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Recent advances in biosensor devices for HER-2 cancer biomarker detection

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The human epidermal growth factor receptor 2 (HER-2) protein is a member of the epidermal growth factor receptor (EGFR or ErbB) family and is a transmembrane tyrosine kinase receptor. HER-2 is highly regulated in ovarian, lung, gastric, oral, and breast cancers. The low specificity, complexity, expensiveness and the lack of sensitivity are essential restrictions in traditional diagnosis methods such as FISH, immunohistochemistry and PCR and these disadvantages led to the need for more studies on alternative methods. Biosensor technology has greatly affected the quality of human life owing to its features including, sensitivity, specificity, and rapid diagnosis and monitoring of different patient diseases. In this review article, we examine various biosensors, considering that they have been categorized based on the transducers used including piezoelectric biosensors, optical sensors such as fluorescence and surface plasmon resonance, and electrochemical types for the diagnosis of HER-2 and the effectiveness of some drugs against that. Attention to developing some types of biosensor devices such as colorimetric biosensors for HER-2 detection can be an important point in future studies.

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1. Introduction

In recent years, breast cancer has been a primary reason for death among women and more than 2 million new patients who have breast cancer were distinguished, and an estimated 627 000 women died.[1] Tumor markers are highly utilized in the detection and prognosis of cancers,[2] although there are no specific tumor markers for breast cancer to date. The human epidermal growth factor receptor 2 (HER-2) protein is a member of the epidermal growth factor receptor (EGFR or ErbB) family and a transmembrane tyrosine kinase receptor and is highly regulated in ovarian, lung, gastric, oral, and breast cancers.[3] The primary role of HER-2 that is expressed in some organs, is facilitating uncontrolled or excessive tumorigenesis and cell growth.[4] The epidermal growth factor receptor family includes HER1 (EGFR), HER-2 (erbB2), HER3 (erbB3), and HER4 (erbB4).[5,6] These RTKs are transmembrane single subunit glycoproteins with intracellular tyrosine kinase, a catalytic domain, an extracellular ligand-binding domain, and a transmembrane domain. HER-2, also known as receptor tyrosine-protein kinase erbB-2, is a member of the EGFR family of receptor tyrosine kinases. The HER-2 protein is one of the tumor biomarkers which show overexpression in about 25–30% of breast cancer patients.[7] The low specificity and the lack of sensitivity results in the traditional diagnosis method leading to unsuitable clinical outcomes.[8] Also, the absence of a non-invasive way for accurate detection of cancer biomarkers in the bloodstream is the main concern. Standard methods, including immunoassay techniques utilized for the diagnosis of HER-2 often demonstrate low sensitivity and distinguish low-level proteins. However, immunopolymerase chain reaction methods have high sensitivity; their applications are limited because of complexity.[9] Other methods such as magnetic resonance imaging (MRI), mammogram, biopsy, and molecular breast imaging (MBI) are often used after the symptoms of

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breast cancer have been exhibited, and the biopsy technique is invasive.[10] Therefore, more rapid and sensitive methods are required to fulfill the rapid diagnosis needed in cancer diagnosis.

2. Conventional methods for detection of the HER-2 biomarker

Heterodimerization of HER-2 with other members of the EGFR family, routinely causes HER-2 up regulation and this process leads to the autophosphorylation of tyrosine residues within the cytoplasmic domain of the heterodimer and begins several signalling pathways because of tumorigenesis and cellular proliferation. Up regulation of HER-2 has been approved in a different set of solid tumours, including biliary tract cancer (BTC), bladder cancer, colorectal cancer (CRC), gastric and gastro-oesophageal junction (GEJ) cancers, non-small-cell lung cancer (NSCLC) and breast cancer.[11] HER-2 expression can be shown on cell membranes of epithelial cells in the placenta, urinary tract, gastro-intestinal tract, respiratory tract, skeletal muscle cells, reproductive tract, skin, breast and heart cells.[12] In recent studies, the appropriate clinical test detection of HER-2 levels in patients serum samples and routine devices for the determination of HER-2 levels have been developed. In fetal tissue, the HER-2 level is usually higher than in healthy adult tissue. Approximately 50% of breast cancers have a low level of HER-2 and absence of HER-2 amplification can be demonstrated. Circulating HER-2 extracellular domain (HER-2 ECD) levels were introduced as a surrogate for HER-2 tissue expression to monitor breast cancer patients for early responses to HER-2-targeted therapies because they are released into blood after cleavage and shedding from the tumor cell surface.[13] The current methods such as (1) evaluating the fluorescence *in situ* hybridization (FISH), chromogenic *in situ* hybridization (CISH), gene copy number by southern blot analysis, and polymerase chain reaction (PCR), (2) evaluating protein expression by immunohistochemical or western blot tests and (3) assessment of messenger RNA through PCR or Northern blot analysis can be used for determining the HER-2 status of patients.[14–16] Three of the mentioned tests have gained US Food and Drug Administration (FDA) approval for patient care purposes: ELISA, immunohistochemical analysis, and FISH. Existing detection technologies involve amplification of the HER-2 gene by fluorescence *in situ* hybridization (FISH) and use immune histochemistry (IHC) to measure the expression of the receptor within the cell membrane for HER-2 analysis.[17] ELISA is a monoclonal method that can be accomplished using either cell lysates on fluids or tissues. ELISA can be done on serum at any time during the disorder and it benefits from being a quantitative test. Also, ELISA is appropriate for monitoring advanced-stage disease. But, serum ELISA levels depend on the time of illness, tumor burden, and other reasons, including the phase of the menstrual cycle.[18] Serum HER-2 ECD levels were evaluated using both the HER-2 assays to compare the two ELISA methods. Moreover, baseline serum HER-2 ECD levels were determined with two monoclonal antibodies directed against the ECD of the HER-2 antigen, utilizing the direct chemiluminescence method.[19] IHC tests demonstrate the intensity of the expression and location of unique proteins on pathological tissue sections. IHC analysis evaluates the actual HER-2 receptor on the cell membrane *via* the anti-HER-2 antibody receptor.[20] IHC is less expensive and more accessible than FISH, but it is less sensitive and false-positive assay results are possible. FISH quantifies the number of HER-2 gene copies that are located on chromosome 17.[21] FISH is selected as a standard gold test; although, due to its time consumption and higher cost, as well as the need for a fluorescence microscope, usually only some cases are evaluated by this technique.[22] However, these three methods have been universally approved but because each of them has its own disadvantages, new methods such as biosensors can be used in the diagnosis of HER-2.

3. Biosensor technology

Biosensor devices have highly affected the quality of human life *via* their sensitivity, specificity, and ability to rapidly diagnose different patient diseases.[23] Moreover, biosensors are used step by step to develop advanced detection methods. A biosensor consists of three important parts: a signal-processing unit, a bio receptor, and a transducer in tight connection with the bio receptor. Also, the biosensors have appropriate values of assay time, specificity, accuracy, robustness, reproducibility and sensitivity.[24] DNA detection is one of the important subjects in genetics, biotechnology, virology, parasitology and diagnosis. Multiple DNA biosensors have been fabricated for the detection of specific DNA. Also, many biosensors are excellent devices for screening the efficiency of some drugs to find the best drugs. Electrochemical sensors, as the most effective approach, involve reacting chemical solutions with sensors to produce electrical signals proportional to the analyte concentrations. Electrochemistry-based methods have excellent advantages due to their capacity to measure electrochemical signals at a specific reduction potential.[25] The use of piezoelectric materials to build appropriately excellent structures for modern industrial products has also been highly crucial in the scientific community. In this review article, we will review these biosensors, considering that they have been categorized based on the transducers used including piezoelectric biosensors, optical sensors such as fluorescence, colorimetric and surface plasmon resonance, and electrochemical types for the diagnosis of HER-2 and the effectiveness of some drugs against that.

3.1 Electrochemical sensors

A chemical sensor is a device that transforms chemical information, such as complete compositional analysis or the amount of a specific sample component into an analytically detectable signal. In electrochemical biosensors (ECBs), the transducer changes the chemical signal to an electrical signal which allows for the quantitative and qualitative recognition of the target markers. Electrochemical sensors have some advantages including requiring no sample preparation, fast detection, inexpensiveness, rapid responses, and being simple to use.[26,27]

It has been demonstrated that numerous electrochemical biosensing methods have been established for various working electrodes for different biomedical and biological applications.[28] The working electrode is the electrode in an electrochemical biosensor on which the reaction of interest is occurring.[29] Commonly the working electrodes consist of materials ranging from inert metals such as platinum, gold, or silver to inert carbon including glassy carbon, boron doped diamond, and mercury drop and film electrodes. So, in recent years, electrochemical devices with various electrodes have been developed for HER-2 biomarker detection (Table 1).

Self-assembled monolayers (SAMs) can function as screen-printed electrodes (SPE) in electrochemical sensors to prepare an oriented and organized layer for various applications.[44] Ferreira *et al.*[30] fabricated two biosensors. In the first one, a sensor modified with 1-mercapto-6-hexanol (MCH) and thiolated DNA aptamers specific for HER-2 can make a SAM deposit on the SPE electrode and in the second one 1,6-hexanethiol (HDT) and the same aptamer have been used to generate a ternary SAM and finally induce biosensor operation. In this ECB the electrochemical impedance spectroscopy (EIS) technique has been selected to diagnose the HER-2 biomarker from 1 pg mL^{-1} to 1 μg mL^{-1}. Metal–organic frameworks (MOFs) have been utilized as a potential material in drug delivery, sensing, and magnetism.[45] Aptamers are single-strand oligonucleotides (DNAs or RNAs) which are fabricated synthetically in the laboratory, and display high specificity to bind with different targets, such as proteins, exosomes, circulating tumor cells (CTCs), and circulating tumor DNA (ctDNA).[46] Gu *et al.*[31] prepared a new ECB which was modified with carbon dots/MOF on an Au electrode and incubated with a HER-2 aptamer. This electrochemical aptasensor demonstrates suitable sensing performances against HER-2 cells with low detection limits (LOD) of 19 fg mL^{-1} (Fig. 1). In electrochemical biosensors metal nanoparticles (MNPs) are extensively used because of their properties such as low toxicity, biocompatibility, high surface area and excellent conductivity. Quantum dots (QDs) are crystalline nanoparticles that can be relevant as electrochemical detection labels in cancer biomarker assays because of the excellent electroactivity of the employed metals.[47] In a study, magnetic beads (MBs) were suspended in EDC/NHS solution and deposited on a screen-printed carbon electrode (SPCE) and HER-2 analyte solution was added to this modified electrode. Finally, the QD solution was immobilized on MBs/SPCE. In this immunosensor the evaluation of the concentration of the extracellular domain of HER-2 (HER-2-ECD) was determined by differential pulse anodic stripping voltammetry (DPASV) with 0.29 ng mL^{-1} LOD.[32] Moreover, PbS QDs are useful materials for the sensitive recognition of staphylococcal enterotoxin B (SEB) with a modified glassy-carbon electrode (GCE).[48] Dithioglycerol (DTG) and thioglycerol (TGL) are capping agents to generate PbS QDs and this material can be linked with antiHER-2 antibodies *via* the use of carbonylimidazole (CDI).[33] Azizah Nor Haiza Lah *et al.*[33] prepared a sandwich immunosensor based on pbS QDs to assess the HER-2 biomarker level with SWV which was detected in a linear range from 1–100 ng mL^{-1}. MnO_2 nanosheets have attracted high attentions due to their properties such as large interesting physical, specific surface and chemical attribute.[49] Different studies have reported the use of MnO_2 nanosheets in the electrochemical or fluorescence bioassay of analytes.[50,51] A peptide that can sensitively detect HER-2 was modified on a gold electrode to capture HER-2. Then, the functionalized MnO_2 nanosheets were linked to the electrode by the binding between the HER-2 aptamer and HER-2 on the MnO_2 nanosheets. In this study, the square wave voltammetry (SWV) data have shown electrochemical currents at 0.22 V with 0.05 pg mL^{-1} LOD in spiked human serum samples.[34] Iron oxide nanomaterials display enzyme-mimic attributes against chromogenic substances and are suitable as capture agents and catalysts in evaluating microRNA and Abs in biological samples.[52,53] In a new strategy, iron oxide that is conjugated with AuNPs and loaded with anti-HER-2 Abs can be immobilized on the electrode. A positive HER-2 assay produced a sixfold increase in current output compared to the negative

Table 1 Various type of electrochemical biosensors[a]

Sensing platform	Target	Type of electrode	LOD	References
MCH/thiolated DNA aptamers	HER-2 marker	SPE	179 pg mL^{-1}	30
Carbon dots/MOF	HER-2 cells	Au	19 fg mL^{-1}	31
MBs/QDs	HER-2-ECD	SPCE	0.29 ng mL^{-1}	32
pbS QDs	HER-2 marker	SPCE	0.28 ng mL^{-1}	33
MnO_2 nanosheets	HER-2 aptamer	Au	0.05 pg mL^{-1}	34
Au–Fe_2O_3	HER-2 marker	STE	0.4 U ml^{-1}	35
AuNP/anti-HER-2Abs	HER-2 marker	Au	0.5 pg mL^{-1}	36
MnFePBA@AuNP	HER-2 marker	Au	0.247 pg mL^{-1}	37
ErGO-SWCNTs	HER-2 DANA probe	GCE	50 fg mL^{-1}	38
AuNP/PANI	SK-BR3 breast cancer cell	—	2 cells per mL	39
AuNP/AuNPs	HER-2 marker	MW-CILE	7.4 ng mL^{-1}	40
antiHER-2/APTMS-Fe_3O4	HER-2 marker	GCE	2.0×10^{-5} ng mL^{-1}	41
MWCNT	HER-2 DANA probe	GCE	6.34×10^{-11} M	42
rGO/chitosan	HER-2 marker	—	0.21 ng mL^{-1}	43

[a] Sreptavidin-modified electrode (STE), MW-CILE (multiwall-carbon ionic liquid electrode), multi-walled carbon nanotubes (MWCNTs), and reduced graphene oxide (rGO).

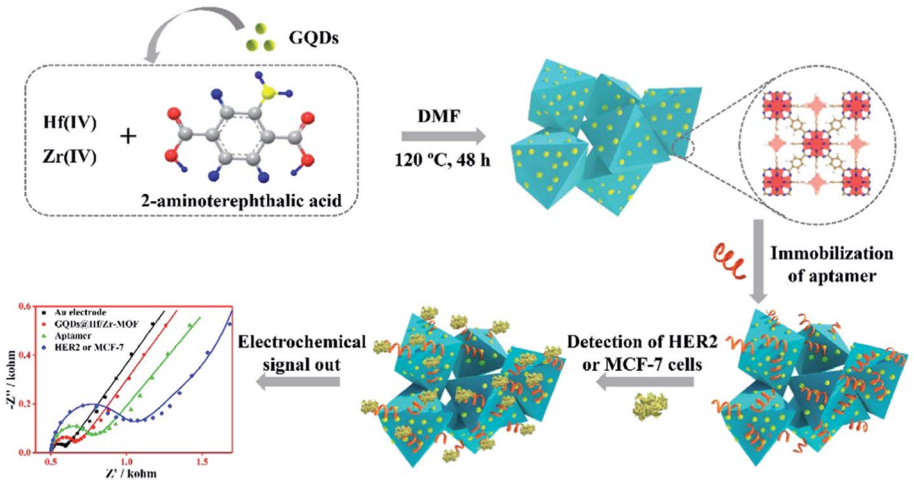

Fig. 1 Schematic demonstration of the fabrication procedure of a CDs@ZrHf-MOF-based aptasensor for the detection of HER2.[31] Copyright 2021, Elsevier. Adapted with permission from ref. 31.

biological variant or negative target.[35] The best method for the design of a precise and sensitive immunosensor for the detection of various analytes requires careful selection of both signal amplification and ligand binding strategies.[54] Immunoassays based on colorimetric assay or fluorescence are usually difficult to amplify. Electrochemical immunoassays are highly attractive for their unique advantages such as low cost, high sensitivity and good portability. Usually, for diagnosis, on the other hand, DNA-based signal strategies are easy and versatile to amplify.[55] Previous studies have combined the DNA-based signal amplification methods with special immunoassays including, immunoassays with rolling circle amplification (RCA) (immuno-RCA) and immunoassays with PCR (immuno-PCR).[56] However, these methods are sensitive; they are not commonly used due to their complexity. A polycytosine DNA sequence increases electrochemical biosensors efficiency by its appropriate affinity ligand for inorganic nanomaterials.[57] Li *et al.*[36] conjugated AuNPs with anti-HER-2 Abs and these nanoparticles operate as a supporting matrix to the modified polycytosine DNA sequence. A sandwiched immunocomplex interaction occurred between the anti-HER-2 antibodies on the AuNPs and a peptide towards HER-2 immobilized on the gold electrode. Electrochemical impedance spectroscopy (EIS)-based sensors have attracted more attention because of the feasibility of label-free diagnosis of a marker binding to a detector layer at the electrode surface that can be detected *via* the changes in resistance.[58] PB analogue (PBA) or Prussian blue (PB) have received considerable attention in many fields because of their special structure.[59] MnFe PBA has been studied extensively due to its low cost, the promotional synergistic effect between the two elements as well as because of its environmental friendliness.[60] Zhou *et al.*[37] modified an Au electrode with MnFePBA@AuNP to easily bind the electrode surface with an aptamer. EIS technique demonstrates the signal variation between the bare electrode, modified electrode and after adding different concentrations of HER-2. Carbon nanomaterials, containing carbon dots, nanoporous carbon, single- and multi-walled carbon nanotubes, nanodiamonds, graphene oxides, and fullerene are studied in the field of electrochemical biosensors.[61] Some kinds of graphene and carbon nanotubes are the most widely used carbonaceous materials in electrochemical sensing. Densely packed AuNPs placed on a composite including electrochemically reduced graphene oxide and single-walled carbon nanotubes (ErGO-SWCNTs) can be immobilized on a glassy carbon electrode (GCE) and be better linked with an aptamer.[38] This sensor can detect HER-2 levels with electrochemical techniques such as EIS, cyclic voltammetry (CV), and differential pulse voltammetry (DPV) with 50 fg mL^{-1} LOD. In recent years, the application of new materials of nanocomposites with exceptional specificity and sensitivity is important in HER-2 detection because accurate evaluation of HER-2 positive cells is necessary to identify patients who may benefit from therapeutic drugs like trastuzumab or Herceptin. Enhancement of electrochemical signals by a new nanocomposite such as graphene nanostructured polyaniline (PANI) can be the best way to improve stability and conductivity, and caused more HER-2 antigen markers to bind on the electrode.[39] The carbon ionic liquid electrode (CILE) has excellent benefits like easy preparation, low cost, wide electrochemical windows, renewable surface, antifouling effect and high conductivity and it has been widely utilized in the field of electrochemical sensing.[62] The gold nanoparticles (GNP) can grow on the MW-CILE (multiwall-carbon ionic liquid electrode) *via* the electrodeposition method.[40] GNPs decrease the resistance of electrodes and increase MW-CILE conductivity. GNPs/MW-CILE layers are coated by CV and EIS techniques and then the anti-HER-2 antibodies are deposited on the modified electrode. Finally, the interaction of Abs and various concentrations of antigens are monitored by the change of the impedance response.[40] Magnetic nanoparticles (MNPs) have great properties including high magnetization and ease of manipulation with inexpensive and simple permanent magnets compared to non-magnetic particles.[41] The amino-functionalized silane monomers such as 3 aminopropyltrimethoxysilane (APTMS) are used as outer

coatings to separate the metal oxide from external media and add surface functional groups to the magnetite core (Fe_3O_4). A sandwich-type of biosensor is prepared with a (I) platform bioconjugate (PB) as functionalization of 3-aminopropyltrimethoxysilane (II) magnetite nanoparticles with antibody (antiHER-2/APTMS-Fe_3O_4) and (III) HER-2 antigens on the modified GCE electrode. Finally, the label bioconjugate (LB) as a magnetic AuNP self-assembled with thiolated antibodies and hydrazine (antiHER-2/Hyd@AuNPs-APTMS-Fe_3O_4) was employed to produce a sandwich biosensor and DPV signals were obtained by the evaluation of HER-2 Ag with 2.0×10^{-5} ng mL^{-1} LOD.[41] Anti-HER-2 antibodies can be conjugated on the iron oxide nanoparticles (Fe_3O_4 NPs) by using polyethylene glycol (PEG). PEG is used to equip enough space to link more antibodies to NPs and allow them to stand aside and cause a more specific combination with the biomolecules.[63] Also, these bioconjugates enhance the sensitivity of the biosensor *via* loading as much Abs on the electrode surface and then HER-2 biomarkers can be detectable over the ranges of 0.01–10 ng mL^{-1}. CNTs can increase the sensitivity of electrochemical DNA sensors. A number of studies using nanocomposites, graphene-like materials and CNTs as modified materials for DNA sensors have been reported.[64,65] CNTs are commonly functionalized *via* special materials such as porphyrin (aromatic and planar molecule) which allows them to bind with CNTs strongly by π–π conjugation, and a porphyrin/CNT material complex has been widely synthesized for different applications in various fields.[66] The flattening of porphyrin molecules can decrease the distance between CNTs and porphyrin planes. The HER-2 specific DNA probe linked tightly onto CNT modified electrode *via* π–π stacking interaction and this hybridization with the target DNA probe can be measured with EIS[42] (Fig. 2). Conjugation of chitosan with reduced graphene oxide (rGO) can generate a useful electrode material that possesses good attributes such as good stability, high binding of amine groups as aptamer binding sites, high homogeneity, and large surface area.[43] Aptamer molecules can be linked on the modified surface with rGO-Chit film by using a glutaraldehyde (GLA) linker to produce an electrochemical HER-2 sensor. The electrochemical signals of this sensor can be increased by the interaction of methylene blue (MB) and a large number of free guanine bases of the aptamer.[43] Data have shown that the rGO/Chit electrode has an excellent response to HER-2 in comparison with the electrodes fabricated using bare rGO (Table 1). According to studies performed to detect HER-2 by using electrochemical biosensors, we can point to two common limitations of studies, including a confined or limited temperature range and cross-affectability of different gases.

3.2 Optical sensors

3.2.1 Surface Plasmon Resonance (SPR). Surface plasmons (SPs) are light waves trapped on metal–dielectric surfaces. Many studies have recently demonstrated that SPs can be produced easily from nanohole arrays built in noble metal thin films that have been utilized to obtain a label-free specific biosensor.[67,68] In many biosensors, SPs are used because of their resonant interactions with electrons of the metal conduction band[67,69] (Fig. 3). Surface plasmon resonance (SPR)-based optical biosensors are fully automated, sensitive, exhibit label-free sensing, portable, adapted for use in microfluidics and biochips and now being applied routinely to define high- and low-affinity small molecule binding and kinetics of a wide variety of macromolecular interactions. SPR sensors enable a direct diagnosis of a target marker such as HER-2 and do not work with labelled molecules, overcoming conventional ELISA method limitations. However, the important disadvantages of SPR that affect its results are a long calibration process, sensitivity to motion and temperature and being bulky in size.

SPR-based nanohole arrays exhibit some properties such as allowing better potential for miniaturization and an easier experimental setup that operates in a collinear transmission mode.[70] Using nanohole arrays on a silver or gold thin film can create a sensitive optical sensor and SPR can detect the HER-2 biomarker at 3.0 ng mL^{-1} concentration, suggesting suitable applicability in breast cancer prognosis and diagnosis.[71] To biomarker detection, cancer cell lysate from biopsies is an interesting biosample in the various types of cancers. Lack of effective surface chemistry to suppress fouling is an important disadvantage for biomarker analysis using cell lysates.[72] High fouling of biofluids on surfaces resulted in an increasing nonspecific response of plasmonic sensors and SPR. To solve this problem, PEG, peptides and monolayer poly (carboxybetaines), are used for decreasing nonspecific adsorption and low fouling surface chemistry.[73] These new ultra-low fouling ionic liquids have a high effect in decreasing the nonspecific adsorption of the cell lysate and maintaining the activity of recognized molecules or Abs when bound on the surface of SPR.[74] This new ionic liquid monolayer can eliminate nonspecific adsorption of MCF-7 cells lysates in SPR sensing. In SPR, the surface of chip was modified with ultra-low fouling ionic liquids with anti-HER-2 and finally was measured the HER-2 Ag.[72] SPR methods are limited to use in the laboratory. So, recent research studies have demonstrated that the transposition of the SPR principle to optical fibers have many critical assets including flexibility, remote control, and miniaturization.[75] Previous studies reported that optical fiber SPR has high potential features in detecting molecules of interest in body fluids, biomarkers in tissues and identification of circulating cells.[76,77] In the Optical fiber-based surface plasmon resonance (OF-SPR) the optical fibers were covered with a sputtered gold film and antiHER-2 ssDNA aptamers were biofunctionalized. Then, these gold-coated optical fibers with directly bound onto the gold surface.[78] HER-2 concentrations were carefully distinguished at 0.6 μg mL^{-1}.[79] A novel and specific label-free SPR system based on subwavelength nanohole arrays was combined with a microfluidic system, and applied to measure low concentrations of HER-2 biomarkers in an aqueous solution.[71] Also, one of the new ways to use SPR is to combine it with tilted fiber Bragg gratings (TFBGs). A SPR coupled to TFBG sensor demonstrates an excellent tunable and versatile platform allowing the development of highly sensitive and specific biosensing devices. Lobry and his colleagues[80] prepared a TFBGs-SPR system to recognize the HER-2 biomarker and have

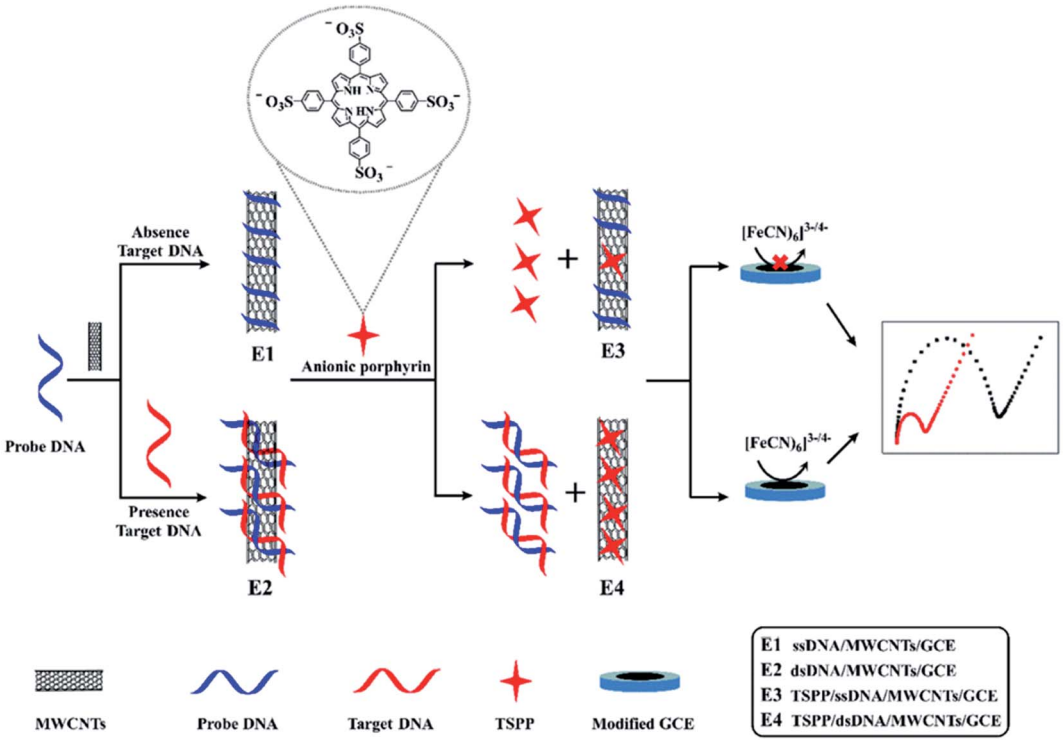

Fig. 2 HER-2 detection DNA probe binds tightly onto a CVT modified electrode *via* π–π stacking interaction and hybridization with the target DNA probe can be measured by EIS.[42]

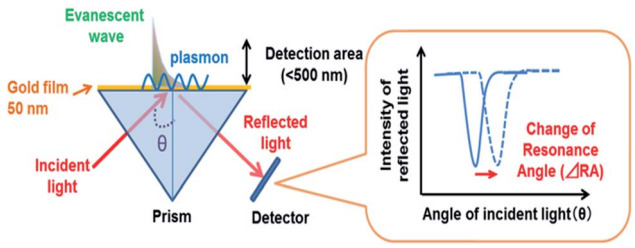

Fig. 3 This scheme illustrates the principle of surface plasmon resonance (SPR) sensors that can detect refractive index (RI) changes within a detection area (<500 nm) as a change of the resonance angle (RA).[69]

shown the HER-2 aptamer–protein interaction with shifting wavelengths. An anthracycline class antibiotic like Doxorubicin (DOX), is a popular anticancer drug that is used to treat various types of cancers such as colon cancer, leukemia, lung cancer, and breast cancer.[81] Resistance to drugs and lacking tumor-specific activity are the main limitations of DOX. To overcome these defects and increase drug activity and selectivity, tumour-specific agents containing hormones, antibodies and peptides have used to induce the specificity of DOX against cancer cells.[82,83] Peptidomimetics and peptides are used as drug carriers because of their easily modified, lower toxicity and the synthesis methods are relatively simple.[84] Compound 5 of peptidomimetics can suppress HER-2 dimerization with other EGFRs and binding to the extracellular domain IV of HER-2.[85] In a study, the HER-2 Ag was immobilized on a carboxymethylated (CM5) dextran sensor chip SPR and the data demonstrated the conjugation of DOX–peptidomimetics binding to the HER-2 extracellular domain with good affinity compared to DOX or compound 5 alone[86] (Table 2).

3.2.2 FRET. Optical biosensors can be commonly divided into two main modes: label-based and label-free. Detection of interaction of the analyzed material with the transducer is a label-free mode. On the other hand, when a label is generated using an optical signal *via* fluorescence, luminescence or colorimetry, are label-based sensing methods. The dimerization of HER-2 with receptors on the cell membrane is a crucial step in activating cell signaling pathways. Fluorescence resonance energy transfer (FRET) is an excellent way to monitor receptor dimerization because of its unique ability to live cells detection[87,88] (Fig. 4). But it is also important to note that one of the main drawbacks of fluorescence biosensors is that not all compounds are fluorescent and this reason has reduced the variety of studies. Migration and invasion enhancer 1 (MIEN1) is a novel gene that is highly expressed in the HER-2 subtype of breast cancer tissues and it operated as a main regulator of cancer cell invasion and migration to induce systemic metastases.[89,90] Isoprenylation at the C-terminal tail of MIEN1 has a role in the translocation to the inner leaflet of the plasma membrane and is a post-translational modification and it operates as a membrane-bound factor.[91] But precisely which molecular events at the membrane interact with MIEN1-driven breast cancer cell motility is vaguely understood. Also, in studies that have been approved, MIEN1 as a new interacting partner of Annexin A2 (AnxA2), is a member of the annexin

Table 2 Optical sensors[a]

Working surface	Type of optical	Identification value	Target	References
Nanohole arrays/Au	SPR	3.0 ng mL^{-1}	HER-2 Ag	71
AntiHER-2Ab/ionic liquids	SPR		HER-2 Ag	72
ssDNA aptamers/Au	OF-SPR	0.6 μg mL^{-1}	HER-2-target DNA	79
DOX–peptidomimetics	SPR	1 μM	HER-2 extracellular domain	86
MIEN1–AnxA2	FRET	—	MIEN1–AnxA2	93
MnCuInS/ZnS	FRET	1 ng mL^{-1}	HER-2-target DNA	98
QDs	FRET	—	HER-2 positive cells	96

[a] Fluorescence resonance energy transfer (FRET) and Surface Plasmon Resonance (SPR).

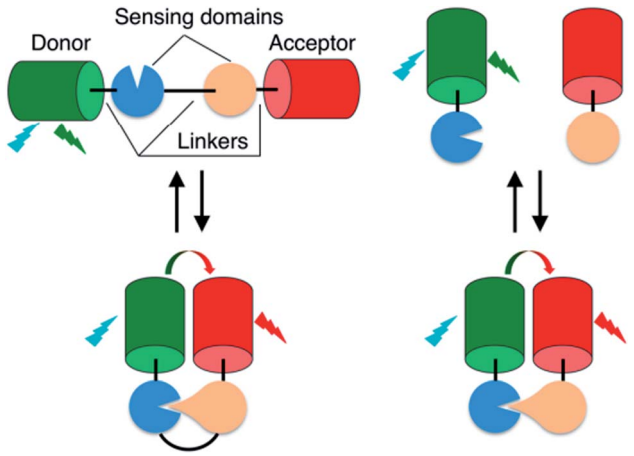

Fig. 4 The principle of a fluorescence resonance energy transfer (FRET) biosensor.[88]

family of Ca^{2+}-dependent phospholipid binding proteins.[92] FRET detection is carried out through fluorescence lifetime imaging microscopy (FLIM) assay to evaluate and prove the interaction of AnxA2 and MIEN1. The lifetime decays of the donor (MIEN1) and donor–acceptor (MIEN1–AnxA2) pair were demonstrated by labelling of cells with donor Alexa-488 and acceptor fluorophore Alexa-594.[93] Semiconductor nanoparticle quantum dot (QD) fluorophores in fluorescence biosensors have some features including strong intensity and narrow emission profile of QDs, in tandem with their broad UV excitation spectra. The long term photostability and size-tunability have caused QD fluorophores to be excellent quantitative and qualitative probes for a number of applications both in the micro and macro size regime. "Lab-on-a-chip" (LOC) or microfluidic systems have some specific properties such as low cost, small sample size, and short analysis times.[94] "Nano-bio-chip" (NBC) sensors that have a nanoparticle (nano) and size-tunable nano-net within agarose microspheres can generate a fluorescent transduction signal for the detection of biological analytes.[95] QDs have excellent fluorescence features and make critical progress against the completion of a harmonized nano-bio analysis system. Jokerst *et al.*[96]prepared a NBC sensor based on QDs for the quantification of HER-2 positive cells. Moreover, in recent studies, biosensing in the near infrared (NIR) region has attracted a lot of attention because of its low-background interference.[97] So, QD-based FRET biosensing in the NIR region can be developed for biomarker detection. Xing *et al.*[98] fabricated a new NIR FRET biosensor based on MnCuInS/ZnS nanocrystals and AuNPs as a unique donor–acceptor pair. The merging of AuNPs and MnCuInS/ZnS has increased the FRET efficiency in the presence of the HER-2 biomarker.

3.3 Piezoelectric biosensors

A quartz crystal microbalance (QCM) is a piezoelectricity-based biosensor device with fantastic features such as ease-of-use, label-free and low-cost for qualitative and quantitative evaluation of binding affinity.[99] In the past, a QCM has been usually used for studying the interaction between purified antigens and antibodies. Today, the use of cells and synthetic polymer-based antibodies mimics the sensor detection elements to monitor specific cancer cells and the affinity of antibodies for a cell membrane receptor.[100,101] A suspension of human ovary adenocarcinoma cells (SKOV3) HER-2 positive cells was modified on a QCM COP-1 chip and were bound to Herceptin monoclonal antibodies known as trastuzumab with a mean dissociation constant (KD) value of 7 ± 1 nM (ref. 102) (Fig. 5). In some studies, Au coated quartz crystal can be used as a transducer in a QCM biosensor to detect some molecule binding events.[103] Shang *et al.*[104] fabricated a QCM piezoelectric immunoassay with immobilization of GPYELWELSH and QLGPYELWELSH that are two HER-2 mimotope-derived peptides on the gold surface. These peptides havethree parts:

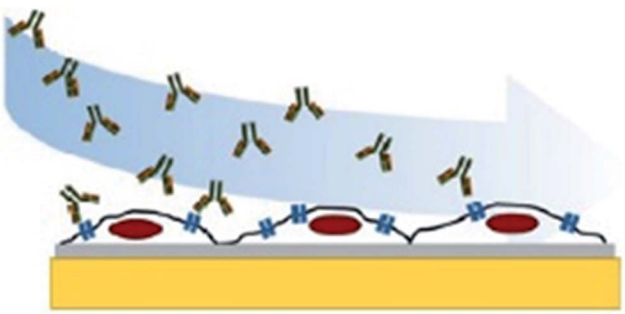

Fig. 5 Schematic illustration of trastuzumab (green/yellow) binding to a HER2 receptor (blue) on SKOV3 cells attached to a QCM cell chip.[102]

(1) a spacer sequence (GSGSGS or RGRGRG) to diminish the steric hindrance between immobilized peptides and Herceptin, (2) the functional HER-2 mimotope-derived peptide sequence, and (3) surface coupled amino acids [Cysteine (C) or Arginine (R)] to easily bind on the Au surface. The linear operating range of the piezoimmunosensor assay was (0.038–0.859 nM) and with a detection limit of 0.038 nM.[104] This immunosensor can be a suitable device for the diagnosis of a broad range of HER-2 biomarkers. The results of the piezoelectric methods for detecting HER-2 are excellent in terms of sensitivity, but due to few studies in this case, these reports cannot be relied on and more studies should be done.

4. Conclusion

Analytical diagnosis tests founded upon whole cell-based assays are critical in fundamental studies of biomolecular recognition and in early-stage drug development. The HER family is the main mediator for normal cell development and growth. The HER-2 receptor is overexpressed in adenocarcinoma (colorectal, lung and endometrial cancers) and breast cancers. Diagnosis of the high-expression of HER-2 helps to determine Herceptin therapy and to predict prognosis. FISH, PCR and immunohistochemical assays are routine methods for assessing HER-2 concentrations. Some limitations such as time consumption, complexity, requiring expert people and being expensive have led to more studies of alternative methods in recent years. In comparison with conventional tests as mentioned, biosensors have high specificity and sensitivity in drug discovery and clinical diagnosis, and the detection of infections. As mentioned, in electrochemical biosensors, different studies that have used various nanoparticles can monitor detection of HER-2 sensitively and specifically. Moreover, optical types including FRET, SPR and piezoelectric are developed because of their label-free sensing feature. Almost all of the studies cited in this review study have proven to be relatively sensitive and also cheaper than serological methods. Other types of biosensors such as colorimetric sensors can be developed in the future to detect a HER-2 marker and studies on this type of biosensor are few. Moreover, in this review article, another important point for future studies can be to use more sensitive and easy to synthetize nanomaterials.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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