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Application of various optical and electrochemical aptasensors for detection of human prostate specific antigen: A review

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ABSTRACT

Early stage detection of prostate cancer, one of the main causes of mortality among men, is of great importance for better treatment of the patients. Prostate specific antigen (PSA) is a glycoprotein which has been considered as the most potential serological biomarker for the detection of prostate cancer. Among the various techniques employed for PSA detection, aptamer-based biosensors (aptasensors) have achieved notable attention because of their unique features and great potentials as diagnostic tools. A variety of strategies such as integration of nanomaterials (NMs) into the structure of aptasensors have also been applied for enhancing the sensitivity of PSA detection. This article reviews recent advances in various optical and electrochemical aptasensors used for PSA detection.

1. Introduction

Early detection of cancer usually increases the likelihood of successful treatment and quality of life in cancer patients (Wardle et al., 2015). The detection of cancer biomarkers in blood or serum samples has emerged as a powerful medical tool for early diagnosis, prognosis, and monitoring of treatment response in these patients (Nagpal et al., 2016).

Prostate specific antigen (PSA) has been established to be the most potential biomarker for diagnosis of prostate cancer, the second primary cause of cancer death among men (Afkham et al., 2018; Ankerst et al., 2016; Lu Chikezie and Madu, 2010). Moreover, it is used as an ideal biomarker for diagnosis of other prostatic diseases, such as prostatitis and prostatic hyperplasia (Gamé et al., 2003). PSA is a 33-KDa single chain glycoprotein with chymotrypsin-like protease activity that is secreted by prostate gland (Heidenreich et al., 2014; Wu et al., 2001). It may exist in two main forms in human serum, including free PSA and conjugated form with plasma proteins (Sarkar et al., 2002). The serum concentration of PSA below 4 ng/mL has been considered as normal levels in men, while any concentration above the cut-off value is suspected to the appearance of prostate cancer or other prostate disorders (Okuno et al., 2007).

Currently, different traditional methods, including Enzyme-linked immunosorbent assay (ELISA) (Acevedo et al., 2002), chemiluminescent immunoassay (Albrecht et al., 1994), polymerase chain reaction (PCR) (Gewanter et al., 2003), and radioimmunoassay (Graves et al., 1992) have been proposed for PSA detection. Nonetheless, these approaches are time consuming, expensive, inconvenient, and require complicated instruments (Kavosi et al., 2015). Besides, these traditional techniques are not sensitive enough and suffer from the disadvantages of antibodies associated with their preparation, stability, and, modification (Srivastava et al., 2018). Accordingly, development of novel and effective approaches for determination of PSA is of great importance for early diagnosis and monitoring of treatment responses in these patients.

Biosensors are compact analytical devices which have recently attained considerable success for determination of PSA due to their rapid, real-time, reliable, cost-effective, and sensitive detection ability (Abolhasan et al., 2019; Y.-W. Huang et al., 2013; Yousefi et al., 2019). The application of nanomaterials (NMs) in biosensors construction has provided more sensitive and swifter nano-biosensors with synergetic functions for detection of biomarkers (Golichenari et al., 2018). Among

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various biorecognition elements (enzymes, antibodies, and etc.) in biosensors, aptamers have wide range of applications and great potential for the detection of cancer-specific biomarkers (Dehghani et al., 2018; Yousefi et al., 2019).

Aptamers are high affinity and short single-stranded DNA or RNA molecules produced by a combinatorial technique called systematic evolution of ligands by exponential enrichment (SELEX) (Catuogno and Esposito, 2017). Due to their several unique features, including target versatility, easy production and modification, high affinity and selectivity to their targets, stability and cost-effectiveness, aptamers have been widely used for biomarker detection (Song et al., 2008). According to these advantages, aptamers are also suggested as interesting substitute to antibodies (C.-C. Chang et al., 2016).

To the best of our knowledge, only two review articles concerning aptamer-based biosensors (aptasensors) and PSA have been published so far. Jolly and coworkers have reviewed different biosensors and also some examples of aptasensors for detection of PSA in prostate cancer (Jolly et al., 2015a). Additionally, in 2018, Chang et al. summarized different electrochemical PSA biosensors such as aptasensors based on their assay strategy (direct, competitive and sandwich detection) (Chang et al., 2018). In this review, we first discussed about aptamers selected against PSA. Then, we attempted to describe and compare the performances of recently developed PSA optical and electrochemical aptasensors with different detection methods. Moreover, we particularly emphasized on the prominent role of nanostructured aptasensor platforms (nano-aptasensors) developed for highly sensitive and selective detection of PSA. We further made a critical comparison between commercially available kits used for PSA detection with the established aptasensors. A concluding section summarized the current status, addresses current challenges, and gave an outlook on potential future trends.

2. Aptamers selected against PSA

To develop highly sensitive and effective aptasensors for the detection of PSA, aptamer selection against PSA is inevitable and play a critical role in the development of these aptasensors. Therefore, several researches have been focused on characterization and selection of PSA aptamers (Table 1). Savory et al. (2010) selected the first DNA aptamer against PSA using a genetic algorithm (GA) which showed high affinity to PSA. Furthermore, Park et al. (2016) have demonstrated a novel microfluidic SELEX method for selecting a highly specific PSA aptamer based on an acoustofluidic separation (acoustophoreis). This is the best DNA aptamer with an affinity (Kd) of 0.7 nM against PSA. Recently, a PSA-specific DNA aptamer was screened by Fernández and coworkers for the establishment of an electrochemical aptasensor for the PSA assay. This aptasensor showed a sensitive detection with a LOD of 0.66 ng/mL (Díaz-Fernández et al., 2019). Svobodova et al. (2013) also isolated 2′F-modified RNA aptamer against PSA whit an affinity of 630 nM.

3. Optical PSA aptasensors

According to their method of signal transduction, biosensors are usually classified into different types such as electrochemical and optical (Damborsky et al., 2016). During the past few years, great advances have been made in optical biosensors, which are useful medical tools for diagnostics and analytical purposes (Perumal and Hashim, 2014). Measuring different features of analyte and capability of label-free and real-time detection are advantages of these transducers (Perumal and Hashim, 2014).

The use of NMs for signal amplification purposes has recently attracted extensive attention because of critical requirement for ultra-sensitive biosensors and the trend towards assay miniaturization (Lei and Ju, 2012). These NMs offer potential benefits for improving the limit of detection (LOD) and capability of single-molecule detection (Mokhtarzadeh et al., 2015; Turner, 2013). A number of recent studies has developed successful optical aptasensors such as chemiluminescence, electrochemiluminescence, fluorescence, surface plasmon resonance (SPR), surface-enhanced Raman spectroscopy (SERS), and Light scattering techniques for detection of PSA (Table 2). In the following part, several representative examples of these sensing platforms for PSA detection will be discussed.

3.1. *Luminescent based PSA aptasensors*

Luminescence is the process of emission of light by a substance with no involvement or generation of heat (Murthy and Virk, 2014). Depending on the source of energy, luminescence is classified into several subtypes. For example, chemiluminescence (CL) is the production of light by chemical reactions; however, in electrochemiluminescence (ECL) the light emission is generated by electrochemical reactions (Han et al., 2016). Among the optical biosensors for the aim of biomarker detection, luminescence-based techniques are especially attractive due to their high sensitivity, selectivity, and wide quantitative linear range (Kulmala and Suomi, 2003; Roda et al., 2016). A number of luminescent based aptasensors have been designed for detection of PSA.

3.1.1. *Chemiluminescence based PSA aptasensors*

Recently, a dual-aptasensor was constructed for simultaneous detection of trace levels of PSA and vascular endothelial growth factor (VEGF) using guanine (G)-based intra chemiluminescent resonance energy transfer (Intra-CRET) system (Chong et al., 2019). CRET is the energy transferred between chemiluminescent donor and acceptor molecule and is a sensitive, cost-effective, and simple system that these features make it an attractive optical analytical scheme in bioassay (Dong et al., 2017). The CL intensity was improved with the elevation of VEGF, however, that became weaker by increasing the PSA concentration. The LOD for this sensing platform was as low as 0.6 ng/mL and showed good accuracy, precision, and reproducibility for PSA detection.

Table 1
Available aptamers specifically for PSA detection.

Aptamer type	Sequences	Affinity (Kd)	References
DNA	TTTTTAATATCCGGGGAACGTCGTGGCCCTTT	100 nM >	Savory et al. (2010)
DNA	SH-GCAATGGTACGGTACTTCCTATGGCGATGTGTTGGCTGTGTGTGGGGTGCAAAAGTGCACGCTACTTTGCTAA-MB	0.36 ± 0.08 μM	Li et al. (2018)
DNA	GGGCGGGGCGGACGAGACAGTAAGGGCTGTGGGTGTGGTG	0.7 nM	Park et al. (2016)
RNA	CCGUCAGGUCACGGCAGCGAAGCUCUAGGCGCGGCCAGUUGC	_	Jeong et al. (2010)
RNA	2′F-AGCUCCAGAAGAUAAAUUACAGGUACGGUUCACGCCUGUCUCAUGCUGACUAAGAAAGUUUAGCAACUAGGAUACUAUGACCC	630 nM	Svobodova et al. (2013)
DNA	_	177 ± 65 nM	(Díaz-Fernández et al., 2019)

Table 2
Optical aptasensors for PSA detection.

Detection methods	Strategy/nanomaterial	Aptamer type	Aptamer sequence	Limit of detection (LOD) (pg/ml)	Linear range (LR)/(pg/ml)	References
Chemiluminescence (CL)	Guanine CL reaction based on the chemiluminescent resonance energy transfer (CRET)	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	1000	1900 to 125000	Cha et al. (2014)
CL	Guanine CL reaction	DNA	GGGGGGTTTTTAATTAAAGCTCGCCATCAAATAGCTTTAAAAAAAA A	600	1000 to 100000	Chong et al. (2019)
[a]CL	Magnetic Fe3O4 graphene oxide (GO) nanoparticles	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	500	1600 to 50000	Choi & Lee (2013)
[a]Electrochemiluminescence (ECL)	Competitive aptasensor using GO@AuNRs multilabeled with glucose oxidase (GOD) and streptavidin toward luminol-based ECL system.	DNA	TTATTAAAGCTCGCCATCAAATAGC	0.17	0.5 to 5000	Cao et al. (2018)
[a]ECL	CdTe quantum dots (QDs)/gold nanorods (AuNRs)	DNA	ATT AAA GCT CGC CAT CAA ATA GC	500	1000 to 1000000	Lu et al. (2018a)
[a]ECL	Target-triggered signal-on ratiometric ECL based on MOF/Au/G-quadruplex	DNA	_	58	500 to 500000	Shao et al. (2018)
[a]ECL	Switched aptasensor using ferrocene-graphene sheets for high-efficiency quenching of ECL from Au-CdS flower-like 3D assemblies	DNA	TTATTAAAGCTCGCCATCAAATAGC	0.38	1 to 25000	Yang et al. (2017a)
[a]ECL	ECL ratiometry based on a closed biopolar electrode (BPE)/Au@g-C3N4 Pt-PAMAM-DNAzyme, and Ru(bpy)$_3$ $^{2+}$	DNA	ATT AAA GCT CGC CAT CAA ATA GC	100	100 to 200000	Wang et al. (2016b)
[a]Fluorescent	Based on the Tb-MOFs@AuNPs Platform (Tb-metal–organic frameworks)	DNA	TTATTAAAGCTCGCCATCAAATAGC	360	1000 to 100000	Qu et al. (2019)
[a]Fluorescent	QD-MSNs (mesoporous silica nanoparticles)/ molybdenum disulfide nanosheets (MoS2)	DNA	ATT AAA GCT CGC CAT CAA ATA GC	0.0009	0.001 to 100	Sun et al. (2019)
Fluorescent	Three-in-one" nanohybrid of MOF@AuNP@GO	DNA	_	10	10 to 10000	Huang et al. (2018)
[a]Fluorescent	QDs/electrospun nanofibers (NFs)/AuNPs	DNA	_	0.46	1 to 100000	Yang et al. (2017c)
[a]Fluorescent	gold-upconversion-nanoparticle (Au-UCNP)	DNA	_	0.032 aM (about 9.1 × 10^{-7} pg/mL)	0.04–1 aM	Hao et al. (2017)
[a]Fluorescent	Label-free turn-on sensing based on aggregation-induced emission–silica nanospheres (SiO2 NP)	DNA	TTATTAAAGCTCGCCATCAAATAGC	500	500 to 50000	Kong et al. (2017)
[a]Fluorescent	Aptamer-functionalized MoS2 nanosheet	DNA	TTATTAAAGCTCGCCATCAAATAGC	200	500 to 300000	Kong et al. (2015)
Fluorescent	On-chip FRET graphene oxide aptasensor	DNA and RNA	TTTAATTAAAGCTCTCCATCAAATAGCTTTTTTTTTT	_	_	Ueno et al. (2015a)
Fluorescent	On-chip FRET graphene oxide aptasensor	DNA	TTTAATTAAAGCTCTCCATCAAATAGC	_	_	Ueno et al. (2015b)
SPR	Two-dimensional nanocomposite of MoS2 QDs and g-C3N4 nanosheets decorated with chitosan-stabilized AuNRs	DNA	TTA TTATTA AAT TAA AGC TCG CCA TCA AAT AGC TTT	770	1000 to 250000	Duan et al. (2018)
[a]SERS	Magnetic nanoparticles (MNPs) core-AuNPs satellite assemblies	DNA	ATT AAA GCT CGC CAT CAA ATA GC	5	5–500	Yang et al. (2017b)
[a]Resonance light scattering (RLS)	Aptamer modified AuNPs	DNA	ATT AAA GCT CGC CAT CAA ATA GC	32	130 to 110000	Chen et al. (2012)
[a]Light scattering (LS)	Target stimuli-responsive assembly of AuNPs	DNA	AAAAAAAAAAAAAAAAATTAAAGCTCGCCATCAAATAGC	2	10 to 20000	Liu et al. (2019)

[a] These aptasensors have been successfully tested in real clinical samples.

3.1.2. Electrochemiluminescence based PSA aptasensors

Decorated graphene oxide (GO) with different metal nanoparticles have been widely used in sensing platforms, greatly increasing their catalytic activity (Liu et al., 2011). Comparing with gold nanoparticles, gold nanorods (AuNRs) exhibit good biocompatibility, stability, catalytic activity, and were used for signal amplification by improving the loading capacity of biological molecules (Parab et al., 2010). In a study (Cao et al., 2018), a competitive and sandwich type ECL based nano-aptasensor was developed for PSA assay with the low detection limit and wide linear range of 0.17 pg/mL and 0.5 pg/mL to 5 ng/mL, respectively. In this approach, glucose oxidase (GOD), streptavidin, and biotinylated DNA were loaded on GO coated with AuNRs and formed GO@AuNRs-GOD-SA-biotin-DNA nanocomposites, which were used as signal-amplifying probes. In the absence of PSA, the signal probes attached to the HS-DNA (S1)-PSA aptamer and enhanced ECL intensity. However, upon adding PSA, signal probes were separated from the electrode and resulted in weak ECL response. Due to its excellent sensitivity, selectivity, stability, and practicality in real samples, this aptasensor can be a promising choice for PSA detection in clinic.

Cadmium sulfide (CdS) flower-like three dimensional (3D) assemblies have unique optical features and potential photocatalytic activity. However, similar to other types of semiconductors, low electron conductivity is their major shortcoming which can enhanced by employment of AuNPs (Shi et al., 2010). An “off-on” signal switch ECL aptasensor was fabricated by Yang et al. (2017a) for rapid PSA detection. They used ferrocene-graphene (Fc- GNs) nanosheets for high-efficiency quenching of ECL from AuNPs supported on CdS flower-like 3D assemblies (Fig. 1). By adding PSA, the Fc-GNs was desorbed from electrode surface and led to the ECL signal enhancement. The designed nano-aptasensor showed a highly sensitive detection ability of PSA down to 0.38 pg/mL concentration. Besides, it could be effectively used to the quantification of PSA in human serum samples, suggesting its potential application in bioanalysis.

Wang et al. (2016b) constructed a spatial-resolved ECL ratiometry for PSA detection using Au@ graphitic carbon nitride (g-C3N4) nanocomposites and Ruthenium (II) tris-(bipyridine) $(Ru(bpy)_3^{2+})$ as two effective ECL emission substances on the cathode and anode of bipolar electrode (BPE), respectively. The sensitivity of the sensor was enhanced three times because no optical filter was employed in the detection. Pt-PAMAM-DNAzyme was prepared as sensing probe and integrated with the cathode surface through DNA hybridization between probe DNA and PSA aptamer. This aptasensor provided a LOD of 0.1 ng/mL and had potential application for PSA assay in human serum samples.

3.2. Fluorescent based PSA aptasensors

Fluorescence is itself a form of luminescence, which is the most common optical technique used in protein detection (Valeur and Berberan-Santos, 2011; Wang et al., 2016a). In the few past years, this technique has attracted extensive attention due to its high sensitivity, simplicity, high signal production, reproducibility, and non-destructiveness (Hotzer et al., 2012; Wang et al., 2015a). Generally, two strategies are employed in the development of fluorescent based aptasensors (Bostan et al., 2018). The first one is called ‘signaling aptamers’ that is based on the direct labeling of an aptamer with fluorophores, whereas in the fluorescence resonance energy transfer (FRET) the aptamer is labelled with a fluorescence quenching molecule. Taking advantages of fluorescence method and aptamers, some fluorescent based aptasensors have been fabricated for PSA assay.

Silica nanospheres (SiO2 NPs) have been recognized as an efficient platform for covalent coupling of different biomolecules for fluorescent biosensing (Zhang et al., 2016). In a study (Kong et al., 2017), for the first time a sensitive and label-free fluorescence aptasensor was designed based on aggregation-induced emission (AIE)-SiO2 NPs for turn-on detection of PSA (Fig. 2). The positively charged SiO2 NPs probe adsorbed the negatively charged PSA aptamer to form SiO2 NP-PA nanocomposite. Binding of PSA to the aptamer resulted in the release of PSA aptamer away and aggregation of negatively charged tetraphenylethylene derivative 3 (TPE3) on the surface of SiO2 NPs to form AIE-SiO2 NP nanocomposite, which emitted strong fluorescence. The constructed aptasensor provided a detection limit of 0.5 ng/mL for PSA and efficiently applied in serum samples, indicating its promising use in real clinical samples. It is also suggested that this technique can provide

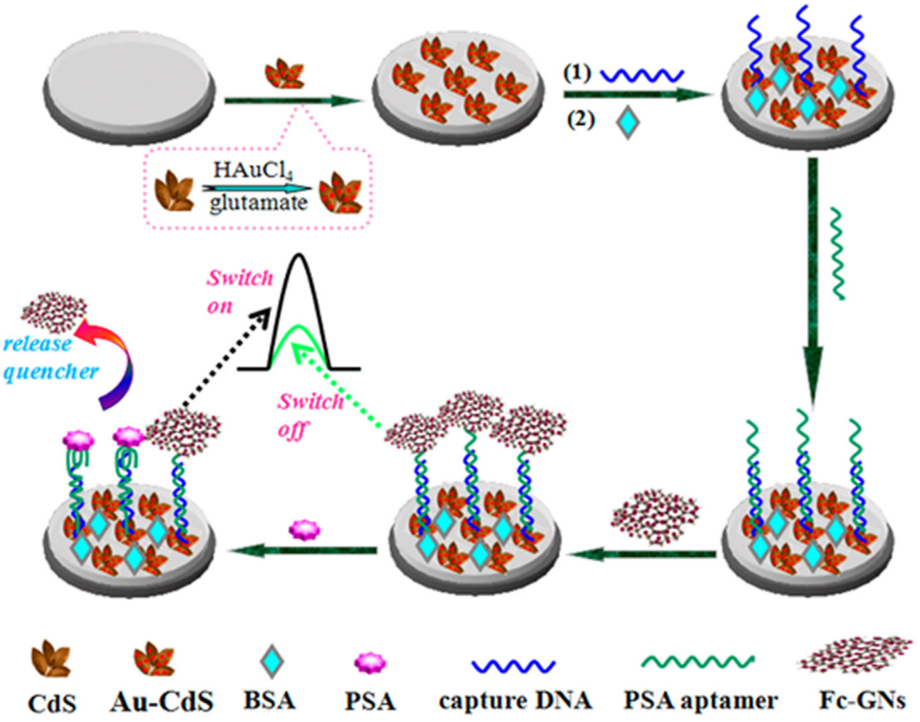

Fig. 1. Schematic illustration of ECL aptasensor for PSA detection. Reprinted with permission from (Yang et al., 2017a).

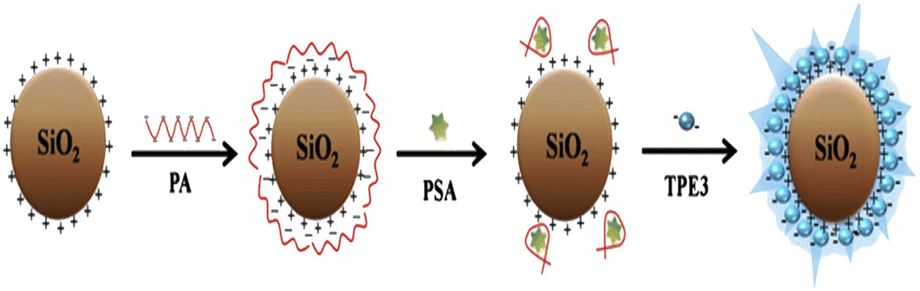

Fig. 2. Schematic illustration of AIE-SiO_2 NP-based label-free fluorescent aptasensor for the sensitive turn-on for detection of PSA. Reprinted with permission from (Kong et al., 2017).

opportunities to design simple, rapid, and low-cost nanoprobes for a wide range of targets.

Upconversion nanoparticles (UCNPs) have gained lots of attentions because of their fluorescence stability and unique optical features such as long lifetime and sharp emission bands (Sadeghi et al., 2018). Hao et al. (2017) designed an ultrasensitive fluorescent aptasensor for simultaneous detection of PSA using Au-UCNP assembled pyramids. In the presence of PSA, the formation of aptamer-target complex changed the pyramid structure, and these variations were noted fluorescence intensity. Their proposed strategy reached an excellent LOD of 0.032 aM. In addition, the successful application of this ultrasensitive biosensor in serum samples demonstrated its usefulness in clinical practice.

Furthermore, FRET-based biosensors are highly sensitive and specific tools that have been widely used for detection of target proteins (Kim et al., 2009). In an experiment, a FRET-based on-chip aptasensor was fabricated using GO, as an excellent acceptor, for sensitive thrombin (TB) and PSA detection (Ueno et al., 2015b). A double strand DNA (dsDNA) was used as an effective spacer, which separated the dye from the GO surface. They indicated that longer spacer could enhance the fluorescence intensity and improve the sensitivity of the platform.

Sun and coworkers fabricated a turn-on aptasensor that could detect PSA and carcinoembryonic antigen (CEA) using combined effects of FRET system and internal filter effect (IFE) (Sun et al., 2019). Mesoporous silica nanoparticles (MSNs) and CdTe quantum dots (QDs) was employed for the fluorescence signal amplification in the platform and molybdenum disulfide nanosheets (MoS_2) was used as an efficient quencher with the aim of higher sensitivity. This ultrasensitive platform showed a detection limit as low as 0.9 fg/mL and achieved reliable results in clinical serum samples.

Another FRET based aptasensor was established through the interaction of dispersed AuNPs with Tb-metal–organic frameworks (Tb-MOFs). By adding the PSA, aptamer–PSA complex released from AuNPs and caused the emission recovery of Tb-MOFs. The system was reported to have detection range from 1 to 100 ng/mL and a LOD of 0.36 ng/mL. Moreover, this platform could successfully detect PSA in human urine samples and had several advantages including easy operation, low costs, and good sensitivity and selectivity (Qu et al., 2019).

3.3. SPR/SERS based PSA aptasensors

Surface plasmon resonance (SPR) biosensors are potential analytical techniques for measurement of analyte-ligand interactions and biomarker detection due to their high sensitivity, specificity, and capability of label-free and real-time sensing (Miyazaki et al., 2017; Taylor et al., 2008). SPR biosensors sense any change in a refractive index proportional to the amount of analyte over the course of the reaction (Nguyen et al., 2015). SPR-based aptasensors have been greatly developed in various fields, especially in detection of cancer-specific biomarkers (Dehghani et al., 2018).

For example, a two-dimensional g-C_3N_4 nanocomposite embedded with MoS_2 QDs and chitosan-stabilized Au nanoparticles (CS-AuNPs) (denoted as MoS_2QDs@g-C_3N_4@CS-AuNPs), have been applied for designing both SPR and electrochemical aptasensor for determination of trace levels of PSA (Duan et al., 2018). In comparison with other 2D NMs, g-C_3N_4 is cost-effective and environment-friendly nanocomposite, which provides a large scaffold to composite with different nanoparticles (Lv et al., 2017; Wang et al., 2015b). This bifunctional platform showed and a low detection limits of 0.71 pg/mL and 0.77 ng/mL, deduced from electrochemical impedance spectroscopy (EIS) and SPR, respectively. Moreover, it showed suitable selectivity, reproducibility, and promising applicability in clinical samples.

Surface-enhanced Raman scattering (SERS) has also gained great interest for the development of cancer biosensors because of its sensitivity, excellent reproducibility, and ability for rapid detecting (Jayanthi et al., 2017; Yang et al., 2017b). In a study, magnetic nanoparticles (MNPs) core-AuNPs satellite assemblies as an ultrasensitive SERS-based magnetic aptasensor was employed for PSA assay with a low detection limit of 5.0 pg/mL and linear range of 5–500 pg/mL (Fig. 3) (Yang et al., 2017b). In addition to the high sensitivity, rapid detection, low sample consumption, and easy of separation are other

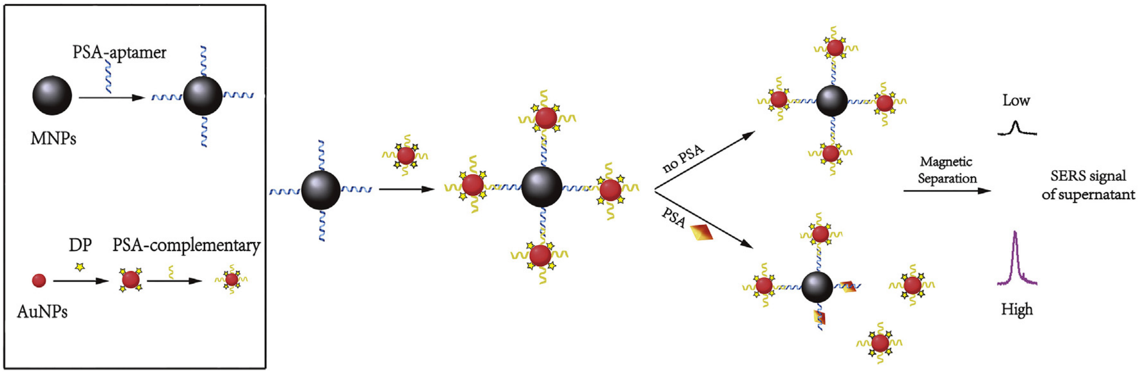

Fig. 3. Scheme of SERS-based magnetic aptasensor for the detection of PSA. Reprinted with permission from (Yang et al., 2017b).

advantages of this technique. Furthermore, it didn't need any immobilization process, solved the difficulty of slow reactions between aptamer and target, and demonstrated good accuracy and reliability in human serum samples.

3.4. Brief overview of optical PSA aptasensors

Generally, optical detection methods including CL, ECL, fluorescence, SPR, and SERS have been applied for designing PSA aptasensors which have notable merits such as feasibility of quantitative analysis without requirement of advanced tools. Resonance light scattering (RLS) (Chen et al., 2012) and light scattering (LS) (Liu et al., 2019) are other optical aptasensors designed for PSA detection with a LOD of 0.032 ng/mL and 2 pg/mL, respectively (Table 2). Fluorescent based aptasensors are the most prevalent optical detection methods for determination of PSA due to their excellent properties such as high sensitivity and ease of detection (Emrani et al., 2016). Based on the reported LODs, among optical aptasensors, the fluorescent based aptasensors also showed the highest sensitivity (0.032 aM) for PSA detection, while CL had the lowest sensitivity (1 ng/mL). In spite of the successful application of luminescent and fluorescent based aptasensors for PSA detection, the intrinsic fluorescence of serum proteins can influence the outcome of the sensor and accordingly the fluorophores with time-resolved fluorescence features must be employed (Alexiev et al., 2017). Besides, the interaction between coexisting biomarkers in complex samples scan limit the application of SPR aptasensors for PSA assay. Development of specific PSA aptamers against particular target may overcome this problem.

4. Electrochemical PSA aptasensors

Electrochemical aptasensors are analytical devices incorporating an aptamer as the biorecognition element integrated on an electrochemical transducer surface to produce measurable electrical signals (Meirinho et al., 2016). These sensors are highly applicable and very attractive means for early detection of cancer biomarkers as they are simple, rapid, portable, inexpensive, highly sensitive, and selective towards their targets (Meirinho et al., 2016; Mustafa Oguzhan, 2017). A list of instances of the various accessible electrochemical aptasensors reported for detection of PSA using electrical impedance spectroscopy (EIS), voltammetry, and other techniques is provided in Table 3. Some of these platforms are discussed in the following parts.

4.1. Electrical impedance spectroscopy based PSA aptasensors

Electrical impedance spectroscopy (EIS) aptasensors are among the most widely used platforms for PSA detection because of their high sensitivity, selectivity, and label-freeness. Lu et al. (2018b) developed a label-free and in-line EIS based aptasensor in which reduced graphene-oxide (rGO) thin films were employed as the transducer for PSA detection. This aptasensor could detect PSA concentrations as low as 33 pM with a wide detection range of 0.033–330 nM. In addition, because of rGO stability in human serum, this sensor can be a promising tool to detect PSA in real samples.

In another approach, a high selective and sensitive impedimetric aptasensor platform was designed based on TiO2 nanoparticles, SF nanofibers and AuNPs, which had a LOD of 0.8 fg/mL for PSA detection using EIS technique (Fig. 4). The MCH/apta/AuNP/SF-TiO2/GCE aptasensor had high selectivity, sensitivity, reproducibility, and needs low cost and sample volume. It also has been successfully tested in real samples. However, the main drawback of this method was its time-consumingness (Benvidi et al., 2017).

In addition, a label-free electrochemical aptasensor was fabricated based on the interaction of thiol terminated PSA with DNA aptamer (5′-HS–(CH2)6–TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT-3′) immobilized onto the AuNPs/fullerene C60-chitosan-ionic liquid/multiwalled carbon nanotubes/screen printed carbon electrode. The detection of PSA was carried out by both EIS and differential pulse voltammetry (DPV). The limit of detection for this sensitive platform was 0.5 pg/mL in the range of 1–200 pg/mL by DPV method, while it was 1.5 ng/mL in the range of 2.5–90 ng/mL by EIS (Jalalvand, 2019). It also successfully detected PSA in real serum samples and had the ability of wider application for other targets.

Heydari-Bafrooei and Shamszadeh, 2017 introduced another label-free electrochemical aptamer-based biosensor for PSA detection. Both DPV and EIS analytical methods were employed for the detection using rGO-MWCNT/AuNPs nanocomposite modified platform which significantly improved the conductivity and sensitivity of the established aptasensor. According to the obtained data, the proposed aptasensor had a low LOD of 1 pg/mL and the wide detection ranges of 0.005–20 ng/mL and 0.005–100 ng/mL were identified for DPV and EIS methods, respectively. Additionally, the developed biosensor was effectively used for PSA detection in complex real samples.

4.2. Voltammetry based PSA aptasensors

As shown in Table 3, several voltammetric aptasensors, such as Cyclic voltammetric (CV), DPV, square wave voltammetry (SWV), and Linear sweep voltammetry (LSV) are also available for PSA assay.

For example, Srivastava and coworkers prepared a label-free aptasensor by means of GQDs-AuNRs modified screen-printed electrodes (SPE). In this work, the aptamer was immobilized on the surface of SPE and three electrochemical methods, including CV, DPV and EIS were employed for PSA detection that had an almost same LOD of 0.14 ng/mL. The aptasensor also showed promising potential for PSA assay in real human serum with excellent sensitivity and repeatability (Srivastava et al., 2018).

In another experiment, Zhang et al. (2018a) fabricated an electrochemical aptasensor using hemin-functionalized graphene-conjugated palladium nanoparticles (H-Gr/PdNPs) for amplification of the sensor sensitivity (Fig. 5A). They immobilized the PSA aptamer (5′-biotin-TTT TTA ATT AAA GCT CGC CAT CAA ATA GCT TT-3′) with biotin-streptavidin interaction on the surface of electrode and a LOD of 8 ng/mL was reached by DPV technique. They also suggested that the aptasensor could be a promising alternative for PSA assay in clinic because of its high stability, specificity, and low LOD. Nevertheless, frequent pretreatment and modification of the GCE and capability of single biomarker detection are the limitations of this platform.

A signal-on built in-marker electrochemical aptasensor was designed by Sattarahmady et al. (2017) for PSA assay based on DPV technique. They used hairbrush-like gold nanostructure to improve the aptamer-PSA binding. This biosensor showed a detection limit of 50 pg/mL with a wide linear range of 0.125–128 ng/mL and could efficiently detect PSA in patients' serum samples.

In another study (Zhao and Ma, 2018), an ultrasensitive electrochemical aptasensor was employed for detection of PSA using enzyme-free recycling amplification strategy. The aptasensor was designed based on the target-induced catalytic hairpin assembly and bimetallic catalyst. As shown in Fig. 5B, in the presence of PSA, the complementary DNA of aptamer (C-apt) was released and triggered the catalytic assembly between hairpin DNA and help DNA that led to generation of many opened hairpin capture DNA, which associated with the Au/Pt-polymethylene blue (PMB) composite to enhance electrochemical signal. The sensing platform showed a low LOD of 2.3 fg/mL using SWV technique and had a good accuracy, selectivity, and sensitivity for detection of the target of interest in real serum samples.

Miao et al. (2018), reported another aptasensor for quantification of PSA in human serum. In this work, DNA tetrahedron molecular layer modified gold electrode provided the recognition element for PSA capture. Then, an exonuclease-aided target recycling amplification was implemented to achieve enhanced electrochemical signals from silver nanoparticles (AgNPs). The designed LSV aptasensor displayed a highly

Table 3
Electrochemical aptasensors for PSA detection.

Detection methods	Strategy/nanomaterial	Aptamer type	Aptamer sequences	Limit of detection (LOD) (pg/mL)	Linear range (LR) (pg/mL)	References
[a]Electrochemical impedance spectroscopy (EIS)	Label-free detection based on immobilization of thiol terminated PSA binding DNA aptamer onto AuNPs/fullerene C60-chitosan-ionic liquid (C60-CS-IL)/multiwalled carbon Nanotubes (MWCNTs)	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	0.5	1 to 200	Jalalvand (2019)
[a]EIS	Titanium oxide nanoparticles (TiO2)/silk fibroin nanofiber (SF)/AuNPs	DNA	TTT TTA ATT AAA GCT CGC CAT CAA ATA GCT TT G	0.0008	0.0025 to 25 and 25 to 25000	Benvidi et al. (2017)
EIS	Two-dimensional nanocomposite of MoS2 QDs and g-C3N4 nanosheets decorated with chitosan-stabilized AuNRs	DNA	TTA TTATTA AAT TAA AGC TCG CCA TCA AAT AGC TTT	0.71	1 to 1000	Duan et al. (2018)
[a]EIS	label-free detection using reduced graphene-oxide (rGO)/MWCNT/AuNP	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	1	5 to 100000	Heydari-Bafrooei and Shamszadeh. (2017)
[a]EIS	Glassy carbon electrode modified with TiO2-rGO hybrid nanosheets	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	1	3 to 1000000	Karimipour et al. (2018)
EIS	Label-free detection using rGO	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	33 pM (937.2 pg/mol)	924 to 924000	Lu et al. (2018b)
[a]EIS	Label-Free detection based on graphene quantum dots (GQD)/AuNRs	DNA	TTTTGCCATCGGGGCCATGTTCAA	140	400 to 11600	Srivastava et al. (2018)
[a]EIS	label-free detection with antifouling chemistry	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	-	-	Jolly et al. (2015b)
EIS	Aptamer- molecularly imprinted polymer (MIP) hybrid receptor sensor based on the amalgamation of biomolecular recognition elements and molecular imprinting	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	1	100 to 100000	(P. Jolly et al., 2016)
EIS combined with Quartz Crystal Microbalance with Dissipation mode (QCM-D)	Functionalization of gold sensor surface via thiol chemistry with different ratios of thiolated-DNA aptamer and 6-mercapto-1-hexanol (MCH)	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	37 nM (1050800 pg/mol)	-	Formisano et al. (2015)
[a]Cyclic voltammetry (CV)	Label-Free detection based on GQD/AuNRs	DNA	TTTTGCCATCGGGGCCATGTTCAA	140	400 to 11600	Srivastava et al. (2018)
[a]Differential pulse voltammetry (DPV)	Label-free detection based on immobilization of thiol terminated PSA binding DNA aptamer onto AuNPs/C60-CS-IL/MWCNTs/SPCE	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	1500	2500 to 90000	Jalalvand (2019)
[a]DPV	label-free detection using rGO/MWCNT/AuNPs	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	1	5 to 20000	Heydari-Bafrooei and Shamszadeh. (2017)
[a]DPV	Label-free detection using gold nanospears	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	50	125 to 200000	Rahi et al. (2016)
[a]DPV	Signal-on detection based on hairbrush-like gold nanostructure	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	50	125 to 128000	Sattarahmady et al. (2017)
[a]DPV	Label-Free detection based on GQD/AuNRs	DNA	TTTTGCCATCGGGGCCATGTTCAA	140	400 to 11600	Srivastava et al. (2018)
[a]DPV	Based on hemin-functionalized graphene-conjugated palladium nanoparticles (H-Gr/PdNPs)	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	8	25 to 205000	(Zhang et al., 2018a)
[a]DPV	AuNPs@GMCs (graphitized mesoporous carbon nanoparticles)	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	250	250 to 200000	Liu et al. (2012)
[a]DPV	Label-free detection based on mesoporous silica thin film (MSF)-coated Au	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	280	1000 to 300000	Argoubi et al. (2018)

(*continued on next page*)

Table 3 (*continued*)

Detection methods	Strategy/nanomaterial	Aptamer type	Aptamer sequences	Limit of detection (LOD) (pg/mL)	Linear range (LR) (pg/mL)	References
[a]DPV	label-free detection based on AuNPs/rGO/thionine (THI) nano composites	DNA	ATT AAA GCT CGC CAT CAA ATA GC	10	50 to 200000	Wei et al. (2018)
[a]Square wave voltammetry (SWV)	Enzyme-free recycling amplification via target-induced catalytic hairpin assembly/Au/Pt-polymethylene blue (PMB) composite	DNA	–	0.0023	0.01 to 100000	Zhao & Ma (2018)
SWV	Label-free and “off-on” detection using an aptamer capture	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	In the ng/mL range	1 ng/mL up to 10 µg/mL	Souada et al. (2015)
SWV	Self-assembly of thiolated aptamers on gold-covered surface using methylene blue (MB) as redox label	DNA	TT TTT AAT TAA AGC TCG CCA TCA AAT AGC TGG GGG	80	0 to 100000	Crulhas et al. (2017)
[a]Linear sweep voltammetry (LSV)	based on exonuclease-aided target recycling amplification/silver nanoparticles (AgNPs)		–	0.11	1 to 160000	Miao et al. (2018)
[a]Photoelectrochemical (PEC)	competitive-displacement reaction strategy based on target-induced dissociation of AuNPs-coated graphene nanosheet (GN) from CdS quantum dots-functionalized mesoporous titanium dioxide (CdS QDs/TiO2)	DNA	–	0.52	1 to 8000	Cai et al. (2018)
[a]PEC	Signal-on sensor using aptamer capped glucose-loading mesoporous silica nanoparticle (MSN) and rGO functionalized iron oxyhydroxide (FeOOH) as the photoactive material	DNA	ATT AAA GCT CGC CAT CAA ATA GC	0.3	1 to 100000	Zhou et al. (2017)
[a]PEC	rGO-BiFeO3/Hybridization chain reaction (HCR)	DNA	ATT AAA GCT CGC CAT CAA ATA GC	0.31	1 to 100000	Zhou et al. (2018)
[a]PEC	Signal-on aptasensor based on p-type Cu-doped Zn0.3Cd0.7S, rolling circle amplification (RCA), and hemin/G-quadruplex,	DNA	ATTAAAGCTCGCCATCAAATAGCTTATTATGTCCGTGCTAGAAGGAAACAGTTAC	16.3	50 to 40000	(Zhang et al., 2018b)
[a]Chronocoulometry	2,4,9-trithiaadmantane/HCR	DNA	–	0.05	0.1 to 100	Ding et al. (2018)
Memristive	Label-Free/Si-nanowires	DNA	TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT	23 aM (0.00065 pg/mL)	33 aM to 330 fM	Tzouvadaki et al. (2016)

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[a] These aptasensors have been successfully tested in real clinical samples.

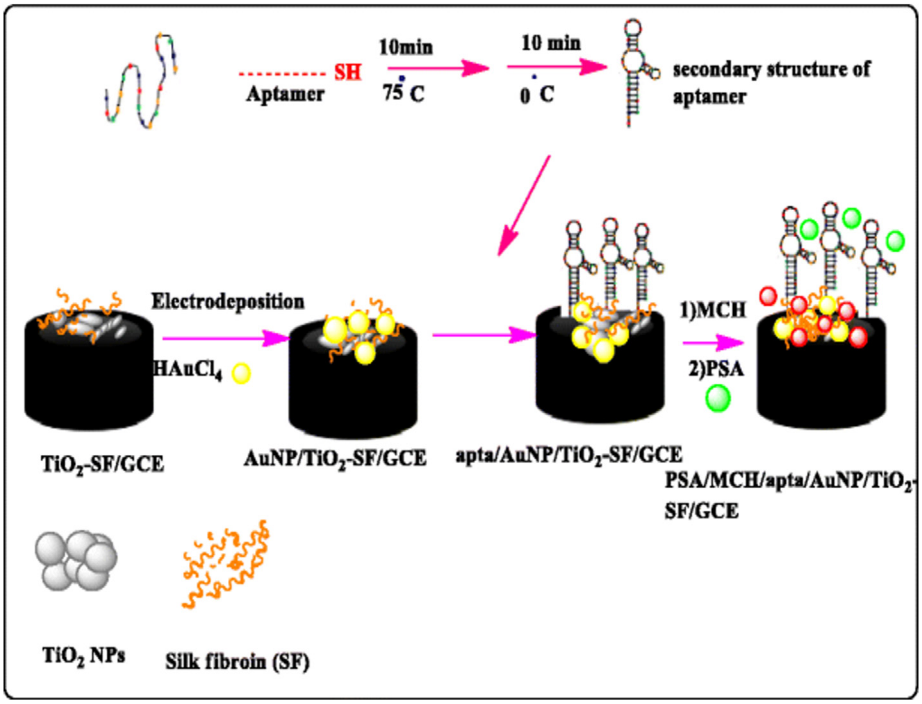

Fig. 4. Schematic illustration of the fabrication of MCH/apta/AuNP/SF-TiO2/GCE aptasensor for PSA detection. Reprinted with permission from (Benvidi et al., 2017).

sensitive detection of PSA down to 0.11 pg/mL. Furthermore, the proposed sensor had an excellent detection capability in biological samples and avoided the use of multiple reagents which reduced the costs.

4.3. PEC electrochemical PSA aptasensors

Photoelectrochemical (PEC) method, which possess the advantages of both fluorescence and electrochemical biosensors, has become a popular detection method because of its simplicity, high sensitivity, cost-effectiveness, and low background signals (D. Dong et al., 2004; N. Hao et al., 2019; C. Li et al., 2015).

A displacement reaction-based PEC aptasensor was developed by Cai et al. (2018) for PSA assay by using exciton-plasmon interaction (EPI) between AuNPs/Graphene Nanohybrids (GN) and CdS QDs functionalized with mesoporous titanium dioxide (TiO2) which prevented the use of natural enzymes. Briefly, to design this sensor,

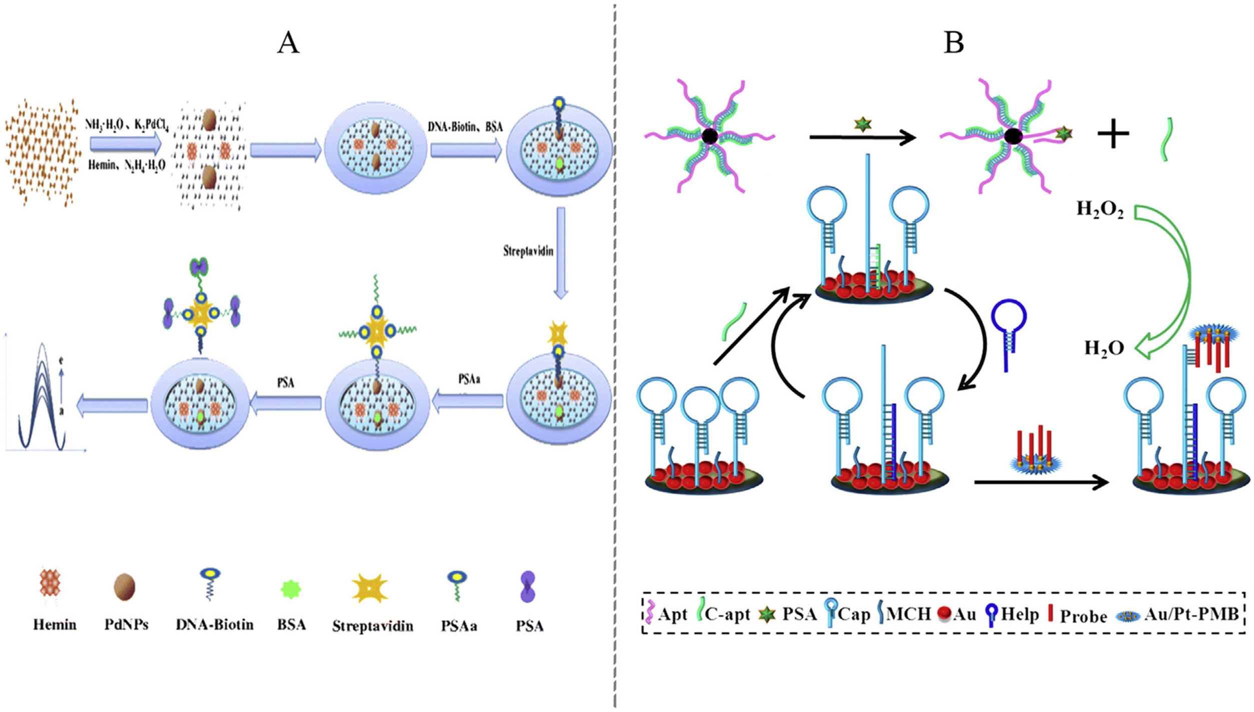

Fig. 5. (A) Schematic illustrations of H-Gr/PdNP nanocomposites based electrochemical PSA aptasensor. (B) The target-induced catalytic hairpin assembly and Au/Pt-PMB composites strategy-based PSA aptasensor. Reprinted with permission from (Zhang et al. 2018a) and (Zhao and Ma, 2018).

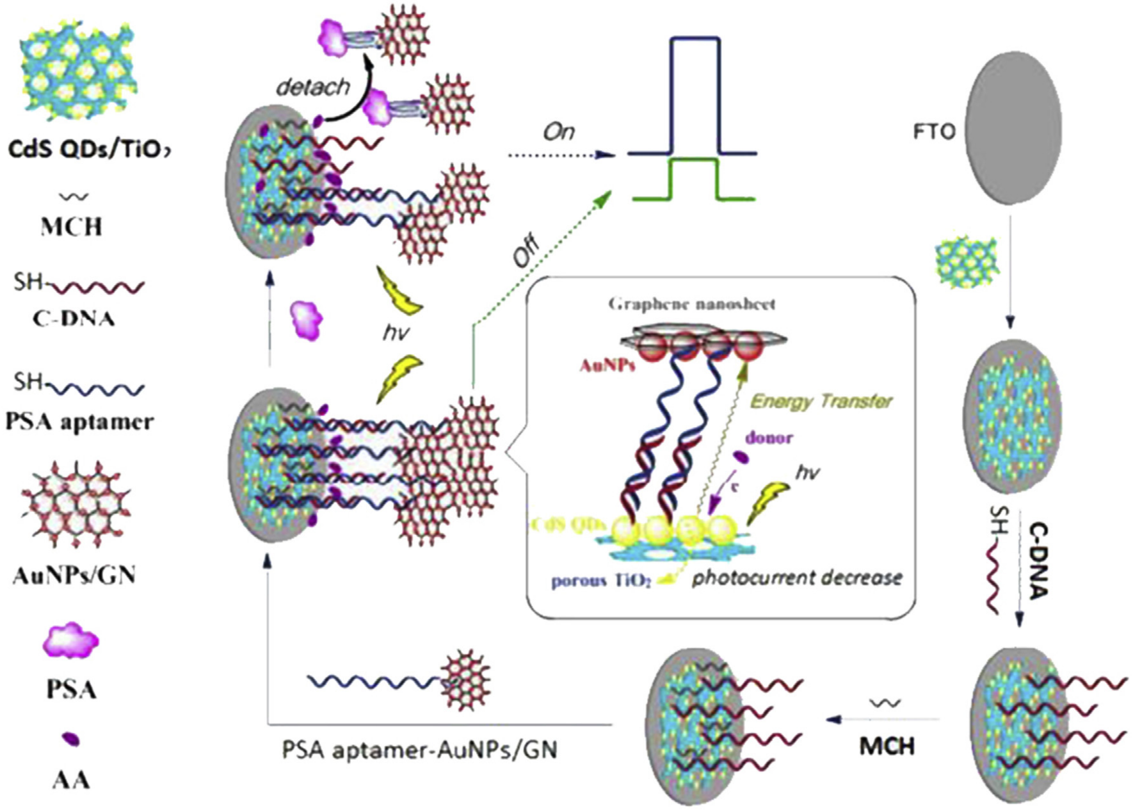

Fig. 6. Schematic illustration of PEC based aptasensor for detection of PSA. Reprinted with permission from (Cai et al., 2018).

AuNPs/GN-aptamer was attached to the CdS QDs/TiO2-conjugated capture DNA by hybridization chain reaction (HCR) strategy (Fig. 6). By adding PSA, AuNPs/GN was dissociated from the electrode that resulted in the improvement of the photocurrent. The competitive-displacement reaction could efficiently increase the sensitivity of the platform and decreased the labeling process of the biomolecules. The assay was shown to have a low LOD of 0.52 pg/mL within a wide linear range of 1 pg/mL to 8 ng/mL. Furthermore, the aptasensor reached accurate results in clinical serum samples.

Zhou et al. (2017) introduced another signal-on PEC aptasensor for PSA assay using rGO functionalized iron oxyhydroxide (FeOOH) as photoactive material and bioresponsive controlled release system. As the recognition probe, they employed glucose-loading MSN blocked by the aptamer. By addition of PSA, the aptamer-analyte combination caused obvious increase in photocurrent. This system provides a LOD of 0.3 pg/mL and was reliable system for PSA determination in complex biological samples because of its beneficial features such as convenient, efficient, low bio-toxicity and low cost. However, the artificial transferring of the glucose released from MSN to the electrolyte was the limitation of this method which may easily solved using magnetic bead or microfluidic device.

4.4. Other electrochemical PSA aptasensors

Another electrochemical PSA aptasensor was constructed by Ding and coworkers using chronocoulometry that had a LOD of 0.05 pg/mL. This work benefited from 2,4,9-trithiaadmantane that was functionalized via DNA probes, and HCR as signal amplification strategy (Ding et al., 2018). Because of the stable surface anchor of 7-hydroxycarbonyl-2,4,9-trithiaadmantane, this platform had high resistance to non-specific adsorption, that make it suitable sensor to apply in real clinical samples.

Tzouvadaki et al. (2016) developed a label-free ultrasensitive electrochemical aptasensor for PSA detection based on memristive properties of silicon nanowires functionalized with DNA aptamer. The proposed aptasensing platform reached a superior LOD of 23 aM which could be easily integrated with POC devices.

4.5. Brief overview of electrochemical PSA aptasensors

In general, among the several electrochemical analysis methods, namely, impedometry, voltammetry, PEC, and others, the EIS and DPV were the most widely used detection methods for PSA assays due to their potential properties like high sensitivity and selectivity and the memristive based aptasensor showed the lowest LOD (23 aM) for PSA detection.

5. Comparison of the performance of PSA aptasensors

In this review, numerous optical and electrochemical aptasensors with various detection methods have been developed for PSA assay that we tried to compare their performance in Tables 2 and 3. Most of them showed good sensitivity, selectivity, accuracy, and repeatability for PSA detection. The advantages and disadvantages of optical and electrochemical biosensing techniques for PSA assay is also compared in Table 4. In addition to the detection method, the structural features of an aptamer such as type (DNA or RNA), length, its functionalization and its affinity to the target of interest play a key role in an aptasensor development (Reich et al., 2017). As shown in Tables 2 and 3, DNA aptamers have been used for development of all the PSA biosensing platforms because of their several beneficial properties such as more stability, lower costs, easy modification and functionalization, and simple selection process (M. Li et al., 2018; J. Liu et al., 2009; Q. Zhu et al., 2015). However, RNA aptamers are not suitable for designing reusable aptasensors because they easily degrade by ribonucleases (Radi, 2011). According to the literature, the aptamer with 5′-TTTTTAATTAAAGCTCGCCATCAAATAGCTTT-3′ sequence is the most frequent anti-PSA aptamer used for designing the aptasensors. The length

Table 4
Comparison of the advantages and disadvantages of optical and electrochemical methods for PSA detection.

Principle	Advantages	Disadvantages	References
Optical aptasensors	- Real-time - Quantitative - Direct and label-free detection - No warm up time required	- Have not been used in clinic - Commonly expensive - Time-consuming fabrication - Low portability - Fluorescent- and SPR-base methods have limitation for multiple analyte detection which is highly rewarded in clinical diagnosis	(Dehghani et al., 2018; Jamali et al., 2014; Vigneshvar et al., 2016)
Electrochemical aptasensors	- Cost-effective and highly sensitive - Simple and rapid - Quantitative - Reusable and robust - Disposable - Easy to miniaturize - Independent of sample turbidity in view of high-throughput - Low sample volume is needed - Very suitable for point-of-care diagnostic tools - Comparability with novel microfabrication technologies - Fast response	- Have not been used in clinic - At higher currents, control on the surface of working electrode is limited - False positive results originated from electrolytes - Limited control on the working electrode, when higher currents are being induced	(Bostan et al., 2018; Dehghani et al., 2018; Hayat and Marty, 2014; Jamali et al., 2014)

of an aptamer also can affect their immobilization ability on surface, and accordingly long aptamers can be detached easily from the support surface than shorter ones (Steel et al., 2000). The comparison between results of different PSA aptasensors also shows that their functionalization with various nanomaterials have led to advances in amplified biosensing. Some other factors such as type of sample (buffer/serum), platform compositions, and other signal amplification strategies can affect the aptasensors performance. As a result, it is possible to enhance the applicability of the PSA aptasensors by individually optimizing these factors.

6. Comparison of PSA commercial detection kits with the established aptasensors

At the present time, antibody based colorimetric assay techniques like ELISA are the most common commercial kits for PSA detection (Table 5). Compared with aptamer-based biosensors, antibody-based detection methods require a larger sample size, sophisticated instruments, and protocols, costly antibodies, and long-term incubation periods (Xu et al., 2017; X. Zhu et al., 2017). Moreover, variable affinity of antibodies towards their targets and, therefore, limited LOD and sensitivity are other limitations of the available kits. To the best of our knowledge, RayBiotech is one of the most sensitive ELISA kits for human PSA assay with a LOD of 0.16 pg/mL, however, the developed aptasensors could detect PSA even in the range of 0.032 attomolar (approximately 9×10^{-7} pg/mL). The determination of trace levels of PSA is critical for early diagnosis and prognosis of prostate cancer and also in predicting the outcome of a particular therapy. As a result, the developed aptasensors or nano-aptasensors with different detection methods could be more sensitive than the commercial detection kits for PSA assays and unlike the antibody based colorimetric assay techniques, they could be novel promising approaches for point-of-care testing in clinical diagnostics that is currently at the nascent phase.

7. Conclusion and future perspectives

Over the last few years, there have been great advances in development of various aptasensors with different signal transductions for highly sensitive and selective detection of PSA as the main biomarker in early diagnosis of prostate cancer. Unique characteristics of aptamers in comparison with antibodies including high sensitivity and stability, cost-effectiveness and ease of synthesis have made them appropriate and useful choices for establishment of a wide variety of PSA aptasensors. In spite of the successful application of PSA aptamers in numerous sensing platforms and their applicability in real clinical samples, they still haven't found their proper place in clinical laboratories as commercial diagnostic tools. Additionally, a great effort is still necessary for development of convenient PSA aptasensors for point-of-care diagnostics. It has been demonstrated that the use of NMs in the structure of aptasensors have largely improved their sensitivity and specificity for PSA detection. In this regard, nano-aptasensors have achieved limit of detection in the femtomolar or even attomolar range,

Table 5
Comparison of analytical performance of various PSA commercial detection kits.

Commercial PSA kits	Assay sensitivity (pg/ml)	Assay range (pg/ml)	Sample types	Detection methods	Assay time
Invitrogen	8	10.24 to 2500	Supernatant, Plasma, Serum	Colorimetric	4 h 45 min
LifeSpan BioSciences	8	10.24 to 2500	Cell Culture Supernatants, Plasma, Serum	Colorimetric	_
RayBiotech	8	8 to 2000	Cell Culture Supernatants, Plasma, Serum	Colorimetric	_
Fitzgerald	< 1.47	_	_	_	_
RayBiotech	0.16	0.16 to 2500	Cell Culture, Supernatants, Plasma, Serum	qPCR	_
R&D Systems	69	900 to 60000	Cell Culture Supernatants, Serum, EDTA Plasma, Heparin Plasma	_	4.5 h
Bioassay Technology Laboratory	30	50 to10000	serum, plasma, cell culture supernatants, cell lysates, tissue homogenates	_	_
ALPCO	1000	2000 to 120000	Serum	_	2 h 20 min
BosterBio	500	1000 to 32000	Serum	Colorimetric	
Elabscince®	190	310 to 20000	Serum, plasma and other biological fluids	Colorimetric	4.5 h

which is offering novel promises for early stage diagnosis of prostate cancer or other prostate diseases in vitro and in vivo. Nonetheless, the safety of NMs for human body remains a major concern that must be noticed for in vivo detection of PSA. Furthermore, more research efforts are needed to accelerate the implementation of these sensing platforms for detection of PSA in vivo, as many of the reported aptasensors have been designed for in vitro quantification of their targets. In addition, other protein biomarkers are also present in prostate cancer, therefore, development of aptasensors for multiple detecting of biomarkers is required for proper diagnosis. However, the main challenge is the interference of the developed aptasensors with other biomarkers existing inside the tumor cells. To sum up, given the recent growth in the field of aptamer-based platforms, extensive progresses are likely to be occurred in the future in parallel with lab-on-a chip devices and miniaturized platforms like microfluidics aptasensors with potential clinical diagnostic applications.

Conflict of interest

Authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Farzaneh Ghorbani: Conceptualization, Writing - original draft. **Hossein Abbaszadeh:** Project administration, Writing - original draft. **Jafar Ezzati Nazhad Dolatabadi:** Supervision. **Leili Aghebati-Maleki:** Writing - review & editing. **Mehdi Yousefi:** Writing - review & editing.

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References

Abolhasan, R., Mehdizadeh, A., Rashidi, M.R., Aghebati-Maleki, L., Yousefi, M., 2019. Application of hairpin DNA-based biosensors with various signal amplification strategies in clinical diagnosis. Biosens. Bioelectron. 129, 164–174. https://doi.org/10.1016/j.bios.2019.01.008.

Acevedo, B., Perera, Y., Ruiz, M., Rojas, G., Benitez, J., Ayala, M., Gavilondo, J., 2002. Development and validation of a quantitative ELISA for the measurement of PSA concentration. Clin. Chim. Acta 317 (1–2), 55–63.

Afkham, A., Aghebati-Maleki, L., Siahmansouri, H., Sadreddini, S., Ahmadi, M., Dolati, S., et al., 2018. Chitosan (CMD)-mediated co-delivery of SN38 and Snail-specific siRNA as a useful anticancer approach against prostate cancer. Pharmacol. Rep. 70 (3), 418–425. https://doi.org/10.1016/j.pharep.2017.11.005.

Albrecht, S., Brandl, H., Steinke, M., Freidt, T., 1994. Chemiluminescent enzyme immunoassay of prostate-specific antigen based on indoxyl phosphate substrate. Clin. Chem. 40 (10), 1970–1971.

Alexiev, U., Volz, P., Boreham, A., Brodwolf, R., 2017. Time-resolved fluorescence microscopy (FLIM) as an analytical tool in skin nanomedicine. Eur. J. Pharm. Biopharm. 116, 111–124. https://doi.org/10.1016/j.ejpb.2017.01.005.

Ankerst, D.P., Gelfond, J., Goros, M., Herrera, J., Strobl, A., Thompson Jr., I.M., et al., 2016. Serial percent free prostate specific antigen in combination with prostate specific antigen for population based early detection of prostate cancer. J. Urol. 196 (2), 355–360. https://doi.org/10.1016/j.juro.2016.03.011.

Argoubi, W., Sánchez, A., Parrado, C., Raouafi, N., Villalonga, R., 2018. Label-free electrochemical aptasensing platform based on mesoporous silica thin film for the detection of prostate specific antigen. Sensor. Actuator. B Chem. 255, 309–315. https://doi.org/10.1016/j.snb.2017.08.045.

Benvidi, A., Banaei, M., Tezerjani, M.D., Molahosseini, H., Jahanbani, S., 2017. Impedimetric PSA aptasensor based on the use of a glassy carbon electrode modified with titanium oxide nanoparticles and silk fibroin nanofibers. Mikrochim. Acta 185 (1), 50. https://doi.org/10.1007/s00604-017-2589-1.

Bostan, H.B., Taghdisi, S.M., Bowen, J.L., Demertzis, N., Rezaee, R., Panahi, Y., et al., 2018. Determination of microcystin-LR, employing aptasensors. Biosens. Bioelectron. 119, 110–118. https://doi.org/10.1016/j.bios.2018.08.003.

Cai, G., Yu, Z., Ren, R., Tang, D., 2018. Exciton-plasmon interaction between AuNPs/graphene nanohybrids and CdS quantum dots/TiO2 for photoelectrochemical aptasensing of prostate-specific antigen. ACS Sens. 3 (3), 632–639. https://doi.org/10.1021/acssensors.7b00899.

Cao, J.T., Yang, J.J., Zhao, L.Z., Wang, Y.L., Wang, H., Liu, Y.M., Ma, S.H., 2018. Graphene oxide@gold nanorods-based multiple-assisted electrochemiluminescence signal amplification strategy for sensitive detection of prostate specific antigen. Biosens. Bioelectron. 99, 92–98. https://doi.org/10.1016/j.bios.2017.07.050.

Catuogno, S., Esposito, C.L., 2017. Aptamer cell-based selection: overview and advances. Biomedicines 5 (3), 49. https://doi.org/10.3390/biomedicines5030049.

Cha, T., Cho, S., Kim, Y.T., Lee, J.H., 2014. Rapid aptasensor capable of simply diagnosing prostate cancer. Biosens. Bioelectron. 62, 31–37. https://doi.org/10.1016/j.bios.2014.06.015.

Chang, C.-C., Chen, C.-Y., Chuang, T.-L., Wu, T.-H., Wei, S.-C., Liao, H., Lin, C.-W., 2016. Aptamer-based colorimetric detection of proteins using a branched DNA cascade amplification strategy and unmodified gold nanoparticles. Biosens. Bioelectron. 78, 200–205. https://doi.org/10.1016/j.bios.2015.11.051.

Chang, Y., Wang, M., Wang, L., Xia, N., 2018. Recent progress in electrochemical biosensors for detection of prostate-specific antigen. Int. J. Electrochem. Sci. 13 (5), 4071–4084. https://doi.org/10.20964/2018.05.24.

Chen, Z., Lei, Y., Chen, X., Wang, Z., Liu, J., 2012. An aptamer based resonance light scattering assay of prostate specific antigen. Biosens. Bioelectron. 36 (1), 35–40. https://doi.org/10.1016/j.bios.2012.03.041.

Choi, H.K., Lee, J.H., 2013. Role of magnetic Fe3O4 graphene oxide in chemiluminescent aptasensors capable of sensing tumor markers in human serum. Anal. Methods 5 (24), 6964–6968. https://doi.org/10.1039/C3AY41683F.

Chong, J., Chong, H., Lee, J.H., 2019. A chemiluminescent dual-aptasensor capable of simultaneously quantifying prostate specific antigen and vascular endothelial growth factor. Anal. Biochem. 564–565, 102–107. https://doi.org/10.1016/j.ab.2018.10.024.

Crulhas, B.P., Karpik, A.E., Delella, F.K., Castro, G.R., Pedrosa, V.A., 2017. Electrochemical aptamer-based biosensor developed to monitor PSA and VEGF released by prostate cancer cells. Anal. Bioanal. Chem. 409 (29), 6771–6780. https://doi.org/10.1007/s00216-017-0630-1.

Damborsky, P., Svitel, J., Katrlik, J., 2016. Optical biosensors. Essays Biochem. 60 (1), 91–100. https://doi.org/10.1042/ebc20150010.

Dehghani, S., Nosrati, R., Yousefi, M., Nezami, A., Soltani, F., Taghdisi, S.M., et al., 2018. Aptamer-based biosensors and nanosensors for the detection of vascular endothelial growth factor (VEGF): a review. Biosens. Bioelectron. 110, 23–37. https://doi.org/10.1016/j.bios.2018.03.037.

Díaz-Fernández, A., Miranda-Castro, R., de-los-Santos-Álvarez, N., Rodríguez, E.F., Lobo-Castañón, M.J., 2019. Focusing aptamer selection on the glycan structure of prostate-specific antigen: toward more specific detection of prostate cancer. Biosens. Bioelectron. 128, 83–90. https://doi.org/10.1016/j.bios.2018.12.040.

Ding, S., Gu, Z., Yan, R., Tang, Y., Miao, P., 2018. A novel mode of DNA assembly at electrode and its application to protein quantification. Anal. Chim. Acta 1029, 24–29. https://doi.org/10.1016/j.aca.2018.04.073.

Dong, D., Zheng, D., Wang, F.Q., Yang, X.Q., Wang, N., Li, Y.G., et al., 2004. Quantitative photoelectrochemical detection of biological affinity reaction: biotin-avidin interaction. Anal. Chem. 76 (2), 499–501. https://doi.org/10.1021/ac035184p.

Dong, J., Lian, J., Jin, Y., Li, B., 2017. Guanine-based chemiluminescence resonance energy transfer biosensing platform for the specific assay of uracil-DNA glycosylase activity. Anal. Methods 9 (2), 276–281. https://doi.org/10.1039/C6AY02964G.

Duan, F., Zhang, S., Yang, L., Zhang, Z., He, L., Wang, M., 2018. Bifunctional aptasensor based on novel two-dimensional nanocomposite of MoS2 quantum dots and g-C3N4 nanosheets decorated with chitosan-stabilized Au nanoparticles for selectively detecting prostate specific antigen. Anal. Chim. Acta 1036, 121–132. https://doi.org/10.1016/j.aca.2018.06.070.

Emrani, A.S., Danesh, N.M., Ramezani, M., Taghdisi, S.M., Abnous, K., 2016. A novel fluorescent aptasensor based on hairpin structure of complementary strand of aptamer and nanoparticles as a signal amplification approach for ultrasensitive detection of cocaine. Biosens. Bioelectron. 79, 288–293. https://doi.org/10.1016/j.bios.2015.12.025.

Formisano, N., Jolly, P., Bhalla, N., Cromhout, M., Flanagan, S.P., Fogel, R., et al., 2015. Optimisation of an electrochemical impedance spectroscopy aptasensor by exploiting quartz crystal microbalance with dissipation signals. Sensor. Actuator. B Chem. 220, 369–375. https://doi.org/10.1016/j.snb.2015.05.049.

Gamé, X., Vincendeau, S., Palascak, R., Milcent, S., Fournier, R., Houlgatte, A., 2003. Total and free serum prostate specific antigen levels during the first month of acute prostatitis. Eur. Urol. 43 (6), 702–705. https://doi.org/10.1016/S0302-2838(03)00158-1.

Gewanter, R.M., Katz, A.E., Olsson, C.A., Benson, M.C., Singh, A., Schiff, P.B., Ennis, R.D., 2003. RT-PCR for PSA as a prognostic factor for patients with clinically localized prostate cancer treated with radiotherapy. Urology 61 (5), 967–971.

Golichenari, B., Nosrati, R., Farokhi-Fard, A., Abnous, K., Vaziri, F., Behravan, J., 2018. Nano-biosensing approaches on tuberculosis: defy of aptamers. Biosens. Bioelectron. 117, 319–331. https://doi.org/10.1016/j.bios.2018.06.025.

Graves, H.C., Wehner, N., Stamey, T.A., 1992. Ultrasensitive radioimmunoassay of prostate-specific antigen. Clin. Chem. 38 (5), 735–742.

Han, S., Zhang, Z., Li, S., Qi, L., Xu, G., 2016. Chemiluminescence and electrochemiluminescence applications of metal nanoclusters. Sci. China Chem. 59 (7), 794–801. https://doi.org/10.1007/s11426-016-0043-3.

Hao, N., Lu, J., Chi, M., Xiong, M., Zhang, Y., Hua, R., Wang, K., 2019. A universal photoelectrochemical biosensor for dual microRNA detection based on two CdTe nanocomposites. J. Mater. Chem. B 7 (7), 1133–1141. https://doi.org/10.1039/C8TB03195A.

Hao, T., Wu, X., Xu, L., Liu, L., Ma, W., Kuang, H., Xu, C., 2017. Ultrasensitive detection of prostate-specific antigen and thrombin based on gold-upconversion nanoparticle assembled pyramids. Small 13 (19). https://doi.org/10.1002/smll.201603944.

Hayat, A., Marty, J.L., 2014. Aptamer based electrochemical sensors for emerging environmental pollutants. 2 (41). https://doi.org/10.3389/fchem.2014.00041.

Heidenreich, A., Bastian, P.J., Bellmunt, J., Bolla, M., Joniau, S., van der Kwast, T., et al., 2014. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur. Urol. 65 (1), 124–137. https://doi.

org/10.1016/j.eururo.2013.09.046.

Heydari-Bafrooei, E., Shamszadeh, N.S., 2017. Electrochemical bioassay development for ultrasensitive aptasensing of prostate specific antigen. Biosens. Bioelectron. 91, 284–292. https://doi.org/10.1016/j.bios.2016.12.048.

Hotzer, B., Medintz, I.L., Hildebrandt, N., 2012. Fluorescence in nanobiotechnology: sophisticated fluorophores for novel applications. Small 8 (15), 2297–2326. https://doi.org/10.1002/smll.201200109.

Huang, X., He, Z., Guo, D., Liu, Y., Song, J., Yung, B.C., et al., 2018. Three-in-one" nanohybrids as synergistic nanoquenchers to enhance No-wash fluorescence biosensors for ratiometric detection of cancer biomarkers. Theranostics 8 (13), 3461–3473. https://doi.org/10.7150/thno.25179.

Huang, Y.-W., Wu, C.-S., Chuang, C.-K., Pang, S.-T., Pan, T.-M., Yang, Y.-S., Ko, F.-H., 2013. Real-time and label-free detection of the prostate-specific antigen in human serum by a polycrystalline silicon nanowire field-effect transistor biosensor. Anal. Chem. 85 (16), 7912–7918. https://doi.org/10.1021/ac401610s.

Jalalvand, A.R., 2019. Fabrication of a novel and ultrasensitive label-free electrochemical aptasensor for detection of biomarker prostate specific antigen. Int. J. Biol. Macromol. 126, 1065–1073. https://doi.org/10.1016/j.ijbiomac.2019.01.012.

Jamali, A.A., Pourhassan-Moghaddam, M., Dolatabadi, J.E.N., Omidi, Y., 2014. Nanomaterials on the road to microRNA detection with optical and electrochemical nanobiosensors. Trac. Trends Anal. Chem. 55, 24–42. https://doi.org/10.1016/j.trac.2013.10.008.

Jayanthi, V.S., Sankara A, P.K., Das, A.B., Saxena, U., 2017. Recent advances in biosensor development for the detection of cancer biomarkers. Biosens. Bioelectron. 91, 15–23. https://doi.org/10.1016/j.bios.2016.12.014.

Jeong, S., Han, S.R., Lee, Y.J., Lee, S.W., 2010. Selection of RNA aptamers specific to active prostate-specific antigen. Biotechnol. Lett. 32 (3), 379–385. https://doi.org/10.1007/s10529-009-0168-1.

Jolly, P., Formisano, N., Estrela, P., 2015a. DNA aptamer-based detection of prostate cancer. Chem. Pap. 69 (1), 77–89. https://doi.org/10.1515/chempap-2015-0025.

Jolly, P., Formisano, N., Tkáč, J., Kasák, P., Frost, C.G., Estrela, P., 2015b. Label-free impedimetric aptasensor with antifouling surface chemistry: a prostate specific antigen case study. Sensor. Actuator. B Chem. 209, 306–312. https://doi.org/10.1016/j.snb.2014.11.083.

Jolly, P., Tamboli, V., Harniman, R.L., Estrela, P., Allender, C.J., Bowen, J.L., 2016. Aptamer-MIP hybrid receptor for highly sensitive electrochemical detection of prostate specific antigen. Biosens. Bioelectron. 75, 188–195. https://doi.org/10.1016/j.bios.2015.08.043.

Karimipour, M., Heydari-Bafrooei, E., Sanjari, M., Johansson, M.B., Molaei, M., 2018. A glassy carbon electrode modified with TiO2(200)-rGO hybrid nanosheets for aptamer based impedimetric determination of the prostate specific antigen. Mikrochim. Acta 186 (1), 33. https://doi.org/10.1007/s00604-018-3141-7.

Kavosi, B., Salimi, A., Hallaj, R., Moradi, F., 2015. Ultrasensitive electrochemical immunosensor for PSA biomarker detection in prostate cancer cells using gold nanoparticles/PAMAM dendrimer loaded with enzyme linked aptamer as integrated triple signal amplification strategy. Biosens. Bioelectron. 74, 915–923. https://doi.org/10.1016/j.bios.2015.07.064.

Kim, G.I., Kim, K.W., Oh, M.K., Sung, Y.M., 2009. The detection of platelet derived growth factor using decoupling of quencher-oligonucleotide from aptamer/quantum dot bioconjugates. Nanotechnology 20 (17), 175503. https://doi.org/10.1088/0957-4484/20/17/175503.

Kong, R.M., Ding, L., Wang, Z., You, J., Qu, F., 2015. A novel aptamer-functionalized MoS2 nanosheet fluorescent biosensor for sensitive detection of prostate specific antigen. Anal. Bioanal. Chem. 407 (2), 369–377. https://doi.org/10.1007/s00216-014-8267-9.

Kong, R.M., Zhang, X., Ding, L., Yang, D., Qu, F., 2017. Label-free fluorescence turn-on aptasensor for prostate-specific antigen sensing based on aggregation-induced emission-silica nanospheres. Anal. Bioanal. Chem. 409 (24), 5757–5765. https://doi.org/10.1007/s00216-017-0519-z.

Kulmala, S., Suomi, J., 2003. Current status of modern analytical luminescence methods. Anal. Chim. Acta 500 (1), 21–69. https://doi.org/10.1016/j.aca.2003.09.004.

Lei, J., Ju, H., 2012. Signal amplification using functional nanomaterials for biosensing. Chem. Soc. Rev. 41 (6), 2122–2134. https://doi.org/10.1039/C1CS15274B.

Li, C., Wang, H., Shen, J., Tang, B., 2015. Cyclometalated iridium complex-based label-free photoelectrochemical biosensor for DNA detection by hybridization chain reaction amplification. Anal. Chem. 87 (8), 4283–4291. https://doi.org/10.1021/ac5047032.

Li, M., Guo, X., Li, H., Zuo, X., Hao, R., Song, H., et al., 2018. Epitope binning assay using an electron transfer-modulated aptamer sensor. ACS Appl. Mater. Interfaces 10 (1), 341–349. https://doi.org/10.1021/acsami.7b17324.

Liu, B., Lu, L.S., Hua, E., Jiang, S.T., Xie, G.M., 2012. Detection of the human prostate-specific antigen using an aptasensor with gold nanoparticles encapsulated by graphitized mesoporous carbon. Microchim. Acta 178 (1–2), 163–170. https://doi.org/10.1007/s00604-011-0709-x.

Liu, G., Feng, D.-Q., Li, Z., Feng, Y., 2019. Target-activatable gold nanoparticle-based aptasensing for protein biomarkers using stimuli-responsive aggregation. Talanta 192, 112–117. https://doi.org/10.1016/j.talanta.2018.08.034.

Liu, J., Cao, Z., Lu, Y., 2009. Functional nucleic acid sensors. Chem. Rev. 109 (5), 1948–1998. https://doi.org/10.1021/cr030183i.

Liu, S., Tian, J., Wang, L., Luo, Y., Lu, W., Sun, X., 2011. Self-assembled graphene platelet-glucose oxidase nanostructures for glucose biosensing. Biosens. Bioelectron. 26 (11), 4491–4496. https://doi.org/10.1016/j.bios.2011.05.008.

Lu Chikezie, O., Madu, Y., 2010. Novel Diagnostic Biomarkers for Prostate Cancer, vol. 1.

Lu, H.J., Zhao, W., Xu, J.J., Chen, H.Y., 2018a. Visual electrochemiluminescence ratiometry on bipolar electrode for bioanalysis. Biosens. Bioelectron. 102, 624–630. https://doi.org/10.1016/j.bios.2017.12.008.

Lu, X., Miodek, A., Munief, W.M., Jolly, P., Pachauri, V., Chen, X., et al., 2018b. Reduced graphene-oxide transducers for biosensing applications beyond the Debye-screening limit. Biosens. Bioelectron. https://doi.org/10.1016/j.bios.2018.09.045.

Lv, S., Li, Y., Zhang, K., Lin, Z., Tang, D., 2017. Carbon dots/g-C3N4 nanoheterostructures-based signal-generation tags for photoelectrochemical immunoassay of cancer biomarkers coupling with copper nanoclusters. ACS Appl. Mater. Interfaces 9 (44), 38336–38343. https://doi.org/10.1021/acsami.7b13272.

Meirinho, S.G., Dias, L.G., Peres, A.M., Rodrigues, L.R., 2016. Voltammetric aptasensors for protein disease biomarkers detection: a review. Biotechnol. Adv. 34 (5), 941–953. https://doi.org/10.1016/j.biotechadv.2016.05.006.

Miao, P., Jiang, Y., Wang, Y., Yin, J., Tang, Y., 2018. An electrochemical approach capable of prostate specific antigen assay in human serum based on exonuclease-aided target recycling amplification. Sensor. Actuator. B Chem. 257, 1021–1026. https://doi.org/10.1016/j.snb.2017.11.064.

Miyazaki, C.M., Shimizu, F.M., Ferreira, M., 2017. 6 - surface plasmon resonance (SPR) for sensors and biosensors. In: Da Róz, A.L., Ferreira, M., de Lima Leite, F., Oliveira, O.N. (Eds.), Nanocharacterization Techniques. William Andrew Publishing, pp. 183–200.

Mokhtarzadeh, A., Ezzati Nazhad Dolatabadi, J., Abnous, K., de la Guardia, M., Ramezani, M., 2015. Nanomaterial-based cocaine aptasensors. Biosens. Bioelectron. 68, 95–106. https://doi.org/10.1016/j.bios.2014.12.052.

Murthy, K.V.R., Virk, H.S., 2014. Luminescence phenomena: an introduction. Defect Diffusion Forum 347, 1–34. https://doi.org/10.4028/www.scientific.net/DDF.347.1.

Mustafa Oguzhan, C., 2017. Electrochemical aptasensors for early cancer diagnosis: a review. Curr. Anal. Chem. 13 (1), 18–30. https://doi.org/10.2174/1573411012666160601142051.

Nagpal, M., Singh, S., Singh, P., Chauhan, P., Zaidi, M.A., 2016. Tumor markers: a diagnostic tool. Natl. J. Maxillofac. Surg. 7 (1), 17–20. https://doi.org/10.4103/0975-5950.196135.

Nguyen, H.H., Park, J., Kang, S., Kim, M., 2015. Surface plasmon resonance: a versatile technique for biosensor applications. Sensors 15 (5). https://doi.org/10.3390/s150510481.

Okuno, J., Maehashi, K., Kerman, K., Takamura, Y., Matsumoto, K., Tamiya, E., 2007. Label-free immunosensor for prostate-specific antigen based on single-walled carbon nanotube array-modified microelectrodes. Biosens. Bioelectron. 22 (9), 2377–2381. https://doi.org/10.1016/j.bios.2006.09.038.

Parab, H.J., Jung, C., Lee, J.H., Park, H.G., 2010. A gold nanorod-based optical DNA biosensor for the diagnosis of pathogens. Biosens. Bioelectron. 26 (2), 667–673. https://doi.org/10.1016/j.bios.2010.06.067.

Park, J.-W., Lee, S.J., Ren, S., Lee, S., Kim, S., Laurell, T., 2016. Acousto-microfluidics for screening of ssDNA aptamer. Sci. Rep. 6, 27121. https://doi.org/10.1038/srep27121.

Perumal, V., Hashim, U., 2014. Advances in biosensors: principle, architecture and applications. J. Appl. Biomed 12 (1), 1–15. https://doi.org/10.1016/j.jab.2013.02.001.

Qu, F., Ding, Y., Lv, X., Xia, L., You, J., Han, W., 2019. Emissions of terbium metal-organic frameworks modulated by dispersive/agglomerated gold nanoparticles for the construction of prostate-specific antigen biosensor. Anal. Bioanal. Chem. https://doi.org/10.1007/s00216-019-01883-2.

Radi, A.-E., 2011. Electrochemical aptamer-based biosensors: recent advances and perspectives %J. Int. J. Electrochem. 17https://doi.org/10.4061/2011/863196. 2011.

Rahi, A., Sattarahmady, N., Heli, H., 2016. Label-free electrochemical aptasensing of the human prostate-specific antigen using gold nanospears. Talanta 156–157, 218–224. https://doi.org/10.1016/j.talanta.2016.05.029.

Reich, P., Stoltenburg, R., Strehlitz, B., Frense, D., Beckmann, D., 2017. Development of an impedimetric aptasensor for the detection of Staphylococcus aureus. Int. J. Mol. Sci. 18 (11), 2484. https://doi.org/10.3390/ijms18112484.

Roda, A., Mirasoli, M., Michelini, E., Di Fusco, M., Zangheri, M., Cevenini, L., et al., 2016. Progress in chemical luminescence-based biosensors: a critical review. Biosens. Bioelectron. 76, 164–179. https://doi.org/10.1016/j.bios.2015.06.017.

Sadeghi, A.S., Ansari, N., Ramezani, M., Abnous, K., Mohsenzadeh, M., Taghdisi, S.M., Alibolandi, M., 2018. Optical and electrochemical aptasensors for the detection of amphenicols. Biosens. Bioelectron. 118, 137–152. https://doi.org/10.1016/j.bios.2018.07.045.

Sarkar, P., Pal, P.S., Ghosh, D., Setford, S.J., Tothill, I.E., 2002. Amperometric biosensors for detection of the prostate cancer marker (PSA). Int. J. Pharm. 238 (1–2), 1–9.

Sattarahmady, N., Rahi, A., Heli, H., 2017. A signal-on built in-marker electrochemical aptasensor for human prostate-specific antigen based on a hairbrush-like gold nanostructure. Sci. Rep. 7 (1), 11238. https://doi.org/10.1038/s41598-017-11680-5.

Savory, N., Abe, K., Sode, K., Ikebukuro, K., 2010. Selection of DNA Aptamer against Prostate Specific Antigen Using a Genetic Algorithm and Application to Sensing, vol. 26.

Shao, K., Wang, B., Nie, A., Ye, S., Ma, J., Li, Z., et al., 2018. Target-triggered signal-on ratiometric electrochemiluminescence sensing of PSA based on MOF/Au/G-quadruplex. Biosens. Bioelectron. 118, 160–166. https://doi.org/10.1016/j.bios.2018.07.029.

Shi, C., Shan, Y., Xu, J., Chen, H., 2010. Enhanced solid-state electrogenerated chemiluminescence of Au/CdS nanocomposite and its sensing to H2O2. Electrochim. Acta 55 (27), 8268–8272. https://doi.org/10.1016/j.electacta.2010.03.029.

Song, S., Wang, L., Li, J., Fan, C., Zhao, J., 2008. Aptamer-based biosensors. Trac. Trends Anal. Chem. 27 (2), 108–117. https://doi.org/10.1016/j.trac.2007.12.004.

Souada, M., Piro, B., Reisberg, S., Anquetin, G., Noel, V., Pham, M.C., 2015. Label-free electrochemical detection of prostate-specific antigen based on nucleic acid aptamer. Biosens. Bioelectron. 68, 49–54. https://doi.org/10.1016/j.bios.2014.12.033.

Srivastava, M., Nirala, N.R., Srivastava, S.K., Prakash, R., 2018. A comparative study of aptasensor vs immunosensor for label-free PSA cancer detection on GQDs-AuNRs modified screen-printed electrodes. Sci. Rep. 8 (1), 1923. https://doi.org/10.1038/s41598-018-19733-z.

Steel, A.B., Levicky, R.L., Herne, T.M., Tarlov, M.J., 2000. Immobilization of nucleic acids at solid surfaces: effect of oligonucleotide length on layer assembly. Biophys. J. 79 (2), 975–981. https://doi.org/10.1016/S0006-3495(00)76351-X.

Sun, Y., Fan, J., Cui, L., Ke, W., Zheng, F., Zhao, Y., 2019. Fluorometric nanoprobes for simultaneous aptamer-based detection of carcinoembryonic antigen and prostate specific antigen. Mikrochim. Acta 186 (3), 152. https://doi.org/10.1007/s00604-019-3281-4.

Svobodova, M., Bunka, D.H.J., Nadal, P., Stockley, P.G., O'Sullivan, C.K., O'Sullivan, C.K., 2013. Selection of 2'F-modified RNA aptamers against prostate-specific antigen and their evaluation for diagnostic and therapeutic applications. Anal. Bioanal. Chem. 405 (28), 9149–9157. https://doi.org/10.1007/s00216-013-7350-y.

Taylor, A.D., Ladd, J., Homola, J., Jiang, S., 2008. Surface plasmon resonance (SPR) sensors for the detection of bacterial pathogens. In: Zourob, M., Elwary, S., Turner, A. (Eds.), Principles of Bacterial Detection: Biosensors, Recognition Receptors and Microsystems. Springer New York, New York, NY, pp. 83–108.

Turner, A.P., 2013. Biosensors: sense and sensibility. Chem. Soc. Rev. 42 (8), 3184–3196. https://doi.org/10.1039/c3cs35528d.

Tzouvadaki, I., Jolly, P., Lu, X., Ingebrandt, S., de Micheli, G., Estrela, P., Carrara, S., 2016. Label-free ultrasensitive memristive aptasensor. Nano Lett. 16 (7), 4472–4476. https://doi.org/10.1021/acs.nanolett.6b01648.

Ueno, Y., Furukawa, K., Matsuo, K., Inoue, S., Hayashi, K., Hibino, H., 2015a. On-chip graphene oxide aptasensor for multiple protein detection. Anal. Chim. Acta 866, 1–9. https://doi.org/10.1016/j.aca.2014.10.047.

Ueno, Y., Furukawa, K., Tin, A., Hibino, H., 2015b. On-chip FRET graphene oxide aptasensor: quantitative evaluation of enhanced sensitivity by aptamer with a double-stranded DNA spacer. Anal. Sci. 31 (9), 875–879. https://doi.org/10.2116/analsci.31.875.

Valeur, B., Berberan-Santos, M.N., 2011. A brief history of fluorescence and phosphorescence before the emergence of quantum theory. J. Chem. Educ. 88 (6), 731–738. https://doi.org/10.1021/ed100182h.

Vigneshvar, S., Sudhakumari, C.C., Senthilkumaran, B., Prakash, H., 2016. Recent advances in biosensor technology for potential applications - an overview. Frontiers in bioengineering and biotechnology 4, 11. https://doi.org/10.3389/fbioe.2016.00011.

Wang, G., Zhu, Y., Chen, L., Zhang, X., 2015a. Photoinduced electron transfer (PET) based label-free aptasensor for platelet-derived growth factor-BB and its logic gate application. Biosens. Bioelectron. 63, 552–557. https://doi.org/10.1016/j.bios.2014.07.067.

Wang, K., Li, Q., Baoshun, L., Cheng, B., Ho, W., Yu, J., 2015b. Sulfur-doped G-C3N4 with Enhanced Photocatalytic CO2-reduction Performance, vol. 176.

Wang, Y., Li, H., Xu, D., 2016a. Aptamers-based sandwich assay for silver-enhanced fluorescence multiplex detection. Anal. Chim. Acta 905, 149–155. https://doi.org/10.1016/j.aca.2015.12.013.

Wang, Y.Z., Zhao, W., Dai, P.P., Lu, H.J., Xu, J.J., Pan, J., Chen, H.Y., 2016b. Spatial-resolved electrochemiluminescence ratiometry based on bipolar electrode for bioanalysis. Biosens. Bioelectron. 86, 683–689. https://doi.org/10.1016/j.bios.2016.07.067.

Wardle, J., Robb, K., Vernon, S., Waller, J., 2015. Screening for prevention and early diagnosis of cancer. Am. Psychol. 70 (2), 119–133. https://doi.org/10.1037/a0037357.

Wei, B., Mao, K., Liu, N., Zhang, M., Yang, Z., 2018. Graphene nanocomposites modified electrochemical aptamer sensor for rapid and highly sensitive detection of prostate specific antigen. Biosens. Bioelectron. 121, 41–46. https://doi.org/10.1016/j.bios.2018.08.067.

Wu, G., Datar, R.H., Hansen, K.M., Thundat, T., Cote, R.J., Majumdar, A., 2001. Bioassay of prostate-specific antigen (PSA) using microcantilevers. Nat. Biotechnol. 19 (9), 856–860. https://doi.org/10.1038/nbt0901-856.

Xu, H., Kou, F., Ye, H., Wang, Z., Huang, S., Liu, X., et al., 2017. Highly sensitive antibody-aptamer sensor for vascular endothelial growth factor based on hybridization chain reaction and pH meter/indicator. Talanta 175, 177–182. https://doi.org/10.1016/j.talanta.2017.04.073.

Yang, J.J., Cao, J.T., Wang, H., Liu, Y.M., Ren, S.W., 2017a. Ferrocene-graphene sheets for high-efficiency quenching of electrochemiluminescence from Au nanoparticles functionalized cadmium sulfide flower-like three dimensional assemblies and sensitive detection of prostate specific antigen. Talanta 167, 325–332. https://doi.org/10.1016/j.talanta.2017.01.077.

Yang, K., Hu, Y., Dong, N., Zhu, G., Zhu, T., Jiang, N., 2017b. A novel SERS-based magnetic aptasensor for prostate specific antigen assay with high sensitivity. Biosens. Bioelectron. 94, 286–291. https://doi.org/10.1016/j.bios.2017.02.048.

Yang, T., Hou, P., Zheng, L.L., Zhan, L., Gao, P.F., Li, Y.F., Huang, C.Z., 2017c. Surface-engineered quantum dots/electrospun nanofibers as a networked fluorescence aptasensing platform toward biomarkers. Nanoscale 9 (43), 17020–17028. https://doi.org/10.1039/c7nr04817c.

Yousefi, M., Dehghani, S., Nosrati, R., Zare, H., Evazalipour, M., Mosafer, J., et al., 2019. Aptasensors as a new sensing technology developed for the detection of MUC1 mucin: a review. Biosens. Bioelectron. 130, 1–19. https://doi.org/10.1016/j.bios.2019.01.015.

Zhang, G., Liu, Z., Fan, L., Guo, Y., 2018a. Electrochemical prostate specific antigen aptasensor based on hemin functionalized graphene-conjugated palladium nanocomposites. Mikrochim. Acta 185 (3), 159. https://doi.org/10.1007/s00604-018-2686-9.

Zhang, K., Lv, S., Lu, M., Tang, D., 2018b. Photoelectrochemical biosensing of disease marker on p-type Cu-doped Zn0.3Cd0.7S based on RCA and exonuclease III amplification. Biosens. Bioelectron. 117, 590–596. https://doi.org/10.1016/j.bios.2018.07.001.

Zhang, W.-H., Hu, X.-X., Zhang, X.-B., 2016. Dye-Doped fluorescent silica nanoparticles for live Cell and in vivo bioimaging. Nanomaterials (Basel, Switzerland) 6 (5), 81. https://doi.org/10.3390/nano6050081.

Zhao, J., Ma, Z., 2018. Ultrasensitive detection of prostate specific antigen by electrochemical aptasensor using enzyme-free recycling amplification via target-induced catalytic hairpin assembly. Biosens. Bioelectron. 102, 316–320. https://doi.org/10.1016/j.bios.2017.11.044.

Zhou, Q., Lin, Y., Shu, J., Zhang, K., Yu, Z., Tang, D., 2017. Reduced graphene oxide-functionalized FeOOH for signal-on photoelectrochemical sensing of prostate-specific antigen with bioresponsive controlled release system. Biosens. Bioelectron. 98, 15–21. https://doi.org/10.1016/j.bios.2017.06.033.

Zhou, Q., Lin, Y., Zhang, K., Li, M., Tang, D., 2018. Reduced graphene oxide/BiFeO3 nanohybrids-based signal-on photoelectrochemical sensing system for prostate-specific antigen detection coupling with magnetic microfluidic device. Biosens. Bioelectron. 101, 146–152. https://doi.org/10.1016/j.bios.2017.10.027.

Zhu, Q., Liu, G., Kai, M., 2015. DNA aptamers in the diagnosis and treatment of human diseases. Molecules 20 (12), 20979–20997. https://doi.org/10.3390/molecules201219739.

Zhu, X., Kou, F., Xu, H., Lin, L., Yang, G., Lin, Z., 2017. A highly sensitive aptamer-immunoassay for vascular endothelial growth factor coupled with portable glucose meter and hybridization chain reaction. Sensor. Actuator. B Chem. 253, 660–665. https://doi.org/10.1016/j.snb.2017.06.174.