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A novel classification of prostate specific antigen (PSA) biosensors based on transducing elements

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ABSTRACT

During the last few decades, there has been a tremendous rise in the number of research studies dedicated towards the development of diagnostic tools based on bio-sensing technology for the early detection of various diseases like cardiovascular diseases (CVD), many types of cancer, diabetes mellitus (DM) and many infectious diseases. Many breakthroughs have been developed in the areas of improving specificity, selectivity and repeatability of the biosensor devices. Innovations in the interdisciplinary areas like biotechnology, genetics, organic electronics and nanotechnology also had a great positive impact on the growth of bio-sensing technology. As a product of these improvements, fast and consistent sensing policies have been productively created for precise and ultrasensitive biomarker-based disease diagnostics. Prostate-specific antigen (PSA) is widely considered as an important biomarker used for diagnosing prostate cancer. There have been many publications based on various biosensors used for PSA detection, but a limited review was available for the classification of these biosensors used for the detection of PSA. This review highlights the various biosensors used for PSA detection and proposes a novel classification for PSA biosensors based on the transducer type used. We also highlight the

advantages, disadvantages and limitations of each technique used for PSA biosensing which will make this article a complete reference tool for the future researches in PSA biosensing.

Keywords: Prostate cancer; Biosensor; PSA

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1. Introduction

Today prostate cancer causes the fatality to approximately 10% of all cancer patients [1]. During the last few years, the frequency of prostate cancer in men has been increasing hastily and this accords with the increasing usage of prostate specific antigen (PSA) as a biomarker. PSA is considered as the utmost significant biomarker for prostate cancer determination. It is a glycoprotein (93% peptide, 7% sugar) produced by the prostate gland. It has another important function that is the liquefaction of the seminal fluid. While determining the prostate cancer, a

total PSA level in serum is measured. If the measurement is above 10.0 ng mL^{-1}, it is considered as positive and indicates high probability of prostate cancer. If the total PSA level is below 4.0 ng mL^{-1}, the result is regarded as negative and denotes low possibility of prostate cancer; and if the total PSA value is between 4.0 ng mL^{-1} and 10.0 ng mL^{-1}, the result is in the so-called "gray zone", and free PSA/total PSA ratio specifies cancer specificity [2]. The normal values for PSA in different countries are shown in Table 1. Usually the PSA tests are conducted in dedicated centralized laboratories where they use large automated analyzers and equipment. This requires transportation of the sample, which in turn takes long waiting times and increased costs. To overcome this disadvantage, POCT (Point of Care Testing) is introduced. In POCT setup, the diagnostic testing is carried outside the clinical laboratory and it will be in close proximity to where the patient is receiving care. POCT helps the patients in many ways, including the ease of use, reduced cost factor, mass screening and increased clinical outcome. When using biosensors as a-point-of-care testing tool, the patient's molecular profile is used for the generation of data, which is then used, for exploring new biomarkers. Some of the major highlights of biosensors include high accuracy, promptness in detection, less instrumentation and technical skills and reproducibility. This review highlights some of the significant PSA biosensor layouts that have lately been related towards the detection of Prostate Specific Antigen from serum and emphasizing the advantages and drawbacks of each biosensor type in association to its appropriateness for use in the POCT procedures of the upcoming methods.

Table 1:

2. Past and present of PSA as cancer biomarker

Regarding the discovery of PSA in blood, there have been numerous controversies existing. The first report regarding the properties of PSA was made by Rubin Flocks, an American urologist in the year of 1960 [3]. But it was by T. Ming Chu and his research group who discovered that the PSA could be invoked as a biomarker for prostate cancer detection [3]. This remarkable discovery in turn resulted in a series of studies conducted by the coworkers of Chu, Lawrence D. Papsidero, Manabu Kuriyama and Wang [4, 5]. Later they developed a sensitive ELISA (Enzyme-Linked Immunosorbent Assay) immunoassay, which can be used for detecting PSA content in blood, and executed early studies investigating the potential clinical applications of PSA as a biomarker in diseases affecting the prostate. But still there were many limitations pointed out for using PSA as a diagnosing tool for prostate cancer. The main issue was the overlapping of PSA level during the occurrence of other prostate related diseases like benign prostatic hyperplasia, and prostatitis. Due to this many researchers and clinicians disagree for using PSA as a first line diagnostic tool for prostate cancer. Nevertheless, in early 1990s, it was proved that PSA can be used a biomarker for diagnosing prostate cancer and this led to the approval of the PSA test by the United States Food and Drug Administration (FDA) [6].

3. Disadvantages of currently available PSA immunoassays

There are various PSA testing procedures available currently in the market. But all of them are carried out at centralized dedicated laboratories or hospitals by using automated high-through-put systems. The main benefits of such setups are the ability of the device to uncover the analytes with low detection limits. Table 2, gives a brief introduction to various PSA tests nowadays done by companies and their detection limits. Having a small detection limit, in the range of 0.05–0.005 ng mL^{-1} and high dependability of the results makes such methods undeniable in the field

of clinical diagnosis. But on the other hand it is questioning the very basic point of early diagnosis. The foremost disadvantages of such large detection systems are the time and effort a patient or doctor has to spend to undergo the test and get the results. The sample has to be sent to the centralized laboratories and has to wait for the results to be finalized. This will increase the overall treatment cost and finally the time in-between the evaluation of test results and the clinical action acquired towards the obtained test result, which is otherwise known as therapeutic turnaround time (TAT) [12], is often delayed several weeks [7]. Here comes the importance of Point of Care Techniques. To make the most out of a biomarker, the detection system should be able to deliver the results within a matter of seconds to minutes. It should be just an easily portable device, which contains less complicated mechanism, even the patient can himself handle it. It should be either reusable or it can be made available to patients at affordable costs. With such a system, patient involvement will be transfigured through a decline in the sum of clinic visits, diminished diagnostic costs, improved patient gratification and enhanced clinical output.

Table 2:

4. PSA biosensors: A new trend in the point-of-care PSA measurement

A biosensor is a detection device which uses a living component or a biomolecule as a mode of sensing and a physicochemical method to express it [8]. It contains a biological component (eg. antigen, antibody, DNA, enzymes, etc.), which takes part in the corresponding reaction. A transducer component, then converts this biological response into corresponding electrical signal [9]. Figure 1 provides a brief idea about the various classifications of biosensors in general. The sample analyte is reacted with the components in the bio-receptor. The transducer converts the resulting signal to a readable form, which in turn is amplified and displayed. An ideal biosensor

should possess the following qualities: The biomolecule utilized for the detection process should be highly specific. Stability of the sensor is an essential aspect. Parameters like change in pH, buffer or temperature should not affect the reaction. The output of the sensor should be precise, reproducible and linear. Electrical noise should not affect the sensor output. The components of the biosensor should be in appropriate size and shape with respect to the application. It should not cause any harmful side effects in the body. Altogether an ideal biosensor should be small, easy to use and less expensive [10]. Since biosensors are mainly used for mass screening purposes, it should be reusable too. Coming to the biosensors used for detection of PSA from the blood, there have been countless methods adopted so far. But one thing was common in all the sensors; all of them exclusively make use of the attachment of Prostate Specific Antigen using high-affinity integral antibodies in order to shape the recognition elements of the sensing devices. There are a limited number of review articles published on the classification of biosensors used for PSA detection. In the year 2007, Healy et al., [1] reported the classification of PSA biosensors into label based signal transduction and label free PSA biosensors. In the present review, we propose a novel classification for PSA biosensors based on the transducer type used. We also highlight the advantages, disadvantages and limitations of each technique used for PSA biosensing which will make this article a complete reference tool for the future researches in PSA biosensing.

Fig. 1:

5. Classification of PSA biosensors

Biosensors are classified according to transducer type or according to the nature of their biological component. Table 3 gives a general outline of the classification on PSA biosensors

based on transducer element. In this review, we are describing some of the major PSA biosensors reported under the classification based on transducing element.

5.1.1. Electrochemical biosensors for PSA detection

One of the most common and major types of biosensors in use today is the electrochemical biosensor. This is mainly due to their advantages like small size, portability and being more economical when compared with the other types of biosensors. The portability and small size enable electrochemical biosensors to be used as a point-of-care device by the patient himself at home or in a doctor's clinic. They also take the advantage of sensing parameters without causing any damage to the sensing element. This property makes the electrochemical biosensors a suitable candidate for PSA sensing applications. They utilize redox reactions to measure the amount of an analyte present.

Table 3:

The sample is quantified in response to the potential difference or using the current flowing through the system owing to the oxidation and reduction reactions comprising the analyte. A novel dual function electrochemical biosensor based on a sandwich immune binding format for the detection of PSA and telomerase activity has been recently reported [11]. This dual biosensor works on a single electrode, but with two different reactions, a conventional sandwich immunoreaction for the detection of PSA and a telomerization reaction for DNAzyme.

Fig 2:

The target protein PSA is first captured on the Ab1 coated gold electrode, which in turn forms a mutual sandwich immunocomplex with biotinylated Ab_2 (Fig. 2). When the sensor comes in contact with biological analyte, a series of enzymatic reaction is triggered. This finally catalyzes

the reduction of H_2O_2 and then generates a cathodic current which is measured and compared with the reference. This generated cathode current is proportionate to the amount of PSA present in the serum. A direct dependency between the obtained peak currents and the logarithm of prostate specific antigen levels was achieved in a varying range from 0.14 ng mL^{-1} to 1400 ng mL^{-1}.

In PSA electrochemical biosensors, a bio electrochemical component functions as the main transduction element and the measurement of electrical properties for obtaining the quantitative information from the biological system is generally electrochemical in nature [10]. The generated signal after the reaction may be a measurable current (amperometric), a measurable potential or a charge accumulation (potentiometric) in the electrodes which can be detected and calculated from the resulting parameters.

Based on this principle, electrochemical PSA sensors are classified into two. Potentiometric PSA biosensors mainly use ion-selective electrodes for the detection an electrical response and amperometric PSA sensors measured current which is generated when a potential is applied between the two electrodes. The electrochemical PSA sensors do not experience the disadvantages of optical sensors. They have more steady output, have elevated sensitivity, firm response and suffer from lesser interferences. Despite of these advantages electrochemical biosensors has some drawbacks like narrow or limited temperature range and short life span. Various PSA biosensors which use potentiometric and amperometric approaches are discussed below.

5.1.1.1. Potentiometric biosensors for PSA detection:

The working principle of potentiometric PSA biosensors is that they use conventional ion-selective electrodes so as to transduce the biological response into an electrical signal. They have advantages like simplicity and clear principles of operation. With the usage of modern silicon technologies, potentiometric PSA biosensors can be easily mass fabricated for commercial applications. Their applications can vary from simple disposable sensing device to advanced analyzers and monitors. Rebelo, T.S., et al., [12] reports a potentiometric biosensor for the detection of PSA with a detection limit of 2 ng mL^{-1}. Protein Imprinted Materials (PIM) with charged binding sites are used for the development of this potentiometric biosensors. Surface imprinting technology over graphene layers was utilized for the formation of charge binding sites (C/PIM), to which the protein was attached covalently [12]. Potentiometric PSA sensors often provide the benefit of choosiness, ease of use and accuracy. The method of molecular imprinting over graphene layers resulted in a low-cost material that was effectively related to fabricate PSA sensors of potentiometric application. Another appealing potentiometric biosensor was reported for double biomarkers detection by varying the applied bias in the detection process [13]. In this photoelectrochemical biosensor, the nanocomposites of TiO_2 mesocrystals and dual disk electrodes acts as an excellent photoelectrochemical sensing matrix. Prostate specific antigen and human interleukin-6, the two major biomarkers in serum for prostate cancer, were immobilized onto the separate disks of modified electrode via glutaraldehyde bridges (Fig. 3). Then two other photosensitizers, graphitic carbon nitride and CS-AgI labeled different antibodies were self-assembled onto the electrode surface by corresponding competitive immune recognition reaction. The photocurrents changing with target antigen concentration at different critical voltages enables the user to selectively and quantitatively determine the specific targets.

Fig 3:

The proposed biosensor revealed reasonable performances comprising wide linear range, low detection limit and decent selectively. The results demonstrated that this potentiometric addressable photoelectrochemical biosensing strategy not only owned unlimited potential as a new point-of-care diagnostic tool for early detection of prostate cancer but also can be conveniently expanded to multiplex biosensing by simply changing biomarkers.

5.1.1.2. Amperometric biosensors for PSA detection

The working principle of amperometric PSA biosensors is that a current is produced when a potential is applied between two electrodes. The generated current will be proportional to the amount of analyte present in the sample applied. The main advantages of these sensors are their quick response times and vibrant ranges, which are similar to the potentiometric biosensors. They are highly sensitive and more appropriate for mass production than the potentiometric biosensors [14, 15]. Kenzo Maehashil et al., [15, 16] reported an amperometric label-free PSA biosensor with high sensitivity using microelectrodes reformed by single-walled carbon nanotubes (SWNTs). By using thermal, chemical vapor deposition technique, the SWNT electrodes were directly fabricated on platinum electrodes. After this stage the SWNT were further modified with linkers and immobilized with PSA antibodies. SWNTs are covalently anchored with monoclonal PSA antibodies using a linker. For the measurement 1 ng mL^{-1} of prostate specific antigen is introduced to the sensor setup. The corresponding electrochemical current is considerably increased signifying the formation of antigen-antibody complex. The set-up is tested with bovine serum albumin to determine the selectivity of the device. The proposed PSA sensor successfully detected the PSA range of 0.25–1 ng mL^{-1} [15].

Notwithstanding various advantages for amperometric based biosensors, they have some serious limitations like the interloping from chemicals present in the sample matrix to the analyte to be tested. This can be primarily challenging when comes to the testing of biological samples in specific. This limitation due to matrix interference can be overcome by optimizing the parameters like pre-concentration, derivatization and extraction. Even though, the direct use of biosensors in a matrix is desirable in order to avoid the time spent for complex sample preparation steps [17].

5.1.2. Mechanical biosensors for PSA detection

Recent developments in the area of micro and nano fabrication facilitate a broad range of the latest technologies, including the advancement in the field of mechanical devices and nano sized robots. The vital problems in biological physics and bioengineering concerning the development of applied micro- and nano-electromechanical biosensors have come to an end with the introduction of standard wafer-scale semiconductor processing techniques. This also facilitated the mass production of nano and mechanical biosensors for various diagnostic purposes. Microelectromechanical systems (MEMS), are the broad category of technology using microscopic devices, principally those with moving parts. It combines at the nano-scale into nanoelectromechanical systems otherwise known as NEMS systems, which are the type of devices incorporating mechanical and electrical functionality at the nanoscale level [18]. Recent advancements in MEMS/NEMS based systems comprising cantilevers and other small scale structures, have been a great inspiration for various research findings in the field of biosensing applications [19-21]. When most of the current biosensing units rely on biomarkers and fluorescent labeling techniques which require more effort, chemical reactions and time

consuming procedures, this mechanical based MEMS/NEMS systems can be utilized to develop ultrasensitive means of labelfree mass detection. The main advantage of this technique is that, it can be tailored to distinctive forms and dimensions and designed in combinations with large numbers of elements [22].

In a broad spectrum, mechanical PSA biosensors exploit the characteristics of reduced physical size of the components. Mainly in mechanical biosensors, the minimum measurable mass is proportional to the total mass of the device. Second property, which makes them unique, is their ability to be displaced or deformed uniformly in all dimensions according to the corresponding reaction. They have high mechanical compliance, which can be tailored according to the application. This property converts an applied force into a measurable displacement which then can be converted to electrical signals and measured. The heightened force responsivity unlocks new openings for quantifying the miniscule forces that control biological interactions. For example, nanomechanical sensors can detect events like rupturing of individual hydrogen bonds with forces of ~10 pN. They can also exhibit fast response times. This allows biological processes in fluids to be studied on the time scales of milliseconds or shorter [23].

5.1.2.1. Cantilever PSA biosensor

There are many classifications of mechanical biosensors, but for the detection of PSA micro-cantilever mechanical biosensors are mostly reported. During the biological reaction, cantilever based sensors react in two different ways. One method is the static deflection where the binding of the biological analyte on one side of the cantilever causes alteration in the surface stress, which then further develops into a detectable deflection; and the other is the dynamic method where binding on a cantilever produces deviations of its mass and subsequently changes the resonant frequency. Various physical methods can be employed to sense the cantilever motion.

They can be mechanical, optical or electromagnetic in nature. The resulting signal is converted to an electrical response and calculated for the quantification. Cantilever devices are mostly fabricated using MEMS photolithography processes which enable them to be tailored in various shapes and forms [24].

Wu et al., [25] reported micro cantilever based PSA biosensors which can detect PSA in a wide range varying from 0.2 ng mL^{-1} – 60 μg mL^{-1} by keeping human plasminogen and human serum albumin (HSA) as a backdrop. The micro cantilever is fabricated using a covalently linked polyclonal prostate specific antigen as a ligand to the cantilever surface. Silicon nitride coated with gold nanoparticls is used as the substrate for the cantilever. When the sensor comes in contact with the PSA antigen, it reacts with polyclonal antibody and forms the antigen-antibody complex (Fig. 4). This reaction triggers the altering of the intermolecular nanomechanical interactions inside the self-assembled monolayer of the micro cantilever. The force generated is directly proportional to the amount of the antigen added and the resultant bending of the cantilever is measured and converted to electrical signals.

Fig. 4:

5.1.3. Optical biosensors for PSA detection

Due to various limitations of electrical and mechanical biosensors, optical biosensors is considered for the sensing of various biological components for diagnostic and analytical purposes [26]. Fluorescence, absorbance, chemiluminescence and surface plasmon resonance (SPR) are some of the widely used techniques for optical biosensing. Different methods used for optical PSA biosensing are reported below.

5.1.3.1. Fluorescent biosensors for PSA detection

Use of fluorescent biosensors is widely accepted method for detecting biologically significant molecules and various biochemical reactions for diagnostic purposes. Latest advancements and investigations in the field of fluorescent biosensors have led to many breakthroughs in understanding the role of different biomolecules and the intercellular relationship of various biological components in disease diagnosis including cancer markers. Even though there have been many recent discoveries in the field of PSA fluorescent biosensing, logical design approaches of these fluorescent biosensors are yet to achieve. Their inability to be used in multiplexed assays still remains as a major drawback. Fabrication of fluorescent biosensors generally requires some basic strategies. The main task is to select receptor molecule which has specificity and appropriate affinity to the target molecule. Once the correct receptor molecule is finalized, the signal transduction task, which will be triggered in response to the corresponding biological reaction, has to be incorporated. This can be either through direct or indirect fluorescent method [27]. Since many of the biomolecules possess fluorescent properties, for others to get the effect, an auto-fluorescent protein (AFP) probe or label has to be covalently attached to the respective position in order to visualize the species of interest [28]. Especially after the introduction of fluorescent nanoparticles, like luminophore doped nanoparticles and quantum dots, due to their narrow emission peaks, PSA biosensing using the fluorescent method is widely accepted among researchers in this field [1].

A novel aptamer-functionalized Molybdenum disulfide (MoS_2) nanosheet fluorescent biosensor that detects PSA was reported by Kong et al. [29]. Aptamers are generally very short, single-stranded DNA or RNA molecules which are produced from an in vitro selection process. In

sensing applications, aptamers possess a lot of reasonable advantages when compared with the antibodies. They have good stability for long term storage purposes, lack of immunogenicity, they can be easily tailored based on the application, low processing cost and low toxicity are some of them. Other major advantages of aptamers which makes them applicable for biosensing are their ability to denature and renatured many times without losing their binding ability with targets.

The binding of the aptamer to the target PSA persuades a rigid aptamer structure which makes the incorporation with the MoS_2 nanosheet feeble. This affects the discharge of the aptamer probe from the nanosheet surface and reestablishes the quenched fluorescence (Fig. 5). This method has the benefit of the simple design and swift detection of PSA. The biosensor has the merits of high sensitivity and high selectivity with a detection limit for the PSA of 0.2 ng mL^{-1}. The biosensor was also effectively applied to the detection of PSA in human serum samples with satisfactory results. The dye-labeled DNA probe was adsorbed on the surface of the MoS_2 nanosheet and the fluorescence of the dye was then quenched. In this work, the MoS_2 nanosheet acted as a nano platform to adsorb aptamer molecules and was further employed as a biological probe.

Fig. 5:

5.1.3.2. Surface plasmon resonance (SPR) biosensors for PSA detection

Surface plasmon resonance (SPR) biosensors are another classification of optical biosensors. They work on the basis of utilizing surface plasmon polaritons, a special type of electromagnetic waves in order to make the connection between the analyst and the bio recognition probe, which are immobilized on the sensor surface [30]. SPR biosensors are able to directly detect

concentrations in the nano molar range, which makes them perfectly suitable for detection of medium sized proteins such as prostate specific antigen [31, 32].

A PSA biosensor based on surface plasmon-enhanced fluorescence spectroscopy is illustrated in the Figure 6. A glass prism attached with a gold film coated with f-PSA at concentrations between 3 and 300 nM were used as sandwich immunoassay. The sensor is enhanced with fluorescence spectroscopy (SPFS), where the capture of fluorophore labeled biomolecules is detected through the intensity of the fluorescence light discharged from the sensor surface. A flow cell is attached to the sensor surface through which the analyte passes at a predetermined rate. The lens is used to collect the emitted fluorescent light which is passed through the flow cell. The resultant signal is filtered and detected by a photomultiplier tube [33]. This method has the advantage of having a durable intensity of the electromagnetic field supplemented with the resonant excitation of surface plasmons.

Fig. 6:

Figure 7 illustrates another type of surface plasmon resonance PSA biosensor reported by Uludag et al., [34]. Here the working principle is same as previously explained, but additionally they used gold nanoparticles in order to enhance and amplify the sensor signal. This will increase the refractive index of the sensor surface. Because of the biocompatible nature of gold nanoparticles, it won't interfere with the biological nature of PSA antibodies, which makes them special with respect to other nanoparticles. One of the main disadvantages of surface plasmon resonance PSA biosensors is the variation of the sensitivity of the sensor with respect to the refractive index of the sample, buffer solution, and the running buffer. This may create noise in the obtained output. In order to rectify this a sandwich assay is performed instead of a direct

assay. This sensor was able to detect at the range of 0.29 ng mL^{-1} to 2.3 ng mL^{-1} PSA with the addition of 40 nm Au nanoparticles. Some of the major disadvantages of surface plasmon resonance technology are their limitation to measure one parameter at a time and they require noble metal surfaces for proper functioning.

Fig. 7:

5.1.3.3. Chemiluminascence PSA biosensor

Luminescence is defined as the emission of light energy from an electronically excited compound or substance returning to its ground state. Based on the source of energy used for excitation, luminescence is classified into various types. Chemiluminascence happens during a chemical reaction in an electronically excited state [35]. This principle is made used in the fabrication of chemiluminascence biosensors where the binding of target molecules triggers the photochemical emission.

This can be either direct or with the use of an enzyme labeling. In this method, there is minimal background hindrances compared to other methods due to the absence of emission filters and excitation light sources [36-38]. Figure 8, shows the schematic diagram of the steps used in the fabrication of an electro generated chemiluminescence peptide based biosensor (ECL-PB) for the detection of prostate-specific antigen reported by Qi et al., [39]. The obtained results of this study show that the electrochemiluminescence (ECL) intensity was directly proportional to the concentration of the PSA present. This method has a particularly low detection limit of 8×10^{-13} ng mL^{-1} and was able to measure PSA concentration in a range of.08 ng mL^{-1} to 5 ng mL^{-1}.

Fig. 8:

5.2. Other types of PSA biosensors

There are also other types of biosensors used for the detection of prostate specific antigen for diagnostic purposes. In specific, with the high photo stability and narrow emission peaks, fluorescent sensing using nanoparticles, such as quantum dots and luminophore-doped nanoparticles, have provided an appealing ground of research for PSA biosensor development. Surface-enhanced Raman spectroscopy biosensor using labeled antibodies, which are attached to gold nanoparticle probes, were used for PSA detection by [40]. An electrochemical biosensor which can concurrently detect vascular endothelial growth factor (VEGF) and PSA based on graphene oxide/ssDNA/PLLA nanoparticles was recently reported [41]. Although biomarkers have various advantages, occasionally it gives false positive rates, which may hinder with the final outcome. As a solution to this problem, DeLuna et al., [42] introduced a novel label-free photonic-crystal biosensor imaging system for the detection of prostate cancer cells using a Photonic- Crystal-based biosensor in a Total-Internal-Reflection (PC-TIR) configuration. They demonstrated the use of refractive index (RI) to achieve label-free detection of prostate cancer cells in contradiction of non-cancerous prostate epithelial cells. Sana et al., [43] managed to detect PSA concentration as low as 0.5 ng mL^{-1} using photonic crystal (PhC) based double nanocavity resonator biosensor. Real-time PCR for PSA detection [44], Nanowire field effect transistors (NW-FETs) PSA biosensor [45], (3D) electrochemical immunosensor [46], bead-based electrochemical impedance spectroscopy (BEIS) [47] etc. are some of the latest additions to the list which are not discussed here.

5.3. Limitations of PSA biosensing

Despite of all the breakthroughs in the area of PSA biosensing, there are still many issues, which require a great deal of attention. Even though PSA is considered as the most reliable biomarker

for prostate cancer in the last 25 years, there has been many limitations reported for this test method. Mainly its low specificity and sensitivity, which ranges from 20 to 40% and 70 to 90%, respectively, and the variation in the cutoff values which is based on the geographical area of the patient [48]. All the reported biosensors faced a similar problem in the detection of PSA mainly because of the fact that non-cancerous conditions may also result in the elevated level of PSA. In conditions like inflammation, infection and trauma of the prostate gland and benign prostatic hyperplasia are more common causes of elevated serum PSA than cancer [49]. Future techniques for PSA sensing should find an appropriate solution for this problem or an alternative biomarker for PSA with more specificity has to be introduced.

5.4. Future viewpoints and conclusions

The fundamental goal of cancer biosensor technology is to bring point of care advantage to the diagnostic field. PSA is recognized as the most relevant biomarker for the early detection of prostate cancer. Biosensor technology has developed to a point where the PSA testing has been moved to near patient diagnostic methods from large centralized high throughput laboratories. In future these sensors can be developed in the form of hand held devices where the patient can test and see the results by himself without medical assistance. The evolution of hand held glucometers are a good example of this. This type of biosensors will revolutionize the health care industry by reducing the treatment cost and by improving the clinical outcomes. There have been various biosensors used for the detection of PSA from blood and some reviews have been published on various types of PSA biosensors. However, in this review we introduce a novel classification for PSA biosensors based on the transducer type used.

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Figure captions

Fig. 1: Basic classification of biosensors [68]

Fig 2: The process and assay mechanism of dual functional electrochemical biosensor based on a sandwich immune binding format for the detection of PSA and telomerase activity. (reprinted with permission from [11] .Copyright (2014) Elsevier

Fig 3: Working principle of the potentiometric immunosensor and detect mechanism of prostate-specific antigen and human interleukin-6. (DDCE) Dual-Disk glassy Carbon Electrode, (PAAD) Polyamidoamine Dendrimers, (CAM) Cube Anatase TiO_2 Mesocrystals. (reprinted with permission from [13] Copyright (2016) American Chemical Society

Fig. 4: Mechanism of PSA sensing using micro cantilever biosensor. Adapted with permission from Macmillan Publishers Ltd: Nature Biotechnology [25], copyright (2001)

Fig. 5: Scheme of fluorescent biosensing using PSA using MoS_2 nanosheets (reprinted with permission from [29]) Copyright (2014) Elsevier

Fig. 6: PSA biosensor using Surface Plasmon Resonance Technology (reprinted with permission from [33]) Copyright (2009) American Chemical Society

Fig. 7: Surface plasmon resonance technology for PSA biosensor using gold nanoparticles (reprinted with permission from [34]) Copyright (2012) American Chemical Society

Fig. 8: Schematic diagram of the steps used in the fabrication of an electro generated chemiluminescence peptide based biosensor for PSA detection (reprinted with permission from [39]) Copyright (2014) American Chemical Society

Figures

Figure 1

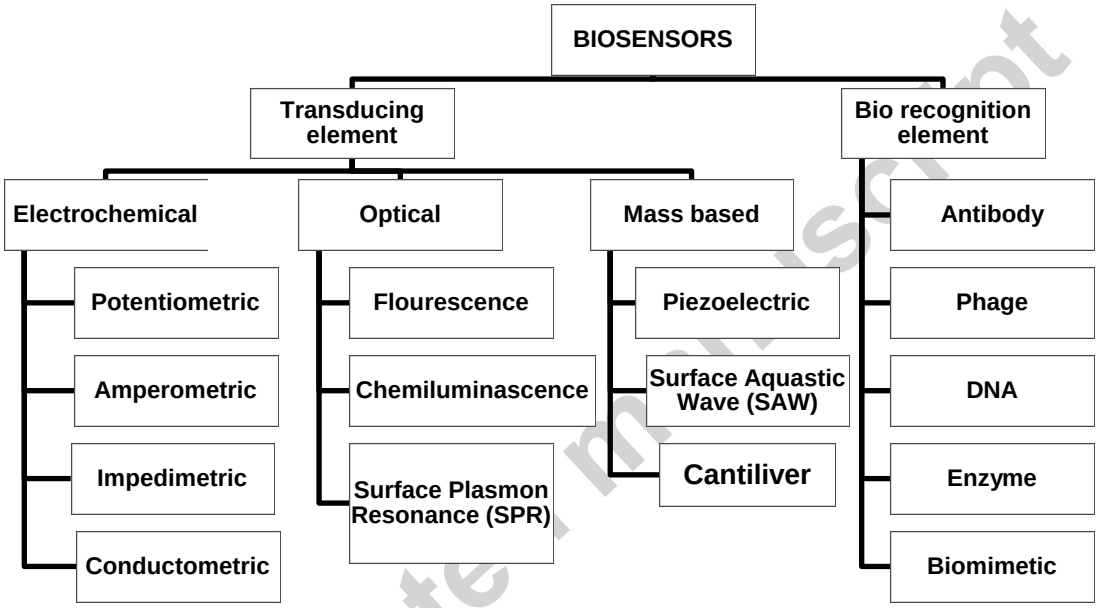


Figure 2

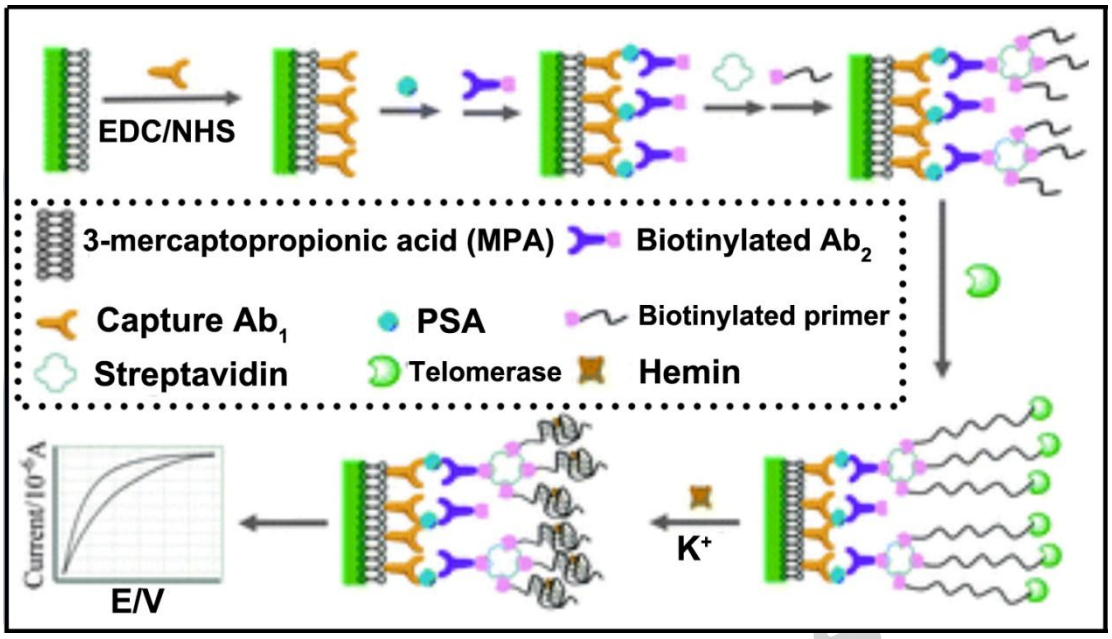
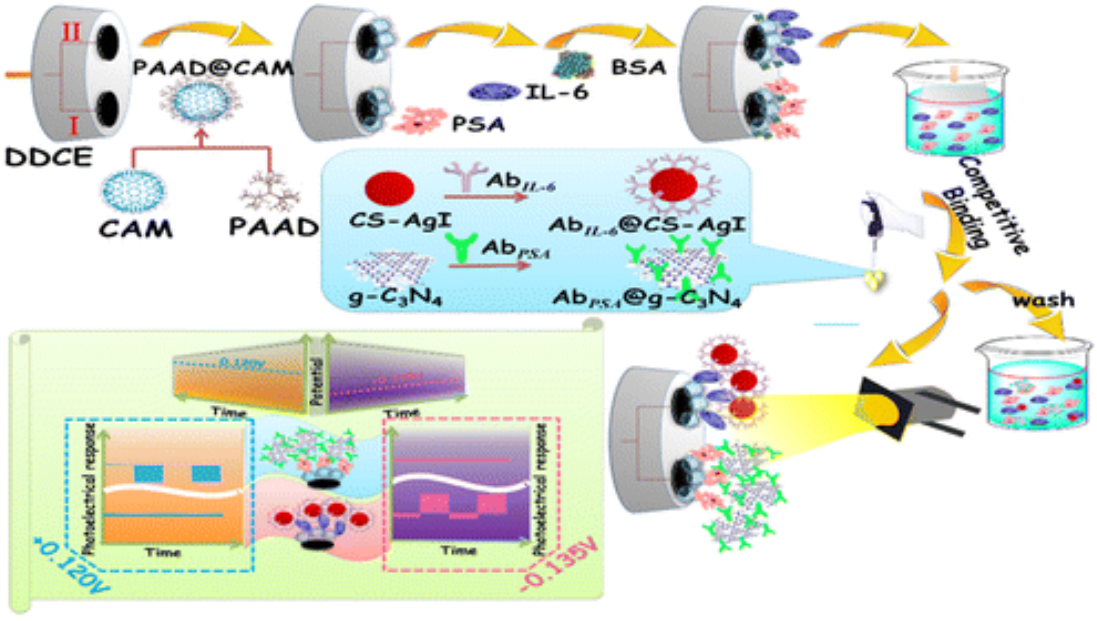

EDC/NHS
3-mercaptopropionic acid (MPA)
Biotinylated Ab2
Capture Ab1
PSA
Biotinylated primer
Streptavidin
Telomerase
Hemin
K+
Current/10-4A
E/V

Figure 3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DDCE
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g-C3N4
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Competitive Binding
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Potential
Time
Photoelectrical response
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-0.135V

Figure 4

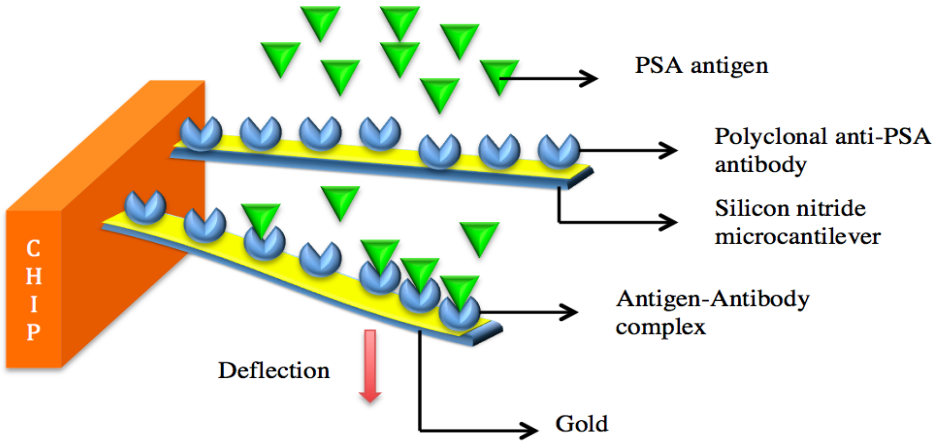


Figure 5

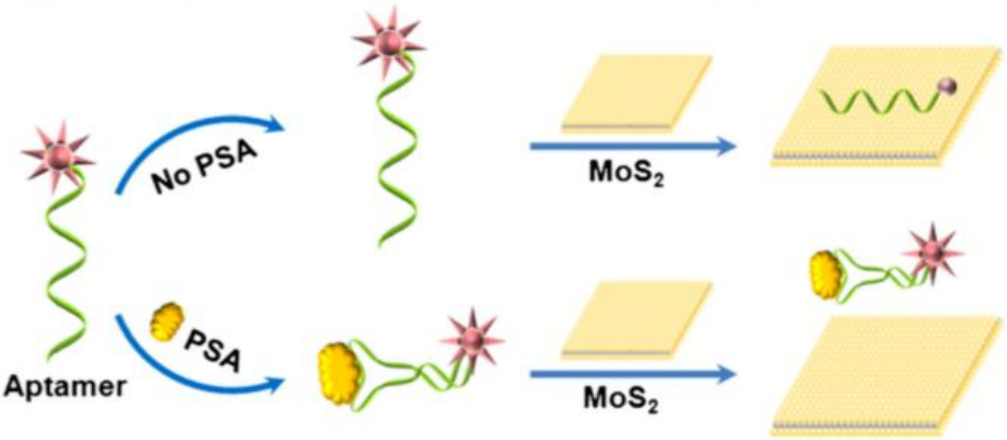
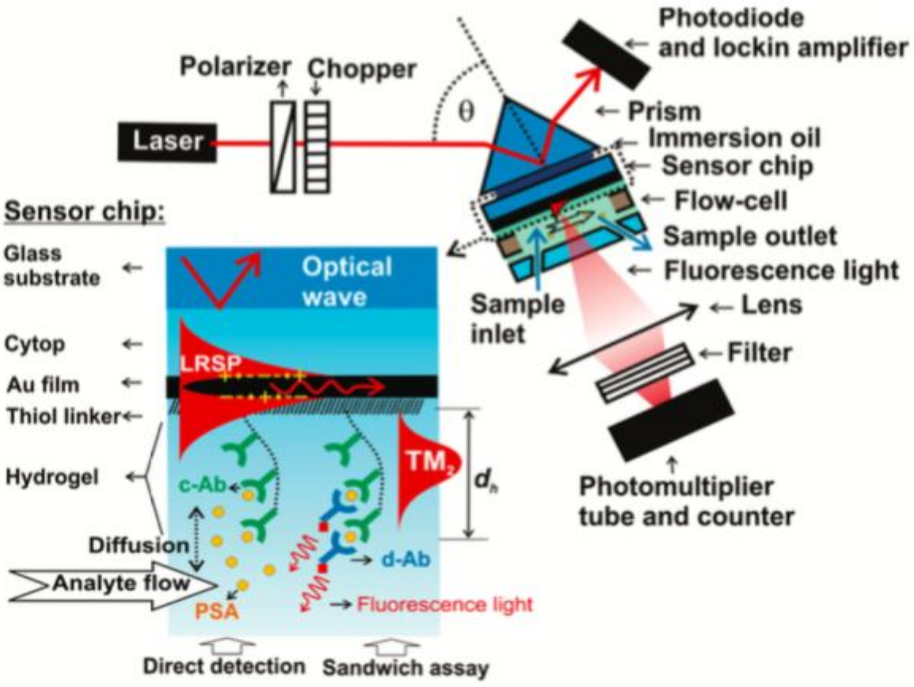


Figure 6


Photodiode
and lockin amplifier
Polarizer
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Laser
Prism
Immersion oil
Sensor chip
Flow-cell
Sample outlet
Fluorescence light
Sensor chip:
Glass substrate
Optical wave
Sample inlet
Lens
Filter
Cytop
LRSP
Au film
Thiol linker
Hydrogel
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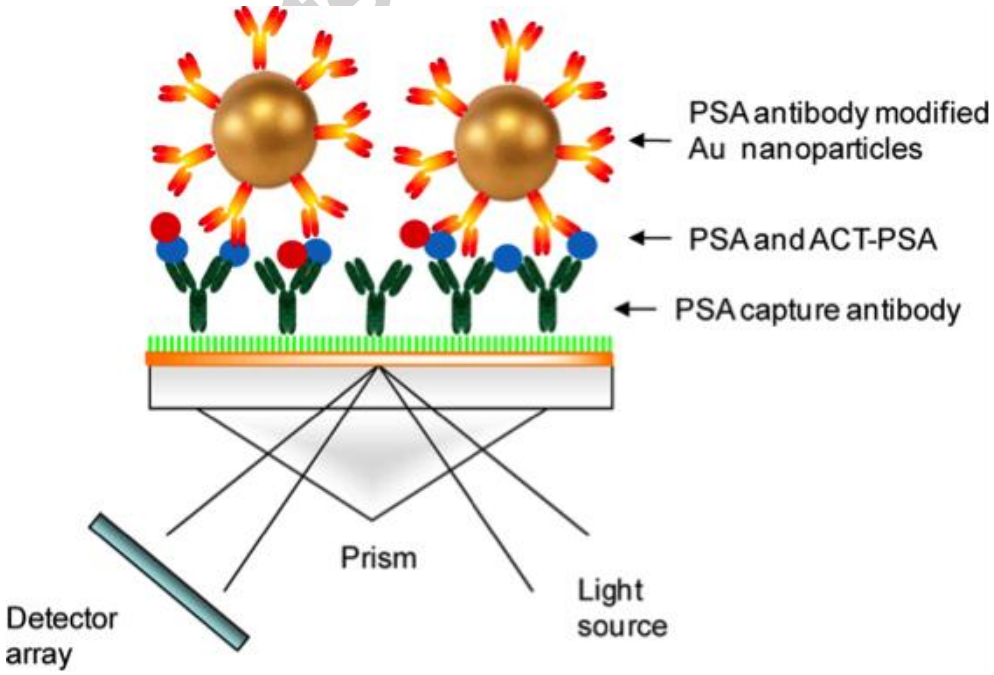
Photomultiplier tube and counter
Diffusion
d-Ab
Analyte flow
PSA
Fluorescence light
Direct detection
Sandwich assay

Figure 7


PSA antibody modified
Au nanoparticles
PSA and ACT-PSA
PSA capture antibody
Prism
Light
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Detector
array

Figure 8

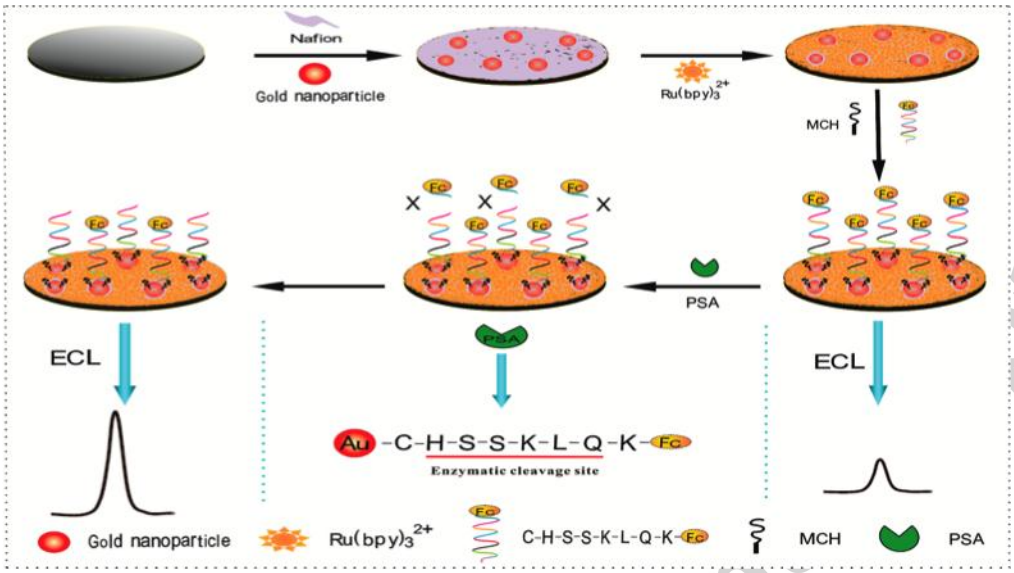


Table captions

Table 1: PSA normal values in different countries (ng mL^{-1}) from age group 30-80

Table 2: Commercially available PSA detection kits

Table 3: Common PSA detection assays and their methods

Tables

Table 1

Country	30–39	40–49	50–59	60–69	70–79	Ref
Arabs*	.49	.55	1.12	2.76	4.14	[50]
Saudi Arabia		2.85	3.99	5.41	6.29	[51]
China	–	–	2.15	3.20	4.10	[52]
Korea	–	–	2.0	2.4	3.9	[53]
Singapore	1.4	1.7	2.3	4.0	6.3	[54]
India	0.8	1.14	1.31	1.41	1.68	[55]
Japan	–	–	2.0	3.0	4.0	[56]
Turkey	–	1.7	2.0	2.9	3.5	[57]
Asian Americans	–	2.0	3.0	4.0	5.0	[58]
African Americans	–	2.0	4.0	4.5	5.5	[59]

*Arab men (Kuwaitis and Omanis)

Table 2

Name	Manufacturer	Principle	Storage	Approximate time required	Sensitivity	Specificity
(f-PSA) ELISA Kit Protocol	Phoenix Pharmaceuticals	f-PSA ELISA	2-8°C	2 hours	0.1 ng mL^{-1}	S*
CANCHECK - PSA	Zephyr Biomedicals	Immunochromatography	4-30°C	20 minutes	100%	)0%
Bi-1-st PSA test device	Ekoweb	Membrane based immunoassay	2-30°C	2 hours	NS	3.5%
Blue Screen (PSA) Deluxe Plate	Philippine Blue Cross Biotech Corporation	Chromatographic immunoassay	NS	30 minutes	NS	S
"See Now" PSA	CAMP Medica Group	Ag-Ab Reaction	5-25°C	20 minutes	NS	)0%

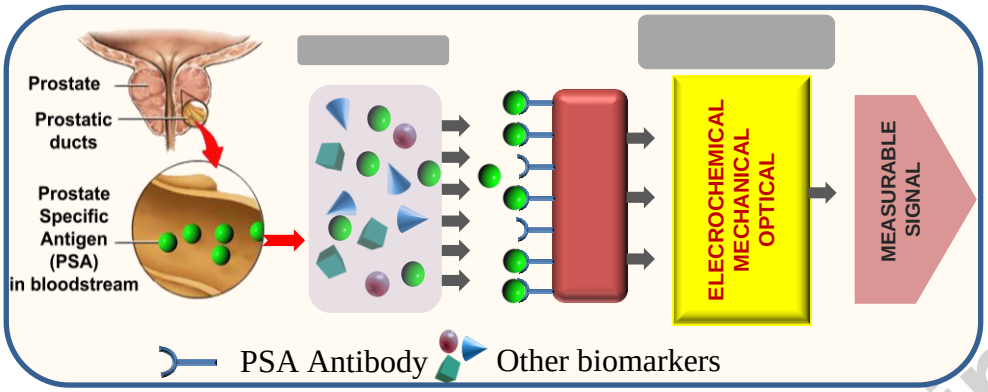
SD Bioline PSA	Standard Diagnostics INC	Immunochromatography	2-8°C	30 minutes	NS	3.9%
PSA Ultra Semi-Quantitative Rapid Test	Homemed (Pty) Ltd	Chromatographic immunoassay	2-30°C	1 hour	98.7%	3.5%

Data obtained from product catalogue. *NS-Not specified

Table 3

Transducer Used	Assay method used or nanostructure used	Detection Range/LOD	Reference
Electrochemical	Sandwich immune binding format	0.14 to 1400 ng mL^{-1}	[11]
Electrochemical	Peptide Biosensor Based on in Situ Silver Deposition	0.001 to 30 ng mL^{-1}	[60]
(3D) Electrochemical immunosensor	Graphene (GR)-based gold (Au) composite	0–10 ng mL^{-1}	[46]
Potentiometric	Molecular imprinting	2 ng mL^{-1}	[12]
Amperometric	Single-walled carbon nanotubes (SWNTs)	0.5 to 5 ng mL^{-1}	[16]
Cantilever	Antigen-Antibody reaction	0.2 to 60 μg mL^{-1}	[25]
Fluorescence	MoS2 nanosheet	0.2 ng mL^{-1}	[29]
Time Resolved Fluorescence	Europium (III) chelate-dyed polystyrene nanoparticles	0.21 ng mL^{-1}	[61]
Surface Plasmon Resonance	Sandwich assay Gold nanoparticles (AuNPs)	0.29 to 2.3 ng mL^{-1}	[34]
Chemiluminescence	Gold nanoparticles (AuNPs)	0.08 to 5 ng mL^{-1}	[39]
Capillary-based	Pt@AuNPs Sandwich assay	0.02 to 2.5 ng mL^{-1}	[62]
Bead-based Electrochemical Impedance Spectroscopy (BEIS)	Magnetic beads	>100 ng mL^{-1}	[47]
Nanowire field effect transistors (NW-FETs)	Schottky contacts (Si-Ti)	23 ng mL^{-1}- 500 ng mL^{-1}	[45]
Surface-Enhanced Raman Scattering	Gold nanoparticles	1.0 pg mL^{-1}	[40]
Silicon Nanobelt Field-Effect Transistor	Label-free detection	50 - 500 ng mL^{-1}	[63]
Microelectrode-Based Impedimetric	Gold nanoparticles	1 ng mL^{-1}–100 ng mL^{-1}	[64]
Colorimetric	Magnetic beads	10 ng mL^{-1}	[65]
Piezoelectric	Lead titanate zirconate (PZT) ceramic resonator	0.25 ng mL^{-1}	[66]
UV light-assisted molecular immobilization (LAMI)	Thiol groups	0.23 ng mL^{-1}	[67]

Graphical abstract



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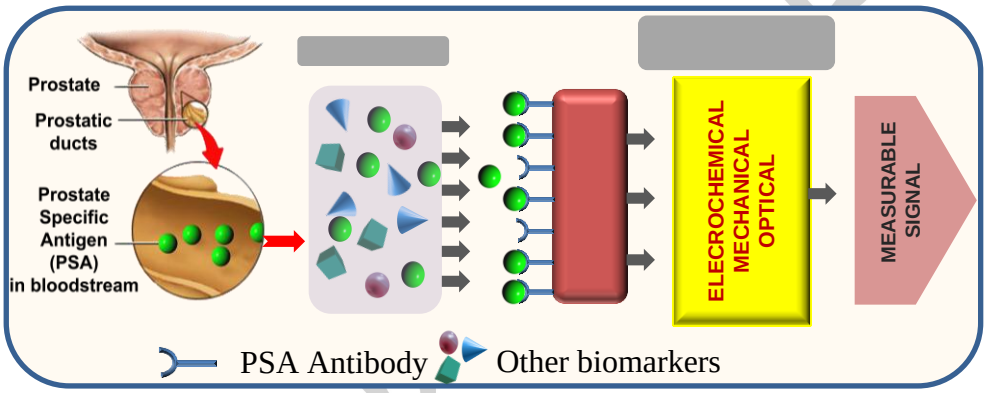

JPEG file

Highlights

- A novel classification for PSA biosensors based on the transducer element is introduced.
- A detailed review of various PSA biosensors with their working mechanism is explained.
- Advantages and limitations of various PSA sensors described.