



# Label-Free LSPR Prostate-Specific Antigen Immune-Sensor Based on GLAD-Fabricated Silver Nano-columns

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## Abstract

Label-free detection of biomarkers has been recently noticed and optical biosensors showed great potential to be the method of choice in such situation. Here, we used glancing angle deposition (GLAD) method in which silver nano-columns stabilized by a self-assembled monolayer (SAM) of 11-mercaptoundecanoic acid (MUA) and 6-mercaptohexanol to investigate the capability of localized surface plasmon resonance (LSPR)-based silver nanochips to detect prostate-specific antigen (PSA). Using different standard solutions of PSA, limit of detection (LOD) of the nano-sensors has been calculated to be 850 pg/ml. The selectivity of the nano-sensors has also been evaluated. We showed that these nano-sensors could detect PSA in clinically acceptable sensitivity and specificity without any complicated laboratory equipment.

**Keywords** Prostate-specific antigen · LSPR · Immune-sensor

## Introduction

Prostate cancer is known as the most common malignancy in men, accounting as a major cause of cancer deaths in western countries [1]. It also accounts for the most cases of diagnosed cancer among American men, with an estimated lifetime risk of approximately 12.9%.

Prostate-specific antigen (PSA) is an FDA-approved tumor marker which has been exploited to monitor patients with prostate cancer since 1986. PSA measurement has profoundly enhanced the capability of diagnosis, treatment, and patients follow-up [1]. Thanks to the results of PSA screening, it is estimated that 16% of men would be diagnosed with PC; however, the mortality of this disease is only 3.4% [2].

PSA, which is produced in both normal and cancerous prostate tissue, is a 33-kDa serine-protease of the tissue kallikrein family. This protease is secreted into the seminal fluid, accounting as the major protein in semen, where it liquefies

semen from its gel form. In normal condition, PSA is confined in the prostate gland and only a minute amount enters into the blood vessel. In some medical conditions, the normal architecture of prostate disrupts so that PSA leaks to the circulation, which leads to the elevated levels of PSA in serum. The most common causes of disruption in prostate are prostate cancer, benign prostate hyperplasia (BPH), or prostatitis [3].

Now it is obvious that PSA levels in blood have strong relation with cancer risk in men, but there are some challenges regarding precise grading of each stage and related amount of PSA in serum. In the guidelines of prostate cancer screening, it is recommended that men with the serum PSA level of 4 ng/ml or above must undergo biopsy. Using the cut-off of 4 ng/ml has always met some controversies such as low sensitivity (21%), but the specificity of such cut-off seems quite well and calculated about 91% in several large studies. [4].

Quantification of cancer biomarkers is currently performed by several conventional methods, most of which are based on immunoassay, such as enzyme-linked immunosorbent assay (ELISA). These methods have many advantages including low detection limits, reliability, and the capability of high-throughput sample processing [5]. Despite acceptable sensitivity and specificity, these methods have some disadvantages regarding the measurement of some proteins like PSA.

Most of these methods require complicated laboratory facilities, are technically complex, are time consuming, and need highly trained operator [6].

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As an alternative, biosensors are being developed in recent years. Biosensing is a process in which a biological element as a recognizer interacts with an analyte. It has been proven that biosensors are able to minimize the expenses of each test, improve sensitivity, increase simplicity, and miniaturize the volume of materials required for each measuring unit. Moreover, biosensors offer faster analysis procedure, making them an ideal device in emergency situations [7]. Optical biosensors show numerous advantages including direct and rapid quantitation, high specificity, easy miniaturization, and in some platforms possibility of real-time monitoring of the patients [8].

Localized surface plasmon resonance (LSPR) has emerged as a leader among label-free biosensing techniques in that it offers sensitive, robust, and facile detection [9]. This technic is based on specific characteristic of metallic or metalized nanostructure materials, in which the signals are generated when the incident photon frequency resonates with the collective oscillation of free electrons. The LSPR extinction spectrum, which can be monitored in the ultraviolet (UV)–visible region, is known to be associated with the composition, size, shape, orientation, and local dielectric environment of nanoparticles. In particular, the peak wavelength of the LSPR extinction spectrum ( $\lambda_{\text{max}}$ ) is highly sensitive to even subtle changes of the local refractive index near the nanoparticle surface induced by bio-molecular interactions. This optical property enables noble metal nanoparticles to serve as biosensors that can transform biological recognition information into analytically useful signals in the form of LSPR  $\lambda_{\text{max}}$  shifts [9, 10].

There are several fabricating methods to construct LSPR sensors; most of them are based on lithography such as electron beam lithography (EBL) and nano-sphere lithography (NSL) [11, 12]. Nano-sphere lithography is a relatively inexpensive method, with low efficiency in producing large-scale various nanostructures with repetitive manner. Despite being very efficient for fabricating various nanostructures, EBL cannot be used for massive production, because it is considered to be very expensive along with the time consuming procedure for production of a micro-scale area [13].

Glancing angle deposition (GLAD) is an inexpensive method, with enough efficiency for fabricating nanostructures; beside it is capable of producing remarkably diverse shapes. In this method, physical vapor deposition is used in which the rotating substrate is exposed to vapor flux with a large deposition angle ( $> 75^\circ$ ) with respect to the substrate normal [14, 15]. By adjusting different parameters of GLAD such as deposition angle, deposition rate, and speed of substrate rotation, it is possible to fabricate a variety of nanostructures [13]. Despite several advantages, due to inherent broadness of plasmonic peaks of nanostructures fabricated by GLAD, there are limited cases reported using this protocol as a method of choice for constructing LSPR-based biosensors.

In this paper, an LSPR-based biosensor for detection of PSA has been constructed. We could successfully manage to fabricate silver nanostructures using GLAD with narrow plasmonic peaks and comparable sensitivity with respect to the other fabrication methods such as lithography.

## Experimental Design

### Materials

High-purity silver granules (99.99%), 11-mercaptoundecanoic acid (MUA), 1-ethyl-3-[3dimethylaminopropyl] carbodiimide hydrochloride (EDC), and N-hydroxysuccinimide (NHS) were purchased from Merck (KGaA Darmstadt, Germany). 6-Mercaptohexanol (6-hydroxyl-hexanethiol) was also purchased from Sigma-Aldrich (St. Louis, MO, USA).

Anti-PSA monoclonal antibody and high-purity PSA were purchased from Abcam (Cambridge, MA, USA). All of the other materials and reagents were also obtained from Sigma-Aldrich (St. Louis, MO, USA). In order to minimize the influence of environmental contaminations, most of the experiments were performed under a laminar flow hood.

### UV-visible spectroscopy

Each step of surface modification was followed by a washing step in which pyrogen-free water has been used to remove unbounded molecules. Afterward, the silver nano-columns were immediately exposed to  $\text{N}_2$  stream to be dried. Then, the substrates were examined using a UV-visible spectrometer and the extinction spectra of the substrates in air were taken from 200 to 800 nm and the corresponding LSPR peak wavelengths were collected. The spectrometer light was emitted perpendicularly onto the substrates' surface.

### Deposition of Silver Nano-column on Glass Substrate

Pieces of microscope cover glass ( $0.6 \text{ cm} \times 2.5 \text{ cm}$ ) were used as substrate for depositing silver nano-columns. Glass slide substrates were cleaned by piranha solution ( $\text{H}_2\text{SO}_4:\text{H}_2\text{O}_2 = 3:1$ ) at  $80^\circ \text{C}$  for 30 min, and then, the slides were washed by water and dried under  $\text{N}_2$  stream. Silver nano-columns were deposited on glass substrate by GLAD method optimized in our laboratory in which the parameters used for deposition of silver nano-column including deposition rate and thickness, azimuthal rotation speed, and glancing angle were optimized at  $0.1 \text{ nm/s}$ ,  $t = 400 \text{ nm}$ ,  $\varphi = 2 \text{ rpm}$  and,  $\theta = 84^\circ$ , respectively [16].

## Reproducibility Study of the Nanostructures

One of the most critical characteristics of any diagnostic device is its reproducibility. By far, most of the LSPR-based biosensors show great reproducible results [17]. To evaluate the reproducibility of deposited nanostructures, six randomly selected silver nano-columns were examined by UV-visible spectroscopy.

## SAM Formation, Stability Study, and Surface Functionalization

Deposited silver nano-columns formed on glass substrate should be stabilized by a SAM. In this step, silver nano-columns were soaked in a 1 mM ethanolic solution of MUA for 2 h. Then, two different strategies have been used, one of which with MUA as the only stabilizing agent and the other with the mixture of 1:4 solutions of 1 mM 6-mercaptohexanol and 1 mM MUA. Then, the substrates were incubated in 1:1 solutions of EDC 45 mM and NHS 20 mM in PBS (10 mM, pH = 6.5) for 1 h in order to activate the carboxylic acid groups of SAM. Afterward, SAM-coated substrates were immersed in 1 mL of four different concentrations of anti-PSA antibody solution in PBS for 1 h, so that the optimal concentration of antibody has been determined.

## Sample Preparation and Detection of PSA

Commercial PSA (Abcam) were prepared in different concentrations based on clinical significances. Then, the antibody-immobilized substrates were exposed to different concentrations of PSA for 1 h. LSPR peak wavelength of each substrate was measured after PSA interaction with antibody-immobilized substrates. The difference between this LSPR peak wavelength and the LSPR peak wavelength of antibody-immobilized substrate was reported as  $\Delta\lambda_{\max}$ . Moreover, the selectivity of the biosensors was evaluated using similar and frequent antigens found in circulation. The schematic representation of surface modification and PSA detection are shown in Fig. 1.

## Stability studies

One of the most important challenges of GLAD-made silver nano-columns is their stability. We used a SAM of MUA to stabilize our nano-structures. In order to examine the stability of silver nano-columns, a bare and a SAM-functionalized silver substrate have been immersed in PBS solution for 24 h and then the LSPR spectra of the substrates in PBS solution were measured at special time steps during 24 h.

## Results and Discussion

### Deposition of Silver Nano-column

For fabricating of LSPR biosensor, here we used GLAD as the method of choice. Using GLAD with described parameters, 400 nm of silver (Ag) was deposited on glass substrates. The refractive index sensitivity of the nano-columns produced by these parameters was 134 nm/RIU. Figure 2 shows the top view SEM image of fabricated silver nano-columns in which a compact array of nano-columns could be seen (Fig. 2a). The UV visible absorbance spectrum of fabricated Ag nano-columns is also shown in Fig. 2. Strong plasmonic peak around wavelength of 382 nm with width of 126 nm has been recorded for Ag nano-columns, which is suitable for sensing experiments based on our coworker's previous results [13]. According to the histogram, the size diameter of silver nano-columns is in the range of 10 to 120 nm (Fig. 2c).

### Reproducibility of Fabricated Nano-columns

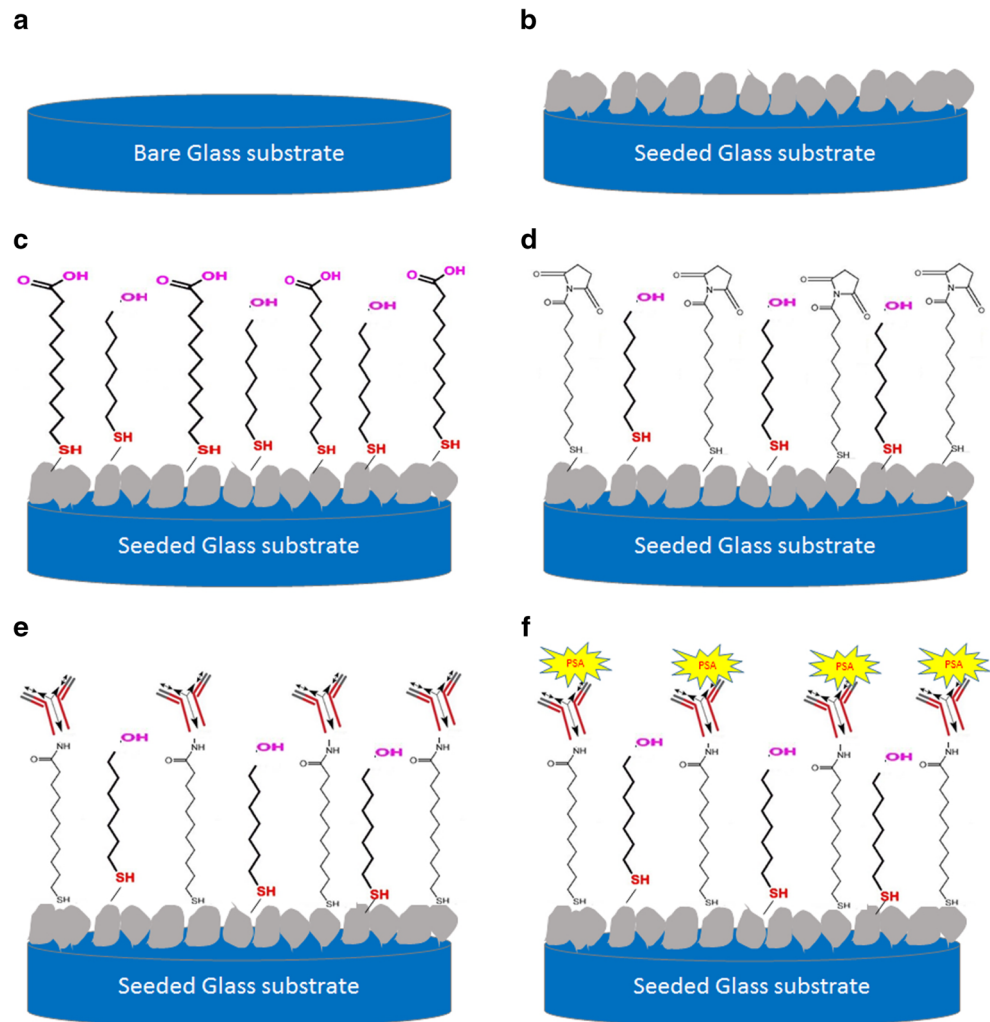
One of the most critical factor in LSPR biosensing is reproducibility, which is mainly affected by the method of fabrication. The more uniform the nanostructures, the more reproducible the results. As long as GLAD is a physical procedure, then the reproducibility of fabricated nanostructures is remarkably high; beside it is possible to build nanostructures in large scale. The reproducibility of fabricated nano-columns was evaluated using six different randomly selected substrates. The LSPR spectra of each sample are shown in Table 1. As the data shows, the LSPR spectra of the nano-columns exhibit remarkable reproducibility, with almost the same LSPR peak wavelength located in a small range of 380–385 nm.

### SAM Formation and Optimum Antibody Concentration

As previously described, we used two different solutions for stabilizing step and each step was followed by incubation in four different concentrations of anti-PSA antibody. In first strategy, we used MUA as the only solvent by which the stabilization procedure had been performed. This methodology was frequently used elsewhere for LSPR biosensing [18, 19], and the results are shown on Table 2. For each sample, 10 ng/ml of PSA had been incubated for 1 h on antibody-coated silver nano-column.

In the second strategy, we used MUA and 6-mercaptohexanol for stabilizing procedure. The results showed that stabilizing by a mixture of 6-mercaptohexanol

**Fig. 1** Schematic representation of coimmobilization of silver nanoparticles using MUA and 6-mercaptohexanol. **a** Silver nano-columns were stabilized by MUA and 6-mercaptohexanol. **b** Stabilized nano-columns were activated by EDC:NHS. **c** Activated nano-columns were coated by antiPSA antibody. **d** Anti-PSA-coated nano-columns were exposed to PSA for recognition step



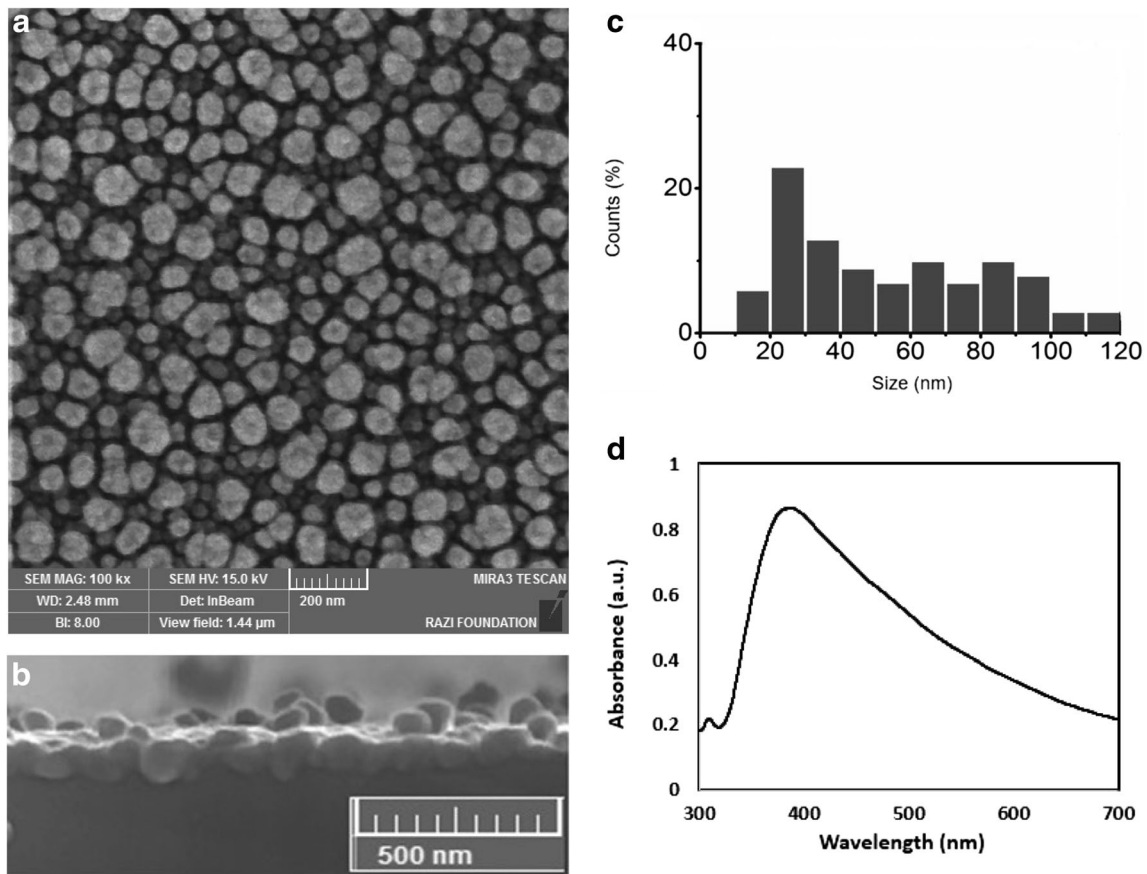
and MUA had greater LSPR shift in functionalization and PSA binding steps (Table 3). MUA alone as stabilizing agent aggregate in a condensed fashion on the surface of silver substrate, so the correct orientation of antibody in the next steps would encounter with steric hindrance. 6-Mercaptohexanol fits itself between compact arrays of MUA molecules which results in less condense formation of MUA on silver substrate. This situation facilitates correct orientation of antibodies as recognizing agent on activated silver nano-columns, enhancing the capability of nano-sensor to detect small amounts of analytes.

In both procedures, 10 nM of antibody showed greater LSPR shift and better response to PSA binding step. These results demonstrate that higher concentrations of antibody (as recognizing agent) in a defined range would result in better response in recognition step (here, PSA binding step). It should be noted that when the concentration of antibody rises to higher level, the LSPR response to the antigen binding step drops, leading to lower amount of LSPR red shift, hence decreased sensitivity. When excessive amounts of antibodies are

used to functionalize the surface, steric hindrance may occur, making it more difficult for PSA to bind to the surface of the activated silver nano-column. It is clear that maximizing the red shift help increase the sensitivity of the biosensor, enabling it to detect trace amount of PSA in biological samples. As the results indicate, there is slight difference in observed red shift between 10 and 20 nM concentration of antibody, so we used 10 nM for the following steps of our experiments.

### Stability of Silver Nano-columns

In biosensing procedures, substrates usually undergo incubation steps in different solvents, which may lead to unwanted changes in their composition. It is clear that any unwanted structural changes in nanoparticles would lead to a change in LSPR spectra. In LSPR biosensing, silver-based nanoparticles should be stable in oxidative environment of different solvents. Therefore, the stability of silver nano-columns must be investigated throughout incubating steps.



**Fig. 2** **a** SEM image of silver nano-column fabricating by GLAD. **b** Side view SEM image of the nano-columns. **c** Absorbance spectra of silver nano-column and **d** size distribution of fabricated nano-columns

Figure 3a shows the results of our stability experiments in which a bare silver nano-column immersed in PBS and the extinction LSPR spectra of the nano-column have been collected during 24 h. As the figure shows, after 1-h incubation, there is a dramatic reduction in peak intensity and a little blue shift is also observed. This blue shift is caused by oxidation of the substrates in aqueous phase. At the end of 24-h incubation, there is greater reduction in peak intensity (about 40%), which probably originates from detachment of silver nanoparticles from the glass surface.

On the other hand, a SAM-functionalized silver nano-column was immersed in PBS in similar condition to check if the SAM could improve the stability of nano-column. As Fig. 3b shows, during incubating steps, there is no significant reduction in peak intensity, implying that the SAM-functionalized silver nano-column is stable against unwanted changes caused by solvents.

### Surface Modifications and LSPR Effect

After each step of surface modifications, LSPR spectra were measured. According to the results obtained in previous step, we chose second strategy for stabilizing procedure and 10 nM antibody for activation of nano-columns. The responses of the nano-biosensors are shown in Fig. 3. As this figure shows, before modification, the LSPR  $\lambda_{max}$  of the bare silver nano-column was measured at 382.35 nm (curve A). A representative LSPR  $\lambda_{max}$  of the silver nano-column after modification with MUA:6-mercaptohexanol and activation (by EDC and NHS) was 401.80 nm with a corresponding LSPR  $\Delta\lambda_{max}$  of + 19.45 nm (curve B). After that, the nano-columns were incubated in a solution of 10 nM anti-PSA antibody and the LSPR  $\lambda_{max}$  shifted to 411.91 nm, with an additional 10.11 nm red shift (curve C). After incubation in 10 ng/ml PSA, the LSPR wavelength shifted to + 23.13 nm, showing

**Table 1** Reproducibility of silver nanostructures

Nano-column	1	2	3	4	5	6
$\lambda_{max}$ (nm)	382.22	383.44	381.09	380.85	384.23	382.55
Absorbance at $\lambda_{max}$ (a.u.)	0.9244	0.8932	0.8955	0.9112	0.8966	0.9332

**Table 2** LSPR response to PSA binding to antibody-coated silver nano-column stabilized with MUA

Antibody concentration(nM)	$\Delta\lambda_{\max}$ (nm)	
	Antibody	PSA
1	1.24	− 5.77
10	7.34	11.44
20	12.50	12.02
40	14.55	2.60

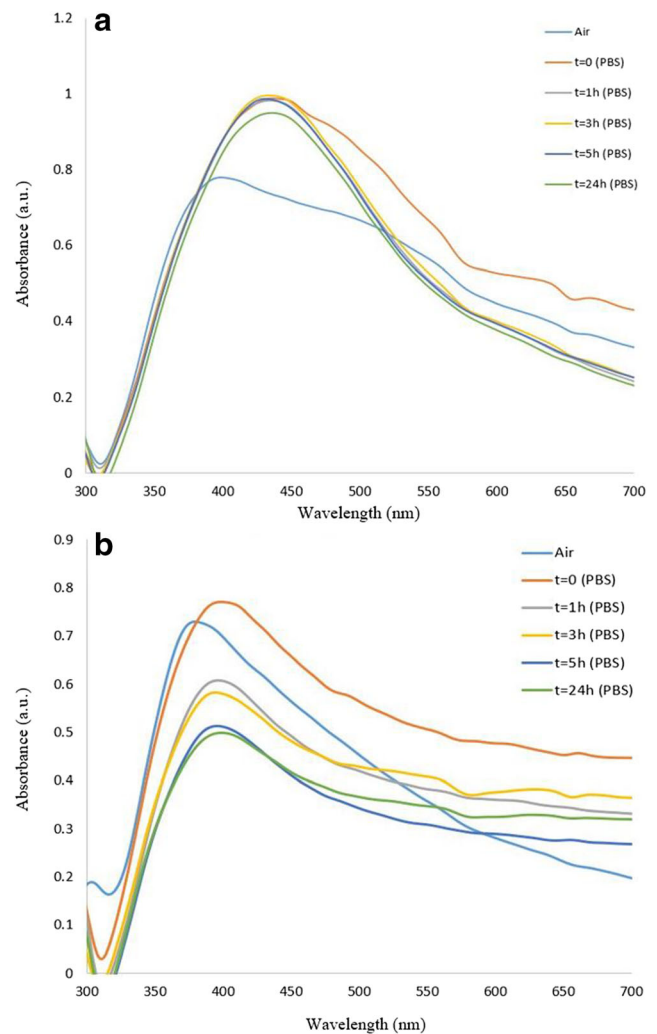
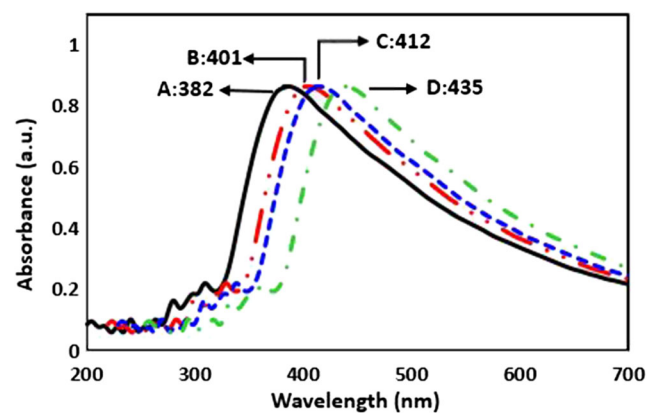
a  $\lambda_{\max}$  of 435.04 nm (curve D). These experimental data have clearly demonstrated that the biosensors used in this paper were successfully able to detect PSA in buffer solution.

## Calibration Curve

In order to construct a calibration curve, the anti-PSA-coated nano-biosensors were exposed to standard solutions of PSA ranging from 0.5 to 24 ng/ml in optimal condition and then the corresponding LSPR wavelength shifts for each solution were recorded. As seen in the Fig. 4, LSPR values increase stepwise in response to increasing concentration of PSA standard solutions, with the coefficient of determination of  $R^2 = 0.997$ , demonstrating excellent fitting. It is also shown that our nano-biosensors react even to the concentration of 3 ng/ml, a value that is under the critical laboratory concentration of PSA. The LOD of the biosensors was also calculated based on EC value in which 10% of maximum signal is considered the signal related to the minimum detectable concentration. Using EC value, the LOD of nano-sensor is calculated to be 850 pg/ml. The LOD of some other nano-sensors with different detection method developed for PSA quantification is seen in Table 4. According to the clinical range of PSA (4–10 ng/ml), it seems that our nano-sensor can reliably detect PSA in its clinically important levels. As it represented in calibration curve, our nano-biosensors show predictable reaction in critical levels of PSA, again demonstrating their excellent potential as future diagnosis tools.

**Table 3** LSPR response to PSA binding to antibody-coated silver nano-column stabilized with MUA and 6-mercaptohexanol

Antibody concentration (nM)	$\Delta\lambda_{\max}$ (nm)	
	Antibody	PSA
1	1.77	− 7.43
10	10.45	22.21
20	14.53	21.77
40	16.77	3.75

**Fig. 3** UV-visible spectra of bare silver-nano-column substrate (a), and SAM-functionalized substrate (b), before and after immersing in PBS solution for various incubation times**Fig. 4** LSPR spectra for sequential steps of co immobilization of silver nano-column using MUA and 6-mercaptohexanol followed by activation and detection steps. **a** Bare silver nano-column  $\lambda_{\max} = 382.35$ . **b** Silver nano-column after formation of a SAM by MUA and 6-mercaptohexanol and surface modification by EDC:NHS  $\lambda_{\max} = 401.80$ . **c** SAM-coated anti-PSA antibody  $\lambda_{\max} = 411.91$ . **d** Antibody-immobilized substrate exposed to 10 ng/ml PSA  $\lambda_{\max} = 435.04$

**Table 4** LOD of different biosensors made for PSA detection

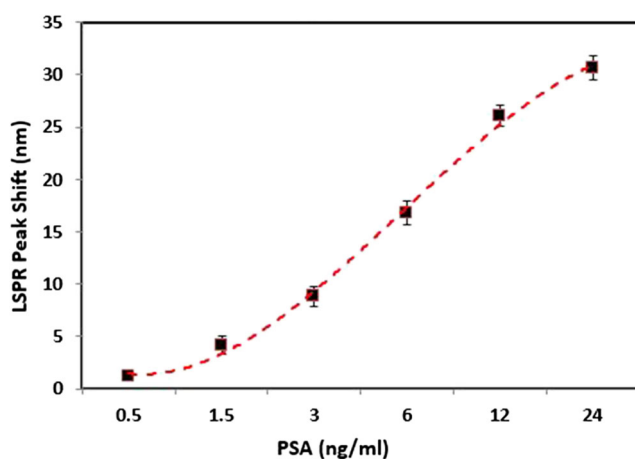
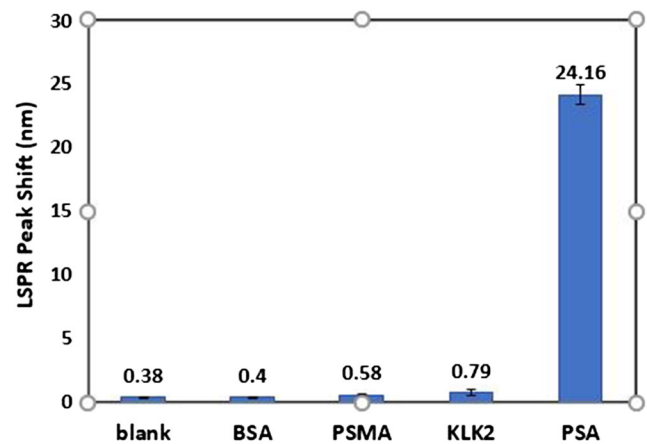
Detection method	Sensing element	LOD (pg/ml)	Reference
Electrochemical	Antibody	5000	[20]
Electrochemistry	Antibody	6	[21]
Optical	Antibody	18,000	[22]
LSPR	Antibody	340	[16]
LSPR	Antibody	850	This study

## Selectivity and Negative Control

Bovine serum albumin (BSA) as the most abundant protein in blood circulation, *PSMA* (prostate-specific membrane antigen), *KLK2* (Kallikrein-2) as the most similar human protein to the PSA, and deionized water as negative control (blank) were used to assess the selectivity of the nano-sensor. For this purpose, we used 10 ng of each control solution to see if the silver nano-column reacts with its target selectively or not. Having exposed controls with nano-sensors, no significant shift in LSPR peak was observed. As the Fig. 6 implies, our nano-sensors react in a target specific manner, showing no significant cross-reaction to non-specific targets. One of the most important characteristics of any diagnostic tool is specificity, which is mainly determined by its selectivity. Lower selectivity may lead to more false positive results; hence, the higher the specificity, the lower the false positive results (Fig. 6). The nano-sensors used in this study have been proved to be specific, making them promising tools for constructing new reliable PSA quantification device.

## Conclusion

A nano-sensor should be sensitive, rapid, target-specific, label-free, easy to use, and financially affordable to be

**Fig. 5** Calibration curve of anti-PSA modified nano-biosensors exposed to different standard solutions of PSA**Fig. 6** Selectivity of nano-sensors to some related antigens and negative control. Concentration of each sample was 10 ng/ml

popularly used as a diagnostic device. The LSPR methodology seems to have all of the above characters, which makes it an ideal technique for constructing nano-biosensors. In this paper, we used an LSPR biosensor for detection of PSA. Briefly, piranha-treated glass substrates were used as surface for silver deposition. Having deposited silver on glass substrate, the surfaces were stabilized by a mixture of 11-mercaptoundecanoic acid (MUA) and 6-mercaptohexanol, followed by an activation step with EDC-NHS. Then, the anti-PSA antibody has been conjugated to the activated surfaces and the optimum concentration of anti-PSA antibody as recognizing agent was also determined. Using 10 nM anti-PSA antibody as the optimum concentration, we were able to plot calibration curve and calculate LOD. Serum biomarkers like PSA are routinely quantified by complicated methods based on immunoassay such as ELISA and chemiluminescence, both of which are time consuming and require dedicated laboratory facilities. Here we evaluated LSPR-based nanostructures with the capability of sensitive detection of PSA along with the fact that these nano-sensors are very easy to be handled, cheap, and easily miniaturized; therefore, the need for the availability of complex laboratory equipment has been eliminated. Here, we utilized a SAM of MUA and 6-mercaptohexanol to stabilize silver substrate in order to minimize possible oxidation and detachment of silver nanostructures. The biosensors we used for our experiments were successfully able to detect PSA in buffer solution in a selective manner. Nowadays, there is a growing interest in using portable device capable of measuring bio analytes in home. Portable glucometers are good examples of such devices. This concept is known as point-of-care testing (POCT) in which the patients do not need to refer to the medical laboratories to be evaluated for some biomarkers. As long as these sensors can be simply miniaturized, so they seem to be an ideal candidate for building POCT devices for PSA quantification.

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