Chapter 18
Emerging Trends in Nanobiosensor

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18.1 Introduction to Nanobiosensors

Nanobiosensors are emerging as a powerful tool in area of sensing and diagnostics. These sensors are developed due to integration of nanotechnology with biosensors. These nanomaterial-based biosensors are much more sophisticated, reliable, and sensitive in comparison to traditional biosensors. A wide range of nanobiosensors is available nowadays in order to address various diagnostic problems. These highly sensitive nanobiosensors are particularly attractive for providing detection of extremely low concentration of analyte. They have applications in clinical diagnosis, environmental monitoring, food analysis, forensic sciences, and drug delivery systems. The clinical application includes detection of presence of pathogens and biomarkers, analysis of drugs in body fluids, monitoring of oxidative stress, and sensing of nucleic acids. In the near future, this technology is going to revolutionize personalized diagnostics based on point-of-care (POC) system. Nanobiosensors can also be used for food analysis to detect contaminants including pathogenic microbes and pesticides. Environmental applications include detection of pollutants, pesticides, toxins, and heavy metals.

Most common nanomaterials used to develop biosensors are carbon nanotubes, graphene, nanowires, quantum dots, and nanoparticles which have the capability of biological and chemical functionalization. With rapid progress in the area of nanobiosensor and its integration with microfluidics, electronics, and mechanical devices, the new generation of applications like lab on a chip devices (LOC), microarray, biochips, and drug delivery systems are going to be advanced. In this chapter, various nanomaterials, their application in nanobiosensing, and recent advancement in nanobiosensor applications with future perspectives are discussed.

18.2 Nanomaterials for Biosensing Applications

It is highly desirable to enhance feature of biosensors like sensitivity and rapidity to detect analyte at very low concentration for the development of LOC and point-of-care (POC) applications in diagnostics, environmental monitoring, and food analysis. Use of carbon nanotubes, graphene and its derivatives, nanowires, quantum dots, and metal nanoparticles (Fig. 18.1) have resulted in rapid nanobiosensors with much enhanced sensitivity due to catalytic activity, electrical feature, optical properties, and very high surface area-to-volume ratio of these nanomaterials. Minute size and disposability of nanobiosensors make the nanomaterials attractive for biosensing applications. Table 18.1 represents an overview of many nanomaterials used in developing nanobiosensors with enhanced features.

In this section, nanomaterial like carbon nanotube, nanowires, quantum dots, graphene and its derivatives and metal nanoparticles (gold, silver, and magnetic) are discussed. These materials are categorized as one dimensional (1D), two dimensional (2D), and three dimension (3D) on the basis of quantum confinement with novel magnetic, catalytic, and optical properties.

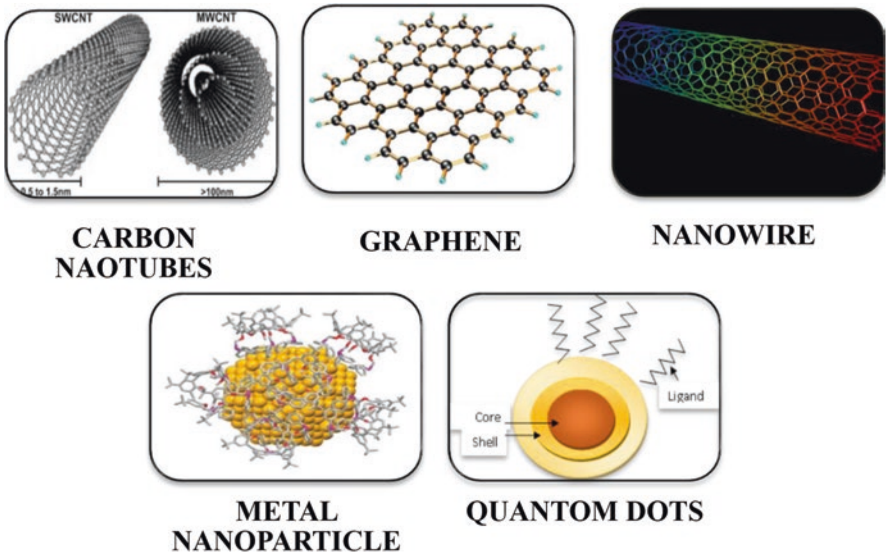

Fig. 18.1 Types of nanomaterials used in biosensor

Table 18.1 Nanomaterials used in developing Nanobiosensors

Nanomaterial used	Method of synthesis	Properties	References
Carbon nanotube	Carbon vapor discharge (CVD), carbon arc discharge, laser ablation method and n-hexane pyrolysis	Good mechanical strength, high thermal stability	Ibrahim and Saeed (2013), Salvetat et al. (1999)
Nanowires	Vapor-liquid-solid method, solution liquid-solid, electrochemical deposition, and vapor phase epitaxy	Large surface area to volume ratio, high flexibility, and low thermal conductivity	Dasgupta et al. (2014)
Quantum dots	Physical methods used are molecular beam epitaxy (MBE), ion implantation, e-beam lithography, and X-ray lithography and chemical methods include colloidal synthesis	High molar extinction coefficients and high photostability	Altintas et al. (2017)
Metal Nanoparticles	1. MNP: Chemical method involves co-precipitation, thermal decomposition, hydrothermal synthesis, and micro-emulsion physical methods involve laser evaporation and milling, hydrothermal synthesis 2. Silver NP: Conventional physical methods including spark discharging evaporation-condensation, pyrolysis, and laser ablation 3. GNP: Turkevich and brust-schiffrin method, microwave, biological methods	High surface-to-volume ratio, high mechanical strength, good optical properties and good catalytic activity, good thermal conductivity	Khan et al. (2017)
Graphene	Scotch tape method, exfoliation, Chemical vapor deposition, intercalation method	Good thermal conductivity, stiffness, impermeability, and electrical conductivity	Randviir et al. (2014), Zheng et al. (2015)

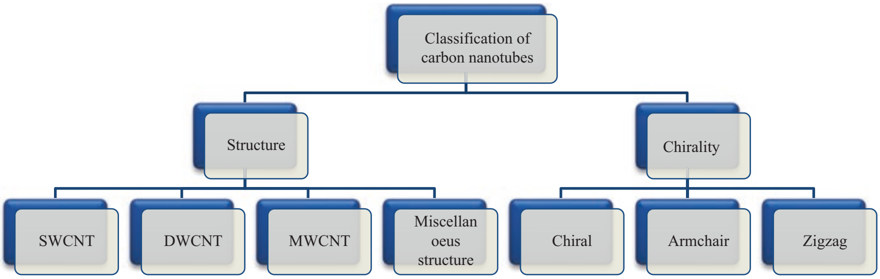

Fig. 18.2 Classification of carbon nanotube based on structure

18.2.1 Carbon Nanotubes

Carbon nanotubes (CNTs) are tubular carbon-based fiber structure with diameter in <1 nm to 50 nm range. These structures were first observed by Iijima in 1991 and made huge impact on nanoscience and nanotechnology. The carbon nanotubes are considered to be rolled form of graphene sheets in which electrons in sp^2 hybridized carbon atoms get delocalized. The electrical properties of carbon nanotube are exhibited due to delocalization of free valence electrons and making it suitable for use in transistors and emitters. CNTs are highly narrow, tubular, lightweight, and highly flexible material with high strength (Salvetat et al. 1999).

Carbon nanotube is categorized into single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs), multiwalled carbon nanotube (MWCNT), and several other structures (Varshney 2014) as in Fig. 18.2.

The various synthesis methods of carbon nanotube are derived from basic idea:

$$\text{Carbon source} \xrightarrow[\text{catalyst}]{\varnothing} \text{Carbon nanotube}$$

The four major methods for synthesis of carbon nanotube are carbon vapor discharge (CVD), carbon arc discharge, laser ablation method, and n-hexane pyrolysis (Ibrahim and Saeed 2013).

18.2.2 Nanowires

Nanowires have two-dimensional quantum confinement but one unconfined direction available for electrical conduction. Synthesis of nanowire follows top-down and bottom-up approaches, which include various methods like vapor-liquid-solid method, solution liquid-solid method, electrochemical deposition, and vapor phase epitaxy (Dasgupta et al. 2014). Nanowires' properties are solely dependent on their diameter, composition, and catalyst used. Some of the properties include large surface area-to-volume ratio, high flexibility, and low thermal conductivity.

18.2.3 Graphene

Graphene (GN) is a two-dimensional nanomaterial with planar monolayer sheet. Here, carbon atoms are sp^2 hybridized and densely packed in honeycomb crystal lattice. Graphene was discovered by A. K. Geim and K. S. Novoselov in 2007. It is gaining worldwide attention because of its chemical inertness, high electron mobility, high flexibility, and optical transmittance (Randviir et al. 2014). Overlapping of delocalized pi electron system allows free movement of electrons without scattering and contributes to electronic property of graphene (Zheng et al. 2015).

18.2.4 Nanoparticles

Nanoparticles are nanoscale particles with size range less than 100 nm. Some of the features of nanoparticles are high surface-to-volume ratio, high mechanical strength, good optical properties, and good catalytic activity. High surface area-to-volume ratio is related to high sensitivity towards target analyte. These nanoparticles (Nikam et al. 2014; Khan et al. 2017; Prasad et al. 2016) have enhanced optical and thermal properties depending on size, shape, and interparticle distance.

Silver, gold, and magnetic nanoparticles are most commonly used for biosensing applications. Silver and gold nanoparticles are generally synthesized by chemical methods. Magnetic nanoparticles (MNP) are synthesized by chemical and physical methods using materials with magnetic properties at room temperature such as metals like iron, cobalt, nickel, alloys (CoPt, FePt, FeNi), and metallic oxides.

18.2.5 Quantum Dots

Brus in 1983 first characterized quantum dots (QDs) which behave like artificial atoms due to quantum confinement effects. Quantum dots are fluorescent semiconductor crystals of size ranging 2–10 nm, consisting of a semiconductor core coated by a shell and exhibiting discrete energy levels. Core is usually made of elements from groups II or VI or groups III or V. Colloidal quantum dot can be synthesized through chemical method like colloidal synthesis and physical methods like molecular beam epitaxy (MBE). The properties of quantum dots vary with its composition and size. QDs are capable of absorbing white light and re-emitting different colors. Florescence of quantum dots are determined by their band gaps. With the increment in size of quantum dot, distance between conduction band and valence band increases and thus affecting its fluorescence. At size range 2–4 nm, they emit fluorescence in higher frequency range giving blue color, while at size more than 6 nm, they exhibit red color. Building a shell of larger band gap semiconductor material around QDs can improve fluorescence quantum yield (Altintas et al. 2017).

18.3 Application of Nanomaterials in Biosensing

Highly sensitive nanobiosensors commonly comprise of a nanomaterial along with biological recognition molecule. These recognition biomolecules are immobilized with nanomaterials like CNT, graphene, metal nanoparticles, nanowires, and quantum dots to develop nanobiosensors. The nanomaterials are known for their unique properties which are quite different from bulk.

18.3.1 Carbon Nanotube (CNT)-Based Nanobiosensors

Features of CNT like chemical species adsorption, better electron transfer rate, and modification of the resistivity as well as band gap make it an ideal material for sensing applications. Fusion of CNT with biosensing devices has facilitated the development of highly sensitive electrochemical nanobiosensors for various applications like detection of viruses, cancer, and chemical pollutants.

Bhattacharya et al. (2011) has developed a CNT-based highly sensitive biosensor for virus detection (avian metapneumovirus (aMPV)) utilizing chemical functionalization for carbon nanotubes to tailor the interactions with viruses and respective antiviral antibodies. In this nanobiosensor, formation of antigen-antibody complex is reflected by variation in conductance.

Lung cancer can be diagnosed by detecting volatile organic compounds (VOCs) 1, 2, 4-trimethybenzene (TMB) and decane in breath. Liu et al. (2010) has reported an organic material-functionalized single-walled carbon nanotube (SWNT) biosensor to detect these VOCs. This SWNT-based sensor is reported to be useful for noninvasive lung cancer screening depicted in Fig. 18.3.

CA-125 antigen is a biomarker for ovarian cancer which is difficult to detect at early stages. Mandal et al. (2017) have developed an interdigitated nanobiosensor for detection of this antigen by coating electrode surface with CA-125 antibody-functionalized CNTs (Fig. 18.4). This sensor is reported to be capable of detecting the ovarian cancer antigen from a micro volume of sample. Enhanced sensitivity of this nanobiosensor is the result of higher capacitance values, high surface-to-volume ratio, and better electron transfer rate of CNT.

Baldo et al. (2016) have reported cost-effective and fast MWCNT-based amperometric immunosensor for detection of arginase (ARG-1). Human arginase-1 is reported to be an important biomarker in several pathological conditions like autoimmune inflammation in the central nervous system, acute liver injury, different types of cancers, and obstructive nephropathy. To develop nanobiosensor for ARG-1, anti-ARG1 antibody has been immobilized on MWCNT-NHS-sensitive layer to work as resistor. This device is capable to detect ARG-1in the range 30–100 ng/mL which is comparable to ELISA.

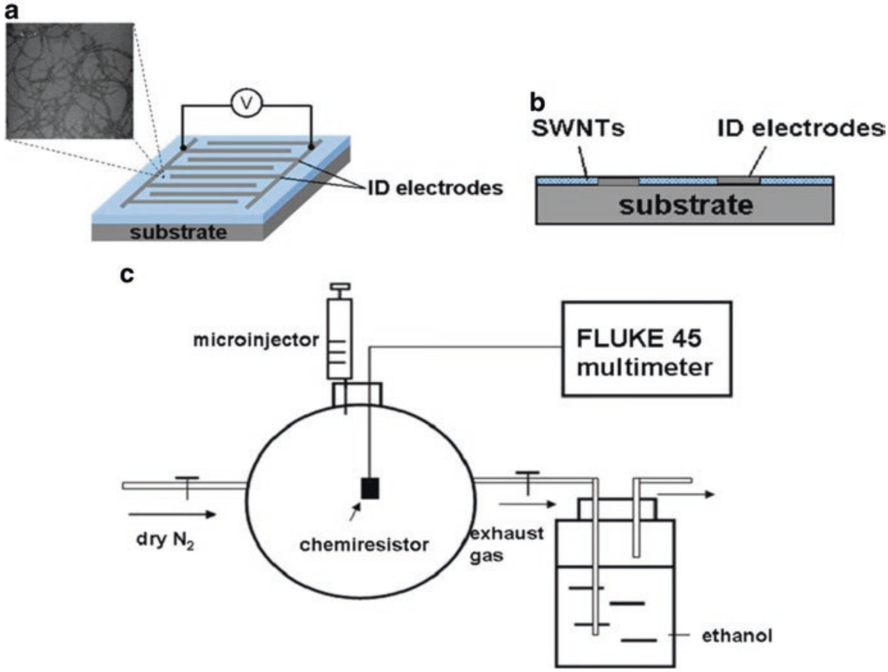

Fig. 18.3 Schematic of the test device. (**a**) the interdigitated electrode coated with SWNTs, (**b**) cross-section view of the electrode, and (**c**) the ichnography of test device. (Reprinted from Physica E: Low-dimensional Systems and Nanostructures, 44, Liu et al. (2010), Single-walled carbon nanotube-based biosensors for the detection of volatile organic compounds of lung cancer, 367–372, Copyright (2018), with permission from Elsevier)

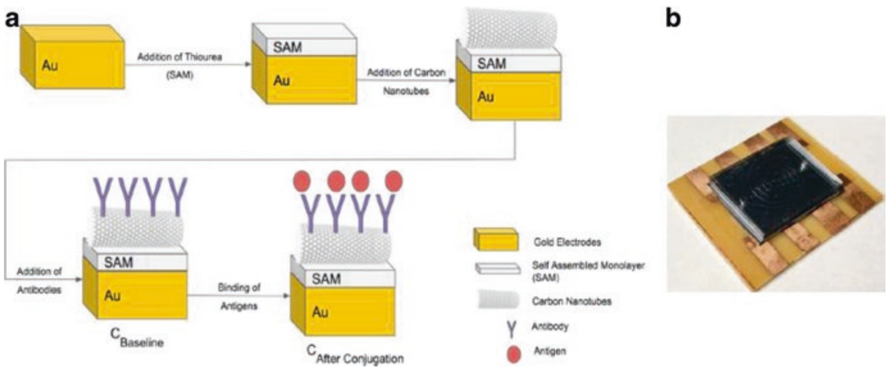

Fig. 18.4 (**a**) Flow diagram of various layer formations on top of the sensor (**b**) real image of the biosensor. (Reprinted from Mandal et al. (2017), Copyright (2018), with permission from Elsevier)

A disposable CNT-based field effect transistor (FET) biosensor for the detection of domoic acid (DA) has been developed by Marques et al. (2017). Domoic acid is a neurotoxin associated with shellfish poisoning in seawater. To develop nano-FET for DA, CNT dispersion is deposited on FET surface and anti-DA immobilized on this FET. As sample containing DA is tested on the nanobiosensor, drain current (I_d) is found to be reduced. With increase in concentration of DA, I_d reduced further. This CNT-based nano-FET has been capable of detecting domoic acid in the range of 10–500 ng/L.

For detection of urea in biological samples like blood or urine, a highly sensitive CNT-FET biosensor is developed by Melzer et al. (2016) using the principle of enzyme-substrate interaction. To develop this nanobiosensor, MWCNT solution drop is casted on gate electrode. The selective detection is reported to be achieved by immobilizing urease enzyme on the biosensor surface. This nano-FET is further modified with polymeric ion-selective membranes and pH-sensitive layers. In this work, concentration of the urea-urease interaction product is detected by the change in respective pH value of electrolyte, which is further reflected by modification in drain current (I_d).

18.3.2 Nanowire-Based Biosensors

Efficient transport of electrons and optical excitation are the unique factors which enable nanowire to be used in biosensors. Most commonly used nanowires in biosensors involve metallic, semiconducting, insulating, and molecular nanowires, which act as promising tool for field use applications such as label-free DNA sensing, virus detection, and environmental monitoring (Patolsky et al. 2006).

Organophosphorus pesticides (OP) are widely used in agriculture. Long-term exposure to low concentration of these OP compounds can damage immune and nervous system (Ghorab and Khalili 2015). An ultrasensitive palladium-copper nanowire-based electrochemical biosensor has been reported for quantitative determination of organophosphate pesticide (malathion) in fruits and vegetables based on the principle of inhibition of acetylcholinesterase (AChE) activity. On exposure to malathion, activity of AChE inhibited resulting in decrease in current. The bimetallic nanomaterials combination used in this nanobiosensor showed chemical stability as well as produced synergistic effect between catalytic activity and conductivity. The result was achieved due to good catalytic property, electron mobility, and high surface area of nanowires (Song et al. 2017).

Food-borne pathogens cause disease outbreaks every year. *E. coli, Salmonella, Listeria monocytogenes, Shigella,* and *Staphylococcus aureus* found in milk, meat, fruits, and vegetables release deadly toxins which can be fatal for humans. Ali et al. (2018) devised an impedance-based electronic biosensor consisting of interdigital silver electrodes with silver nanowires uniformly decorated on the facilitating electrical connection between electrodes. This biosensor measured variation in impedance

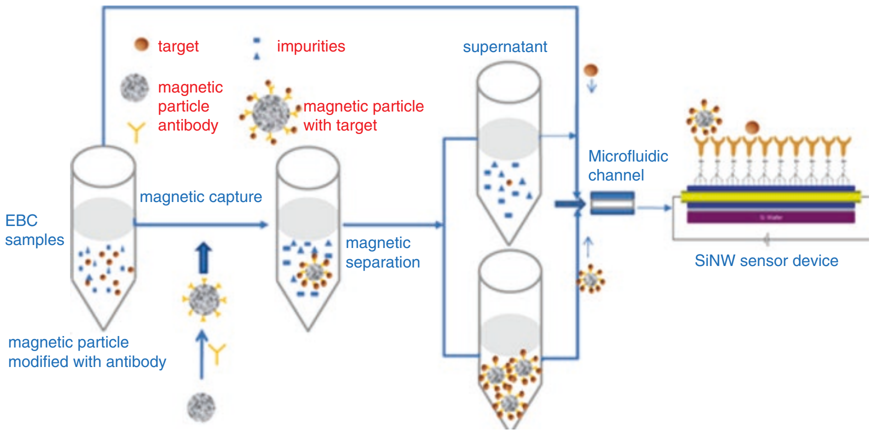

Fig. 18.5 Experimental procedure of virus and 8 iso PGF 2a detection in EBC samples using the SiNW sensor device with and without the magnetic concentrating; EBC samples collected were diluted 100-fold and transported to the sensor device at a flow rate of 170 μL/min. (Reprinted (adapted) with permission from Shen et al. (2012), Copyright (2012) American Chemical Society)

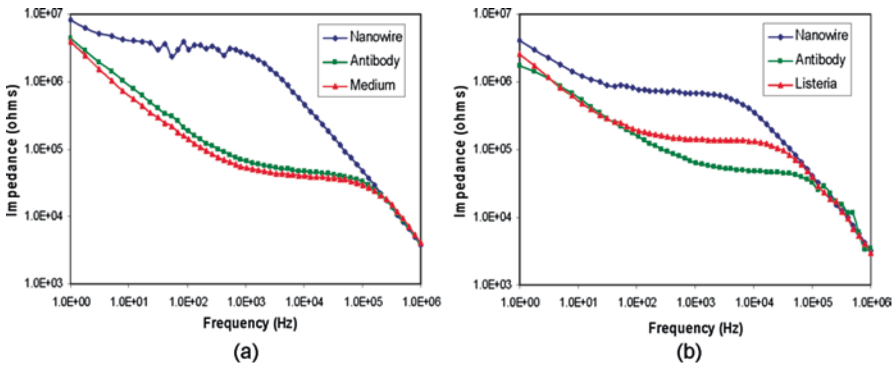

Fig. 18.6 Typical impedance spectra of a TiO_2 nanowire bundle microelectrode-based impedance immunosensor for antibody immobilization and sample detection: (**a**) detection of growth medium without bacteria (control) and (**b**) detection of *Listeria monocytogenes* at a concentration of 4.65 × 103 cfu/mL. (Reprinted (adapted) with permission from Wang et al. (2008). Copyright (2018) American Chemical Society)

depending on the concentration of three different bacteria, namely, *Escherichia coli* strains JM 109 and DH5-α and *Salmonella typhimurium*.

A nano-FET device based on silicon nanowire (SiNW) has been developed by Shen et al. (2012) for selective detection of influenza virus (H3N2) from exhaled breath condensate samples collected from the flu patients. In this device, SiNW functionalized with H3N2/H1N1 antibodies has been used for selectively detecting the virus antigen through change in conductance due to antigen-antibody interaction (Fig. 18.5).

TiO_2 nanowire bundle has been employed in an impedance immunosensor for *Listeria monocytogenes* detection. The nanostructured TiO_2 properties such as large surface area, good biocompatibility, ease of fabrication, and good chemical and photochemical stabilities have been found suitable for nanobiosensor development. TiO_2 nanowire is immobilized with monoclonal antibodies to specifically capture *L. monocytogenes*. This nanowire-antibody-bacteria complex caused change in impedance correlated to bacterial number (Fig. 18.6) (Wang et al. 2008).

Nanowires have also been used for detection of DNA for application in agriculture, forensics, paternity, and medicine. Rahman et al. (2016) has developed SiNW-based electrical nanobiosensor for early-stage diagnosis of dengue virus. In this sensor, single-stranded DNA-functionalized SiNW has been used between source and drain of FET. Alteration in current level between source and drain terminal after hybridization of target DNA with immobilized probe DNA is used as the main working principle in this sensor. The nanobiosensor's sensitivity and stability is enhanced using oxygen plasma technology for efficient use in point-of-care devices.

A glucose sensor has been reported by Liu et al. (2017) based on 3D copper foam (CF)-supported copper oxides nanowire arrays and nanoflowers. These nanostructures exhibited enhanced electrochemical catalytic activity toward glucose oxidation through the enormously increased surface area. The resulting nanosensor for glucose detection reported to provide high sensitivity, selectivity, reproducibility, and stability.

18.3.3 Graphene-Based Nanobiosensors

Graphene (GN) and its water-soluble derivative graphene oxide (GO) are, nowadays, very popular material to develop nanobiosensors for various applications like DNA, glucose, cholesterol, and dopamine sensing. Graphene is capable of improving overall performance of biosensor due to its large surface area, excellent electrical conductivity, and great electron mobility, resulting in enhancement of its selectivity and sensitivity (Suvarnaphaet and Pechprasarn 2017).

Graphene oxide (GO) is found to be useful to develop nanobiosensors due to its capability of excellent biomolecular adsorption and mediating capacity for chemical reactions. It is also reported that GO shows electrocatalytic activities toward small molecules like dopamine, hydrogen peroxide, and NADH, and there is direct electrochemistry of enzymes with graphene oxide. So enzyme biosensors have been developed based on graphene oxide. Several DNA sensors have also been developed on the basis of adsorption of single-stranded DNA (ss-DNA) on GO. As both ss-DNA and GO are negatively charged, high salt concentration is used to screen the electrostatic repulsion between them. The attractive forces between DNA and graphene oxide include hydrophobic interaction, π-π stacking, van der Waals forces, and hydrogen bonding. While probing the interaction between DNA and GO, Liu et al. (2013) explained the mechanisms of DNA sensing on the surface of graphene oxide. GO possesses strong fluorescence quenching ability, and it has strong affinity toward single-stranded DNA (ss-DNA) as well. DNA and aptamers labelled with fluorophore have been used extensively with GO to develop nanobiosensors for detecting nucleic acids, small molecules, and proteins.

Zhang et al. (2015) have reported the development of enzyme-modified graphene solution-gated transistor sensor for glucose sensing. Regular monitoring of glucose level in body is required in disease like diabetes mellitus. This nanosensor has been developed by surface modification of the graphene gate electrode using enzyme glucose oxidase (GOx). Catalysis of glucose oxidation with GOx resulted in generation of H_2O_2 and potential drop on gate electrode, which further affected channel current. Another method reported by Zhu et al. (2016) involved a graphene-based nano-FET for affinity-based detection of glucose. In this sensor, graphene functionalized with boronic acid is used for specific binding with glucose. After interaction with glucose, changes in electrical properties of graphene and detectable signal production have been reported. Kwak et al. (2012) have developed a flexible glucose nanobiosensor using graphene-based FET. In this nano-FET, enzyme GOx is used to functionalize graphene to induce the catalytic reaction of glucose. For this purpose, PET has been used as a flexible substrate and graphene film as channel in FET. Source and drain electrodes have been developed by silver paint and epoxy resin on the PET substrate. Through the measurements of differential drain-source current and Dirac point shift, fabricated nano-FET device detected the presence of glucose.

A rapid and highly sensitive nanobiosensor for multicolor fluorescent analysis of DNA has been designed by He et al. (2010) based on very high quenching efficiency of graphene oxide. Binding of fluorescent ss-DNA probe with graphene resulted in quenching of fluorescence, while strong emission obtained after hybridization of probe with complementary target. The large surface area of GO is exploited in this nanobiosensor for simultaneous quenching of several DNA probes labelled with different dyes. This led to the development of a multicolor sensor for detection of several DNA targets in single sample.

A graphene-based electrochemical biosensor has been developed by Rasheed and Sandhyarani (2014) for low concentration detection of BRCA1 gene related to breast cancer. This biosensor used sandwich method in which there is hybridization of capture probe (DNA-c) and reporter probe (DNA-r) with target probe DNA (DNA-t) on graphene-modified glassy carbon electrode in a sandwich arrangement. The electrochemical detection performed with chronoamperometry and cyclic voltammetry as shown in Fig. 18.7.

A method of nonenzymatic and electrochemical detection of cholesterol has been developed by graphene modification with β-cyclodextrin (Grp-β-CD) (Agnihotri et al. 2015). Redox indicator methylene blue (MB) after adding to Grp-β-CD forms a complex Grp-β-CD-MB. Working mechanism of this nanosensor is based on electrochemical detection of replacement of methylene blue by cholesterol molecule using differential pulse voltammetric (DPV) technique.

Biosensor for sensitive and rapid detection of dopamine (DA) is required for clinical and other applications. DA is an electroactive neurotransmitter, so electrochemical sensing can be used to detect it. Yang et al. (2012) have used this approach

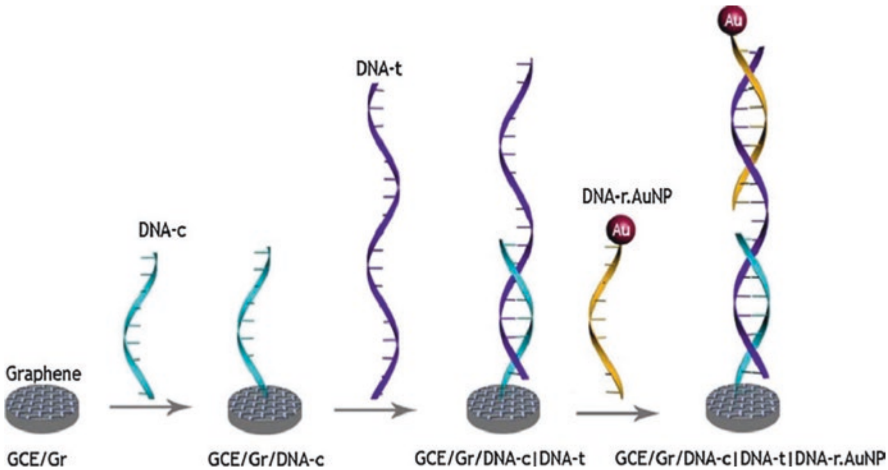

Fig. 18.7 The schematic representations of the various stages of sensor fabrication. (Reprinted from Rasheed and Sandhyarani (2014), Copyright (2018), with permission from Elsevier)

to develop a disposable working electrode based on reduced graphene oxide and gold nanoparticles on ITO-coated glass substrate for sensing presence of DA in meat samples. This sensor is found to have good selectivity for DA against other electrochemical interfering species like uric acid (UA) and ascorbic acid (AA).

18.3.4 Metal Nanoparticles-Based Nanobiosensors

Size-related properties of metal nanoparticles have been assisting in scientific researches for development of novel sensing techniques. Localized surface plasmon resonance, fluorescence enhancement/quenching, surface-enhanced Raman scattering (SERS), and electrochemical activity-related properties have been explored for metallic nanoparticles to be used in a wide range of applications such as pathogen testing, biomarker identification, and DNA testing (Doria et al. 2012). Gold, silver, and magnetic nanoparticles have been used to develop several nanobiosensors (Malik et al. 2013). Applications of metal nanoparticles in nanobiosensors are summarized in Table 18.2.

Gold nanoparticle (GNP) is known for its unique optical, electrical, and catalytic properties. Nanobiosensors based on GNP are developed for applications in diagnostics; environmental contaminants such as heavy metal ions, pathogens, and toxins; and food applications (Paul and Tiwari 2015). Gold nanoparticle-based nanosensors have also been developed for detecting different classes of enzyme activity in analytes, i.e., hydrolases, transferase, and lyase through colorimetric and fluorescence resonance energy transfer (FRET)-based assays (Hutter and Maysinger 2013).

Table 18.2 Applications of metal nanoparticles in nanobiosensors

Metal nanoparticle	Principle of detection	Applications	References
GNP	Fluorescence quenching	Detection of acryalmide in food based on fluorescent quenching	Asnaashari et al. (2018)
	Aggregation principle	Detection of malathion in food	Bolat and Abaci (2018)
	SPR	Detection of 2,4,6-trinitrotoluene (TNT)	Tan et al. (2016)
	Electrochemical	Label-free detection of DNA	Mohammad et al. (2014)
MNP	Fluorescence quenching	Detection of *E.coli* in food samples	Shelby et al. (2017)
AgNP	Colorimetric	Detection of cadmium and lead in water	Kumar and Anthony (2014)
	Electrochemical	Detection of Human chorionic gonadotropin (hCG) biomarker for prostate tumor and gestational choriocarcinoma in blood and urine; Detection of β-adrenergic agonists like ractopamine (RAC), salbutamol (SAL), and clenbuterol (CLB)	Xia et al. (2017), Wang et al. (2013)

Gold nanoparticle-based nanosensors are mainly based on its fluorescence quenching ability, surface plasmon, and aggregation mechanism. GNP is an excellent material for colorimetric biosensors development due to ease of functionalize and color display depending on state of aggregation, size, and shape.

Asnaashari et al. (2018) have reported a biosensor for acrylamide in food products based on fluorescence quenching of FAM, a fluorophore, using DNA and GNP. Acrylamide is a neurotoxic and carcinogen substance developed in some food products during high temperature processing like roasting, frying, and baking. In this nanosensor, remarkable difference in fluorescence intensity is reported in the presence of acrylamide (Fig. 18.8). Presence of the acrylamide in the sample led to acrylamide-ss-DNA adduct formation, which after binding with GNP surface resulted in quenching of fluorescence from FAM.

A highly sensitive biosensor for detection of malathion on the basis of aggregation of GNP has been developed. *Malathion* is a broad-spectrum organophosphorus pesticide. In this nanosensor, a cationic polymer poly (diallyldimethylammonium chloride) (PDDA) and aptamer are used to control aggregation of GNP. PDDA in free form interacts with GNP leading to its aggregation. In absence of malathion, apatamer binds with PDDA and inhibits aggregation of GNP. But in presence of malathion, apatamer interacts with it and free PDDA causing aggregation of GNP and change of color from red to blue (Bolat and Abaci 2018).

SPR is an optical phenomenon which can be amplified using gold nanoparticles. Biosensors for detecting different analytes are developed using SPR principle in the presence of GNP. A GNP-amplified SPR-based aptamer biosensor has been

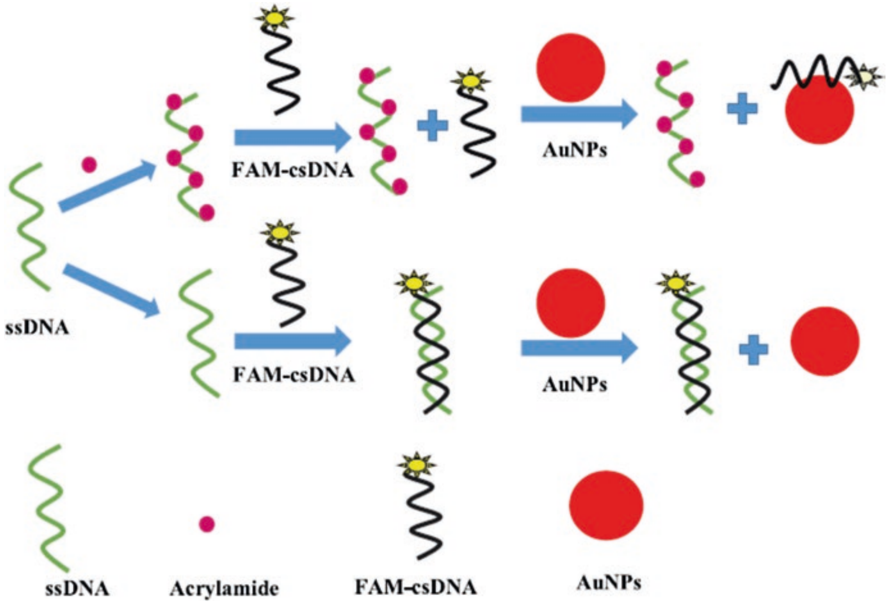

Fig. 18.8 Schematic description of acrylamide detection using fluorescent biosensor. (Reprinted from Asnaashari et al. (2018), Copyright (2018), with permission from Elsevier)

developed for detection of 2, 4, 6-trinitrotoluene (TNT), an explosive. The basic mechanism involved formation of anti-TNT peptide aptamer-GNP complexes from which TNT is capable to bind (Tan et al. 2016).

Electrochemical biosensors work on the principle of generating electrical signals as a result of biological interaction. Conductivity and catalytic property of GNP have been exploited for facilitating electron transfer between the immobilized biomolecules and surface of electrode and as catalyst in electrochemical sensors. This has led to development of GNP-based electrochemical immunosensor and DNA biosensor with enhanced performance. For label-free DNA detection, SiO_2 thin films functionalized with GNP used for attachment of DNA probes. Presence of target DNA was detected by change in capacitance of developed system after hybridization (Mohammed et al. 2014).

Similar to GNP, silver nanoparticles (AgNP) are also being used in several nanobiosensors. A multiplexed, electrochemical immunosensor for simultaneous detection of β-adrenergic agonists: ractopamine (RAC), salbutamol (SAL), and clenbuterol (CLB), has been developed. These β-adrenergic agonists are used as growth promoter in animals. For the development of sensor, silver-palladium alloy nanoparticles (AgPd NP) are used as signal label for antibodies and reduced graphene oxide (rGO) as substrate material for electrode. The immunoreactions at electrode generated strong electrochemical signal which determined the presence of β-adrenergic agonists (Wang et al. 2013).

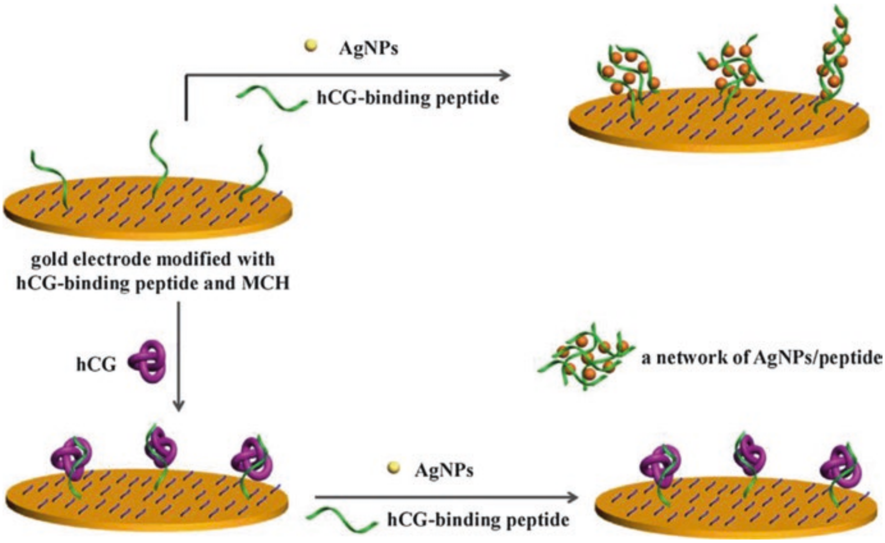

Fig. 18.9 Schematic illustration of the electrochemical method for hCG detection using AgNPs as the redox reporters and hCG-binding peptide as the receptor of hCG and the inducer of AgNPs aggregation. (Reprinted from Xia et al. (2017), Copyright (2018), with permission from Elsevier)

Another silver nanoparticles-based sensor has been reported by Xia et al. (2017) for detection of human chorionic gonadotropin (hCG) which is a biomarker for prostate tumor and gestational choriocarcinoma. The basic principle involved conversion of colorimetric assay of silver nanoparticles to electrochemical signal. The electrode surface in this electrochemical sensor is modified with hCG-specific binding peptides. This hCG-binding peptide induced aggregation of silver nanoparticles on the electrode surface as shown in Fig. 18.9. However, in the presence of hCG, aggregation is found to be inhibited and reflected by attenuation in near-sweep voltammetry (LSV) current.

Surface-modified silver nanoparticles with amino acid-based phenolic ligands have been used to detect mercury, cadmium, and lead toxicants in water samples. These heavy metal ions are known to cause central nervous defects and cancer. These ligands functionalized silver nanoparticles exhibited selective colorimetric change which further measured with UV-Vis spectroscopy in the presence of toxic Cd^{2+}, Hg^{2+}, and Pb^{2+} metal ions in aqueous solution at ppm level (Kumar and Anthony 2014).

Magnetic nanoparticles (MNP)-based nanobiosensor has been exploited for monitoring and separation of various pathogens in the processed food and raw food materials without any filtration or centrifugation procedures and making it practically effortless (Augustine et al. 2016). The basic mechanism for detection involving magnetic nanoparticles is related to formation of bacterium nanoconjugates by conjugation of MNP with appropriate bacterial ligands (Fig. 18.10). These bacterial ligands move under influence of magnetic field and move along with MNP.

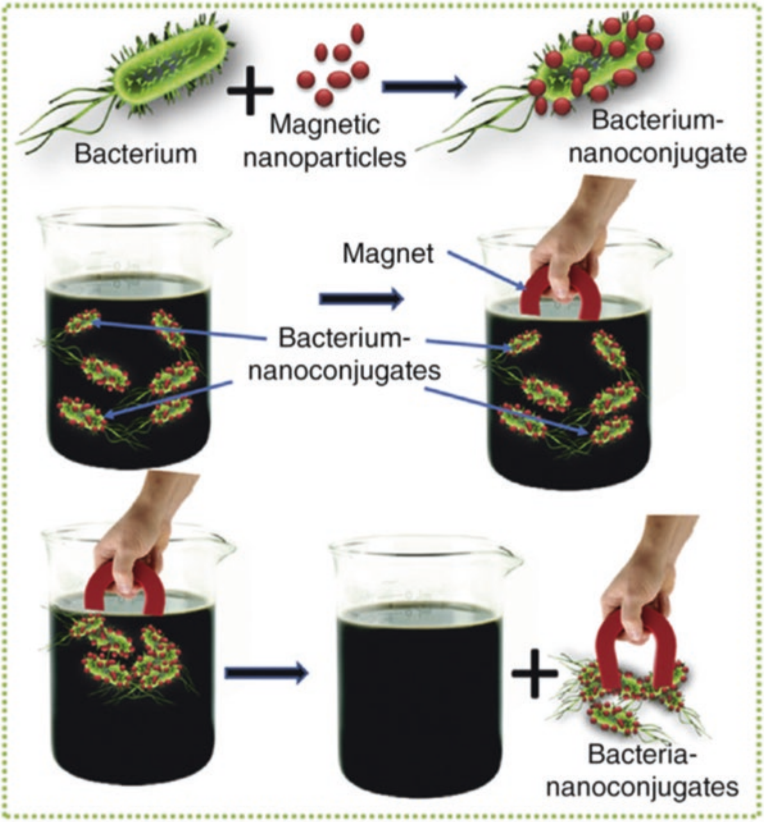

Fig. 18.10 Magnetic nanoparticle-based separation of bacteria from a contaminated solution. (Reprinted from Augustine et al. (2016), Copyright (2018), with permission from Elsevier)

The bacteria bound to MNP can be removed and decontaminated by appropriate sterilization techniques for reuse. MNPs used in electrochemical devices have shown to improve the transduction mechanism through their contact with the electrode surface, transport of a redox-active species to the electrode surface, and formation of a thin film on the electrode surface (Rocha-Santos 2014).

Aljabali et al. (2018) devised a sensitive nanosensor based on antibody conjugated iron oxide nanoparticle for detecting *Serratia marcescens* belonging to enterobacteriacia family found in starchy food causing food-borne infection. Iron oxide nanoparticle coated with *Serratia* antibody has been used to bind with cell wall of the bacteria. The magnetic properties of iron nanoparticle strengthened the detection capability.

Shelby et al. (2017) devised a magneto-fluorescent nanosensor (MFnS) for detection of *E.coli* in food samples (milk and lake water) using magnetic nanoparticles. In this nanosensor, surface of iron oxide nanoparticles conjugated with target-specific antibodies is coated with fluorescent 1,1′-Dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) dye. Magnetic relaxation values are reported to be changed after clustering of MFnS around the surface of bacterial contaminants. Binding of MFnS could also be detected optically due to strong signal produced by it, hence giving a dual mechanism for detection of *E. coli.*

18.3.5 Quantum Dots-Based Nanobiosensors

Quantum dots (QD) are small semiconductor crystals exhibiting unique optical and electronic properties such as broad absorption spectra, photodurability, size-tunable emissions, and large intrinsic dipole moments (Frasco and Chaniotakis 2009; Wen et al. 2017). QDs have advantages over organic fluorophores like narrow emission peaks, longer lifetime, and broad excitation ranges. Quantum dots can also be functionalized by different biological molecules.

Rennin is an enzyme secreted by kidneys for regulating blood pressure. Its evaluation is essential for assessment of rennin-related diseases such as hypertension, congestive heart failure, and cancers. Long et al. (2012) have devised a method for sensitive detection of rennin activity using quantum dots. The QD biosensor for rennin activity has advantages over other methods of rennin detection such as size-dependent emission spectra with narrow bandwidths, good resistance to chemical, and photodegradation. The sensor involved complex of streptadavin-coated QDs from which bioinylated peptide substrates are attached. These bioinylated peptide substrates labelled with Cy5 dye make QD complex to exhibit fluorescence resonance energy transfer (FRET). The QD cleaves from substrate in the presence of rennin and resulting in decreases of FRET efficiency. This results in decrease of Cy5 counts which is directly related to quantity of rennin as shown in Fig. 18.11.

Quantum dots are also used for developing a model nanosensor for protein recognition with potential to be used in future for clinical diagnostics and food analysis. For this purpose, a combination of fluorescent QDs conjugated goat anti-mouse IgG and capture antibody (rabbit anti-mouse IgG antibody) has been used. In this work, use of fluorescent QDs for protein recognition has been successfully demonstrated using UV-illuminated microscope (Xu et al. 2010).

Bhattacharyya et al. (2017) have used fluorescent CdSe QD probes with tunable excitation and emission for tuberculosis volatile organic biomarkers (TB-VOB) detection in the breath (Fig. 18.12). Emission properties of VOB-modified QDs are found to be altered exhibiting peak shift which reflected in the display of completely different colors.

Photoelectrochemical sensors based on quantum dot are gaining attraction as they are being viewed as strong alternative of biochemical and chemical molecules. The QDs are being utilized to develop electrochemical sensors in which electrode with immobilized QDs generates photocurrent upon illumination depending on type and concentration of the analyte (Yue et al. 2013).

A biosensor using fluorescent cadmium-tellurium (CdTe) quantum dots has been developed to identify human T-lymphotropic virus-1. In the developed method, two probes, acceptor and reporter probes, hybridized with target DNA, making a sandwich complex. This complex immobilized on a well having streptavidin in which

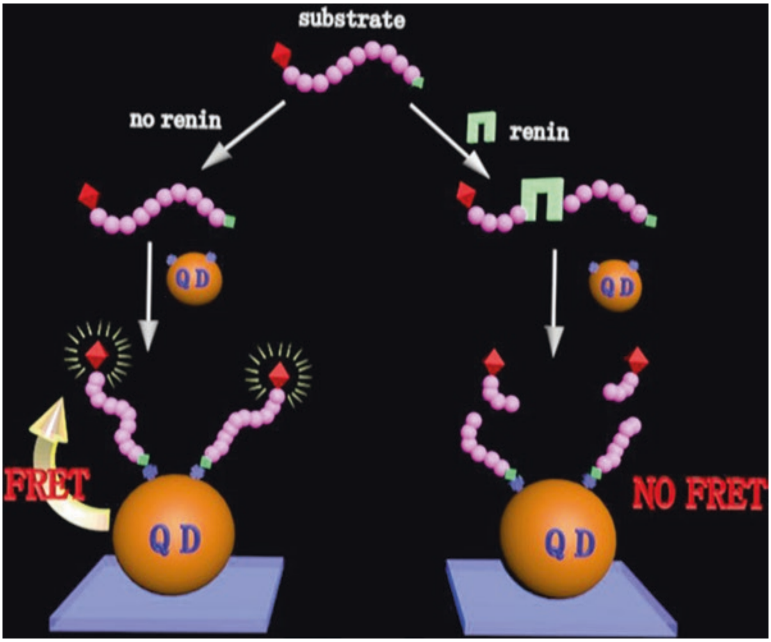

Fig. 18.11 Schematic Illustration of the Single-QD-Based Nanosensor for Renin Assay. (Reprinted (adapted) with permission from Long et al. (2012). Copyright (2009) American Chemical Society)

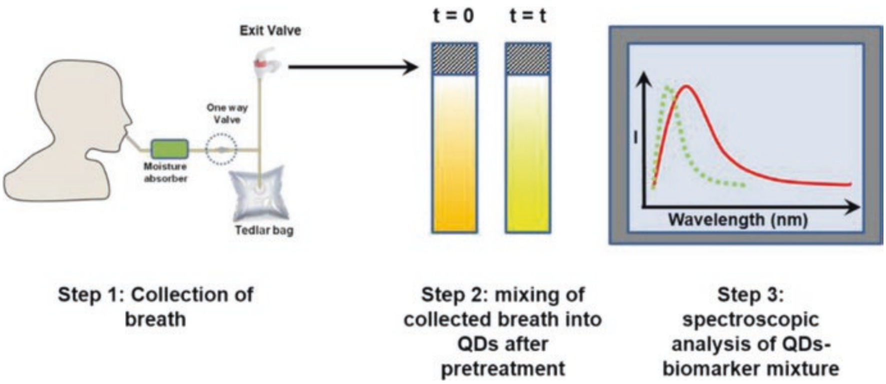

Fig. 18.12 A diagram (schematic) showing proposed method of TB biomarker detection using quantum dots. The methodology involves the collection of breath into a Tedlar bag and subsequent mixing into a QDs (or C-dot) solution. The spectral analysis performed for estimation of VOB concentration and prediction of patient health. (Reprinted from Bhattacharya et al. (2017), Copyright (2018), with permission from Elsevier)

QD solution was added. After conjugation with reporter probe, emission spectra of the quantum dots are found to be modified (Norouzi et al. 2017).

Fluorescence property of the QD has also been utilized in the detection of pesticides trichlorfon (TF). The sensor developed consists of core and multilayered shell structure of CdSe/ZnSe/ZnS QDs, streptavidin (SA), and enzyme AChE (acetylcholine esterase). QD/SA/AChE structure has been used as biosensor for TF. Hydrolytic activity of AChE and enzyme inhibition capability of trichlorfon are used in this sensor to modify the surroundings and the fluorescence of QD (Nguyen et al. 2015).

A nanobiosensor for aflatoxin has been reported using fluorescence property of QD. Fungi *Aspergillus flavus* and *Aspergillus parasiticus* produce aflatoxin B1 (AFB1), a potent carcinogen into infected agricultural products such as oilseed and cereals. Zeng et al. (2015) demonstrated an electrochemical competitive immunoassay for highly sensitive detection of aflatoxins (AFB1) using layer-by-layer (LBL) assembled PbS quantum dots conjugated with monoclonal anti-AFB1 antibody for peanut samples.

Meshik et al. (2014) have developed a QD-based aptamer nanosensor for optical detection of potassium and lead ions which are important for diagnostic purposes. To develop this sensor, thrombin-binding aptamer (TBA), InGaP QD, and GNP quencher have been used, and photoluminescence (PL) is used to measure the efficiency of quenching leading to estimation of ion concentration of analytes.

18.4 Recent Advancement in Nanobiosensor Applications

Recent advancement in nanotechnology has led to designing of innovative biosensing techniques utilizing CNT, graphene, GNP, magnetic nanoparticles, QD, and nanowires. Nanobiosensors are becoming important in the field of diagnostics, food safety, defense, and environmental monitoring. This led to integrating them as biological sensing element with applications like point-of-care (POC) devices, biochips, drug delivery, cancer biomarker detection, and lab on a chip to make them more sophisticated, rapid, cost-effective, and reliable. In this section, an overview of recent advancements in nanobiosensor applications is provided.

18.4.1 Point-of-Care Devices

Point-of-care (POC) devices have important role in diagnostics, especially for disease surveillance and clinical care. It is important to take care of affordability, portability, rapidity, and user friendliness during designing of POC devices (Gonza'lez and Merkoçi 2018; Choi 2010a). POC devices have been classified as small handheld devices and the ones which are used in laboratories. Example of the handheld point-of-care devices includes glucose meter, pregnancy test kit, and bench top devices like testing and electrolyte analysis. It has been noted that these POCs have overcome the problems faced in the conventional method of analysis and diagnosis which are time-consuming and expensive. POC devices are advantageous for rural setup also, where there is lack of facility or people can't afford the expensive diagnostic testing. This impact of POCs in diagnostic has been made possible due to conjugation with nanotechnology. The crucial function in POCs made by nanotechnology is huge improvement in transduction mechanism. The most common transduction mechanisms shown in POC's are optical and electrochemical. Integration of nanomaterial with POC provided very large surface area for biomolecule attachment, increasing specificity and helping in detecting ultra trace concentration, thus performing multiple analysis with small quantity of sample.

Many nanobiosensors developed using nanomaterials such as QDs; gold, silver, and magnetic nanoparticles; carbon nanotubes, and graphene are being used in point-of-care devices for detecting DNA, cancer, pathogenic bacteria, glucose, and hormones (Syedmoradi et al. 2017; Gonza'lez and Merkoçi 2018; Wang et al. 2016). A microfluidic POC device has been proposed for nucleic acid detection from bacteria related to tuberculosis based on a magnetic barcoding strategy. The device contained all the main units of assay loaded onto one chip for performing DNA amplification, MNPs-DNA incubation, washing, and NMR detection (Liong et al. 2013). The fluorescent nanoparticle QD and magnetic particles have been used for *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Klebsiella pneumoniae* detection for magnetic barcode system where the specific bacteria changed the emission spectra of fluorescent QDs (Cihalova et al. 2017). Nanowires employed on paper for recording electrocardiogram (ECG) signal by measuring changes between skin and electrode have shown a possible alternative toward wet gel electrodes (Mostafalu and Sonkusale 2015). However, use of POCs as an ideal diagnostic device holds some challenges like constraints in the development of appropriate sample preparation methods, prevention of nonspecific adsorption, standardization, automation of technology and interpretation of results need to be taken care of (Syedmoradi et al. 2017).

18.4.2 Biochips

The evolvement of biochips is finding major applications in biotechnology industry such as genomics and proteomics (Rao et al. 2012). Biochip consists of multiple tools having sensitive detection capability which has been made possible due to use of nanobiosensing principles.

A highly efficient and reusable Raman spectroscopy (SERS)-active biochip has been developed using laser scribing treatment of silver nanoparticle and graphene (AgNP-GO) composite (Fig. 18.13). AgNP on graphene surface has been used to enhance the Raman signal. By immobilizing biomolecules on graphene, controllable trapping and release of DNA could be obtained in this biochip (Han et al. 2018).

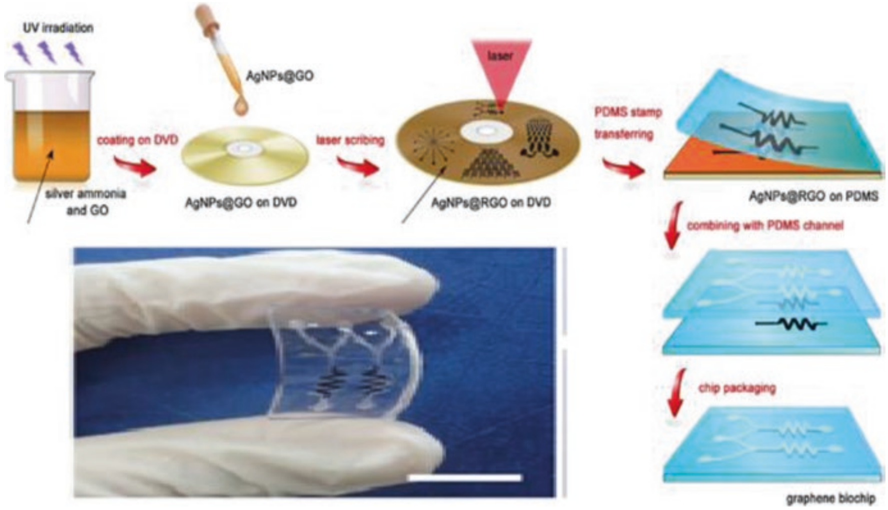

Fig. 18.13 Fabrication of AgNPs@RGO biochip. (**a**) Schematic illustration of the fabrication procedure of an AgNPs@RGO SERS biochip and Photograph of the as-prepared AgNPs@RGO SERS biochip. (Reprinted from Han et al. (2018). Copyright (2018), with permission from Elsevier)

Epidemic caused by Zika virus in 2015 has been a major issue of health concern due to its long-term effects such as severe brain defects and Guillain-Barre syndrome on fetus and adults. Afsahi et al. (2018) devised a graphene-based chip functionalized with anti-Zika NS1 providing early diagnosis for Zika virus. Capacitance of graphene chip functionalized with monoclonal antibodies gets changed after binding with varying doses of antigen (ZIKV NS1).

A biochip for prostate cancer biomarker detection has been fabricated by Lee et al. (2012) by integrating microfluidic system with silicon nanowire (SiNW) array immobilized with PSA and IL-6 antibodies. This biochip has been able to detect PSA and IL-6 in plasma for prostates cancer with fast and multiple analyte detection capability.

18.4.3 Drug Delivery

Automated drug delivery system is the area where biosensors play important role. Application of nanotechnology for biosensing in the drug delivery system is giving new route, as hugely growing population urgently needs rapid and cost-effective methods. Researchers are coming up with miniaturized systems containing nanobiosensors and control unit which can be implanted on humans for detection and monitoring of disease. The role of these biosensors is to provide feedback control by perceiving changes in their surrounding physiological or biological fluid and then taking action by controlled release of one or more drugs at desired site. The selectivity of biosensor is critical as different proteins and chemicals present in its surrounding may affect its parameters like accuracy, selectivity, and sensitivity. A variety of organic and inorganic nanomaterials and devices have been used as drug delivery carriers to enhance the therapeutic activity. The requirement for nanoparticle-based drug delivery system includes biodegradability, biocompatibility, nontoxicity, and functionality.

Noninvasive glucose sensing has been gaining significant attention nowadays. These systems modified with nanoscale materials are implanted or administered into the biological system. Nanosensors based on CNT, quantum dots, and graphene have been widely used as a replacement to current glucose sensors (Cash and Clark 2010). Early detection of cancer biomarkers or tumor cells in system may help in the survival of cancer patients. Nowadays, nanomaterial-based biosensors are being employed for cancer detection and drug delivery monitoring (Salvati et al. 2015). A study has been conducted for potential application of MWCNT-Ti sensors in orthopedics for enhancing osteoblast differentiation to promote bone growth and treat infection or inflammation next to bone implants (Sirivisoot and Pareta 2012). Such advancement in drug delivery system through nanosensors can enhance self-monitoring of disease and illness management.

18.4.4 Cancer Biomarker Detection

Uncontrolled growth of abnormal cells in body organs and system results in cancer. Different forms of cancer including lung, prostate, breast, ovarian, hematologic, skin, and colon cancer can be screened through CT-scan, X-ray, and MRI. Currently, researchers are developing methods for accurate diagnosis of cancer relying on cancer biomarkers detection. The detection of biomarker is helpful to know the progress of disease and its response to treatment. Several biosensors used for cancer screening have become more sensitive and show precise response toward biomarkers detection due to the use of nanomaterials (Choi et al. 2010b). Some of the cancer biomarkers are carcinoembryonic antigen (CEA) for cancers of the gastrointestinal tract; prostate-specific antigen (PSA), a biomarker to screen for prostate cancer; and cancer antigen 125 (CA125), an antigen in patients detected with ovarian cancer. Nanowires, quantum dots, and carbon nanotubes are some of the nanomaterials which have been utilized for detection of these cancer biomarkers (Devi et al. 2015; Jaishree and Gupta 2012).

A gold and magnetic nanoparticle-based enzyme-labelled probe for detection of carcinoembryonic antigen (CEA) has been reported. In this method, GNP coated with antibody, single-stranded DNA (ssDNA), and horseradish peroxidase (HRP) are used. A capture probe developed using MNP functionalized another antibody. The immunoreaction between target antigen and antibody had transduced into optical signals (Liu et al. 2010).

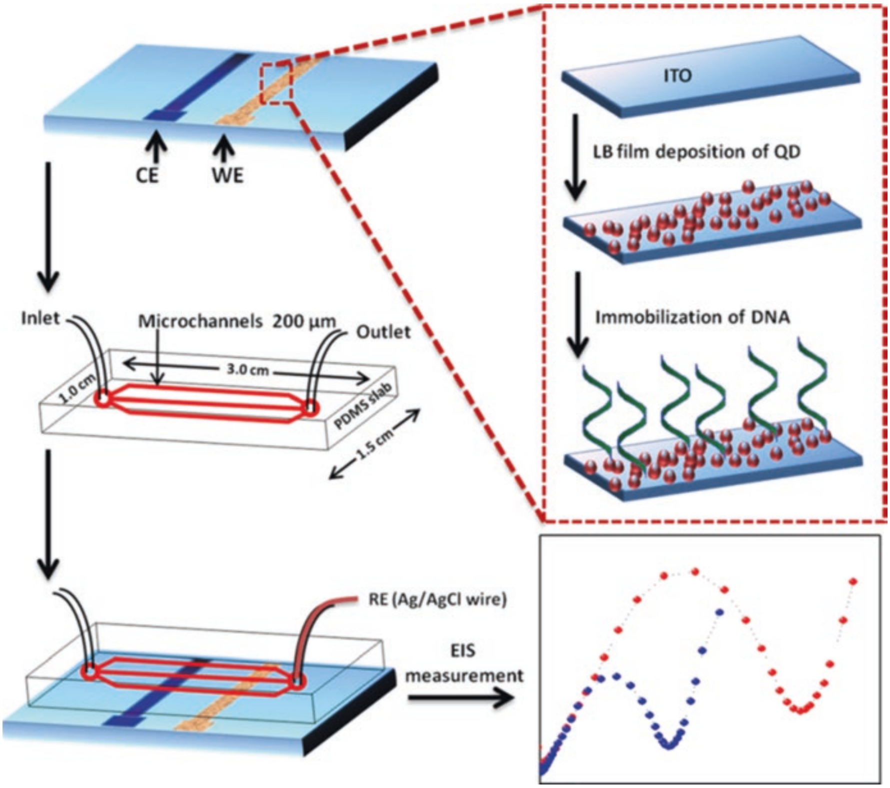

Fig. 18.14 Different steps showing the fabrication of microfluidic biochip for electrochemical detection of DNA hybridization. WE Working electrode, CE counter electrode, RE reference electrode. (Reprinted from Ghrera et al. (2015), Copyright (2018), with permission from Elsevier)

QDs-based nanobiosensor has been developed for detection of mutation in breast cancer cells, BRCA1 and BRCA2. 185delAG I deletion is breast cancer gene associated with risk of developing breast cancer. Amine functionalized DNA attached to QD and emission spectra of this system at 489 nm are found to be stronger for cDNA compared to mDNA (Eftekhari-Sis et al. 2017). Same principle has been used in cadmium selenide quantum dots used in microfluidic sensor for nucleic acid to detect chronic myelogenous leukemia (CML) (Fig. 18.14).The quantification of DNA has been done through measure in interfacial charge transfer resistance (Ghrera et al. 2015).

Carbon nanotube-based biosensors are used for detection of carbohydrate antigen 19-9 (CA19-9), a cancer biomarker for pancreatic cancer. Interdigitated gold electrodes with a thin film sensing unit containing polyethyleneimine and CNT thin film with antibodies anti-CA19-9 have been developed. Binding of CA-19-9 antigen on developed electrode is further studied using impedance spectroscopy (Thapa et al. 2017).

18.4.5 Lab on a Chip

Labs on a chip (LOC) are miniaturized device in which analytical functions are combined for biomolecule detection. The functions like sample pretreatment, recognition of analyte, transduction of the reaction, and amplification of measured signal are integrated in LOC devices. LOC have become meaningful platforms in detection of protein and DNA and diagnostics due to their numerous benefits like low volume of sample, economical, multiple sample detection, and portability (Claussen and Medintz 2012). These miniaturized LOC devices contain nanostructured sensors for detection of analytes for improved transduction mechanism. Chua and Pumera (2013) showed use of chemically modified graphene materials as electrochemical detectors in a lab-on-chip device. Nanomaterials such as quantum dots, GNP, and MNP have been used for labeling of biomarkers to be used in LOC.

For label-free detection of low-density lipoprotein (LDL) cholesterol in human serum, an impedimetric nanobiosensor based on CNT is developed for LOC device applications. In this application, CNT-NiO nanocomposite functionalized with antiapolipoprotein B, is deposited on indium-tin oxide (ITO) substrate to detect LDL by impedimetric method as illustrated in Fig. 18.15. This LOC device convertes the antigen-antibody reaction into measurable electrical signal (Ali et al. 2015).

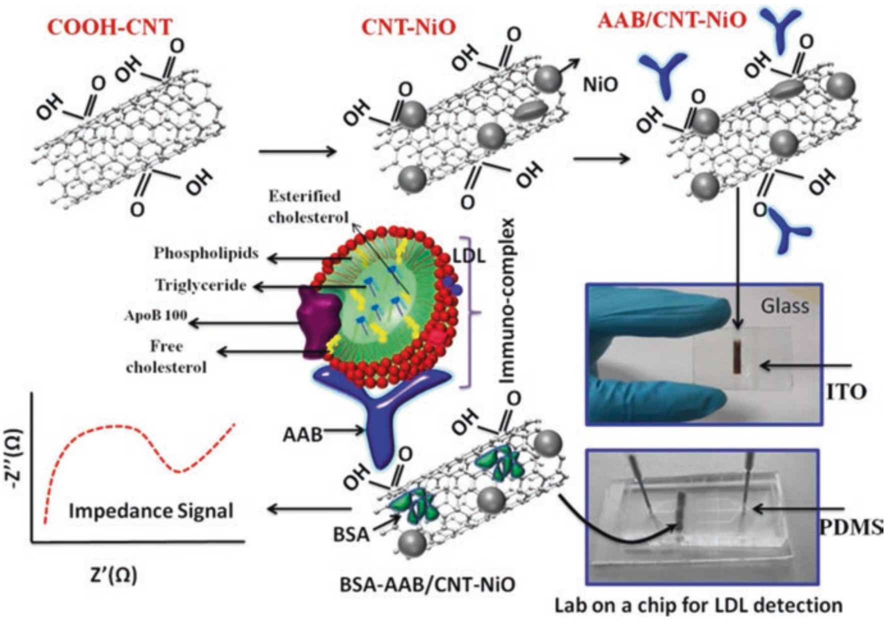

Fig. 18.15 Schematic representation of the Lab-on-a-Chip Fabrication for LDL Detection. (Reprinted (adapted) with permission from Ali et al. (2015), Copyright (2018) American Chemical Society)

An LOC device with nanobiosensing elements for food safety application has been discussed by Yang et al. (2010). In the developed device, anti-SEB antibody-CNT immobilized on polycarbonate strip for detection of staphylococcus enterotoxin (SEB) which is responsible for food-borne intoxication. This LOC device showed potential for sensitive detection of toxin with low volume and sample without power requirement.

In spite of so many advancements in the field of LOC using nanobiosensors, there are some of the current drawbacks including quantification of low concentration of sample, complexity in fabrication procedures, and difficulty in multiplex analysis.

18.5 Future Perspectives

There has been huge growth in the field of nanomaterials in recent years which have attracted attention of researchers to develop novel nanobiosensors by coupling biomolecular recognition elements with nanomaterials like CNT, graphene, metal nanoparticles, and quantum dots. Use of the nanomaterials with high surface area is important in developing rapid and highly sensitive nanobiosensors with applications in clinical monitoring, environmental applications, agriculture, bioprocess control, and food industry applications.

Recent researches are focused on development of miniaturized and portable systems based on electrical, optical, and magnetic sensing. So, the researchers are working toward the design of devices utilizing nanomaterial-based biosensors which fulfil these characteristics. Lab on a chip, point-of-care devices, automatic drug delivery systems, and biochips are examples of such devices in which nanobiosensors are used.

However, this newly growing area of nanobiosensor faces challenges regarding enhanced amplification of signals and enhancement of signal to noise ratio. Interaction mechanisms between nanomaterials and biomolecules are also not fully understood yet. Future work should be focused on understanding the interaction mechanism and using novel techniques to develop more advanced biosensors with the capability of single molecule detection of biomarkers and multiplexed assay feature. There is also requirement of cheap and disposable nanobiosensors for applications in diverse areas. Noninvasive and continuous detection of toxins, biomarkers, hormones, and drugs from body of subject is also a challenging area for nanobiosensors.

However, these nanobiosensors seem attractive as they have potential for delivery of systems like point-of-care diagnostics, automatic drug delivery, and DNA chips that can surpass conventional technologies regarding time, cost, and accuracy.

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