1 Nanobiosensor-Based Diagnostic System: Transducers and Surface Materials

Gorachand Dutta

Abstract

There are increasing needs for the development of simple, cost-effective, portable, integrated biosensors that can be operated outside the laboratory by untrained personnel. The main challenges of point-of-care testing require to implement complex biosensing methods into low-cost technologies. Point-of-care testing is known as medical diagnostic process which is conducted to the near patient and does not need any well-trained personnel. The diagnosis technology should be affordable and disposable to provide the benefits to the large part of the population in developing countries. In this chapter, different nanobiosensors for medical diagnosis using several surface modification strategies of transducers were discussed. A unique redox cycling technology was presented to amplify the signal-to-background ratios for ultrasensitive biomarker detection which are suitable for point-of-site detection such as medical diagnostics, biological research, environmental monitoring, and food analysis. Also, some advanced nanobiosensing technologies including printed circuit board (PCB) were described on the commercial arena for next-generation point-of-care testing.

Keywords

Nanobiosensors · Transducers · Surface functionalization · Point-of-care · Lab-on-a-chip

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1.1 Introduction

Biosensors are detection techniques which utilize one or more biologic recognition elements for specific detection of certain target analyte of interest (Gruhl et al. 2013; Hwang et al. 2018). Major applications for biosensors are clinical diagnosis and disease prevention (Akhtar et al. 2018; Lee et al. 2019a; Li et al. 2019; Wang et al. 2019; Zhang et al. 2019). There has been intense demand of HIV/AIDS, tuberculosis, and vector-borne disease biomarker biosensor (David et al. 2007) for portable devices for rapid and sensitive detection. Various groups and companies in the USA (Whitesides Research Group at Harvard University, Cortez Diagnostics, Inc. California), the UK (Liverpool School of Tropical Medicine and University of Southampton), and France (James P. Di Santo group) have been working on the development of biosensors for HIV/AIDS, tuberculosis, and vector-borne diseases at the point of care. A mobile device named Qpoc Handled Laboratory was designed by the British company QuantuMDx that provides HIV, tuberculosis, and malaria results in 10 min. There has been an increased attempt toward the technological development of biosensing devices for the past about 10 years. In this context, the research on technical feasibility and concept proving in the area of biomolecular electronic devices, technological development of some biosensors and laboratory-level technological development of some biosensors and related biomaterials, was developed. Biosensor technology offers several benefits over conventional diagnostic analysis including simplicity of use, specificity for the target analyte, and capability for continuous monitoring and multiplexing (Chandra et al. 2011; Dutta 2017; He et al. 2018).

A transducer is any device used to convert energy from one form to another (Chandra et al. 2011). A bio-recognition layer and a physicochemical transducer are the two intimately coupled parts in biosensor transducer (Aashish et al. 2018). The biochemical energy converts to an electronic or optical signal. The sensing surface which provides a solid support for the immobilization of the capture biomolecules (i.e., antibody), as well as electron transfer process from the biological/chemical reaction, plays a crucial role for ultrasensitive biomarker detection for POCT. Therefore, selecting an appropriate transducer along with proper surface modifications is an important step to build a highly sensitive biosensor.

Suitable solid surface selection and novel surface chemistry are the most important challenges for developing a viable lab-on-a-chip biosensor (González-Gaitán et al. 2017). There is an increasing demand for a multidisciplinary approach to design and manufacturing of micro-/nanodevices that could be applicable for ultrasensitive biosensing (Khan et al. 2019). Different surface materials were widely used in biosensor to obtain low and reproducible background signal (Zhu et al. 2019). The major requirements for selecting the sensing surface materials depend on (a) biocompatibility with the biological element; (b) nonexistence of diffusion barriers, (c) stability factors with temperature, pH, and ionic strength; (d) specificity and sensitivity of the analyte; and (e) cost-effectiveness for on-site diagnosis.

Over the years, there are increasing needs for the development of a simple, cost-effective, portable, integrated biosensors that can be operated outside the laboratory

by untrained personnel (Eltzov and Marks 2016; Siddiqui et al. 2018; Yang et al. 2016). In recent years, many chip-based biosensors have been reported, and so far, the technology for electrochemical amplification on a chip has always relied on expensive micro- and nanofabrication technologies such as optical and e-beam lithography (Cinel et al. 2012). This approach has several drawbacks even when leading to reliable results in research laboratories. Most of the clinical analysis is carried out in centralized laboratories where high-technology equipment is available and trained personnel perform the assays under almost ideal conditions. However, a large part of the population in developing countries does not have access to state-of-the-art diagnostic methods. It is very important to perform highly sensitive detection of biomarkers with printed and flexible electronics for pint-of-site application. With the rise of printed electronics and roll-2-roll technologies, tools have been developed (Liddle and Gallatin 2011) that could potentially make diagnostics available to a much wider population.

A small instrument can offer very stable voltage/current source and detector that are always unnoticed in electrochemical biosensors (Gu et al. 2019; Nze et al. 2019). Therefore, a combination of new signal amplification technology (i.e., redox cycling) and electrochemical detection can play an important role in the development of ultrasensitive and reproducible biosensors for point-of-care testing. Point-of-care testing (POCT) of biomarkers in clinical samples is of great importance for rapid and cost-effective diagnosis (Akanda et al. 2014; Akanda and Ju 2018; Singh et al. 2013; Xiang et al. 2018). However, up to now it is extremely challenging to develop a POCT technique retaining both simplicity and very high ultrasensitivity and simplicity.

This chapter focuses on the different nanobiosensors for medical diagnosis using several surface modification strategies of transducers. Different transducer effects will be discussed for ultrasensitive biosensing. Also, some advanced nanobiosensing technologies will be explored on the commercial arena for next-generation point-of-care testing.

1.2 Different Transducers for Biosensing with Advanced Surface Materials

Over the past two decades, various transducing systems have been applied for highly sensitive biomarker detection. Gold electrodes were widely used in nanobiosensing for its unique redox property, and the extraordinary affinity of thiol compounds for its surface makes these electrodes very suitable for point-of-care immunodiagnostics (Lee et al. 2019b). Thiolated antibody could be immobilized promptly making the sensor fabrication steps easier for biomarker detection (Wang et al. 2017). To develop a washing-free immunosensing technique without any label, Dutta et al. discovered a rapid measurement of protein biomarkers in whole blood samples (Fig. 1.1) using gold transducer and thiolated capture antibody (Dutta and Lillehoj 2018). Using this nanobiosensor, *Pf*HRP2, a malaria biomarker, was quantified from 100 ng/mL to 100 μg/mL in whole blood samples. This method does not

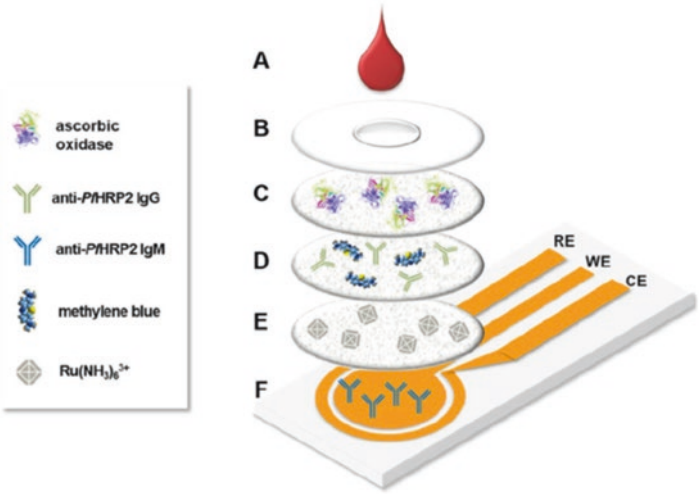

Fig. 1.1 An exploded view of a nanobiosensor using thiolated capture probes and gold transducer. (Reprinted with permission from Dutta and Lillehoj 2018. Copyright (2018) with permission from Nature)

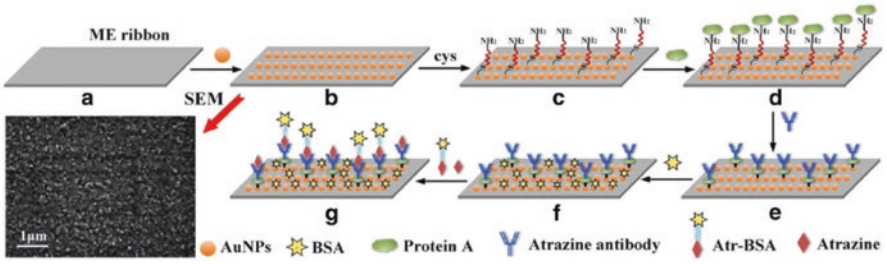

Fig. 1.2 Schematic of the functionalization procedures of the competitive immunoassay (**a**) ME ribbon; (**b**) the AuNP immobilization; (**c**) the SAM formation; (**d**) the protein formation; (**e**) the antibody immobilization; (**f**) BSA coating; and (**g**) atrazine and Atr–BSA competitive mechanism. (Reprinted with permission from Sang et al. 2018. Copyright (2018) with permission from Springer)

require any sample processing, labeling, or washing. Because of excellent stability and very good reproducibility, the device was well suited for point-of-care testing in developing countries.

Sang et al. reported magnetoelastic (ME) nanobiosensor, based on ME materials and gold nanoparticles (AuNPs) (Fig. 1.2), for highly sensitive detection of atrazine employing the competitive immunoassay (Sang et al. 2018). The biosensing results indicated that the ME nanobiosensor displayed strong specificity and stability toward atrazine with detection limit 1 ng/mL. This report also specified a novel convenient method for rapid, selective, and highly sensitive detection of atrazine which has implications for its applications in water quality monitoring and other

environmental detection fields. The competitive biosensing scheme was established by oriented immobilization of atrazine antibody to protein A covalently modified on the AuNP-coated ME material surface, followed by the competitive reaction of atrazine–albumin conjugate (Atr–BSA) and atrazine with the atrazine antibody.

Proa-Coronado et al. reported a reduced graphene coated with platinum nanoparticle-based transducer in back-gated field effect transistor (GFET) nanobiosensors (Proa-Coronado 2018). X-ray photoelectron spectroscopy and cyclic voltammetry techniques were used to prove the adsorption-interaction of CS_2 and human serum albumin biomolecules on rGO/Pt. The local deposition of CS_2, rGO/Pt, and protein G was performed by using a commercial microplotter instrument.

A label-free chemiresistor nanobiosensor employing a SWCN chemiresistor transducer functionalized with antidengue NS1 monoclonal antibodies for rapid detection of the dengue nonstructural protein 1 (NS1) was described by Wasik et al. (Wasik et al. 2018) (Fig. 1.3). A wide range of NS1 was detected with high sensitivity and selectivity with the limit of detection 0.09 ng/mL.

A surface-enhanced Raman scattering (SERS) sensor was reported based on the Ag nanorice@Raman label@SiO2 sandwich nanoparticles that are coupled to a periodic Au triangle nanoarray via the linkage of hepatitis B virus (HBV) DNA (Li et al. 2013) (Fig. 1.4). This nanobiosensor is expected to result in the spatially enhanced electromagnetic (EM) field of the quasiperiodic array, leading to ultrasensitive SERS detection. In the sandwich nanoparticles, malachite green isothiocyanate (MGITC) molecules are chosen as the Raman labels that are embedded between the Ag nanorice core and the SiO_2 shell. The detection limit was 50 aM.

A new nanostructured SERS-electrochemical nanobiosensor was developed for screening chemotherapeutic drugs and to aid in the assessment of DNA modification/damage caused by these drugs (Ilkhani et al. 2016). The self-assembled monolayer protected gold-disk electrode (AuDE) was coated with a reduced graphene

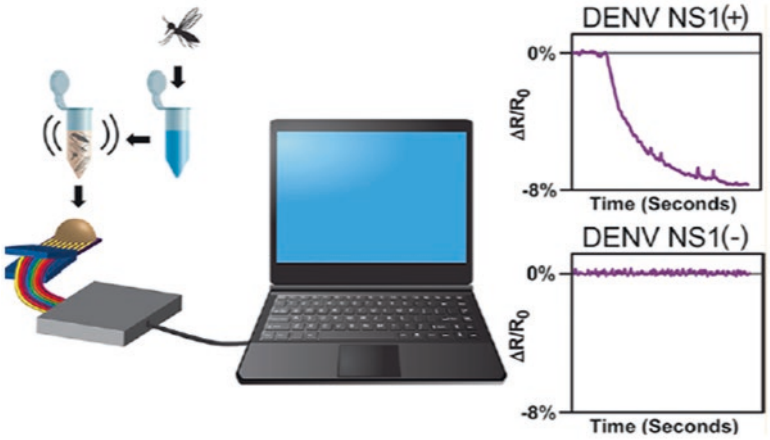

Fig. 1.3 The schematic of a label-free nanobiosensor. (Reprinted with permission from Wasik et al. 2018. Copyright (2018) American Chemical Society)

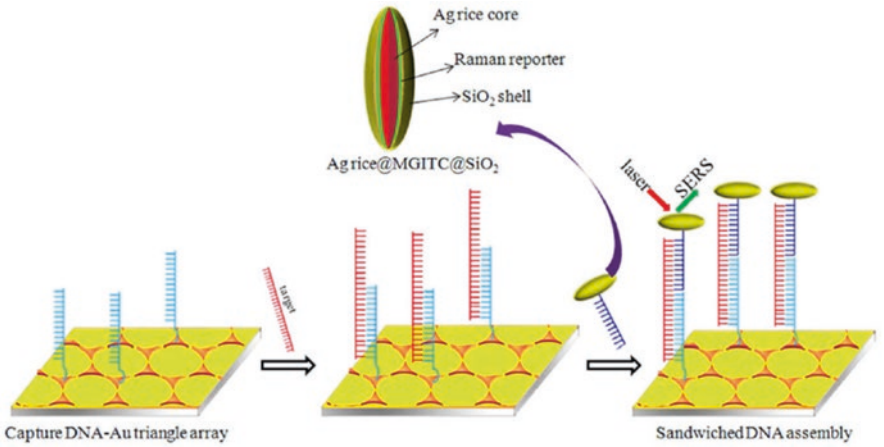

Fig. 1.4 Schematic of the sandwich structure of Ag nanorice@Raman label@SiO2 and the mechanism of SERS sensor. (Reprinted with permission from Li et al. 2013. Copyright (2013) American Chemical Society)

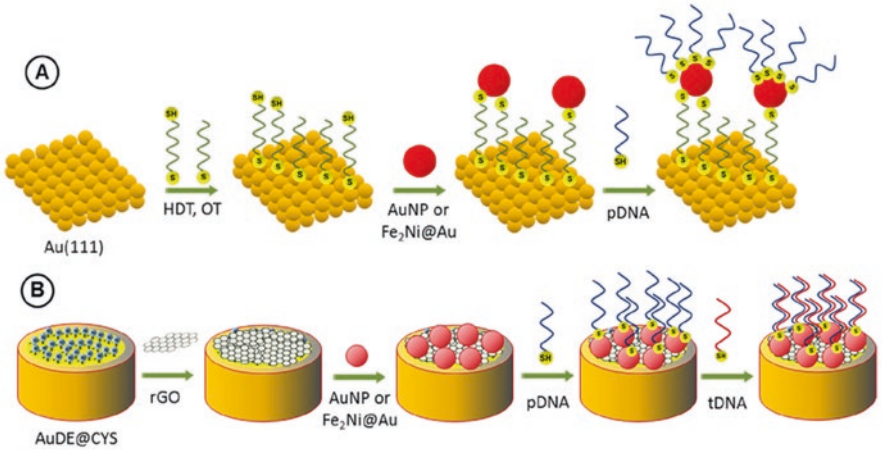

Fig. 1.5 The schematic illustration of SERS/electrochemical nanobiosensors: (**a**) the gold transducer is coated with a SAM of hexanedithiol and octanethiol, and covalently attached AuNPs or Fe_2Ni@Au NPs (magnetic) were functionalized with ssDNA probe; (**b**) SERS/electrochemical nanobiosensor with gold-disk electrode and functionalization of dsDNA. (Reprinted from Ilkhani et al. 2016. Copyright (2016), with permission from Elsevier)

oxide (rGO), decorated with plasmonic gold-coated Fe2Ni@Au magnetic nanoparticles functionalized with double-stranded DNA (dsDNA) (Fig. 1.5). The complete nanobiosensor complex was used to the action of a model chemotherapeutic drug, doxorubicin (DOX), to fit the DNA modification and its dose dependence. These

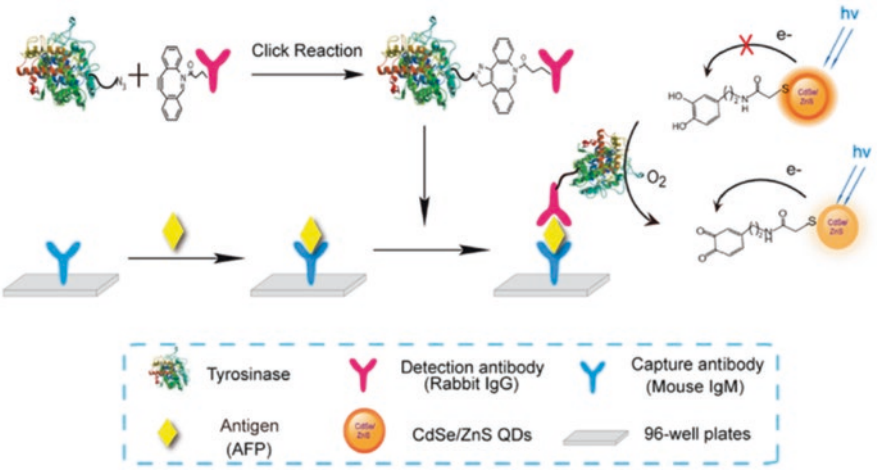

Fig. 1.6 Schematic illustration of the sandwich RMFIA for the detection of disease biomarkers. (Reprinted with permission from Zhang et al. 2016. Copyright (2016) American Chemical Society)

new biosensors are sensitive to agents that interact with DNA and facilitate the analysis of functional groups for determination of the binding mode.

A nanobiosensor for the quantification of acetylcholine (Ach) was reported on the carbon paste electrodes (CPE) modified by copper nanoparticles (Heli et al. 2009) (Fig. 1.6). Cu(III) active species was used to oxidized the Ach. Quantum dots (QDs) have many unique properties and are used in nanobiosensors such as (a) excellent brightness and photostability, (b) wide and continuous excitation spectrum, (c) narrow emission spectrum. A redox-mediated indirect fluorescence immunoassay (RMFIA) for the detection of the disease biomarker α-fetoprotein (AFP) using dopamine (DA)-functionalized CdSe/ZnS quantum dots (QDs) was reported (Fig. 1.6) (Zhang et al. 2016). The detection antibody was conjugated with tyrosinase and used as a bridge connecting the fluorescence signals of the QDs. Different concentration of the disease biomarkers was detected. The immunoassay was sensitive with the detection limit of 10 pM.

1.3 Low Electrocatalytically Active Indium Tin Oxide (ITO) Transducer for Highly Sensitive Biomarker Detection

Indium tin oxide (ITO) is a mixed composition of indium, tin, and oxygen. ITO is widely used in biosensing because of favorable platform in disease diagnosis due to their good electrical conductivity, transparency to visible wavelengths, and high surface-to-volume ratio (Jiaul Haque et al. 2015; Park et al. 2015). In many reported works (Das et al. 2006; Jiaul Haque et al. 2015; Park et al. 2015; Yang 2012), low electrocatalytic indium tin oxide (ITO) electrodes were used to obtain low and reproducible background levels, and low amounts of electroactive species were

modified on ITO electrodes to obtain the rapid electrooxidation of substrate molecules. Also, in highly outer-sphere reactions (OSR-philic species), ITO electrodes reacted very slowly with highly inner-sphere reactions (ISR-philic species) like tris(2-carboxyethyl) phosphine (TCEP) (Akanda et al. 2012, 2013). Overall, the outer-sphere to inner-sphere reaction allowed a very low detection limit even in clinical samples.

ITO electrodes are very low electrocatalytically active in electrochemical detection of biomarkers in real samples with very low interfering effect such as ascorbic acid (AA) and uric acid (UA) (Dutta et al. 2014, 2015; Park et al. 2015). ITO electrodes could be used as biosensing surface by modifying with foreign materials, i.e., reduced graphene oxide (rGO), avidin, streptavidin, silicon layer ((3-aminopropyl) triethoxysilane (APTES)), and gold nanoparticles, to obtain high signal-to-noise ratios (S/N) (Akanda et al. 2012; Aziz et al. 2007; Fang et al. 2018; Singh et al. 2013). A new enzyme-free immunosensor-based ITO electrodes where a unique, competitive electrochemical scheme between MB, hydrazine, and Pt nanoparticles (NPs) was used (Dutta et al. 2017) (Fig. 1.7). This nanobiosensor offers several advantages including rapid electrokinetics, high sensitivity, and good reproducibility. Also, because of ITO electrode, this sensor offers very good detection performance even in real samples with minimal interference species effects.

An ultrasensitive immunosensor was developed based on ITO electrodes for the detection of malaria with fg/mL detection limit (Dutta and Lillehoj 2017) (Fig. 1.8). Here authors used an advanced biosensing technology called redox cycling to amplify the signal-to-background ratios. Real samples were investigated based on a unique electrochemical–chemical–chemical (ECC) redox cycling signal

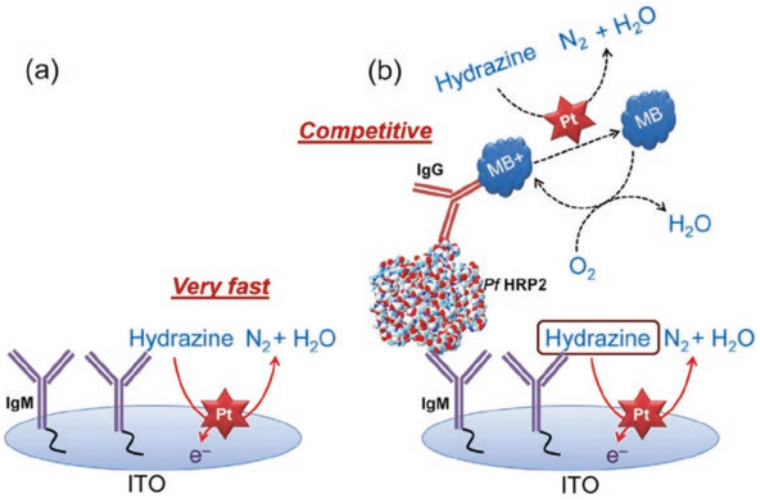

Fig. 1.7 Schematic illustration of an ITO-based nanobiosensor for highly sensitive malaria detection in the absence (**a**) and presence (**b**) of the target antigen with the MB-labeled detection antibody. (Reprinted from Dutta et al. 2017. Copyright (2017), with permission from Elsevier)

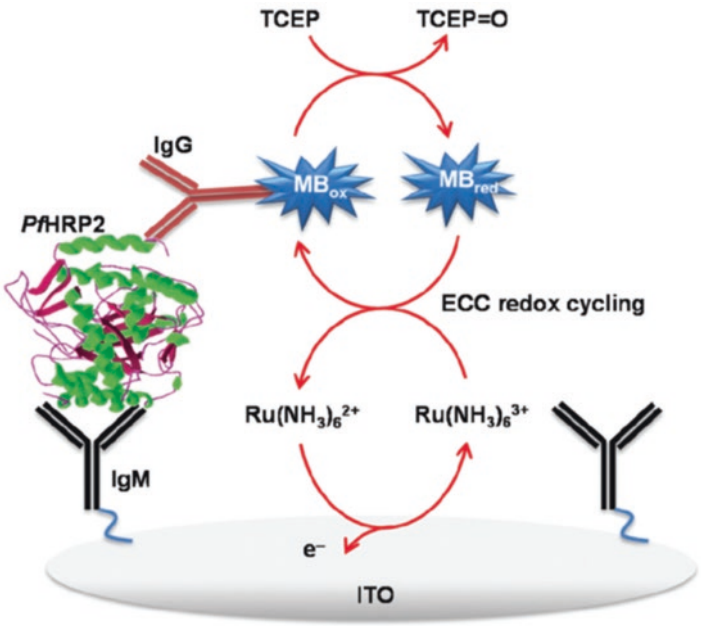

Fig. 1.8 Schematic of the electrochemical immunosensor integrating ECC redox cycling for malaria detection. (Reprinted from Dutta and Lillehoj 2017. Copyright (2017), with permission from the Royal Society of Chemistry)

amplification scheme. This scheme used methylene blue (MB) as a redox indicator which undergoes an endergonic reaction with $Ru(NH_3)_6^{3+}$ and a highly exergonic reaction with tris(2-carboxyethyl)phosphine (TCEP). Malaria biomarker was detected in human plasma and whole blood samples. The detection limit was 10 fg mL^{-1} and 18 fg mL^{-1}, respectively. This nanobiosensor exhibits excellent selectivity, very good reproducibility, and high stability making ITO-based biosensor a promising platform for point-of-care testing, especially for detecting extremely low biomarker concentrations in raw biofluids.

1.4 A Commercial Step for the Nanobiosensor

Commercialization of nanobiosensor devices for disease diagnosis is presently the "holy grail" within the micro total analysis system research community (Lin and Wang 2005; Mahato and Chandra 2019; Mahato et al. 2018). Quite a few nanobiosensors are adopted by the market and reach to the bedside diagnosis although a large variety of highly advanced chips are available and could potentially challenge our healthcare, biology, chemistry, and all related disciplines. Fortunately, the electronics industry already has at its disposal a large industrial base for the manufacturing of printed circuit boards (PCB) at extremely high volumes and at minimal

production costs (Moschou and Tserepi 2017). Over the past 20 years, the rapidly increasing number of publications on lab-on-a-chip systems realized on printed circuit boards (PCB) is indicative of the future commercialization of the nanobiosensor technology and its emerging applications (Dutta et al. 2018b). Indeed, the lab-on-printed circuit board (lab-on-PCB) technology enables the seamless integration of microfluidics, sensors, and electronics and promises the commercial upscalability and standardization of microfluidics, leveraging the well-established PCB industry with standardized fabrication facilities and processes (Dutta et al. 2018a; Ghoreishizadeh et al. 2019; Moschou et al. 2015). The microfluidic devices are seamlessly integrated with PCB sensors and make the technique more useful for complex sample analysis. The amplification reaction can occur on the chip integrated with implanted heaters and will allow the system for point-of-site application (Dutta et al. 2018a; Moschou and Tserepi 2017).

1.5 Conclusions

In this chapter, different nanobiosensors for medical diagnosis using several surface modification strategies of transducers were discussed. A unique redox cycling technology was presented to amplify the signal-to-background ratios for ultrasensitive biomarker detection which is appropriate for point-of-site diagnosis such as medical application, biology-related research, environmental monitoring, and food safety. Also, some advanced nanobiosensing technologies including printed circuit board (PCB) were described on the commercial arena for next-generation point-of-care testing.

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