Peer-reviewed version available at Biosensors 2018, 8, 132; doi:10.3390/bios8040132

Recent progress in surface plasmon resonance biosensors (2016 to mid-2018)

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Abstract

Almost 50 papers on surface plasmon resonance biosensors, published between 2016 and mid-2018, are reviewed. Papers concerning the determination of large particles such as vesicles, exosomes, cancer cells, living cells, stem cells and microRNA are excluded, as these are covered by a very recent review. The reviewed papers are categorized into five groups, depending on the degree of maturity of the reported solution: ranging from simple marker detection to clinical application of a previously developed biosensor. Instrumental solutions and details of biosensor construction are analyzed, including the chips, receptors and linkers used, as well as calibration strategies. Biosensors with a sandwich structure containing different nanoparticles are considered separately, as are SPR applications for investigating the interactions of biomolecules. An analysis is also made of the markers determined using the biosensors. Concluding, there is shown to be a growing number of SPR applications in the solution of real clinical problems.

Keywords: Surface plasmon resonance; cancer markers; biosensors; receptor immobilization; antibodies; nanoparticles

Biosensors are the subject of enormous expectations and are gradually gaining in diagnostic importance. However, there still is a shortage of biosensors offering near 100% sensitivity and selectivity. A limited number of measuring techniques are used successfully in combination with biosensors, the leader among which is ELISA. Surface plasmon resonance (SPR) is still only a promising technique which, so far, has no practical diagnostic applications. However, the number of potential applications of SPR in the solution of real clinical problems is growing. This paper reviews the most recent publications on SPR biosensors, appearing between 2016 and mid-2018. Earlier works are covered in an excellent review by Masson (2017)[1]. This review excludes papers concerning SPR biosensors used for the determination of large particles such as vesicles, exosomes, cancer cells, living cells, stem cells, etc., as well as microRNA—these papers have already been broadly reviewed [2]. Both Masson and Ferhan et al. conclude that future work should focus more on clinical samples than on improving detection specificity and sensitivity.

Table 1. Stages of biosensor development and technical solutions for biosensors

Stage	Marker	SPR type	Fluidic/ Non fluidic	Chip	Linker /receptor	Receptor immobilization	Reference
Cancer markers							
i	HER2	SPR	Micro-fluidic	Nano-whole array	Cysteamina/ Sandwich/ 2Antibodies	Biotin/ streptavidin	[3]
i	CEA	SPR	Fluidic	Slide/Cr/Au	MUA /antibody	EDC/NHS	[4]
i	Cytokeratin 17	SPR	Non fluidic	Optical fiber/Au	S2PEG6COOH/ antibody	EDC/NHS	[5]
ii	Cytokeratin-19	SPR	Both	prism	Cysteamine/ GOCOOOH/ /antibody	EDC/NHS	[6]
iii	PSA	SPRi	Fluidic	Slide/Au	Allyl mercaptan	PSA imprinted polymer	[7]
iv	Rac1, Rac1b	SPR	Fluidic	CM5 chip	Dextran-COOH/ Antibody	EDC/NHS	[8]
iv	5LOX	SPR	Fluidic	CM5 chip	Dextran-COOH/ Antibody	EDC/NHS	[9]
iv	CDK4	SPR	Fluidic	CM5 chip	Dextran-COOH/ Antibody	EDC/NHS	[10]
iv	Laminin-5	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[11]
iv	Collagen IV	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[12]
iv	MMP1	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[13]
iv	20S immune-proteasome	SPRi	Non fluidic	Slide/Au/ array	1-octadecano-thiol / Inhibitor ONX 0914	Hydrophobic interaction	[14]
iv	MMP2	SPRi	Non fluidic	Slide/Au/ array	1-octadecano-thiol / Inhibitor ARP 101	Hydrophobic interaction	[15]
v	podoplanin	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[16]
v	20S proteasome	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Inhibitor PSI	EDC/NHS	[17]
v	Cystatin C	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[18]
Non cancer markers							
i	BSA	SPR	Both	Prism/Au	Cysteamine/ GOCOOOH/ /antibody	EDC/NHS	[19]
i	BSA	SPR	Non fluidic	Slide/Au	mercapto propane sulfonate/ modified GO	EDC/NHS	[20]
i	Cytochrom C	SPRi	Fluidic	Easy2Spot	antibody	Sensor pre-activated G-type Senseye	[21]
ii	Transferrin	SPR	Fluidic	Slide/Au	4-Mercapto phenylboronic	4-Mercapto phenylboronic	[22]
ii	Folic acid	SPR	Fluidic	Prism/Ti/ Au/graphen	FAP	Hydrophobic interaction	[23]
iii	CBP	SPR	Fluidic	CM5 chip	Dextran-COOH/ Antibody	EDC/NHS	[24]
iii	Troponin T	SPR	Fluidic	Slide/Au	Polydopamine/ Epitop/	Polymer Imprinted	[25]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 October 2018 doi:10.20944/preprints201810.0675.v1

Peer-reviewed version available at Biosensors 2018, 8, 132; doi:10.3390/bios8040132

						epitop	
iv	YKL40	SPR	Fluidic	CM5 chip	Dextran-COOH/ Antibody	EDC/NHS	[26]
iv	Mortalin & αSynuclein	SPR	Fluidic	CM5 chip	Dextran-COOH/ Antibody	EDC/NHS	[27]
iv	Fibronectin	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[28]
v	UCHL1	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[29]
v	MMP2 Laminin5 Collagen IV	SPRi	Non fluidic	Slide/Au/ array	1-octadecano-thiol / Inhibitor ONX 0914 Cysteamine/ antibody	Hydrophobic Interaction EDC/NHS	[30]
v	UCHL1	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[31]
v	20S proteasome	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Inhibitor PSI	EDC/NHS	[32]
v	UCHL1	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Antibody	EDC/NHS	[33,34]
v	20S proteasome	SPRi	Non fluidic	Slide/Au/ array	Cysteamine/ Inhibitor PSI	EDC/NHS	[35]

EDC/NHS – covalent amide bond formed due to the EDC/NHS protocol

GO – graphite oxide

A majority of the reviewed papers concern biosensors for the determination of cancer markers. The applied solutions differ in terms of biosensor construction, operational mode and type of SPR technique. These details are given in Tables 1 and 2. Table 2 summarizes the cases in which nanoparticles were applied. In Table 1, biosensors for cancer markers are shown separately.

Table 2. Stages of biosensor development and technical solutions for biosensors with the use of nanoparticles

Stage	Marker	SPR type	Fluidic/ Non fluidic	Chip/NP	Sandwich/ /other	receptors immobilization (chip/antibody)	Reference
ii	Folic acid	SPRi	Non fluidic	Array/Cr/Au/ FA-AuNP	Sandwich	HS-(CH2)11-EG3-NTA/polyhistidine	[23]
ii	Troponin I	SPR	fluidic	Slide/Au/ /HGNP / MMWCNTs-PDA	Sandwich/ / MMWCNTs-PDA	Polydopamine/ Polydopamine	[36]
iii	CEA	SPR	fluidic	Slide/Ti/Au /AuNP	Sandwich	HS-OEG-COOH/ HS-OEG-COOH/ EDC/NHS	[36]
iii	HER 2	SPR	Micro-fluidic	Prism/Au/ SAv-GNPs	Sandwich	MUA/ EDC/NHS/	[38]

						/biotinylated antibody	
iv	Cytochrom C	SPR	fluidic	Slide/Au /AuNR	Sandwich/ /MMP	Straptavidin/ /biotinylated aptamer/ /antibody/MMP	[39]
iv	AFP, CEA CYFRA 21-1	SPR	Micro-fluidic	Prism/Au	Sandwich/ /QD	Hexanedithiol/ /antibody/ DTBE	[40]

SAv-GNPs - Streptavidin decorated gold nanoparticles
FA-AuNP – AuNP functionalized with polyhistidine tagged folic acid binding protein
AuNR – Au nanorods
MMP – micro magnetic particles
QD- quantum dot (CdSe/ZnS core/shell structure)
DTBE - 2,2′ -dithiobis[1-(2-bromo-2-methylpropionyloxy)]ethane
AFP- α-fetoprotein
MMWCNTs-PDA - Polydopamine-wrapped magnetic multi-walled carbon nanotubes
HGNP - hollow gold nanoparticles

The tables do not contain data on the limits of detection and ranges of concentration of the reported biosensors. In our opinion, a more significant piece of information is whether the range of measurable concentration covers the range of concentrations of the marker in cancer samples and a representative level for the healthy population. In some cases, the reported dynamic response range covers several orders of magnitude (e.g. [37]). However, linearity of the analytical response is obtained when the analytical signal is plotted against log marker concentration. In other cases, linearity of the analytical signal against the marker concentration is reported, but in a significantly narrower concentration range. Generally, all calibration graphs represent the Langmuirian curve type, in which the initial sections may approximately follow the strain lines, while the whole curve may be approximately linear when the analytical signal is plotted against log marker concentration (see Fig. 1). Almost all of the reviewed papers containing calibration data report calibration on the basis of a linear calibration graph. Only two papers refer to semi-log calibration [19,24]. This appears to be a reasonable choice, because determination of the logarithm of the marker concentration does not satisfy expectations for clinical results.

Generally, a mature biosensor and a procedure for the determination of a particular marker is developed in several stages. This is clearly visible in the reviewed papers concerning SPR biosensors. The following stages of development of a biosensor and a related analytical procedure can be distinguished:

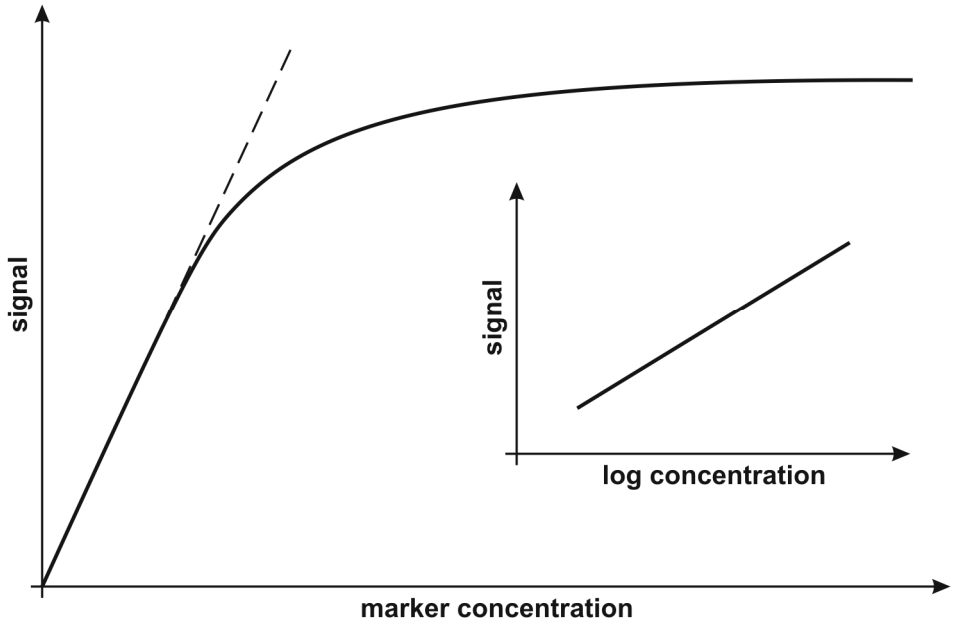

Fig. 1. Typical calibration curves

i. The biosensor is used only for the detection of a marker (as a rule, a cancer marker);
ii. The biosensor is characterized in terms of quantitative marker determination (calibration graph, the marker concentration range covered by the biosensor);
iii. The biosensor and related analytical procedure are validated (precision, recovery, interferences, comparison of results with another procedure such as ELISA, examples of natural samples e.g. blood plasma);
iv. The mature biosensor and the analytical procedure are used for investigation of the marker in significant series of clinical samples, including long control series of healthy donors;
v. A fifth stage may be distinguished when the mature SPR biosensor and procedure are used in clinical investigation.

A majority of the reviewed papers present mature solutions (type iv; see Tables 1 and 2) or are devoted only to the application of previously developed biosensors in clinical investigations (type v). This is the direction recommended in the reviews by Mansson and Ferhan et al.,[1,2] and gives an indication of the future growing significance of SPR.

As regards instrumental solutions, both classical SPR and SPR imaging are equally represented. Surprisingly, none of the reviewed papers used localized SPR. Approximately the same number of reviewed papers reported the use of fluidic and non-fluidic measurement. In two cases the use of both options as alternatives was reported, and in five cases fluidic measurements were performed as microfluidic. There is a significant difference in the arrangement of a fluidic or non-fluidic

measurement: a fluidic measurement is usually performed with *in situ* creation of a biosensor, while in the non-fluidic case the biosensor is prepared *ex situ*. In the fluidic version a biosensor is created during the measurement by sequential introduction of a linker, a receptor and a solution containing the determined marker. Finally, the chip sensor is cleaned to prepare it for the next measurement. A single biosensor usually contains several channels, processed simultaneously for multi-sample measurement or for processing the same solution to gain better precision. The non-fluidic version is usually performed as an array of separated measuring points. Approximately a dozen measuring points are used for a single measurement to improve the precision of the result. Multi-sample measurement is also carried out, as well as the regeneration of the chip after measurement.

A glass slide covered with gold is a typical chip base. Alternatively, a gold-covered glass prism is used. Usually, a chromium—or alternatively, titanium—under-layer is used. Only a few papers report other solutions, such as a gold-covered glass fiber [5], a gold nanohole array [3] or a prism covered with gold and graphene [41]. Frequently, a gold chip surface is covered by a polymer with holes, creating an array of free gold measuring points.

A crucial part of a biosensor is the receptor. The receptor must ensure that only the target marker is captured from the analyzed sample, as well as ensuring suitable effectiveness in terms of the strength of analytical signal sufficient for the determination of a marker in real samples. In the reviewed papers, appropriate antibodies were most frequently used as receptors. The antibody was attached to the gold chip surface via a linker. Most frequently, cysteamine (2-aminoethanethiol) was used as the linker. Cysteamine is fixed onto the gold surface by the thiol group, while the amine group is used for attachment of the antibody. An EDC/NHS protocol is applied for this purpose, with amide bond formation between the antibody's carboxyl group and the linker's amine group. Alternatively, MUA (11-mercaptoundecanoic acid) may be used in conjunction with the EDC/NHS protocol [4]. The amine group of the antibody is used for the junction. Similarly, HS-OEG-COOH [37], S2PEG6COOH [5] (where OEG and PEG denote oxyethylene subunits) and mercapto propane sulfonate [20] have been used. In numerous papers, the commercially available CM5 chip with carboxylated dextran as the linker was employed. Another commercially available chip (Easy2Spot) is supplied in a form ready for antibody bonding [21].

To enhance the SPR signal, a sandwich biosensor may be used [3]. The first antibody captures the marker, while the marker captures the second antibody. The introduction of different nanoparticles in the sandwich can lead to much greater enhancement of the SPR signal (see Table 2). In the simplest solution, the first antibody attached by the EDC/NHS protocol captures the marker, which captures an aggregate consisting of a gold nanoparticle covered by a second antibody attached to the antibody surface by the same EDC/NHS protocol [37]. A similar solution is reported [38] in which the EDC/NHS protocol is used for the first antibody attachment, and a biotinylated antibody attached to streptavidin-decorated gold nanoparticles serves as the second. The preconcentration of the marker with magnetic microparticles covered by the antibody has been reported [39]. Finally, the signal is

created indirectly by a selected aptamer released from the magnetic microparticles–antibody–marker–aptamer structure. A quantum dot having CdSe/ZnS core/shell structure has also been used for SPR signal enhancement in a sandwich configuration [40], as have polydopamine-wrapped magnetic multi-walled carbon nanotubes [35].

Several solutions other than antibodies have been used as receptors. A marker's inhibitor can be used as the receptor, as in the cases of the inhibitor ONX 0914 [14] and the inhibitor ARP 101 [15]; in both cases 1-octadecano-thiol was used as the linker, and the inhibitor was attached to the linker via hydrophobic interactions. A receptor-imprinted polymer may also be used as the receptor [7,25].

In the reviewed papers, the targets of the developed—or merely applied—biosensors are various types of cancer, as well as other diseases. These targets are listed in Table 3. Lung, bladder and breast cancers are most frequently represented. Single papers have been devoted to colorectal, prostate, and head and neck squamous cell cancers, as well as acute leukaemia. Among non-cancer applications, thermal injuries have been most frequently investigated, as well as acute myocardial infarction and acute appendicitis. Single papers have been devoted to apoptosis, asthma, megaloblastic anemia, Parkinson's disease, hypertension, primary renal disease and diabetes. Some biosensors have found applications with several diseases; for example, 20 S proteasome and UCHL1. In the majority of cases, the biosensors were used for the determination of markers in the blood serum or plasma, although in several cases, urine was the target body fluid.

Table 3. Markers and related diseases

Marker	Abbrev.	Cancer /or other disease	Body fluid
Arachidonate 5- lipoxygenase	5LOX/ ALOX5	Breast cancer	Blood plasma
Carcinoembryonic antigen	CEA	Colorectal cancer	Blood serum
Calcium Binding Protein	CBP	Acute myocardial infarction	Blood serum
Chitinase-3-like protein 1	CHI3L1/ YKL-40	Asthma	Blood serum
Collagen IV		Breast cancer/ burns	Blood serum
Cyclin-dependent kinase 4	CDK4	Lung, head and neck cancers	Blood serum
Cystatin C		Bladder cancer	Blood serum, urine
Cytochrom C		Apoptosis	No information
Cytokeratin 17	CK 17	Lung cancer	No information
Cytokeratin 19	CK19	Lung cancer	Blood plasma
Epidermal receptor protein-2 antigen	HER	Breast cancer	No information
Fibronectin		Burns	Blood plasma
Folic acid	FA	Megaloblastic anemia	Blood
20S-immunoproteasom	20Si	Acute leukemia	Blood plasma
Laminin 5		Bladder cancer/burns	Blood plasma
Matrix metalloproteinase-1	MMP1	Bladder cancer/ acute appendicitis	Blood serum
Matrix metalloproteinase-2	MMP2	Burns	Blood plasma
Mortalin/mitochondrial 70kDa heat shock protein,	mtHsp70	Parkinson's Disease	Blood serum
Podoplanin		Bladder cancer	Blood serum, urine

20S-proteasom	20Sc	Burns, acute appendicitis, cryptorchidism	Blood plasma
Prostate specific antigen	PSA	Prostate cancer	Blood serum
Ras-related C3 botulinum toxin substrate 1	Rac1	Non Small Cell Lung Cancer	Blood serum
Ras-related C3 botulinum toxin substrate 1b	Rac1b	Non Small Cell Lung Cancer	Blood serum
Transferrin	Trf	Hypertension, primary renal disease, diabetes.	Artificial urine
Troponin T	TnT	Acute myocardial infarction	Blood serum
ubiquitin carboxyl-terminal hydrolase L1	UCHL1	Burns, cryptorchidism, Acute Appendicitis	Blood serum

Apart from the papers devoted to the determination of particular markers in body fluids, several papers on SPR describe investigations of molecular interactions. One of these [42] describes the interactions of immobilized Cancer Antigen 125 (CA 125) with several aptamers. Elsewhere, the interaction between recombinant Smurf2 protein and CNKSR2 protein was described [43]. Other studies have investigated the parameters of binding between galectin-3 and pectin [44] and the glycosylation-dependent binding of galectin-8 to activated leukocyte cell adhesion molecule (ALCAM) [45]. A further study [46] investigated the affinity and competitive inhibition of nine caffeoylquinic acid compounds (CQAs) against programmed cell death protein 1 (PD-1) and its ligand PD-L1. Another investigation concerned the binding affinities of prostate-specific antigen to six lectins [47], and elsewhere, the ability of nanobody-targeting VEGFR (NTV1) to bind VEGFR2 D3 was demonstrated [48]. Generally, the aim of these papers is to investigate anti-cancer drugs and therapies.

Generally, a majority of the reviewed papers represent validated biosensors and related analytical procedures, which means a shift towards the requirements of medical diagnostics. Evaluation of the results in these procedures is generally based on straight line calibration curves. Approximately a half of the papers are devoted to cancer markers, while fluidic and non-fluidic instrumental solutions appear with roughly equal frequency.

Conflicts of Interest: The authors declare no conflict of interest

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