding shown Au/Ag-SPR sensor had higher sensitivity than Au-SPR sensor will have major application prospects in the future [38]. Molecularly imprinted polymer (MIP) with SPR method was developed for analyses of CA-125 oncomarker appropriately [39]. A immunasensor-based on SPR platform was established for cancer antigen 125 detection in human serum samples. Real-time monitoring, fast operation and cost-effective structure reported as some important advantages of created system [40]. SPR-based immunosensor was settled for detection of CA-125 in human serum samples. Produced biosensor exhibited high sensitivity, reproducibility, and selectivity [41]. An SPRI biosensor was settled for determination of ovarian cancer biomarker properly. Planned system showed standard sensitivity and selectivity and applicable for human serum samples [28]. Multiplexed magnetic nanoparticle-antibody conjugates (MNPs-ABS) based using fluorescence spectroscopy with comparison of surface plasmon resonance (SPR) analysis was applied for determination of CA-125 as an important ovarian cancer biomarkers [42]. SPR platform was applied in research work for ultra-sensitive determination of CA-125. In this study the use of Au/ZnO films significantly improved the SPR signal yield for this bimolecular interaction and presented high sensitivity [43]. Light scattering signals [44], which are interference sources in spectrofluorometric and could be effortlessly identified with a common spectrofluorometric have been applied widely in the investigations of the description of nanomaterials, aggregation of chromophores, and recognition of drugs and biomolecules [45,46]. Accordingly, plasmon resonance scattering (PRS) system designed for determination of CA-125 properly. PRS biosensor revealed high

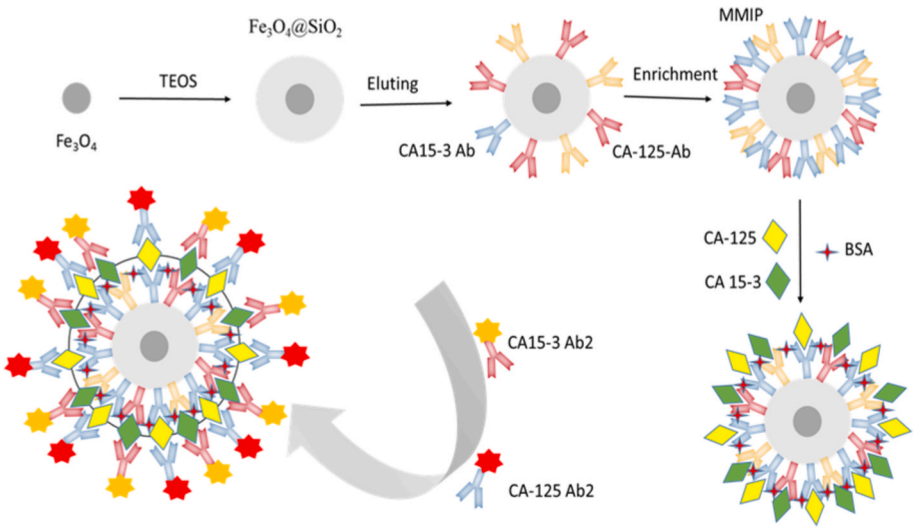


**Fig. 6.** As shown, Ab2 CA15-3 and CdNCs Ab2 CA 125 were added and incubated for 30 min at room temperature. The proposed sandwich immune complex was magnetically separated, washed with PBS, dispersed in 1 ml PBS (0.1 M, pH 7.40) and stored at 4 °C for later use. The magnetic non-molecular imprint polymer (MNIP) was also prepared using the same procedure, but without the CA125 and CA15–3 antibodies (Ab1), reproduced from Ref. [52].

reproducibility, sensitivity, and selectivity, for monitoring of CA 125 in serum samples [47].

### 5.1. Fluorescence resonance energy transfer (FRET)

A novel fluorescence resonance energy transfer (FRET) system settled for rapid and sensitive detection of CA-125 oncomarker. Developed platform was affordable and showed acceptable linearity and selectivity [48]. A paper-based immune-device based on FRET mechanism was fabricated for identification of CA-125 properly. Planned system was applicable several field from clinical chemistry and analytical biochemistry to biodefense related assays. Developed tool presented as a high-throughput, high-performance, fast, unexpansive, point-of-care, highly selective and sensitive detection test [49]. Fluorescence detection based on phosphoserine imprinted SPN nanosensor was investigated for determination of CA 125. Good linearity and LOD with high selectivity and reproducibility discovered by developed biosensor [50]. Aptamer based on label-free probe for near-infrared photoluminescence optical method, Fig. 5 was established for CA-125 antigen detection in biological samples accurately. Experimental outcomes shown the highly selective and sensitive NIR PL responses of biosensor to CA125, with high detection recoveries [51] (Fig. 5).

For simultaneous evaluation of CA125 and CA15–3 oncomarkers a high sensitive molecularly imprinted fluorescence (MIPFL) biosensor was settled correctly. MIPFL method has the potential to be an operational clinical instrument for the appropriate screening of CA-125 and Ca15-3 in human serum samples and MCF-7 cell lines and, OVCAR-3 and can be useful in clinical diagnostics [52] (Fig. 6).

As demonstrated in Fig. 6, proposed sandwich immune complex was magnetically separated, washed with PBS, dispersed in 1 ml PBS (0.1 M, pH 7.40) and stored at 4 °C for later use. The magnetic non-molecular imprint polymer (MNIP) was also prepared using the same procedure, but without the CA125 and CA15–3 antibodies (Ab1) [52].

### 5.2. Chemiluminescence resonance energy transfer (CRET)

A chemiluminescence resonance energy transfer (CRET) platform was advanced for determination of CA-125 biomarker in biological samples. High sensitivity and selectivity reported from established tool [53]. A chemiluminescent (CL) detection device was proposed for carcinoma antigen 125 monitoring in clinical samples. Developed device showed acceptable accuracy, reproducibility and wide range linearity

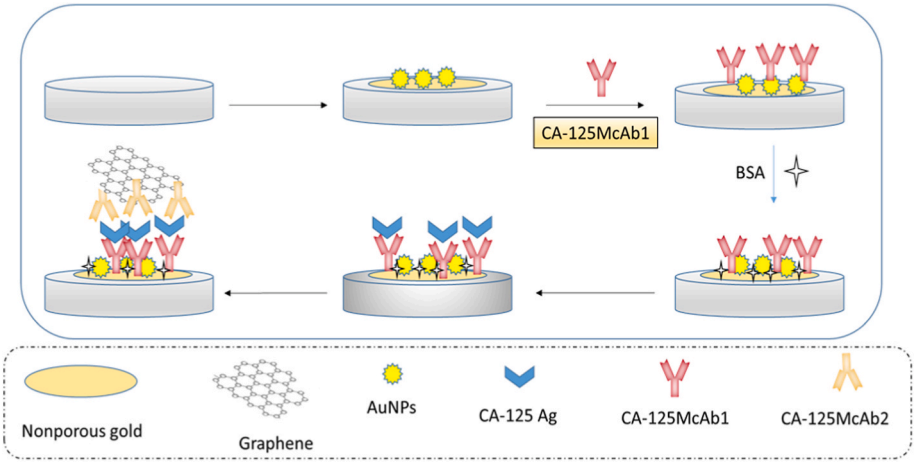


**Fig. 7.** As displayed, the modified electrode was then incubated in 1% BSA solution at room temperature for 1 h to block the possibility of non-specific binding. Subsequently, the electrodes were incubated with various concentrations of CA. 125 solutions. Finally, the prepared RuAuNPs/GR-labeled Ab 25 μL was dropped onto the electrode surface and washed with PBS to remove unbound antibody. Each step was thoroughly washed 3 times with PBS, reproduced from Ref. [55].

and applicable for analysis and screening of a tumor marker [54]. A Highly Efficient Chemiluminescent immunosensor has been successfully engineered to detect CA 125 in practical samples. The explored biosensor provides an encouraging universal platform for bio-sensing of ovarian cancer tumor marker. An ultra-sensitive electrochemiluminescence immunosensor (Fig. 7) was proposed for CA-125 oncomarker appropriately. The ECL system showed good reproducibility, high sensitivity, satisfied selectivity and regeneration and may exhibition an attractive method for other analyte determination [55] (Fig. 7).

As shown in Fig. 7, the cleaned electrodes were assembled with NPG foil. After that, the prosperous Ab1 was dropped on the surface of the NPG electrode. The modified electrode was then incubated in BSA solution at room temperature to block the possibility of non-specific binding. The electrodes were then incubated with different concentrations of CA125 solution. In the next step, RuAuNPs/GR-labeled Ab2 was dropped onto the electrode surface after washing with PBS to remove unbound antibody. Each step was thoroughly washed 3 times with PBS [52].

A spectrum-based ECL/CdSeNCs platform was designed for selectively determining CA125 in human serum. Developed method identified CA-125 selectively, sensitively and rapidly and useable for clinical approaches [56].

Polyamidoamine (PAMAM) dendrimers are a model of a multipurpose and reproducible type of Nano carrier that can be loaded with drugs, and adapted by attaching target-specific ligands that distinguish receptors that are over-expressed on cancer cells [57,58]. PAMAM dendrimers with a high density of cationic charges exhibition electrostatic interactions with nucleic acids such as RNA and DNA, producing dendriplexes that can reserve the nucleic acids from degradation. Based on these characteristics, PAMAM are widely used in the development of biosensors [57,58]. For the example an ultra-sensitive electrochemiluminescence biosystem was fabricated for real-time determination of CA-125 and CA15-3 tumor markers based on PAMAM-CdTe@CdS PAMAM-sulfanilic acid and Ru(bpy)3 $^{2+}$ nanocomposite. As a result, the use of suitable nanomaterials of the prepared biosensor, despite its simple and cost-effective structure, showed good sensitivity, accuracy and specificity [59].

Near-infrared (NIR) spectroscopy is an extremely flexible method of analysis, which can be useful to a broad range of industrial process and research applications [34,60]. Long a staple technology in remote sensing, NIR spectroscopy has become general within industrial markets as a cost-effective tool for evaluating materials to manage costs and improve processes [61]. Capable of examining irregular surfaces, non-destructive, requires little or no sample preparation are important advantages of NIR technology [34,61].

ECL between NIR CdTe/CdS QDs and graphitic carbon nitride (g-$C_3N_4$) was planned as a sandwich method for determination of cancer antigen 125. Created immunoassay presented outstanding analytical performance with excellent selectivity, stability, and reproducibility [62]. Near-infrared (NIR) electrochemiluminescence (ECL) immunoassay was engeenered for selectively detection of CA-125 and useable for early diagnosis and treatment of ovarian cancer [63]. ECL immunosensor developed for the detection of CA72-4 and CA15-3 using CdSe quantum dots and Ru(bpy)3 complex with graphene oxide nanocomposite modified. This bio-device showed satisfactory accuracy with recoveries and acceptable reproducibility and selectivity [64]. A new nano-optical biosensor, involving of a thin sol−gel film containing gold nanoparticles covered by Schiff base ligand, was planned and effectively applied for CA-125 determination in serum samples of individuals suffering OC. The procedure settled in this work could be considered as an excellent contribution to the analytical methods used for CA-125 determination. The technique owns some important features such as accuracy, rapidity, and sensitivity [65]. Some of the most important and up-to-date optical biosensors are summarized in Table 3.

As shown in Table 3, the limit of detection (LOD) results will vary due to the different nature of the kits used by different companies. Also, reporting analytical data is a matter of taste and depends on how the operator calculates the concentration. All of the used units should be approved by IOPAC. In addition, all the units used in the analytical chemistry can be converted to each other using online software and proper formulas.

**Table 3**
Optical biosensor for detection of CA-125.

| Platform/Film | Sample/ Model | Linear range | LOD | Ref |
|---|---|---|---|---|
| SPR/Gold | Blood/Human | 0.25–9.0 mg $mL^1$ | 5 nM | [35] |
| SPR/Au-Cys | Blood/Human | 2.2–150 U $ml^{-1}$ | 150 U $ml^{-1}$ | [36] |
| SPR/Au | Biological/ Human | 5–80 U $mL^{-1}$ | 1.45 U $mL^{-1}$ | [37] |
| SPR/Au–Ag | Biological | _ | 0.8 ng/mL | [38] |
| SPR/Au-SPE | Serum | 0.01 and 500 U $mL^{-1}$ | 0.01 U $mL^{-1}$ | [39] |
| SPR/Gold | Serum | 0.1 and 40 U $ml^{-1}$ | 0.1 U $ml^{-1}$ | [40] |
| SPR/AuNPs | Serum | 1.0–80 U $mL^{-1}$ | 0.4 U $mL^{-1}$ | [41] |
| SPR/Au-Cys | Blood serum | 2–120 pM | 2 pM | [28] |
| SPR/Magnetic | Blood sample | 5.0–40 U $ml^{-1}$ | 0.26 U $mL^{-1}$ | [42] |
| SPR/Gold–Zinc Oxide | Biological | 0.0125 U $mL^{-1}$ to 160 U $mL^{-1}$ | 0.025 U $mL^{-1}$ | [43] |
| PRS | Serum | 1.0–80 U $mL^{-1}$ | 0.4 U $mL^{-1}$ | [47] |
| FRET/AuNPs | Serum | $2.5 \times 10^3$ to $2 \times 10^4$ cells/mL | 0.5 f g/mL | [48] |
| FRET/CuO NPs | Biological | 2.0 10–4 to 100 U $mL^{-1}$ | 3.0 10–4 ng/mL | [49] |
| CRET/GQDs | Biological | 0.1 U $mL^1$ to 600 U $mL^1$ | 0.05 U $mL^{-1}$ | [53] |
| FRET/SPN | Biological | 7.73 $10^{-3}$ $mLU^{-1}$ | 0.49 $UmL^{-1}$ | [50] |
| CL/$SiO_2$NPs | Clinical | 0.5–400 U $mL^{-1}$ | 0.17 U $mL^{-1}$ | [66] |
| ECL/AuNPs/ graphene | Human serum | 0.01–100 U $mL^{-1}$ | 0.005 U $mL^{-1}$ | [55] |
| ECL/CdSeNCs | Human serum | $10^{-4}$ to 1 U $mL^{-1}$ | $5 \times 10^{-5}$ U/mL | [56] |
| ECL/PAMAM-CdTe@CdS | Clinical | 1 μU/mL to 1 U $mL^{-1}$ | 0.1 μU/mL | [59] |
| ECL/NIR CdTe/ CdS QDs | Human serum | 0.0001 U $mL^{-1}$ to 10 U $mL^{-1}$ | 0.034 mU $mL^{-1}$ | [62] |
| NIR-ECL/$AgInS_2$/ ZnS (NCs) | Clinical | $5 \times 10^{-6}$ to $5 \times 10^{-3}$ U/mL | $1 \times 10^{-6}$ U/mL | [63] |
| ECL/GO@CS | Real sample | 100 μU.$ml^{-1}$ −150 U $ml^{-1}$ | 89 μU. $ml^{-1}$ | [64] |
| FTIR/AuNPs-PEG | Clinical | 2.0–127.0 U $mL^{-1}$ | 1.45 U $mL^{-1}$ | [65] |
| FL/GO–$Fe_3O_4$ | Human serum | 0.0005–40 U $mL^{-1}$ | 50 μU $mL^{-1}$ | [52] |

Screen-printed electrode **(SPE);** Fluorescence resonance energy transfer **(FRET),** Chemiluminescence resonance energy transfer **(CRET),** Graphene quantum dots **(GQDs),** plasmon resonance scattering **(PRS),** Chemiluminescence **(CL),** Electrochemical Chemiluminescence **(ECL),** CdSe nanocrystals **(NCs),** Polyamidoamine dendrimer-quantum dots **(PAMAM-QDs),** Near-infrared CdTe/CdS quantum dots **(NIR CdTe/CdS QDs),** Fluorescence **(FL).**

## 6. Conclusion

Ovarian cancer is a growth of cells that forms in the ovaries. The cells multiply quickly and can invade and destroy healthy body tissue. Therefore, rapid, accurate and specific diagnosis can play a very important role in its control and treatment. Due to the limitations of routine methods such as low specificity and sensitivity, biosensors are suitable and reliable tools for detecting CA-125. Optical biosensors are one of the most important types in medical diagnostics and laboratory research. In sum, optical biosensors were formed by a simple preparation process, and revealed short analysis time and good stability, which demonstrate huge potential for the measurement of CA-125 in real samples and cell lines, pathological diagnosis, and promise as an

accessible assay for increasing point-of-care analysis.

## Funding

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## Availability of data and materials

Not applicable.

## Consent for publication

Not applicable.

## Declaration of competing interest

The authors declare that they have no competing interests.

## References

[1] Z.Q. Wang, Characterization of Novel Epigenetic Targets in Ovarian Cancer, 2014.
[2] K.D. Miller, et al., Cancer treatment and survivorship statistics, 2016, CA A Cancer J. Clin. 66 (4) (2016) 271–289.
[3] Y.-S. Wang, et al., CA125-Tn ELISA Assay Improves Specificity of Pre-operative Diagnosis of Ovarian Cancer Among Patients with Elevated Serum CA125 Levels, vol. 9, 2021, 9.
[4] J. Qu, F. Yu, Fabrication of a Highly Sensitive Electrochemical Immunosensor for Human Epididymis Protein 4 (HE4) Detection, vol. 13, 2018, pp. 11193–11202.
[5] D.S. Marques, et al., Osteopontin-c Isoform Levels Are Associated with Sr and Hnrnp Differential Expression in Ovarian Cancer Cell Lines, vol. 39, 2017, 9): p. 1010428317725442.
[6] P. Filippou, et al., A New Enzyme-Linked Immunosorbent Assay (ELISA) for Human Free and Bound Kallikrein 9, vol. 14, 2017, pp. 1–12, 1.
[7] H.G. Huddleston, et al., Clinical Applications of Microarray Technology: Creatine Kinase B Is an Up-Regulated Gene in Epithelial Ovarian Cancer and Shows Promise as a Serum Marker, vol. 96, 2005, pp. 77–83, 1.
[8] B. Ye, et al., Proteomic-based Discovery and Characterization of Glycosylated Eosinophil-Derived Neurotoxin and COOH-Terminal Osteopontin Fragments for Ovarian Cancer in Urine, vol. 12, 2006, pp. 432–441, 2.
[9] D.A. Altomare, et al., AKT and mTOR Phosphorylation Is Frequently Detected in Ovarian Cancer and Can Be Targeted to Disrupt Ovarian Tumor Cell Growth, vol. 23, 2004, pp. 5853–5857, 34.
[10] L.H. Bao, et al., Osteopontin in Metastatic Lesions as a Prognostic Marker in Ovarian Cancers, vol. 14, 2007, pp. 373–381, 3.
[11] R. Bast, et al., Reactivity of a monoclonal antibody with human ovarian carcinoma, J. Clin. Invest. 68 (5) (1981) 1331–1337.
[12] B.W. Yin, K.O. Lloyd, Molecular cloning of the CA125 ovarian cancer antigen: identification as a new mucin, MUC16, J. Biol. Chem. 276 (29) (2001) 27371–27375.
[13] T.J. O'Brien, et al., The CA 125 gene: a newly discovered extension of the glycosylated N-terminal domain doubles the size of this extracellular superstructure, Tumor Biol. 23 (3) (2002) 154–169.
[14] J.A. Gubbels, et al., The detection, treatment, and biology of epithelial ovarian cancer, J. Ovarian Res. 3 (1) (2010) 1–11.
[15] S. Senapati, S. Das, S.K. Batra, Mucin-interacting proteins: from function to therapeutics, Trends Biochem. Sci. 35 (4) (2010) 236–245.
[16] S. Reinartz, et al., CA125 (MUC16) gene silencing suppresses growth properties of ovarian and breast cancer cells, Eur. J. Cancer 48 (10) (2012) 1558–1569.
[17] M. Mascini, S. Tombelli, Biosensors for biomarkers in medical diagnostics, Biomarkers 13 (7–8) (2008) 637–657.
[18] K. Baryeh, et al., Introduction to medical biosensors for point of care applications, in: Medical Biosensors for Point of Care (POC) Applications, Elsevier, 2017, pp. 3–25.
[19] R. Rebelo, et al., 3D biosensors in advanced medical diagnostics of high mortality diseases, Biosens. Bioelectron. 130 (2019) 20–39.
[20] A. Agrawal, et al., Localized Surface Plasmon Resonance in Semiconductor Nanocrystals, vol. 118, 2018, pp. 3121–3207, 6.
[21] M. Sui, et al., Strongly Confined Localized Surface Plasmon Resonance (LSPR) Bands of Pt, AgPt, AgAuPt Nanoparticles, vol. 9, 2019, pp. 1–14, 1.
[22] J. Yuan, et al., Detection of serum human epididymis secretory protein 4 in patients with ovarian cancer using a label-free biosensor based on localized surface plasmon resonance, Int. J. Nanomed. 7 (2012) 2921–2928.
[23] O. Yavas, et al., Self-calibrating On-Chip Localized Surface Plasmon Resonance Sensing for Quantitative and Multiplexed Detection of Cancer Markers in Human Serum, vol. 3, 2018, pp. 1376–1384, 7.
[24] C.L. Wong, et al., Colorimetric Surface Plasmon Resonance Imaging (SPRI) Biosensor Array Based on Polarization Orientation, vol. 47, 2013, pp. 545–552.
[25] A. Sankiewicz, et al., SPR Imaging Biosensor for the Quantitation of Fibronectin Concentration in Blood Samples, vol. 150, 2018, pp. 1–8.
[26] A. Tokarzewicz, et al., SPRI Biosensors for Quantitative Determination of Matrix Metalloproteinase-2, vol. 9, 2017, pp. 2407–2414, 16.
[27] L. Oldak, et al., Two SPRi Biosensors for the Determination of Cathepsin S in Blood Plasma, vol. 225, 2021, 121900.
[28] B. Szymanska, et al., An SPRi Biosensor for Determination of the Ovarian Cancer Marker HE4 in Human Plasma, vol. 21, 2021, p. 3567, 10.
[29] U. Guth, W. Vonau, J. Zosel, Recent developments in electrochemical sensor application and technology—a review, Meas. Sci. Technol. 20 (4) (2009), 042002.
[30] P. Singh, SPR biosensors: historical perspectives and current challenges, Sensor. Actuator. B Chem. 229 (2016) 110–130.
[31] S. Scarano, et al., Surface plasmon resonance imaging for affinity-based biosensors, Biosens. Bioelectron. 25 (5) (2010) 957–966.
[32] R.J. Forster, P. Bertoncello, T.E. Keyes, Electrogenerated chemiluminescence, Annu. Rev. Anal. Chem. 2 (2009) 359–385.
[33] J. Shi, et al., Nanoparticle based fluorescence resonance energy transfer (FRET) for biosensing applications, J. Mater. Chem. B 3 (35) (2015) 6989–7005.
[34] M. Manley, V. Baeten, Spectroscopic technique: near infrared (NIR) spectroscopy, in: Modern Techniques for Food Authentication, Elsevier, 2018, pp. 51–102.
[35] C. Escobedo, et al., Quantification of Ovarian Cancer Markers with Integrated Microfluidic Concentration Gradient and Imaging Nanohole Surface Plasmon Resonance, vol. 138, 2013, pp. 1450–1458, 5.
[36] B. Szymańska, et al., A Biosensor for Determination of the Circulating Biomarker CA125/MUC16 by Surface Plasmon Resonance Imaging, vol. 206, 2020, 120187.
[37] A.C.H. de Castro, et al., Label-free Electrochemical Immunosensor for Detection of Oncomarker CA125 in Serum, vol. 155, 2020, 104746.
[38] R.-m. Yi, et al., Gold nanoparticles-enhanced gold-silver alloy surface plasmon resonance sensor for the detection of C-reactive protein, in: European Conference on Biomedical Optics, Optical Society of America, 2019.
[39] T.S. Rebelo, et al., Molecularly Imprinted Polymer SPE Sensor for Analysis of CA-125 on Serum, vol. 1082, 2019, pp. 126–135.
[40] S. Suwansa-ard, et al., Comparison of Surface Plasmon Resonance and Capacitive Immunosensors for Cancer Antigen 125 Detection in Human Serum Samples, vol. 24, 2009, pp. 3436–3441, 12.
[41] K. Zhang, X. Shen, Cancer antigen 125 detection using the plasmon resonance scattering properties of gold nanorods, Analyst 138 (6) (2013) 1828–1834.
[42] M.K. Pal, et al., Multiplexed Magnetic Nanoparticle-Antibody Conjugates (MNPs-ABS) Based Prognostic Detection of Ovarian Cancer Biomarkers, CA-125, β-2M and ApoA1 Using Fluorescence Spectroscopy with Comparison of Surface Plasmon Resonance (SPR) Analysis, vol. 73, 2015, pp. 146–152.
[43] C.-C. Chang, et al., High-sensitivity detection of carbohydrate antigen 15-3 using a gold/zinc oxide thin film surface plasmon resonance-based biosensor, Anal. Chem. 82 (4) (2010) 1207–1212.
[44] R.F. Pasternack, P.J.J.S. Collings, Resonance Light Scattering: a New Technique for Studying Chromophore Aggregation, vol. 269, 1995, pp. 935–939, 5226.
[45] L.M. Scolaro, A. Romeo, R.F. Pasternack, Tuning Porphyrin/DNA Supramolecular Assemblies by Competitive Binding, vol. 126, 2004, pp. 7178–7179, 23.
[46] X.B. Pang, C.Z. Huang, b. analysis, A Selective and Sensitive Assay of Berberine Using Total Internal Reflected Resonance Light Scattering Technique with Fluorescein at the Water/1, 2-dichloroethane Interface, vol. 35, 2004, pp. 185–191, 1.
[47] K. Zhang, X.J.A. Shen, Cancer Antigen 125 Detection Using the Plasmon Resonance Scattering Properties of Gold Nanorods, vol. 138, 2013, pp. 1828–1834, 6.
[48] S. Hamd-Ghadareh, et al., An Amplified Comparative Fluorescence Resonance Energy Transfer Immunosensing of CA125 Tumor Marker and Ovarian Cancer Cells Using Green and Economic Carbon Dots for Bio-Applications in Labeling, Imaging and Sensing, vol. 96, 2017, pp. 308–316.
[49] S. Ge, et al., A disposable immunosensor device for point-of-care test of tumor marker based on copper-mediated amplification, Biosens. Bioelectron. 43 (2013) 425–431.
[50] S. Büyüktiryaki, et al., Phosphoserine Imprinted Nanosensor for Detection of Cancer Antigen 125, vol. 167, 2017, pp. 172–180.
[51] H. Jin, et al., Aptamer and 5-fluorouracil dual-loading Ag2S quantum dots used as a sensitive label-free probe for near-infrared photoluminescence turn-on detection of CA125 antigen, Biosens. Bioelectron. 92 (2017) 378–384.
[52] D. Bahari, B. Babamiri, A. Salimi, Ultrasensitive molecularly imprinted fluorescence sensor for simultaneous determination of CA125 and CA15–3 in human serum and OVCAR-3 and MCF-7 cells lines using Cd and Ni nanoclusters as new emitters, Anal. Bioanal. Chem. 413 (15) (2021) 4049–4061.
[53] I. Al-Ogaidi, et al., Detection of the Ovarian Cancer Biomarker CA-125 Using Chemiluminescence Resonance Energy Transfer to Graphene Quantum Dots, vol. 50, 2014, pp. 1344–1346, 11.
[54] Z. Fu, et al., Channel and substrate zone two-dimensional resolution for chemiluminescent multiplex immunoassay, Anal. Chem. 79 (2007) 7376–7382, 19.
[55] M. Li, et al., Ultrasensitive electrochemiluminescence immunosensor based on nanoporous gold electrode and Ru-AuNPs/graphene as signal labels, Sensor. Actuator. B Chem. 181 (2013) 50–56.
[56] X. Tan, et al., Spectrum-Based Electrochemiluminescence Immunoassay for Selectively Determining CA125 in Greenish Waveband, vol. 4, 2017, pp. 1714–1718, 7.
[57] N.A.S. Omar, et al., Sensitive Detection of Dengue Virus Type 2 E-Proteins Signals Using Self-Assembled Monolayers/reduced Graphene Oxide-PAMAM Dendrimer Thin Film-SPR Optical Sensor, vol. 10, 2020, pp. 1–15, 1.

[58] C.A. Razzino, et al., An Electrochemical Immunosensor Using Gold Nanoparticles-PAMAM-Nanostructured Screen-Printed Carbon Electrodes for Tau Protein Determination in Plasma and Brain Tissues from Alzheimer Patients, vol. 163, 2020, 112238.
[59] B. Babamiri, R. Hallaj, A. Salimi, Ultrasensitive electrochemiluminescence immunoassay for simultaneous determination of CA125 and CA15-3 tumor markers based on PAMAM-sulfanilic acid-Ru(bpy)32+ and PAMAM-CdTe@CdS nanocomposite, Biosens. Bioelectron. 99 (2018) 353–360.
[60] J.U. Porep, et al., On-line Application of Near Infrared (NIR) Spectroscopy in Food Production, vol. 46, 2015, pp. 211–230, 2.
[61] H.W. Siesler, et al., Near-infrared Spectroscopy: Principles, Instruments, Applications, John Wiley & Sons, 2008.
[62] H. Gao, et al., Electrochemiluminescence immunosensor for cancer antigen 125 detection based on novel resonance energy transfer between graphitic carbon nitride and NIR CdTe/CdS QDs, J. Electroanal. Chem. 886 (2021), 115104.
[63] M. Yin, et al., Electrochemiluminescence ultrasensitive immunoassay for carbohydrate antigen 125 based on AgInS2/ZnS nanocrystals, Anal. Bioanal. Chem. 413 (8) (2021) 2207–2215.
[64] H. Asbaghian-Namin, et al., Electrochemiluminescent immunoassay for the determination of CA15-3 and CA72-4 using graphene oxide nanocomposite modified with CdSe quantum dots and Ru(bpy)3 complex, Microchim. Acta 188 (7) (2021) 238.
[65] M.N. Abou-Omar, et al., Novel optical biosensor based on a nano-gold coated by Schiff base doped in sol/gel matrix for sensitive screening of oncomarker CA-125, ACS Omega 6 (32) (2021) 20812–20821.
[66] Z. Yang, et al., Streptavidin-Functionalized Three-Dimensional Ordered Nanoporous Silica Film for Highly Efficient Chemiluminescent Immunosensing, vol. 18, 2008, pp. 3991–3998, 24.
[67] P. Charkhchi, et al., CA125 and ovarian cancer: a comprehensive review, Cancers 12 (12) (2020) 3730.
[68] X. Zhu, et al., CAR-T cell therapy in ovarian cancer: from the bench to the bedside, Oncotarget 8 (38) (2017) 64607–64621.