

REVIEW

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# AuNPs and 2D functional nanomaterial-assisted SPR development for the cancer detection: a critical review

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## Abstract

Cancer ranks as a leading cause of death and a huge obstacle to rising life expectancy. If cancers are spotted early there's a high chance of survival. The conventional methods relying on the phenotypic features of the tumor are not powerful to the early screening of cancer. Cancer biomarkers are capable of indicating specific cancer states. Current biochemical assay suffers from time and reagents consuming and discontinuous monitoring. Surface plasmon resonance (SPR) technology, a refractive index-based optical biosensor, has significant promise in biomarker detection because of its outstanding features of label-free, sensitivity, and reliability. The nanomaterial features exotic physical and chemical property work on the process of transferring biorecognition event into SPR signal and hence is functioned as signal enhancer. In this review, we mainly discussed the mechanism of gold nanoparticles (AuNPs) and two-dimensional (2D) functional nanomaterial for improving the SPR signal. We also introduced AuNPs and 2D nanomaterial assisted SPR technology in determining cancer biomarker. Last but not least, we discussed the challenges and outlooks of the aforementioned reformative SPR technology for cancer biomarker determination in the clinical trial.

**Keywords:** Cancer biomarker, Gold nanoparticle, 2D functional nanomaterial, Surface plasmon resonance

## Introduction

Cancer ranks as a leading cause of death and a huge obstacle to rising life expectancy, hence a major public health problem worldwide. According to the data from GLOBOCAN, 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 (Siegel et al. 2020a). The global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020 (Sung et al. 2021). Conventional methods, mainly referring to medical imageology, such as computed tomography, positron emission tomography, magnetic resonance imaging, ultrasound, endoscope, etc., rely on the phenotypic features of the tumor and thus are not powerful to the cancer detection at early stage (Roointan et al. 2019). It has been demonstrated by the union international center of

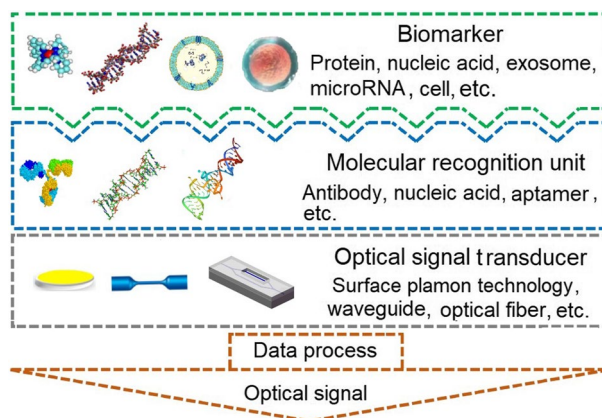


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cancer that one-third of cancers are preventable. If cancers are spotted early there is a high chance of survival.

Cancer involves multi-stage process and its pathogenesis and evolution are closely related to a complicated series of genetic and epigenetic alterations, which leads to the tumor transformation and ultimate malignancy (Huang et al. 2018a). Cancer's onset and progression often associated with some specific molecular alteration, the correlated molecules which are identified as biomarkers (Sveen et al. 2020). The cancer-associated biomarkers are capable of indicating specific cancer states, since their presence and absence and even the concentration change in normal cell often indicate the cancer evolution. As a result, biomarkers play an important role in early diagnosis, assessing the patient's state, and developing an appropriate therapy strategy. Traditional biochemical strategies based on polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) suffer from time and reagents consuming and discontinuous monitoring (Rusling et al. 2010). The demand for fast, real-time, and cost-effective biomarker tests is on the rise (Chen et al. 2020).

Optical biosensors have recently attracted researchers' attention due to their exceptional performance. They are label-free, quick, sensitive, robust and dependable (Khan-sili et al. 2018; Chen and Wang 2020). Biological signal is probed and then transformed to an optical signal including optical absorption, fluorescence, refractive index (RI), et al. Amongst which, optical sensor based on the RI detection is named optical RI sensor. Optical RI sensor makes use of evanescent wave to sense the RI change within a whole sample (bulk sensing) or a small volume very close to the sensor surface (surface sensing) (Chiavaioli et al. 2017). For bulk sensing, evanescent wave with its entire extent of penetration depth interacts with the surrounding volume. The optical RI sensor is only deemed as an optical refractometer. While for surface sensing, only the portion of the evanescent wave probed the RI and thickness of a bilayer which was previously immobilized on the sensing surface. In this case, optical RI sensor is used as an optical biosensor. When it comes to cancer biomarker detection, optical RI sensor served as optical biosensor because detection specificity and affinity are undoubtedly considered in the test.



**Fig. 1** Sketch of the RI-based optical biosensor, whose primary components were molecular recognition unit and optical RI transducer

The recognition element and the signal transducer underlie the RI-based cancer biomarker detection theory (Fig. 1). On one hand, recognition element which normally associated with the transducer enables to identify and capture the biomarker in complex clinical sample with high affinity and specificity. On the other hand, RI variation induced by biomarkers is extremely sensitive, which enables biomarkers to be spotted at very low levels (Kozma et al. 2014; Chocarro Ruiz 2019).

Among different configurations of optical RI transducer, SPR technology which is the earliest commercially available product is the most effective tool for the *in vitro* assay, especially for medical diagnosis (Sanders et al. 2014). For a traditional SPR technology, photonic energy is confined on the gold film surface leading to the intensified light-matter interaction. Nevertheless, it is still challenge to determine the biomarker in clinical sample due to a very low concentration. Recent decades, the advance of nanotechnology benefits SPR technique a lot (Mao et al. 2021; Ye et al. 2018; Li et al. 2017). Nanomaterials with the unique chemical and physical properties, have positive effects on both the recognition and transducing processes and ultimately improve the sensing performance. AuNPs and 2D functional nanomaterials are widely adopted in assistance with SPR for detecting a cancer biomarker. AuNPs features localized SPR (LSPR) effect which is confined on the surface of AuNPs (Saha et al. 2012). The LSPR coupling with the propagating SPR (PSPR) results in an intensified electromagnetic field. Moreover, AuNPs promote biomarkers secretion from cancer cells and hence strengthens the initial weak biological signal (Giljohann et al. 2020).

There have been exploited some 2D functional nanomaterials so far, such as the graphene and its derivatives (Stebunov et al. 2015; Chiu et al. 2017a; Chiu and Huang 2014), molybdenum disulfide (MoS<sub>2</sub>) and its derivatives (Zhang et al. 2015; Chiu et al. 2017b; Chiu and Lin 2018), black phosphorus (BP) (Nangare and Patil 2021; Pandey et al. 2021), antimonene (Pumera and Sofer 2017; Lu et al. 2017) and MXene (Dai et al. 2017; Sang et al. 2016) etc. 2D functional nanomaterials features thermodynamic stability, electronic conductivity, exotic optical property, tunable bandgap, large surface-to-volume ratio, and low loss, etc. Interestingly, these merits benefit the development of biosensor. Thus, the usage of AuNPs and 2D nanomaterial make available the trace amount of a biomarker in broad types of clinical sample, ranging from tears to urine.

In this review, we first reviewed the features and categories of cancer biomarkers and existing biomarkers for monitoring most frequent cancers. Afterward, we explored different approaches for signal amplification based on AuNPs and 2D functional nanomaterials. We introduced the AuNPs and 2D nanomaterial-assisted SPR in determining different cancer biomarkers. Last but not least, we attempted to discuss the challenges and outlooks of the reformative SPR for cancer biomarker detection in clinical trials.

## **Cancer biomarkers**

In this section, we introduced cancer biomarkers in terms of three categories: nucleic acid, protein, and others. For each category, we discussed the most frequent cancers, together with their well-established biomarkers.

### **Nucleic acid biomarkers**

A normal cell transformed to a cancerous cell probably associating with genetic change, such as the activation of oncogenes, the inhibition of tumor suppressor gene, the

alteration of chromosome, and the methylation of nucleic acid, etc. Therefore, nucleic acid is served as biomarker and is preferable in early detection of cancer, since no change of physiological features occur (Huang et al. 2017). For example, the p53 gene is a well-known tumor suppressor gene, the inactivation of which is observed in half of human cancers (Du et al. 2011). The p53 gene mutation is frequently considered as carcinogenesis (Kinzler and Vogelstein 1992).

### **Protein biomarkers**

Functional deviation in protein caused by the expression profile of gene (genetic mutations, alternative splicing, gene duplications) or post-translational change (glycosylation, phosphorylation, and methylation) consequently developed as cancer. Proteins changed significantly at the level of concentration or functional status and, therefore, served as biomarkers (Jayanthi et al. 2017).

Lung cancer is a most prevalent neoplasm and the second deadly cause of cancer-related deaths in both men and women (Boer et al. 2012). Cytokeratin-19 (CK19) antigen and its fragment CYFRA21-1 antigen are the well-established lung cancer-associated biomarkers (Liu et al. 2017a; Pang et al. 2013). Prostate cancer is the most common malignancy in men, ranking second after lung cancer (Rawla 2019). Prostate cancer may be asymptomatic at the early stage and often has an indolent course. Prostate cancers are detected depending on the elevated plasmatic levels of prostate-specific antigen (PSA), a glycoprotein normally expressed by prostate tissue (Hoffman 2011). Testicular tumor is the most common solid malignancy in men ages 15–35 years, and the incidence and mortality rate of which is increasing per year. Human chorionic gonadotropin (hCG) is a hormone essential for the maintenance of pregnancy, yet it is also an important biomarker for testicular tumors (Hoshi et al. 2000).

Colorectal cancer (CRC), is reported as the third most death causing cancer presently (Siegel et al. 2020b). Endothelin-1 (ET-1), a vasoconstrictor peptide chain of 21 amino acids, was shown to be elevated in the blood plasma of Colorectal cancer (CRC) patients (Yanagisawa et al. 1988). The heterogeneous distribution of ET-1 around tumor cells and the addition of ET-1 in growth medium promote tumor growth (Inagaki et al. 1992). Moreover, overexpression of HMGA1b protein in CRC tissues was spotted by the researchers (Huang et al. 2009).

Ovarian cancer and breast cancer are the most common malignant tumors contracted by women all over the world (Stewart et al. 2019; Srnkf and Jemal 2021). Lysophosphatidic acid (LPA) and antigen 125 (CA125) were thought to be indicators in the measurement of ovarian cancer (Mills and Moolenaar 2003; Liu and Xu 2015). Epidermal growth factor receptor 2 (ErbB2, also known as HER2) gene encoding a transmembrane glycoprotein is responsible for breast cancer metastasis and results in overexpression of receptors at the tumor cell surface. The ErbB<sub>2</sub> antigen is broadly adopted in diagnosis of breast cancer (Li et al. 2019a).

### **Other types**

In addition, circulating tumor cells (CTC), exosome and microRNA were recently investigated as cancer biomarkers. When the cancerous tumor is driven to grow, divide and invade the local tissue, some cells slough off the edges of the tumor and travel or lodge

themselves in new tissues. Whatever their path, their origin indicate that they hold information about the tumor (Plaks et al. 2013). Hence, the so-called CTC is deemed as key factor for cancer detection and treatment. Exosomes secreted by eukaryotic cells carry vital molecular information of the parent cell, hence were promoted as non-invasive markers and ultimately developed to exosome-based diagnostic biosensors (Skog et al. 2008; Fais et al. 2016). MicroRNAs are small single-stranded noncoding RNAs usually with 18–25 nucleotides, enabling to regulate multiple biological processes (Bartel, 2004; Esquela-Kerscher and Slack 2006). It has been observed that the expression level of microRNA changed along with tumorigenesis. It is stable under harsh conditions. The use of miRNA for early cancer detection is, therefore, preferred (Petrocca and Lieberman 2009; Wang et al. 2016a).

#### **A panel of biomarkers**

In the clinical diagnosis, a panel of biomarkers is actually recommended and widely adopted as criteria. The elevated level of one biomarker, in some cases, is not uniquely associated with the corresponding cancer types, which makes it non-specific for some organs. For example, CA125 proteins present in epithelial ovarian carcinoma tissue and serum and some other malignant tumor, such as cervical carcinoma, pancreatic cancer and lung cancer. Moreover, the elevated serum levels of CA125 protein may be observed in other physiological conditions, including menstruation, and pregnancy. A panel of biomarkers with ability of improving detection specificity and accuracy, are considered to be more promising than one single biomarker for use in clinical diagnosis. As a result of this tendency, more and more cancer-specific biomarkers must be discovered. To this end, biomolecular techniques, such as genomic profiling, genomic sequencing, protein engineering and so on, will be used.

#### **Molecular recognition element**

Molecular recognition element which determines the detection affinity and specificity is crucial for an SPR-based optical biosensor. It is composed of various bioreceptors (e.g., antibody, enzyme, nucleic acid sequence, peptide, cell receptors, etc.) or chemical synthetic group (e.g., crown ether group, crypt ether group, cyclo-aromatic group, etc.) (Prieto-Simon et al. 2008; Saadati et al. 2019; Pasquarelli 2021). Binding between target analyte and bioreceptor generates a quantifiable signal, which is corresponding to the concentration of the analyte (Estrela et al. 2016). Bioreceptors are bound to the surface of a signal transducer, the process of which named surface functionalization, or molecular immobilization (Khansili et al. 2018). An efficient immobilization strategy features high coverage rate of bioreceptors with good native activity, which contributes to high sensitivity, selectivity, and fast response time (Foubert et al. 2019; Fernandes et al. 2019; Wang et al. 2017; Li et al. 2019b). Therefore, the molecular recognition element is significant in achieving high sensitivity and specificity with prolonged device lifetime.

#### **Immobilization of molecular recognition element**

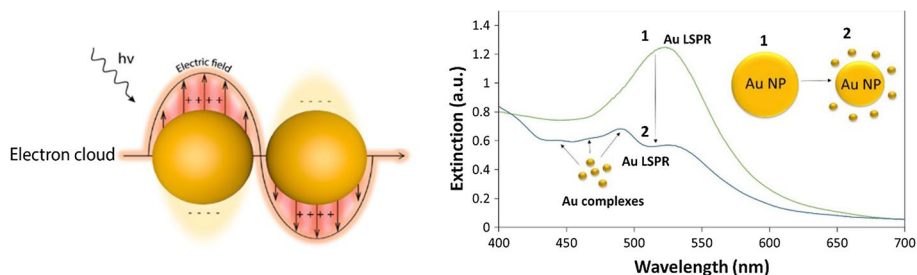
For clinical test, bioreceptors were commonly adopted, considering biocompatibility and nontoxicity. For example, anti-ET-1 antibodies and anti-HMGA1b antibodies were, respectively, selected as bioreceptors in the CRC biomarker detection (Huang et al.

2009). In the ovarian cancer detection, anti-CA125 antibody and anti-ErbB2 antibody were usually used as bioreceptors (Liu and Xu 2015; Li et al. 2019a). Antibody showed highly affinity to its partner antigen (i.e. cancer biomarker), but only when the binding site is fully explored. Antibody with high activity and good orientation enables an adequate exposure of its binding site. The spatial hindering and structure folding prevented the binding site from being exposed. A class of self-assembled monolayer (SAM) covered the sensing surface with active silanol before bioreceptor immobilization. Gold film of an SPR chip is covered with a thiols SAM (Inkpen et al. 2019). Thiol on gold has advantages including easy to preparation, well-defined order and relative inertness of the substrate (Love et al. 2005). EDC ((1-ethyl-3-[3-(dimethylamino) propyl]-carbo-diimide) and NHS (N-hydroxysuccinimide) reagents were used to provide the carbonyl groups, which afterward reacted with amino groups from antibodies (Totaro et al. 2016). Regarding to reformative SPR chip, i.e. extra deposition of dielectric layer (e.g., silicon oxide) on the Au film, silane SAMs with terminal amino and epoxy groups are necessary for attaching antibodies. APTES (3-Aminopropyltriethoxysilane) were intensively investigated and well-understood (Gunda et al. 2014). By the formation of siloxane bonds with surface silanol, the APTES with terminal amino groups were loaded on the sensing surface. Antibodies with carboxyl groups reacted with APTES-amino groups and hence immobilized. EDC and NHS reagents were also used for activating the carboxyl group. Besides, glutaraldehyde (GA), a homo-bifunctional agent enables the cross-link of APTES-amino groups to the antibodies amino group via the formation of reversible Schiff base (Walt and Agayn 1994). Antibodies made use of amino groups to react with GA-aldehyde groups. In comparison with strategy of antibody carboxyl, immobilization approach of antibody amino probably causes improper orientation of antibodies, which leads to mask the binding site.

### Signal amplifier strategy

#### AuNPs

AuNPs feature distinct optical attributes and are biocompatible by utilizing appropriate ligands. AuNPs can be synthesized in a straightforward manner including “top-down” and “bottom-up” approaches (Daniel and Astruc 2004). AuNPs exhibits LSPR at specific operation wavelength, which generates strong surface plasmon absorption bands (Fig. 2). AuNPs enable to improve the SPR signals due to the electronic coupling interaction of



**Fig. 2** Sketch of LSPR effect occurring on AuNPs. Incidence wave excites the collective oscillation of free electrons (left). LSPR effect of distributed AuNPs and aggregated AuNPs are shown (right). The electronic field is considerably reduced as AuNPs aggregate. Reprinted with permission from ref.(Mohammadparast et al. 2019; Garcia-Peiro et al. 2020)

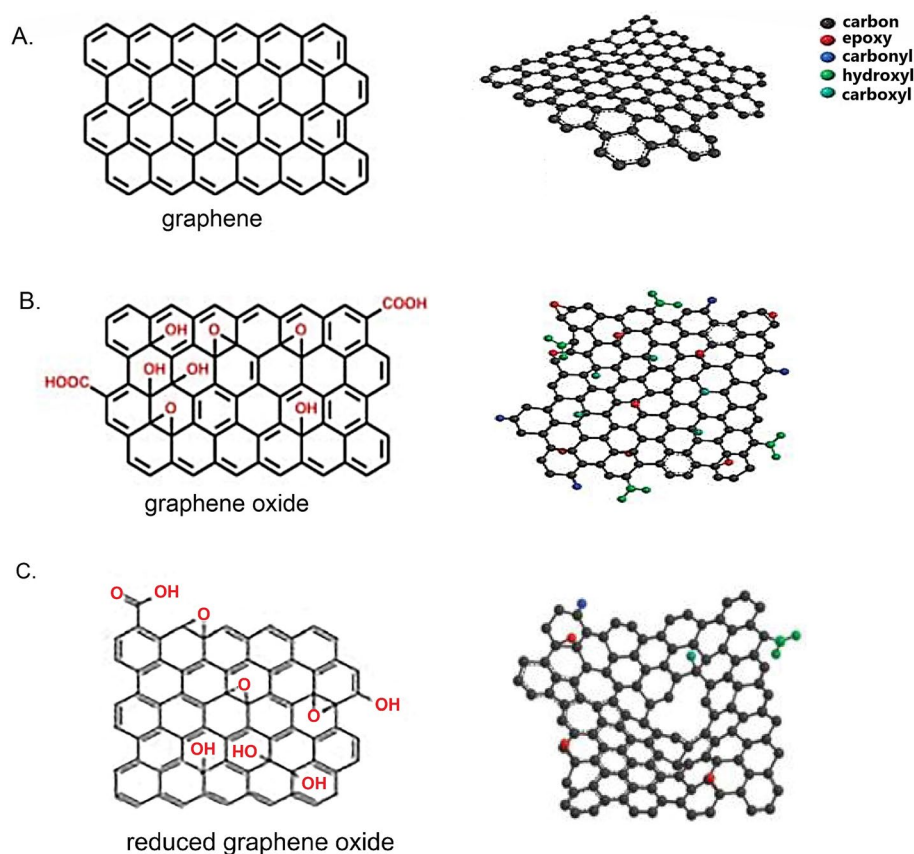


LSPR and PSPR (Hutter et al. 2001). The signal amplification is dependent on many factors, including size, shape, and the gap between AuNPs and Au film (Boer et al. 2012). It has been reported that the AuNPs tagged sensing surface achieved tenfold increase in resonance shift and hence led to 1000-fold improvement in detection sensitivity (He et al. 2000). In some cases, AuNPs promote secretion of biomarkers from cancer cells and hence strengthen the initial weak biological signal (Dreaden et al. 2012). Addition of AuNPs makes the detection more sensitive and selective, which guarantees their usage for trace amounts of a biomarker in broad types of clinical sample, ranging from tears to urine. The native AuNPs are unable to selectively recognize target molecule. AuNPs feature a high surface-to-volume ratio with excellent biocompatibility and hence offer a suitable platform for multi-functionalization with a wide range of ligands for the specific binding and detection of biological targets. It has been reported that AuNPs modified with nucleic acid, aptamer and antibody succeeded in binding to the target analyte specifically. Ohmic loss of gold metal most probably weakens the electromagnetic field, especially when AuNPs aggregate. Addition of metal increases the bandwidth of resonance peak thereby lowering the detection limit. The resultant detection limit is not met with early cancer diagnosis. Therefore, when it comes to the AuNP-based amplification, precisely control over the concentration and distribution of these nanoparticles is still the challenging issue.

### **2D functional nanomaterials**

**Graphene and its derivatives** Graphene is a single atomic layer of carbon atoms, which is arranged in a two-dimensional crystalline hexagonal lattice (Fig. 3A) (Luo et al. 2013). Graphene presents low Ohmic loss and radiative loss in comparison with conventional noble metals. It has been reported that the electromagnetic field confined in the graphene is much stronger than that in noble metals (Naumis et al. 2017). In the terahertz to mid-infrared range, gold film has been replaced by the graphene layer (Gupta et al. 2019). Graphene as an alternative plasmonic material showed advantages, namely, (i) graphene having very high surface-to-volume ratio, which contributes to efficient adsorption of biomolecules, (ii) the combination of graphene on top of the metal film effectively protecting metal from oxidation so as to maintain metal film with stability and quality factor.

Graphene derivative, graphene oxide (GO) is much easier to immobilize bioreceptors due to the oxygenated group (Fig. 3B) (Banerjee xxx). It has been demonstrated that GO is compatible with DNA, amino acid, and peptide (Sharma et al. 2016). GO is considered as hydrophilic derivative of graphene and offers a richer surface functionalization due to oxygenated groups. As mentioned before, cancer biomarkers originate from nucleic acid and protein molecules, which exhibits good hydrophilic property. Serum, urine and body fluid are usually used as test sample in the clinical trial. On one hand, GO layer is easily handled in aqueous medium due to its improved water stabilization. On the other hand, the hydrophilicity promotes GO layer to absorb the receptor molecules. Moreover, oxygenated groups in the hydrophilic zone of the GO molecules enable to react with multiple functional groups, e.g., carboxylic groups with amide bonds. The recognition element or bioreceptor is consequently anchored. To investigate the effect of graphene on the SPR, theoretical calculation and experiment were done recently



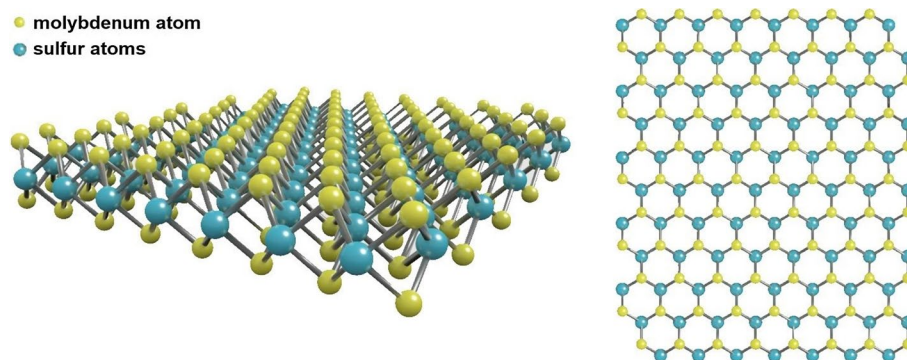
**Fig. 3** Sketch of graphene (A), graphene oxide (B), reduced graphene oxide (C). Reprinted with permission from ref. (Raval 2019)

(Maharana et al. 2015; Nurrohman et al. 2020; Chiu et al. 2019). It should be noted that the electric conductivity of GO is reduced significantly and the sensitivity improvement is due to GO accessibility to bioreceptor.

Reduced GO, abbreviated as rGO, is the reduction product of GO (Fig. 3c). The main goal of reduction process is to produce graphene-like material similar to pristine graphene which is made from direct mechanical exfoliation of highly ordered pyrolytic graphite. Graphene manufactured by rGO (the reduction of GO) becomes much more significant in the graphene research field. Raw material graphite is cheap and can be produced with a high yield by the means of cost-effective chemical methods. Regarding to rGO, most research interests are concentrated on the reduction protocol of GO. The production of rGO is concerned with removing oxygen-containing groups and removing lattice defects. More importantly, rGO is used for recovering the conjugated network of the graphitic lattice. Compared with GO, rGO enables to restore the electric conductivity to the most extent albeit lower than that of the graphene. The plasmonic effect of the rGO is not as high as graphene. Nevertheless, rGO is used as plasmonic material in the biosensing.

*Molybdenum disulfide*  $\text{MoS}_2$  is also a semiconductor material and is classified as the transition metal dichalcogenide group (Fig. 4) (Das et al. 2015). Similar to graphene,





**Fig. 4** Crystal structure of monolayer MoS<sub>2</sub> showing a layer of Mo atoms sandwiched between two layers of S atoms

MoS<sub>2</sub> monolayer is stable in dilute acid and oxygen ambient. MoS<sub>2</sub> monolayer possess unique optical features and has been extensively investigated regarding to SP-enhanced photoluminescence and photosensitivity. Because of its tunable bandgap, high conductivity and optical absorption efficiency, MoS<sub>2</sub> monolayer has recently been applied in the optical biosensing. It has been reported that the MoS<sub>2</sub> monolayer promoted plasmonic wave excitation via charge transfer between MoS<sub>2</sub> compounds and metallic atoms (Kim et al. 2019). As a result, the optical absorption of MoS<sub>2</sub> monolayer (5%) is higher than that of graphene (2.3%). The combination of MoS<sub>2</sub> monolayer to the metallic film generates strong coupling at MoS<sub>2</sub>/metal interface, which leads to an improvement of SPR sensitivity. The MoS<sub>2</sub> layer also protects metal film from oxidation arising from oxygen in air and oxide ion in solution (Wijesinghe et al. 2018). Kim et al. experimentally obtained the SPR responses to the same target analytes utilizing two SPR chips individually based on a bare metal film and a MoS<sub>2</sub> conjugated metal film (Kim et al. 2019). As expected, the MoS<sub>2</sub> conjugated one showed a larger SPR angel shift. In the same year, Kaushik et al. found that MoS<sub>2</sub> monolayer had positive effect on the detection limit of SPR technology (Kaushik et al. 2019).

### Cancer biomarker detection based on the SPR technology

As early as 1980s, the first SPR system for sensing was implemented. In the year of 1990, the first commercial device based on SPR technology was proposed by Biacore company, currently a division of GE Healthcare (Pol et al. 2016). It has been accepted as the most powerful technology for determining affinity, selectivity, and kinetic dynamics of a biological event. So far, such technique performs the excellent capability for bulk sensing in the range of 10<sup>-7</sup> to 10<sup>-6</sup> RIU and that for surface sensing at 1 pg/mm<sup>2</sup>.

### Principle of SPR technology in the cancer detection

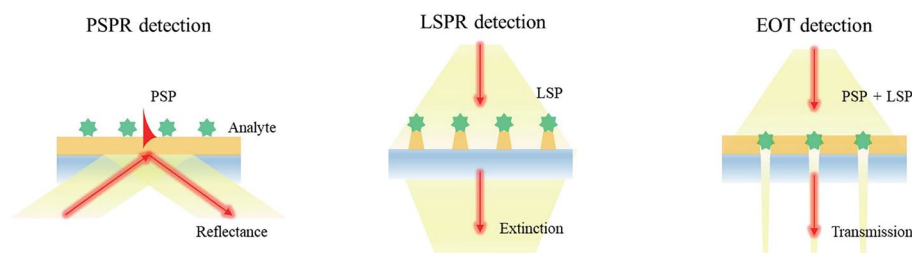
SPR phenomenon arises from the collective coherent oscillation of electrons at the metal surface due to incidence photons interacting with free electrons along with electromagnetic energy transfer (Chen et al. 2021). Electromagnetic field of the incident photon is confined to a subwavelength dimension in the form of surface plasmon

(Chen et al. 2019). SPR technology not only intensifies the optical energy locally, but also confines the optical wave in a subwavelength dimension (Chen et al. 2018). SP wave is sensitive to the RI alteration at the sensing surface caused by the interaction between recognition element and target molecules. PSPR and LSPR are mostly used in SPR sensing. The former is excited on the metal film and propagates along the interface of metal/dielectric to a distance of micrometer. LSPR is inspired on the metallic nanostructure and is strictly confined to the vicinity of the nanoparticle. Recently, researcher observed that an incident light transmitting from a metallic film patterned with periodical arranged subwavelength holes is substantially enhanced (Jia et al. 2022). This phenomenon is named extraordinary optical transmission (EOT) effect, which is considered as the combination of propagating and localized SPR. EOT sensor as a new SPR configuration is applied in the detection of various biological molecules (Xiong et al. 2016; Cetin et al. 2015). Three types of SPR configuration are shown in Fig. 5.

SPR technology is now the most widely used and well-known technique for *in vitro* assays. Recent year, SPR technology has been increasingly utilized for the cancer detection. The reasons can be summarized as: ① metal film as sensing surface shows a good biocompatibility to the loaded analytes; ② it is easier to make a biofunctionalization on a metal film; ③ cancer biomarker is assumed to be directly captured from the complex clinical sample and is loaded upon the sensing surface, which effectively eliminates the pretreatment and reduces the test cost; ④ the SP wave features an intensified field and a small field volume and hence provides a strong response for any RI alteration on the sensing surface within evanescent tail of SP wave. Because of the ultra-high sensitivity, cancer biomarker can be probed in a very low concentration.

#### AuNPs assisted SPR for cancer biomarker detection

In the SPR detection, the intensity of the reflective light is correlated to the incidence angle as the incidence wavelength is fixed. AuNPs exhibit LSPR at specific operation wavelength, which generates strong surface plasmon absorption bands. In the reflective spectrum, a resonance dip appears due to the significantly reduced reflective intensity. Meanwhile, the bandwidth of the resonance dip broadens according to the metallic scattering loss. To date, a variety of AuNPs assisted SPR format are demonstrated. In this section, we will introduce the well-established approaches in the detection of cancer biomarker.



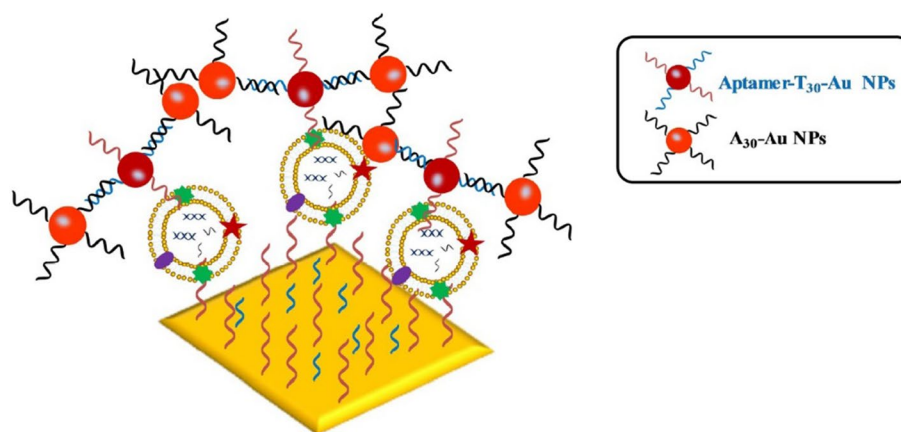
**Fig. 5** Sketch of different SPR configuration for sensing. Reprinted with permission from ref. (Jia et al. 2022)

### ***AuNPs-conjugated format assisted signal amplification***

AuNPs-conjugated system that AuNPs directly labeled to the binding molecules via self-assembled process were widely adopted in the cancer biomarker detection (Englebienne et al. 2001). AuNPs were first modified with specific functional molecules which enabled to bind with the target molecules with high selectivity and affinity. For example, folate receptor linked AuNPs targeting for CTC (Huang et al. 2020a), wheat germ agglutinin linked AuNPs targeting for O-GlcNAc breast cancer biomarker (Gao et al. 2018), DNA linked AuNPs targeting for miRNA let-7a (Nie et al. 2018), aptamer linked AuNPs targeting for breast cancerous exosome (Wang et al. 2019) and streptavidin linked AuNPs targeting for miRNA-21 (Liang et al. 2019), etc. The conjugation of AuNPs with Au film promotes the electromagnetic field coupling between LSPR of AuNPs and SPR of Au film, which results in an improvement of SPR signal. Nevertheless, such signal amplification strategy still faced challenges, such as steric hindrance imposed by the solid sensing surface, stability issue during long-term storage, complicated operation procedure including low flow rate and long hybridization time. Various methods were reported to overcome the problems as illustrated in the following sections.

### ***Dual AuNPs-assisted signal amplification***

Dual AuNPs-assisted signal amplification is widely used in the cancer biomarker detection. Electromagnetic coupling between AuNPs makes field intensification in the gap between adjacent AuNPs (Fig. 6) (Wang et al. 2019; Hutter and Pileni 2003). Addition of dual AuNPs not only promotes the electromagnetic coupling effects between plasmonic nanoparticles, but also generates electromagnetic coupling between Au film and AuNPs. The resultant signal is enhanced greatly. For example, Wang et al. made use of dual-AuNPs conjugation format in the determination of cancerous exosomes. The sensitivity was of  $5 \times 10^3$  exosomes/mL (Wang et al. 2019). It seems that the dual AuNPs conjugation format was preferable for large analytes, such as cell or exosome. Because of the small volume, AuNPs were distributed on the surface of a cell or an exosome. The disadvantage of plasmonic coupling effect of AuNPs was that the background signal was enhanced as well, which reduced the signal-to-noise ratio of the SPR sensor. Electronic



**Fig. 6** Dual AuNPs format for SPR signal enhancing. Reprinted with permission from ref. (Wang et al. 2019)

field enhancement via the AuNPs was unable to differentiate signal from background noise and was only able to improve both the signal and noise without selectivity.

#### ***Functionalized element modified AuNPs-assisted signal amplification***

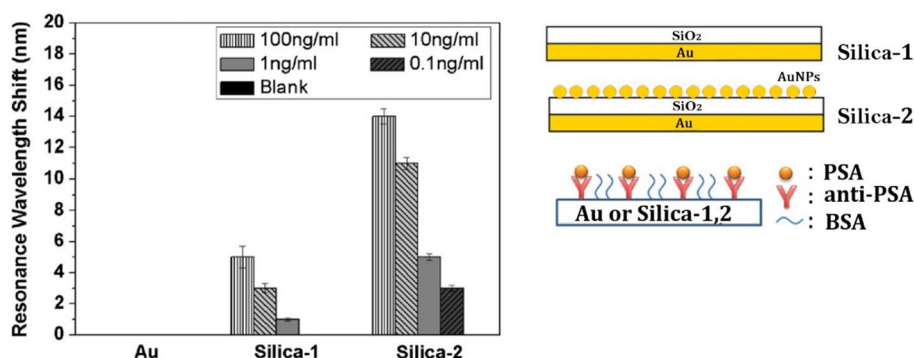
Functional groups modified AuNPs can improve the biological signal by the means of chemical principle. Cell membrane was considered as a functional ligand due to membrane component and structure, wide sources, low cost, long cycle time, and good biocompatibility. Cell membrane-biomimetic technique is applied in the drug delivery, target therapy, and biosensing. Cell membrane conjugation with nanoparticles enables homologous targeting to cell with good response. Membrane is extracting from different type of cell, including red blood cell, platelet and cancer cell. Cancer cell can increase the uptake rate of cancer cell membrane conjugation due to homologous recognition. Accordingly, Chen and co-workers proposed AuNPs conjugating with CTC membrane fragment (Huang et al. 2020a). CTC membrane is first broken into pieces by sonication. JUP protein and folate receptor overexpressed in CTC are considered as marker proteins on the CTC membrane. After sonication, these two marker proteins on the cell membrane surface disperse onto each membrane fragment. The CTC membrane fragments were mixed with the AuNPs and subsequently passed through polycarbonate porous membrane under a high-pressure extruder to obtain membrane fragment coated AuNPs. The membrane-AuNPs conjugates were loaded on the anti-JUP modified gold film of SPR chip. In the presence of CTCs, membrane-AuNPs conjugates targeted the CTCs by the means of both homologous adhesion and specific marker proteins recognition. In this way, the detected target analytes were increased, which improved the biological signal. Moreover, the AuNPs encapsulated in the membrane fragments facilitated the signal amplification.

#### ***Extra dielectric layer between AuNPs and Au film***

It has been demonstrated that the use of silicon oxide ( $\text{SiO}_2$ ) overcoating Au film as substrate for SPR detection significantly increased the changes in SPR angle shift (He et al. 2004). Theoretically, a spacing dielectric  $\text{SiO}_2$  layer between Au film and AuNPs elevates a tunneling barrier for electron leakage and hence an increased charging of the AuNPs, which results in an angle or wavelength shift in an SPR spectrum (He et al. 2004). In the other words,  $\text{SiO}_2$  spacing layer is capable of modulating electromagnetic energy, which contributes to the SPR response in contrast to the electromagnetic coupling effect of AuNPs and bare Au film. For instance, Hyun et al. reported a  $\text{SiO}_2$  layer coating Au film in the combination of AuNPs to enhance the SPR signal in the measurement of PSA (Jung et al. 2009). The sensitivity (0.1 ng/ml) was improved 100-fold in comparison with biochemical method (Fig. 7).

#### ***Addition of metallic material***

Silver nanoparticles (AgNPs) bring a stronger and shaper resonance peak superior to that of the AuNPs (Pastoriza-Santos and Liz-Marzán LM: Colloidal silver nanoplates. 2008). Although silver presents higher conductivity, it is susceptible to the oxidation which ultimately degrades its plasmonic effect. Especially for cancer biomarker detection, test assays are always conducted in the aqueous solution (Cheng et al. 2015). Strategies for

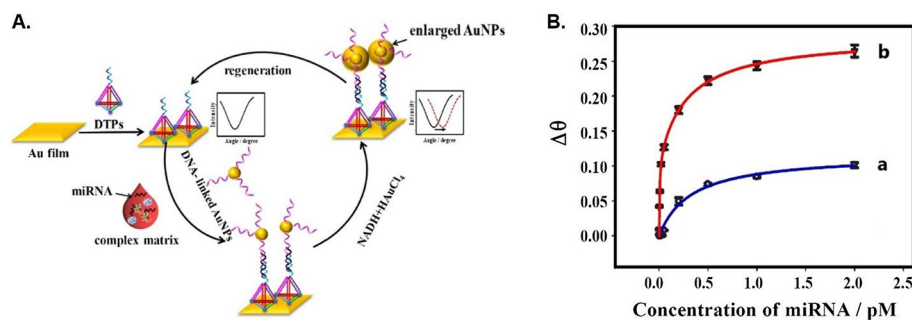


**Fig. 7** Resonances shift of SPR biosensor with bare Au chip, silica-1 chip and silica-2 chip for PSA determination. The results showed that addition of silica layer between Au film and AuNPs significantly increased the resonance wavelength shift attributing to an improvement of sensitivity. Reprinted with permission from ref. (Jung et al. 2009)

protecting AgNPs from oxidation were proposed, amongst which the core-shell structure was most widely used. Ag@AuNPs is defined as AgNP cores wrapped by Au shells (Xia et al. 2011). In this format, AgNPs determine the strong plasmonic effect and Au shell protects the AgNPs from oxidation. Besides, combining AgNPs with AuNPs was reported for cancer detection as well. For example, positively charged AgNPs were attached to the negatively charged DNA strains leading to a further increasing resonance shift. With help of this amplification strategy, the SPR-based detection of miRNA-21 achieved the sensitivity of 0.6 fM (Liu et al. 2017b). In addition, the graphene layer coating on the silver functions as another approach for silver protection. It has been reported that silver was covered with a monolayer CVD graphene and the resulting SPR effect is improved in comparison with the pure silver (Kravets et al. 2014). The combination of graphene with AgNPs probably opens a new avenue for solving the oxidation problem of AgNPs.

#### **Other novel reformative AuNPs-assisted signal amplification**

Single AuNPs-conjugation format has limits as a signal enhancer as aforementioned. Some other reformative AuNPs amplification strategy was reported as well. For example, Wang et al. additionally introduced catalytic growth reagents to enlarge the AuNPs (Nie et al. 2018). The miRNAs from test sample were captured on the DNA tetrahedron probes (DTP) modified gold film. AuNPs linked with DNA to the miRNAs and the sandwich structure was formed by DNA hybridization of target miRNA, DNA-linked AuNPs and DTPs-Au film. The SPR signal was improved by the coupling between LSPR of AuNPs and the surface plasmon wave supported on the gold film. Moreover, catalytic growth reagents promoted the enlargement of AuNPs. The increasing size of AuNPs promoted the effect of electromagnetic coupling once again and hence enhanced the SPR signal further more (Fig. 8). The consequent the mass increasement of AuNPs will cause the change of local refractive index to some extent. The authors did not consider the mass effect. Although it has been demonstrated that the detection limit achieved as low as 8 fM in determining miRNA let-7a, the result is overestimate due to the mass effect. Moreover, hybridization of quantum dots and functional nanomaterial undoubtedly benefit the sensing performance. Specifically, 2D functional nanomaterials hybridization



**Fig. 8** Schematic illustration of reformatory AuNPs-assisted SPR biosensor for determining miRNA. **A** Sketch of catalytic growth of AuNPs enhanced SPR biosensing. **B** Phase shift based on pure AuNPs addition (**a**) and extra catalytic growth of AuNPs (**b**). SPR signal was considerably improved by the catalytic effect. Reprinted with permission from ref. (Nie et al. 2018)

with AuNPs have been extensively explored for cancer biomarker detection (Yao et al. 2016). We will discuss exhaustively in the next section.

### 2D functional nanomaterial-assisted SPR for cancer biomarker detection

It has been reported that graphene opacity is independent of wavelength. The light transmittance through monolayer graphene is about 97.7%. Thus, electromagnetic field is strongly confined in the graphene nanolayer. Addition of graphene improves the SPR angle. One-atom-thick graphene layer absorb 2.3% of incident wave and the absorption increases with thickening of the graphene layer. That is why multi-layer of graphene coated on the gold film widens the resonance curve. As aforementioned, the graphene features the delocalized out-of-plane pi bonds. Compares with the bare gold surface, graphene adsorbs biomolecules more stable and stronger. The improved adsorption efficiency promotes the SPR angle shift. Accordingly, graphene (and its derivatives) is widely used in the SPR detection.

#### Graphene and graphene oxide assisted SPR

Graphene and its derivative (GO) feature strong in-planes bonds and weak out-of-plane p bonds formed by the sp<sup>2</sup> hybridization of carbon atoms (Amieva et al. 2016). Graphene and its derivative (GO) facilitate the adsorption of hydrophobic domains and pi-system, which promotes the bioreceptors to be loaded on the nanosheet easily (Zhong et al. 2015). When graphene and GO nanomaterials are used for biosensing, specific and selective identification of analytes are improved in the tested sample. Take examples of their utility in the cancer biomarker detection. Graphene-coated SPR was utilized for detecting human epithelial-derived tumors and non-small cell lung cancer. GO-coated SPR was reported to detect CK-19 antibodies and hCG antibodies (Chiu et al. 2019, 2018). The resultant minimum detectable concentration normally achieved the value in the order of femtomole and several particle/ml.

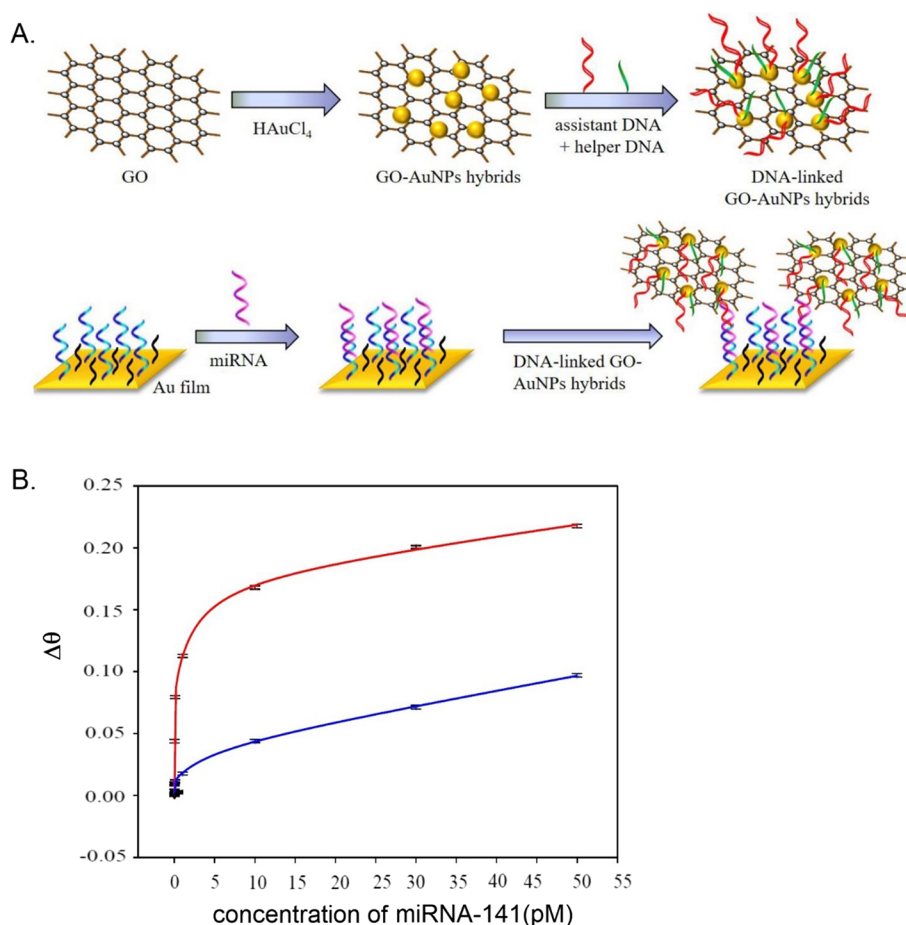
Recently, GO sheets were decorated with AuNPs and produced a GO-gold nanoparticles (GO-AuNPs) composites. GO-AuNPs hybrids were functioned as solid immobilization substrate as well as signal enhancer (Feng et al. 2014; Govindhan et al. 2015). GO features good biocompatibility and large surface area, which promotes the immobilization of bioreceptors. A number of AuNPs are subsequently loaded on the GO sheet to



increase the SPR signal, furthermore. In addition, GO-AuNPs hybrids enable to accelerate electron transfer. Accordingly, the sensing performance is greatly improved. For example, Wang et al. proposed GO-AuNPs hybrids-based SPR biosensor for detecting miRNA-141 (Fig. 9) (Wang et al. 2016b). GO-AuNPs hybrids linking to DNA strands were coupled to the miRNA-141 by the means of complementary pairing of bases. Two years later, the same group proposed double-layer of GO-AuNPs hybrids format (Li et al. 2017). The bottom layer was used as substrate on the Au film and the upper layer used as signal enhancing element. The detection limits of two works were as equal as 1 fM. The preparation of double-layer structure increased the time and economic cost. In our view, it is not necessary to design such a double-layer format.

#### *Molybdenum disulfide assisted SPR*

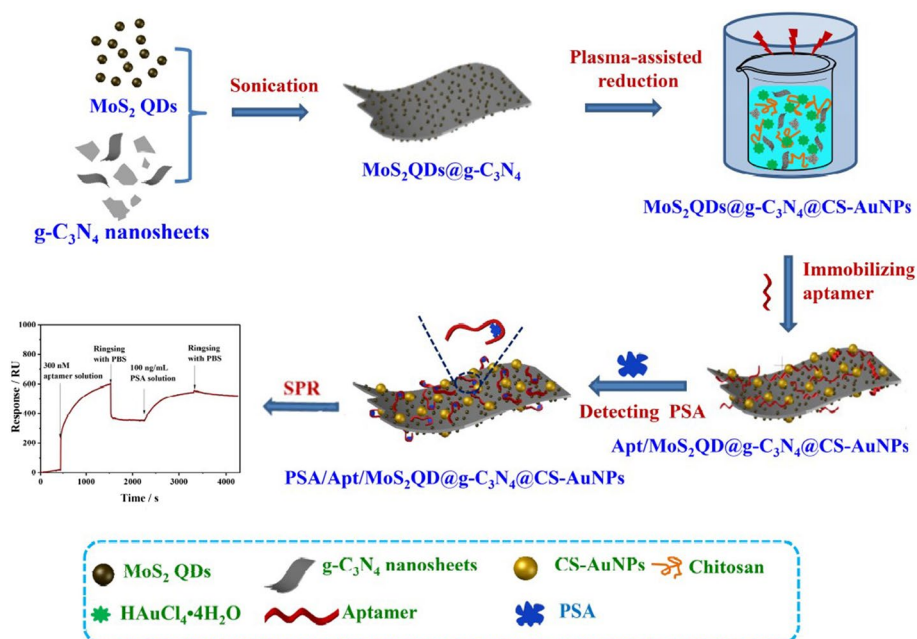
The exploration of new functional nanomaterials has attracted great attentions, and especially graphene-like 2D layered nanomaterials, such as MoS<sub>2</sub> and group functionalized molybdenum disulfide. When it comes to MoS<sub>2</sub> assisted SPR, the gold film was covered by only a MoS<sub>2</sub> layer with Cys linker. Target analytes were captured by the



**Fig. 9** GO-AuNPs hybrids assisted SPR biosensor in the measurement of miRNA. **A** Schematic illustration of GO-AuNPs hybrids synthesis and its usage for SPR signal amplification. **B** Resonance spectrum of bare AuNPs (blue curve) and GO-AuNPs composites (red curve) amplified SPR. Reprinted with permission from ref.(Wang et al. 2016b)

receptors on the MoS<sub>2</sub> layer. In the AuNPs–MoS<sub>2</sub> hybrids, AuNPs were first loaded on the MoS<sub>2</sub> layer in the synthetic process. Tested analytes were captured on the gold film and AuNPs–MoS<sub>2</sub> hybrids were added to amplify the detected signal. Compared with pure MoS<sub>2</sub> layer, AuNPs–MoS<sub>2</sub> hybrids are appealing and exhibit better sensing performance. The MoS<sub>2</sub> layer with high surface-to-volume ratio enables to associate enough AuNPs and the AuNPs enhance the signal by LSPR effect. In both detection format, SPR effect was generated by the gold film. Only in the latter one, LSPR was produced by AuNPs.

The MoS<sub>2</sub>–COOH composite in a multilayer structure was first proposed to be applied for BSA protein detection (Chiu and Lin 2018). Afterwards, a reformative MoS<sub>2</sub>–COOH single layer was reported in determination of lung cancer biomarker CYFRA21-1 (Chiu and Yang 2020). In comparison with multilayer, single layer provided much stronger interfacial interactions and preserved the merits of the original MoS<sub>2</sub>. As a result, the detection limit reached as low as 0.05 pg/mL. Inspired by the concept of AuNPs–GO nanocomposites, AuNPs–MoS<sub>2</sub> hybrids served as signal enhancer was explored by researchers. Wang et al. reported that AuNPs–MoS<sub>2</sub> composites effectively amplified the detectable signal 10<sup>-3</sup> fold when the hybrid composites were introduced to an SPR-based miRNA-141 and miRNA-200 detection (Nie et al. 2017). As alternative to MoS nanosheet, MoS<sub>2</sub> can be used as quantum dots (QD) as well. Zhang et al. made MoS<sub>2</sub> quantum dots hybridization of C<sub>3</sub>N<sub>4</sub> nanosheet (Duan et al. 2018). The addition of AuNPs not only stabilized the hybrid nanosheet, but also assisted to enhance signal (Fig. 10). The hybrid nanosheet-assisted SPR was used for PSA detection. The result showed that both the detection affinity and sensitivity were improved in comparison with the bare sensing chip.

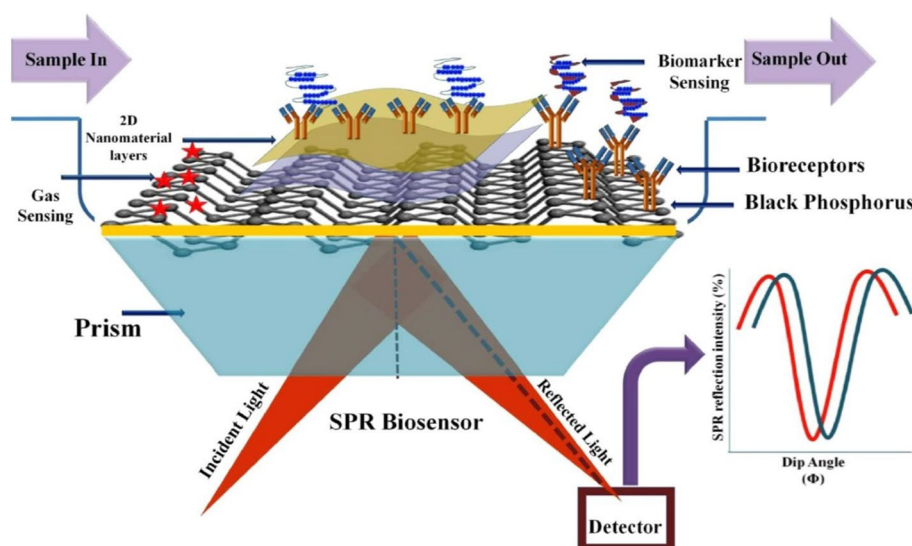


**Fig. 10** Schematic diagram of AuNPs@MoS<sub>2</sub>QD composites assisted SPR biosensor for PSA detection. Reprinted with permission from ref.(Duan et al. 2018)

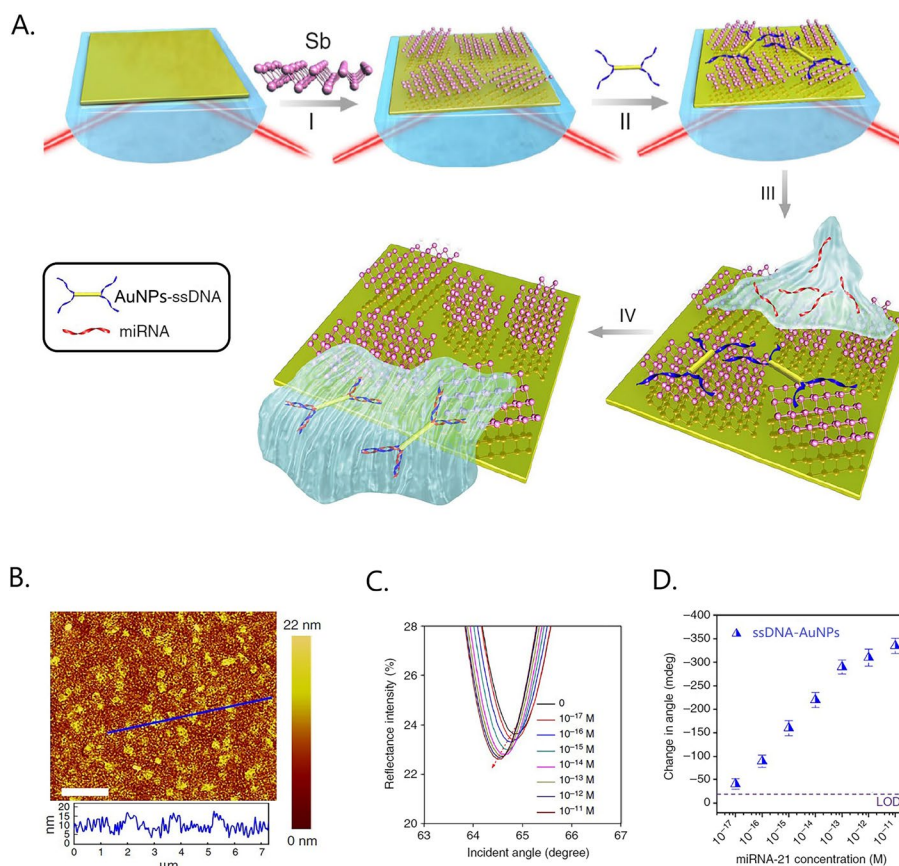
### Other functional nanomaterial assisted SPR

Besides graphene and MoS<sub>2</sub>, black phosphorus (BP), antimonene and MXene have been investigated for biomedical application. BP enables to recognize target analyte with very low concentration due to its 40 times quicker reaction rate and larger adsorption energy in comparison with graphene and MoS<sub>2</sub> counterpart (Nangare and Patil 2021). Regarding to the composition of BP molecule, the presence of active lone electrons from every single phosphorous atom promotes the oxidation of BP, which results in the degradation of BP monolayer. Thus, proper strategy should be proposed to protect BP from oxidation, amongst which the chemical functionalization of BP nanosheet has been suggested as the best method. Huang et al. synthesized a nitrophenyl functionalized BP nanosheet and applied it in the tumor DNA detection (Huang et al. 2020b). Covalent functionalization via direct chemical bond provides high stability of the modified surface. BP has been used in the biomedical field, such as bioimaging, cancer therapy, drug delivery, etc. During 2019 to 2022, the development of BP nanosheet-based SPR sensor for cancer biomarker detection started to gain much attention (Fig. 11). For example, Karki et al. reported the hybridization of titanium disilicide nanosheet and BP nanosheet utilized for various cancer cell detection (Karki et al. 2022).

Antimonene exhibits strong spin–orbit coupling, tremendous stability and hydrophilicity (Lu et al. 2017; Ares et al. 2018). Zhang et al. first reported antimonene nanosheet assisted SPR technology in the measurement of cancer biomarker (Xue et al. 2019). They found that antimonene presents strong adsorption of a DNA molecule through first-principle density functional theory calculation. Motivated by this theoretical finding, they proposed a hybridization of antimonene with AuNPs as amplification format and took advantage of antimonene-modified SPR chip in the measurement of miRNA21 and miRNA55 (Fig. 12). They synthesized the AuNPs–ssDNA complex in advance. Because there is a large adsorption energy between antimonene and ssDNA, AuNPs–ssDNA complexes were easily adsorbed on the



**Fig. 11** Sketch of black phosphorus nanomaterial-based SPR biosensor. Reprinted with permission from ref. (Nangare and Patil 2021)



**Fig 12.** **A** Sketch of AuNPs hybridization with antimonene nanosheet assisted SPR biosensor for determining miRNA. **I** The antimonene nanosheets was assembled on the gold film. **II** AuNPs-ssDNA adsorbed on the antimonene nanosheet. **III** Tested sample of miRNA flowed over the antimonene monolayer surface and paired up to form a double-strand with complementary AuNPs-ssDNA. **IV** Interaction between miRNA and ssDNA led to the release of AuNPs-ssDNA from the nanosheet. **B** AFM images of antimonene on Au film (scale bar = 2 μm). **C** SPR spectrum with miRNA concentrations ranging from 10<sup>-17</sup> to 10<sup>-11</sup> M. **D** Relationship between the SPR angle and miRNA concentration. Reprinted with permission from ref. (Xue et al. 2019).

antimonene nanosheet. In the measurement, target miRNA paired up to generate double-strand with complementary AuNPs-ssDNA. The interaction between miRNA and ssDNA led to desorption of AuNPs-ssDNA from the antimonene and caused a negative shift of the SPR signal. The experimental sensitivity reached the value of 10 aM.

MXene, a new type of transition-metal carbides and carbonitrides material, exhibited metallic conductivity and good hydrophilicity (Huang et al. 2018b). Its derivatives Ti<sub>3</sub>C<sub>2</sub>-MXene has presented superior capacity for loading biomolecules and intensifying localized electromagnetic field (like hotspot) (Dai et al. 2019). Thus, the addition of Ti<sub>3</sub>C<sub>2</sub>-MXene to the SPR device enhances the selectivity for target substance while also improving the measurable signal. Wu et al. proposed a novel 2D amino-functionalized Ti<sub>3</sub>C<sub>2</sub>-MXene-based SPR biosensor for detecting carcinoembryonic antigen (CEA) (Wu et al. 2018). It showed a high selectivity to the CEAs and the low detection limit of 0.15 fM in a linear range of 0.001–1000 pM.

**Table 1** AuNPs and different 2D nanomaterial assisted SPR technology in the detection of cancer biomarkers

Cancer biomarker	Signal amplification	Sensing performance	References
CTC	AuNPs	DL: 1 cell/mL DR: $10^1 \sim 10^5$ cell/mL RR: 93.86% ~ 111.21% RSD: 2.78%	Huang et al. (2020a)
O-GlcNAc	AuNPs	DL: $4.65 \times 10^{13}$ mol/L DR: $4.65 \times 10^{-12} \sim 4.65 \times 10^{-7}$ mol/L RSD: 2%	Gao et al. (2018)
miRNA let-7a	AuNPs	DL: 0.8 fM DR: 0 ~ 2 pM	Nie et al. (2018)
MCF-7 exosome	Dual AuNPs	DL: $5 \times 10^3$ exosomes/mL RSD: 3.3%	Wang et al. (2019)
PSA	AuNPs-SiO <sub>2</sub> layer	DL: 0.1 ng/mL DR: 0.1 ~ 100 ng/mL	Jung et al. (2009)
miRNA-21	Ag@AuNPs	DL: 0.6 fM DR: 0 ~ 10 pM RSD: 2.5%	Liu et al. (2017b)
FAP	Graphene	DL: 5 fM DR: 5 ~ 500fM	He et al. (2017)
exosome	Graphene	DL: 20 exosomes/mL DR: $5 \times 10^3 \sim 5 \times 10^5$ exosomes/mL	Zma et al. (2021)
CK19	GO	DL: 0.05 pg/mL DR: 0.001 ~ 100 pg/mL	Zhong et al. (2015)
hCG	GO	DL: 1.15 pM DR: 1.15 ~ 28.7 pM	Chiu et al. (2018)
CEA	rGO-AuNPs	DL: 0.12 ng/mL DR: 0.6 ~ 80 ng/mL RR: 95.9% ~ 10.5%	Feng et al. (2014)
miRNA141	GO-AuNPs	DL: 0.1 fM DR: 0.1 pM ~ 2 nM RR: 99.4% ~ 101%	Li et al. (2017)
miRNA141	GO-AuNPs	DL: 1 fM DR: 0 pM ~ 50 pM RSD: 1%	Wang et al. (2016b)
CYFRA21-1	MoS <sub>2</sub>	DL: 1 fM DR: 0 pM ~ 50 pM RSD: 4.2% RR: 90% ~ 103%	Chiu and Yang (2020)
PSA	MoS <sub>2</sub> QC-C <sub>3</sub> N <sub>4</sub> -AuNPs	DL: 0.71 pg/mL DR: 1 ~ 250 ng/mL RSD: 1.52% RR: 92.7% ~ 109%	Duan et al. (2018)
tumor DNA	BP	DL: 50 fM DR: 50 fM ~ 80 pM RSD: RR:	Huang et al. (2020b)
ssDNA	BP	DL: 0.2 pg/mL DR: 1 pg/mL ~ 10 mg/mL	Peng et al. (2017)
miRNA-21 miRNA-155	Antimonene	DL: 10 aM DR: 10 pM ~ 10 aM	Xue et al. (2019)
CEA	MXene	DL: 0.15 fM DR: 0.001 ~ 1000 pM	Wu et al. (2018)

DL detection limit, DR dynamic range, RR recovery range, RSD relative standard deviation



At end of the section, we collected the highlighted AuNPs and 2D nanomaterial assisted SPR technologies in cancer biomarker detection (Table 1).

### **Conclusions and future outlook**

Cancer biomarkers which are biological entities enable the early cancer screening which results in a high chance of survival. The well-established cancer biomarkers include DNA, antigen, tumor cell, exosome, and microRNA, etc. Traditional biochemical strategies based on PCR and ELISA suffer from time and reagents consuming and discontinuous monitoring. SPR technology have shown great promise in the detection of cancer biomarkers. Molecular recognition element and surface plasmonic transducer are crucial to the technology. Bioreceptors which are composed of molecular recognition element are immobilized on the gold film in advance. Bioreceptors should keep a good native activity and a high coverage rate and be highly affinitive to the partner cancer biomarker as well. Especially for clinical test, bioreceptors should be biocompatibility and nontoxicity. Antibodies are commonly used as bioreceptors in the cancer detection. The binding site of the antibodies should be exposed adequately and avoid any spatial hindering. Surface plasmonic wave features intensified electromagnetic field and a small field volume and hence offers sensitive response for any alteration within the evanescent field.

Cancer biomarker is normally in a very low concentration at the initial stage of carcinogenesis. SPR as an RI-based transducer provides a good sensing performance, but it is still challenging to implement the early diagnosis of the cancer biomarker. Signal amplification strategy in terms of sensing performance is required to be improved further. Benefiting from the development of nanotechnology, metallic nanoparticles and 2D nanomaterials have been extensively utilized as signal amplification strategy.

SPR detection can be classified as direct assay and indirect assay due to transferring approaches for biological reaction into detectable SPR signal. Direct assays make use of pre-immobilized bioreceptors to capture target molecules, which produces change in SPR signal base on single binding event with analyte. When single binding event does not result in a detectable signal, additional interaction is added to induce a reaction which generates a signal correlating to the tested analyte concentration. The latter detection mechanism is defined as indirect assay. AuNPs worked on the process of biorecognition event transferring into SPR signal. In the direct assay, AuNPs are coupled directly to the analytes. Elimination the secondary binding event reduces the test complexity and reagent, which speeds the test process. In the indirect assay, the addition of AuNPs occurred following the secondary binding event. Experimental process and complexity are both increased which requires both well-trained professionals and well-designed protocols. However, non-specific absorption of substance on the sensing surface seems inevitable in a direct assay, which makes it difficult to decouple from the signal produced by the analyte molecules binding. AuNPs probably enhance both the tested signal and background noise. By comparison, non-specific recognition will be prevented effectively. AuNPs conjugation specifically improve the signal arising from target binding event.

AuNPs enable to improve the SPR signals due to the electronic coupling interaction of LSPR and PSPR. AuNPs as signal enhancers come in a variety of conjugation



formats. AuNPs directly labeled to the binding molecules via self-assembled process were widely adopted in the cancer biomarker detection. Although it is not difficult to make AuNPs modified Au films, there are still problems, such as steric hindrance, stability issues, extra operating procedures, such as low flow rate and extended hybridization time. Reformative AuNPs conjugation scheme were successively reported, such as dual AuNPs-assisted signal amplification, core-shell structure (Ag@AuNPs), SiO<sub>2</sub> layer mediated configuration.

It is worth to mention that cancer cell detection by SPR. Electromagnetic field of the incident wave is confined to a subwavelength dimension in the form of surface plasmonic wave. The electric field amplitude and mode volume determined the wave-matter interaction. CTC is in the micrometric dimension. The mode volume does not overlap with CTC entirely. The sensing area with CTC is only located on the surface of the gold film. Because the covered area and the mass effect of the cells are much higher than of protein molecules, the impact of the RI change is locally higher. The detection can occur with only a low number of hits on the surface. Moreover, AuNPs are added so as to increase the signal-to-noise ratio based on the LSPR effect. Only if the AuNPs are distributed within the range of the evanescent wave into the external medium, can the LSPR be inspired. Only a few AuNPs are loaded on the closest parts of the CTC and serve as signal amplifiers, while the others are ineffective.

2D functional nanomaterials have thermodynamic stability, electronic conductivity, exotic optical property, tunable bandgap, large surface-to-volume ratio, low loss, and so on. So far, graphene and graphene oxide, molybdenum disulfide, black phosphorus, antimonene and MXene have been used for the cancer biomarker detection. These 2D functional nanolayers provide strong adsorption of bioreceptors via  $\pi$ -stacking format, which lead to an improvement of specific and selective identification of cancer biomarker in the tested sample.

Compared with noble metals, graphene presents low Ohmic loss and radiative loss and good tunability. The addition of a graphene nanolayer to bare Au film promotes bioreceptor immobilization while also protecting the Au film from oxidation. Plasmonic wave is much stronger confined in the graphene nanolayer. However, it is difficult to make a bottom-up synthesis of pristine graphene. The pristine graphene has poor solubility, which is easy to be aggregated in the solution. The usage of pristine graphene meets challenge. Reduction of GO becomes much more significant in the graphene manufacturing. Moreover, GO exhibits good performance in biosensing. The oxygenated group increases the solubility and hence the stability of a GO nanocomposite. GO is also compatible with various biomolecules. MoS<sub>2</sub> and graphene belong to Group-IVA (i.e. carbon group) and hence have many similarities in chemical and physical properties. MoS<sub>2</sub> as another plasmonic material is applied in the cancer biomarker detection.

BP classified in the Group-VA is indirect wide bandgap semiconductor. Pristine BP furnishes advantages over graphene, such as simple synthesis, good biodegradability in vivo, and low toxicity to cells. Antimonene, another group-VA element 2D material, was explored very recent year. Until 2019, antimonene nanosheet was first reported in the cancer detection. In the last two years, only dozens of scientific works reported the antimonene-assisted SPR technique. Slow development of the antimonene-based

SPR sensing probably are attributed to the unclear mechanism and synthesis procedure. MXene, a new type of transition-metal carbides and carbonitrides material, exhibits metallic properties for exciting SP wave. MXene hybridized SPR chip started to be reported in the detection of cancer biomarker in the last two years.

Combination of AuNPs with functional nanomaterial opens a new avenue to the SPR technology in the cancer biomarker detection. On one hand, plasmonic coupling between AuNPs and Au film intensified intensifies the electromagnetic field. On the other hand, 2D nanomaterial facilitates molecules immobilization. In this format, AuNPs were first loaded on the nanomaterial layer in the synthetic process. Cancer biomarkers were captured on the gold film. The hybrids were added to amplify the detected signal. Unexceptionally, almost all of the nanomaterials aided SPR sensor to provide quantifiable signals.

Nevertheless, strategies are still in the stage of academic research. Synthesis still face challenges, such as complicated procedure, poor repeatability and stability, etc. Synthesis of nanomaterial and AuNPs necessitates the use of professional personnel with extensive expertise. AuNPs quantity should be controlled carefully to prevent nanoparticles aggregation and make distribution uniformity. That is why the practical applications lags behind the academic discoveries of new materials and innovative properties. Despite extensive academic studies have been done, the commercially available product for determining cancer biomarkers were still in their infancy. A standard manufacturing procedure should be worked out. Furthermore, the SPR biosensor should be highly repeatable with respect to the same sample. It should also work well in the complex context. At current stage, sensing performance, such as sensitivity, selectivity, detection time, and so on, was not adequate for cancer biomarker detection and needed to be improved before it could be utilized in a clinical test. More importantly, the test cost should be cut down so as to compete with the traditional analytical instrument or biochemical test.

In the clinical diagnosis, a panel of biomarkers is actually recommended and widely adopted as criteria. The elevated level of one biomarker, in some cases, is not uniquely associated with the corresponding cancer types, which makes it non-specific for some organs. Thus, more and more cancer-specific biomarkers must be discovered. To this end, biomolecular techniques, such as genomic profiling, genomic sequencing, protein engineering and so on, will be used. POC test has become an irresistible general trend in the near future. It sets the laboratory staffs and facilities free and provides advantages of expanding diagnostic accessibility and reducing costs and time. POC test has become a competitive technology for early diagnosis. SPR biosensor will evolve toward the minimized, convenient, flexible and POC available device. There is still significant effort to be done in developing inexpensive and portable POC devices that can detect new multi-marker panels that indicate improved clinical outcomes in a quantifiable and rigorous manner. As the population shrinking, labor-free clinical tests must be the leading trend. Intelligent detection becomes possible with the help of automated control. Although there is a long way to go, we expect the bright future for nanomaterial-assisted SPR biosensor in cancer marker detection.

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**Author contributions**

Chen Chen conceived, designed, and wrote the manuscript; Kaifei Wang collected literatures of section II (Cancer biomarker) and he also discussed the manuscript; Lei Luo discussed the outlook of the SPR biosensor and edited the manuscript. All authors read and approved the final manuscript.

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**Competing interests**

The authors declare that they have no competing interests.

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