



Nanobiosensors: Point-of-care approaches for cancer diagnostics

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ABSTRACT

Early cancer diagnosis is of prime importance as it paves the way for effective treatment and possible patient survival. The recent advancements in the field of biosensorics have facilitated the development of functionalized nanobiosensors which have the potential to provide a cost-effective, reliable and rapid diagnostic strategy for cancers. These nanoscaled sensing systems utilize electrochemical, optical, mass and calorimetric sensing mechanisms to specifically identify the disease-specific biomarkers. Because of clinical translational utility, the present review aims to describe the recent developments and status of the nanobiosensors as a point-of-care approach for cancer diagnosis. The review also offers important insights into the design, preparation and characterization of these nano-frameworks. In particular, the state-of-art nanobiosensors based on carbon nanostructures, metal nanoparticles, magnetic nanoparticles, silica-based nanomaterials, conducting polymers based nanoparticles and quantum dots, which provide countless opportunities in the field of cancer biosensorics have been summarized. It also showcases the need to perform robust clinical validation of the emerging nanobiosensor strategies that would act as the ultimate point-of-care test for the personalized cancer therapeutics.

1. Introduction

Cancer which resulted in almost 9.6 million deaths in 2018 is considered as a leading cause of mortality around the globe (Bray et al., 2018). One of the primary reasons for such high mortality rate is the lack of an effective approach for early diagnosis of the disease (Sun et al., 2018). At present, the major diagnostic modalities for cancer rely on the conventional approaches that consist of x-ray, plain film and

computed tomography; magnetic resonance imaging, MRI; single-photon emission computed tomography; positron emission tomography; ultrasound and optical imaging. However these strategies are often associated with various limitations such as inability to detect carcinoma at the primary stage; lack of ability to differentiate between malignant or benign tumors; detection of false positive signals; difficulty in detection of tumor pre-seeding of metastatic sites; exposure to high dose of irradiation; limited spatial resolution and complications in

Abbreviations: AFP, α -fetoprotein; AHP, analytic hierarchy process; aM, attomolar; AuNPs, Gold nanoparticles; 4-ATP, 4-aminothiophenol; Au-Ag, Gold-Silver; BRCA1, breast cancer 1; BRET, Bioluminescence resonance energy transfer; CA125, Cancer antigen 125; CA15-3, Cancer antigen 15-3; cAMP, cyclic Adenosine Monophosphate; CBTF, (4-(cyanoethyl)benzoyl)oxy)-2,3,5,6-tetrafluorobenzenesulfonate; CEA, carcinoembryonic antigen; CNT, Carbon nanotubes; CP, Conducting polymer; CRET, Chemiluminescence resonance energy transfer; CYFRA-21, Cytokeratin-19 fragment; DNA, Deoxyribonucleic acid; EDC, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide; EGFR, Epidermal growth factor receptor; ELISA, enzyme-linked immunoassay; EpCAM, Epithelial cell adhesion molecule; EPR, enhanced permeability and retention; FDA, Food and Drug Administration; FRET, fluorescence resonance energy transfer; GO, Graphene oxide; GO-ssDNA, Graphene oxide, single stranded DNA; HeLa, Henrietta Lacks cells; HER2, human epidermal growth factor receptor 2; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IL-6, Interleukin 6; IONPs, Iron oxide nanoparticles; LFA, Lateral flow assay; MB, Magnetic beads miRNAs, microRNAs; MNPs, Metal nanoparticles; MR, Magnetic resonance; MRI, magnetic resonance imaging; MUA, 1-mercaptopundecanoic acid; MUC1, Mucin 1; μ TAS, micro-total analytical systems; NHS, N, hydroxysuccinimide; NPs, Nanoparticles; NSE, Neuron-specific enolase; PAMAM, Polyamidoamine; PCR, polymerase chain reaction; PDA, Polydopamine; PDT, photodynamic therapy; PEDOT:PSS:RGO, Poly(3,4-ethylenedioxythiophene):poly(styrene-sulfonate):reduced graphene oxide; PEG, Polyethylene glycol; PSA, prostate-specific antigen; PTT, photothermal therapy; QDs, Quantum dots; RNA, Ribonucleic acid; SERS, surface enhanced Raman spectroscopy; SIBA, Strand invasion based amplification; SPIONs, Superparamagnetic iron oxide nanoparticles; SPR, Surface plasmon resonance; sulfo-SMCC, sulfosuccinimidyl-4-(maleimidomethyl)cyclohexane-1-carboxylate; SWNTs, Single walled nanotubes; TIR, total internal reflection; TNF, α , Tumor necrosis factor, α ; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, Vascular endothelial growth factor; VEGFR-1, Vascular endothelial growth factor receptor-1

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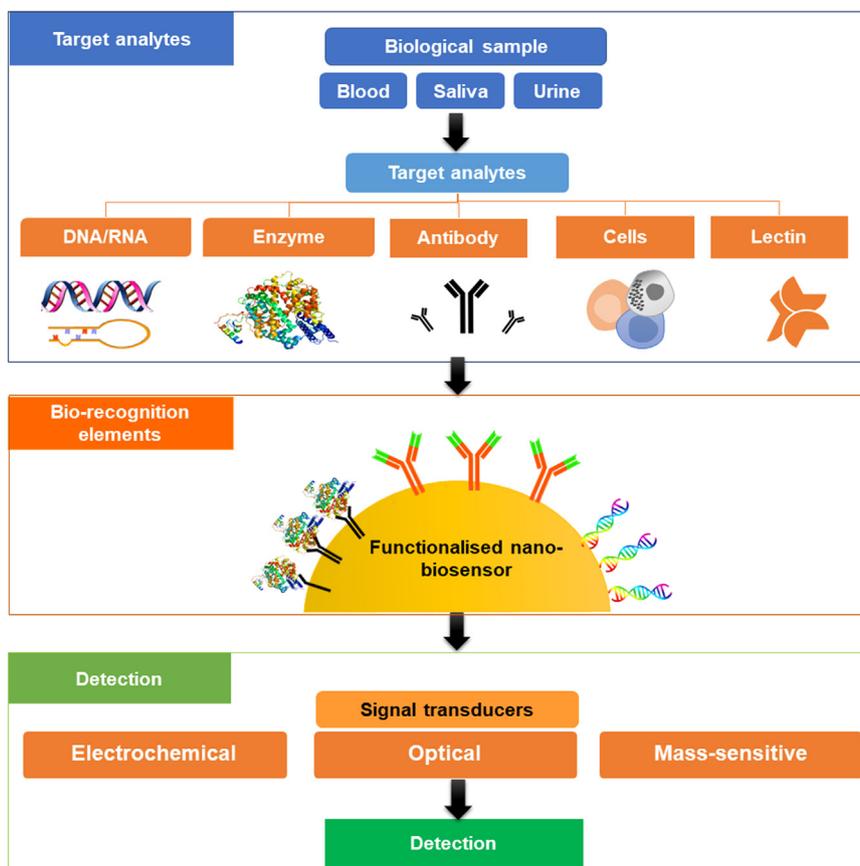


Fig. 1. An outline sketch showing the concept and basic requirements of developing a functionalized nano-biosensor.

the analysis (Arnaud, 2016; Lordick, 2016; Han et al., 2017). Therefore, much scientific attention is now paid towards the transition of the existing investigative technologies into advanced point-of-care tests. These tests are required to be cost-effective, simplified and miniaturized into portable constructs to provide a “fit-for-use” approach both for the patient and the on-site medical staff. Moreover, demonstration of statistical superiority over existing diagnostic modalities by offering real-time results also remains a challenge at the stage of validation and approval. In this regard, various point-of-care approaches such as lab-on-chip, lateral flow assays and electrochemical test strips have been assessed (Campbell et al., 2018).

Of these, strategies utilizing biosensor technology, in particular, the nano-sized biosensing devices have shown a great promise for early prognosis and diagnosis of the disease (Fig. 1). Such nano-scale devices, can be optimized to specifically recognize disease biomarkers for example proteins, circulating tumor cells, circulating nucleic acids and tumor-discarded exosomes (Singh et al., 2018). In addition, the advanced nano-scaled sensorics can assist to achieve higher sensitivity, specificity and multiplexing for complete elucidation of stage and type of cancer. This may utilize all the state-of-the-art platforms such as photoacoustic tomography, Raman spectroscopic imaging and multimodal imaging (Tempany et al., 2015; Rau et al., 2016; Dean-Ben et al., 2017; Zou et al., 2017). In recent years, extensive efforts with different approaches were made to develop a successful point-of-care device for early cancer diagnosis. One such approach is using microfluidics based methodologies like micro-total analytical systems, μ TAS) and lateral flow assays, LFA) (Culbertson et al., 2014; Derda et al., 2015). These microfluidic systems represent an integrated, miniaturized version of all the laboratory processes and offer minimal user intervention (Wu et al., 2017). Incorporation of biorecognition probes and chromatographic techniques further enhances the ability of microfluidic systems to perform qualitative and quantitative determination of the disease-specific

biomarkers. LFAs such as Alere NMP22[®] BladderChek[®] (Wang et al., 2017), OncoE6[™] Cervical Test (Klings et al., 2018) and Medical IVD rapid diagnostic test kits AFP Test kit are some of the commercially available tests for diagnosis of cancer. Apart from this, several minimalistic nucleic acid amplification strategies like SIBA, Strand Invasion Based Amplification) are available that overcomes the limitations of conventional PCR systems (Hoser et al., 2014). The present review aims to provide a comprehensive outline of the nanoscaled biosensors and its translation as point-of-care settings for cancer diagnosis.

2. Nanobiosensors: emerging trends in cancer diagnostics

Nanobiosensors are nano-scaled analytical frameworks that comprise nano-conjugated biological materials as transducing system for the detection of miniscule quanta of any biological, chemical, or physical analytes. The constructs utilize optical, electrochemical, thermometric, piezoelectric, magnetic or micromechanical methods to convey the relevant information in the form of signals (Fig. 2) (Turner et al., 1999; Zhang and Hu, 2010; Hardik et al., 2015). The generated signals precisely depends on the principle of selective bio-recognition of cancer cell associated intracellular or surface biomarkers by the attached antibody or bio-ligands (Salvati et al., 2015; Selvolini and Marrazza, 2017). The nanobiosensors can be further classified on the basis of signal transduction mechanism and bio-recognition elements.

2.1. Signal transduction based nanobiosensors

These nano-frameworks are recognizes a measurable or detectable signal generated due to the interaction of target molecules with the recognition elements (Fig. 3) (Rocchitta et al., 2016). Depending on the type of the recognized signals these biosensors are further sub-classified.

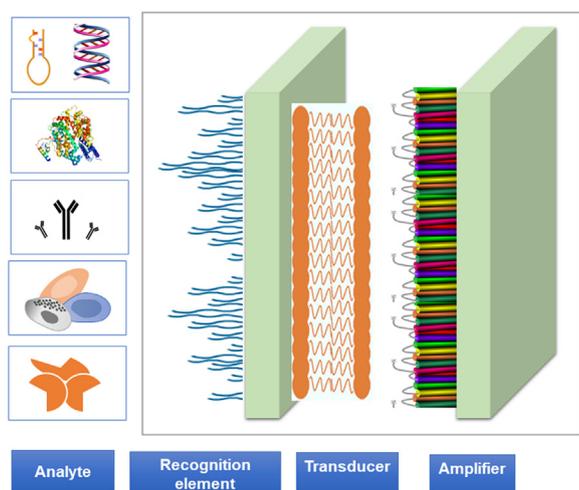


Fig. 2. Figure defining the different components of a nano-biosensor.

2.1.1. Electrochemical nanobiosensors

The electrochemical nanosensors comprise of sensor molecules which are physically adhered to the probe surface. Upon strong and specific interaction of probe with the target analyte initiates a measurable electrochemical signal. Such sensors possess high stability, sensitivity, prompt response and minor intrusions and are considered as the most recognized sensing systems (Hardik et al., 2015; Q. Hu et al.,

2018; P. Hu et al., 2018).

2.1.2. Optical nanobiosensors

Optical nanobiosensors includes a mixed group of sensors that provide in-vivo imaging and multiplexed analyte detection through absorption, luminescence (fluorescence, phosphorescence, fluorescence resonance energy transfer, FRET), Raman spectroscopy, refraction and dispersion. The spectroscopic approaches detect distinctive traits like energy, polarization, amplitude, decay time, and/or phase (Fig. 4) (Damborsky et al., 2016). Recent evidences emerging from different reports suggest that optical nanobiosensors can be effectively used for the detection of cancer biomarkers like cysteine and miRNAs (Borghei et al., 2017; Esmaili-bandboni et al., 2018).

2.1.3. Mass sensitive nanobiosensors

These biosensors rely on the automated recognition of biological entities by means of micro-or nano-dimensional cantilevers. The alteration in the resonating frequency of the unbound cantilever and biomolecule adhered cantilevers due to mechanical excitation indicates the change of mass which is detected. Mass sensitive nanobiosensors generally involves acoustic piezoelectric crystals based sensors (Arlett et al., 2011; Hardik et al., 2015; S. Wang et al., 2015)

2.1.4. Calorimetric nanobiosensor

The rationale of calorimetric nanobiosensors lies within the energy released in the form of heat during different biological processes. These nanobiosensors comprises of a densely packed column with an immobilized enzyme through which the solution containing analyte

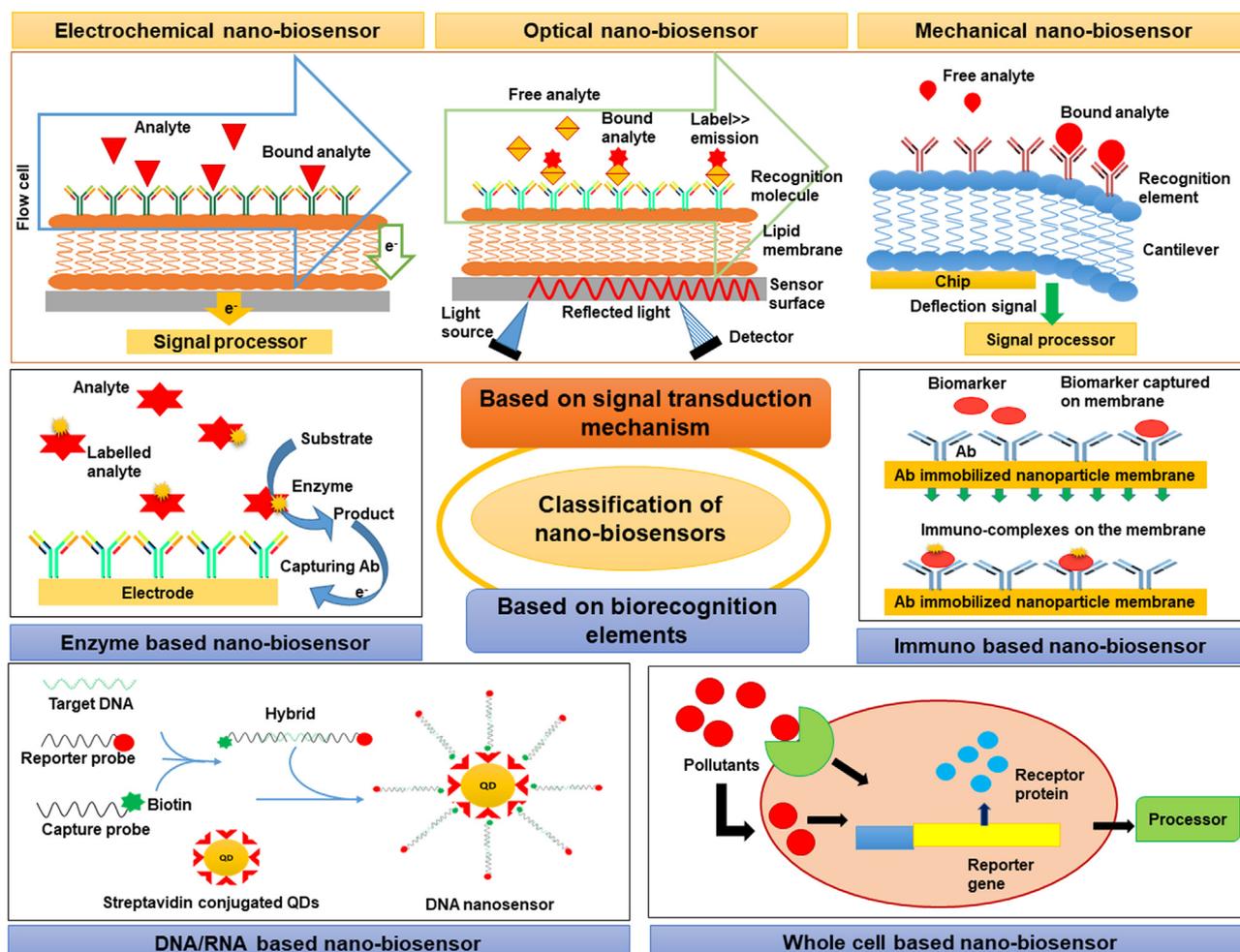


Fig. 3. Diagrammatic illustration of the different classes of biosensors based on the signal transduction mechanisms and the biorecognition molecules.

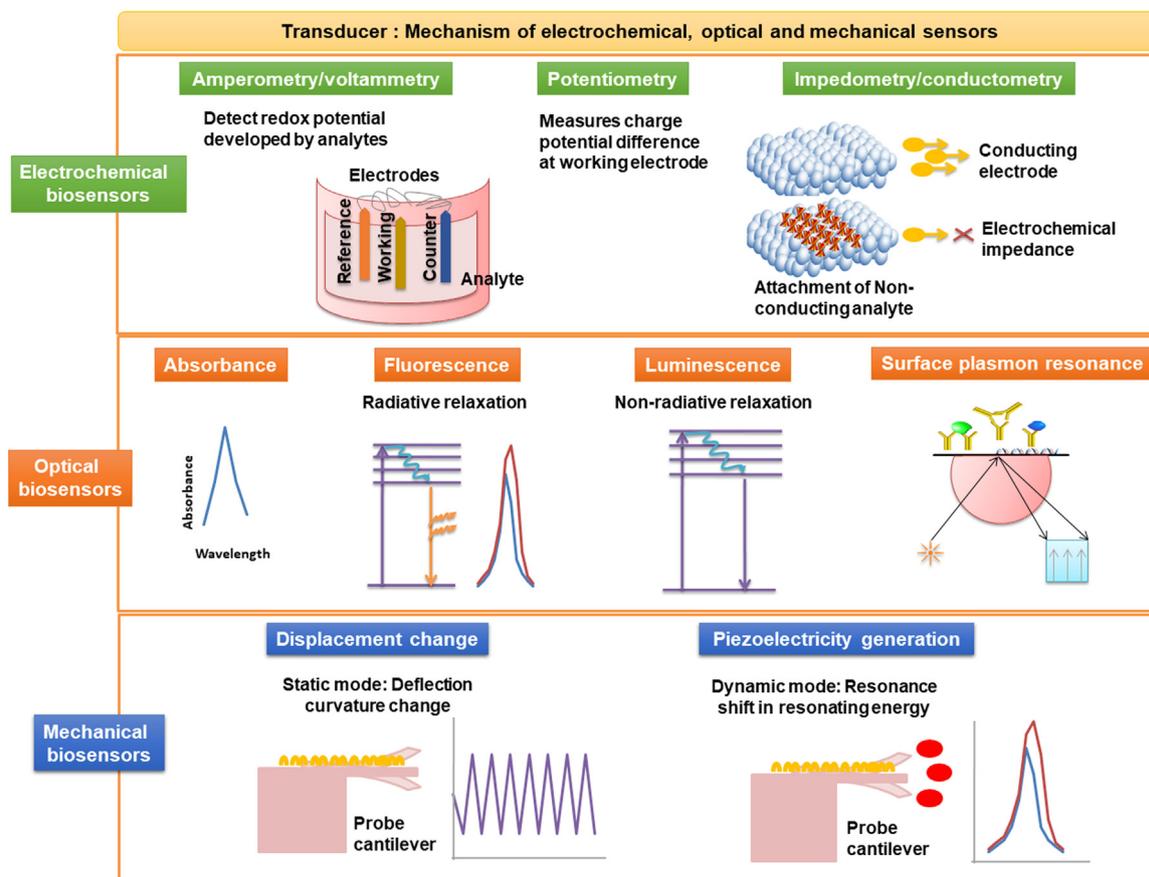


Fig. 4. Figure showing the mechanisms involved in the process of electrochemical, optical, and mechanical sensing.

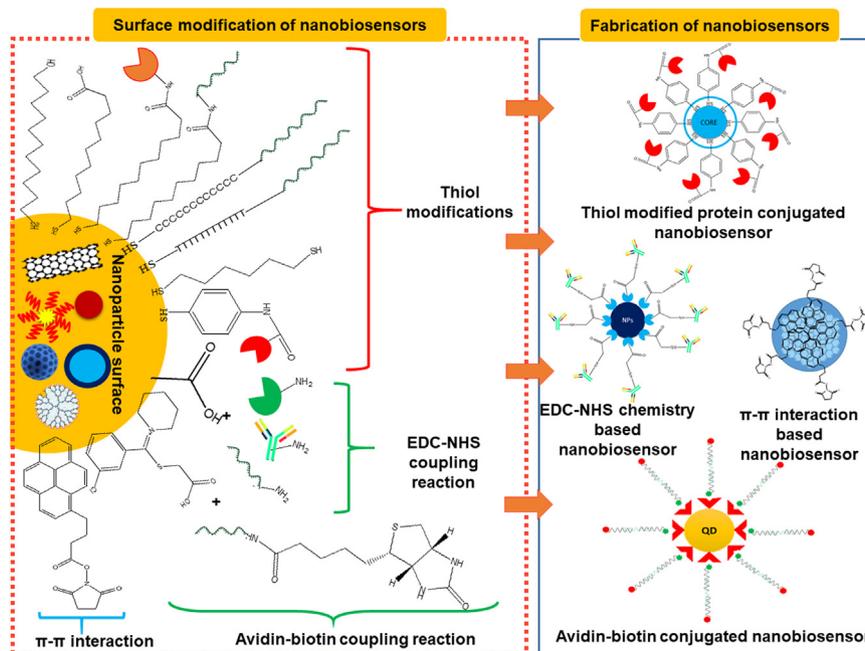


Fig. 5. A brief overview of different surface modification and bioconjugation strategies like thiol modification, EDS-NHS coupling reaction, π - π interaction and avidin-biotin coupling reaction involved in the development of a nanobiosensor.

molecules is passed. The temperature difference before the entry of the solution and after the exit of the solution is measured by the means of thermistors. The change in heat is used as an indicator for the different cellular processes can provide non-damaging metabolic measurements

of live cells (Satvekar et al., 2014).

2.2. Biorecognition based nanobiosensors (Fig. 3)

2.2.1. DNA/RNA nanobiosensors

These are diagnostic devices that are based on the measurement of the responses generated by the nucleic acid conversion processes or by aptamer hybridization (Chandrasekaran, 2017). The involved aptamers are diminutive single-stranded nucleic acid oligomers, DNA or RNA) consist of a highly organised, complex structure that enables association to molecular targets (Abu-Salah et al., 2015; Ilgu and Nilsen-Hamilton (2016).

2.2.2. Immune nanobiosensors

Immune nanobiosensor consists of a surface immobilized antigen or antibody that participates in bio-specific interaction with the target molecules to generate a measureable electrochemical, optical or mechanical signal. Advantages of these nanosensors include escalated specificity, detection and screening of minute amounts of target molecules (Munje et al., 2017; Rodrigo et al., 2014).

2.2.3. Enzyme nanobiosensors

Enzyme nanobiosensor employs immobilized enzymes as recognition elements. The sensors utilize the catalytic activity of enzymes to detect target molecules. However the stability of these nanobiosensors depends precisely upon the physical and chemical conditions, methods used for immobilization and stability of the system (Sassolas et al., 2012).

2.2.4. Whole cell nanobiosensors

Such type of sensors uses live cells or microbes as bio-ligands for detection of intracellular and extracellular biomarkers (Gutierrez et al., 2015; P.-H. Chen et al., 2017; Gui et al., 2017). Earlier studies have evidenced the use of conducting polymer, CP)-gold nanoparticles, AuNPs) nanocomposites and carbon dots for the detection of whole tumor cells (Q. Liu et al., 2015; Pallela et al., 2016).

3. Fabrication of nanobiosensors

3.1. Nanomaterials used as substrates for bio-sensing

The tunable properties such as size, high surface-to-volume ratio, improved sensitivity, specificity and stability, cost-effective commercial-scale fabrication, etc. help nanomaterials to function as optimal substrates for developing biosensors (Yoon, 2013). At present, carbon nanoconstructs, metal and silica-based nanomaterials, magnetic nanostructures, CP nanoparticles and quantum dots, QDs), are some of the most studied nanoparticulate systems for biosensor fabrication (Table 1).

3.1.1. Carbon nanostructures

3.1.1.1. Carbon nanotubes. The Carbon nanotubes, CNTs) are one-dimensional nanostructures that possess excellent electrical and electrochemical properties for real-time, label-free and multiplexed point-of-care biosensing applications. Functioning of CNTs mainly rely on different enzymatic processes that generate electro-active species upon detection of ions, metabolites and protein biomarkers (Ijeomah et al., 2016; Tilmaciu and Morris, 2015; Yang et al., 2015; Zhu, 2017). A number of studies have clearly reported the significant potential of CNT-based optical and immunosensors. Silva et al., documented early, precise and label-free detection of prostate cancer using CNT-based electrochemical nanosensors (Tran et al., 2013; Silva et al., 2016). Similarly, Sardesai et al., assessed the immunosensing ability of an antibody conjugated CNT microwell array (Sardesai et al., 2011). It has been also reported that inherent photoluminescence properties of single walled nanotubes allow these nanoconstructs to penetrate deep in biological tissues for enhanced imaging (Boghossian et al., 2011). Furthermore, CNT-based optical nanobiosensors have been

successfully used for immunoglobulins detection, surface enhanced Raman spectroscopy, SERS)-based biomedical imaging and phototherapy (X. Wang et al., 2012; J. Dong et al., 2018; Williams et al., 2018).

3.1.1.2. Graphene. Another form of carbon based two-dimensional nanomaterial is graphene, which offer attractive properties such as high flexibility of charge transporters at a low concentration, low noise level, cost-effective and environmental friendly nature. Graphene also allows real-time monitoring through adsorption of biomolecules. The adsorption causes structural modifications and significant alterations in the signal conductivity, which is recorded (Gdowski et al., 2014; Lebedev et al., 2016; Suvarnaphaet and Pechprasarn, 2017). Due to the high surface-to-volume ratio these nanosensors offer optimal biomolecule conjugation and detection (Celik et al., 2015; Pasinszki et al., 2017). Apart from the above mentioned attributes, reproducibility, ease of functionalization and biocompatibility are the other added advantages of graphene over other carbon nanostructures (Chauhan et al., 2017; C.S. Park et al., 2016). Studies have shown that graphene based optical nano-biosensors can perform real time analysis of different cancer cell processes (Jin et al., 2014). Moreover, graphene oxide have been demonstrated as an attractive “fit-for-purpose” biosensing nanomaterial for the detection of tumor biomarkers such as CYFRA-21-, BRCA1, p53 and miR-155, prostate-specific antigen, PSA), carcinoembryonic antigen, CEA), AFP, somatostatin receptor subtype 2 and integrin $\alpha\beta3$ (Xie et al., 2011; Mao et al., 2012; Z. Wang et al., 2012; Bianying et al., 2013; Chen et al., 2013; Rasheed and Sandhyarani, 2014; Jia et al., 2014; J. Liu et al., 2015; Xing et al., 2014; Kumar et al., 2016; Hu et al., 2016).

3.1.1.3. Carbon nanodots. Carbon nanodots are zero-dimensional small carbon nanoparticles ranging below 10 nm. These nanodots exhibit exceptional optical and electronic properties due to the optimal quantum confinement and edge effects. In addition, high aqueous solubility, excellent biocompatibility, exceptional biological properties, resistance to photobleaching, low toxicity, and robust chemical inertness make them superior than the conventional nanodots (Shi et al., 2014; Wang and Dai, 2015). Owing to these favourable attributes of carbon nanodots, these nanoconstructs have been successfully used for real-time fluorescent biosensing of alkaline phosphatase activity, cancerous cytosensing (Wu et al., 2013; Qian et al., 2015), electrochemical sensing of DNA (Loo et al., 2016; García-Mendiola et al., 2018), photo-electrochemical sensing of the telomerase activity (S. Liu et al., 2018), and FRET-based immunosensing of tumor markers (Hamd-Ghadareh et al., 2017; Mohammadi et al., 2018).

3.1.2. Metal nanomaterials

Metal nanoparticles, MNPs) have emerged as a promising novel carrier and contrast agents in cancer theragnosis (Vigneshvar et al., 2016). The superior characteristics of MNPs like distinct optical properties, ease of synthesis and availability of a number of adsorption sites for the binding of biological macromolecules, significantly assist in cancer cell imaging and other targeted applications (Hutter and Maysinger, 2013; Lan et al., 2017; Saha et al., 2012). El-Sayed et al. (2005) using anti-epidermal growth factor receptor, (anti-EGFR) as a probe reported effective ability of MNPs to detect and differentiate non-malignant and malignant epithelial cell lines. The nano-silver based MNPs when attached to different biomolecules induces alterations in the refractive index. These alterations cause a shift in the excitation, absorption and scattering) spectrum and allow the real-time monitoring of mammalian cells (Sotiriou and Pratsinis, 2011). Similarly, platinum-based nanoparticles have been utilized to analyse the generated electrochemical single label response for the detection of tumor DNA (Kwon and Bard, 2012).

Moreover, the development of multifunctional hybrid nanoparticle systems further improved the ability of these systems in cancer

Table 1
A summary of recent nanobiosensor studies and their key findings.

S. No.	Type of nano-biosensor	Target biomolecule	Sample type	Detection system/mechanism	Inference	Reference
1.	Electrochemical biosensor	Circulating tumor DNA	Plasma / serum	Framework nucleic acids programmed signal amplification	Demonstrated a valency-controlled signal amplification framework nucleic acids based system for quantitative detection of target analytes like	(Q. Liu et al., 2018)
2.			Serum	Electrochemical detection through peptide nucleic acid	Highly selective biosensor for detection of ds-DNA in femtomolar to nanomolar range.	(Q. Hu et al., 2018)
3.			Urine	Piezoelectric plate sensor coated with a 17-nucleotide locked nucleic acid complementary DNA probe	In situ detection of KRAS G12 V point mutation in urine sample.	(Kirimli et al., 2017)
4.			Target DNA	Gold nanoparticles	Study demonstrated the detection of breast cancer specific gene BRCA1 at minute concentrations (1 pm) without any signal amplification process.	(Yang et al., 2014)
5.			Plasma/ serum	Functionalized nanostructured microelectrodes conjugated with peptide nucleic acid probes	Suggested aDNA clutch probes strategy for sensitive and specific detection of mutated ctDNA at femtomolar range.	(Das et al., 2016)
6.		Circulating tumor-RNA	Blood/ cancer cells	Superparamagnetic nanoparticles based microelectrode biosensor	Demonstrated a velocity valley chip to efficiently capture magnetic nanoparticle-bound circulating tumor cells and prostate specific antigen mRNA in cancer patients.	(Mohamadi et al., 2015)
7.		Circulating Tumor-miRNA	Serum samples	Protein-facilitated electrocatalytic quadroprobe sensor	The biosensor allows instantaneous ultrasensitive profiling of miRNAs directly in serum.	(Labib et al., 2015)
8.			Serum/ plasma	Protein-nanopore-based sensor	For the detection and quantification of sub-picomolar levels of lung cancer-associated micro-RNAs.	(Wang et al., 2011)
9.			Serum	Gold nanoparticles co-functionalized molybdenum nanosheets	A label-free and electrochemical sensing platform for specific detection of mir-21.	(Zhu et al., 2017)
10.			Serum	Gold nano-electrode based electrochemical biosensor	Proposed an ultrasensitive electrochemical miRNA biosensor for direct detection of circulating miRNAs in human serum.	(Hong et al., 2013)
11.		Tumor-associated proteins	Serum	Hybrid Immunosensors of OLED display and protein microarray technology	A multiplex detection array for specific identification of circulating biomarker (HPV16, E2, E6 and E7) for cervical/head and neck cancers	(Katchman et al., 2016)
12.			Urine/serum	Aptamer-modified mesoporous silica nanosensor	For highly specific, reproducible detection and validation of prostate specific antigen.	(Argoubi et al., 2018)
13.			Blood	Aptamer conjugated PASE-modified carbon nanotubes	Selective interaction with the biosensor with IL-6	(Khosravi et al., 2017)
14.		Circulating tumor histones	Tissue/ cells/serum	Hybrid immunosensor of cysteamine capped gold nanoparticles and indium tin oxide	A sensitive detection of prostate cancer antigen positive circulating cells	(Seenivasan et al., 2017)
15.		Tumor exosomes	Tumor Exosomes	Aptamer-magnetic bead bio-conjugates	For the detection of tumor exosomes in complex biological samples	(H. Dong et al., 2018; C. Li et al., 2017)
16.		Circulating Tumor Cells	Circulating tumor cells in a blood mimicking fluid	SERS-based gold-silver-gold core-shell plasmonic nanorods	The developed system could selectively detect circulating tumor cells at minimal concentrations (as low 20)	(Zhang et al., 2017)
17.			Cancer cell lines	Electrochemical cytosensor	Label-free electrochemical cytosensor for specific detection of cancer cells with a lower detection limit of 10 cells mL.	(Shen et al., 2016)
18.			Blood	Aptamer-modified glassy carbon electrode based biosensors	An ultrasensitive cell-specific dual aptamer-modified GCE to detect a single MEAR cell in 10 ⁹ whole blood cells.	(Ou et al., 2014)
19.			Cancer cells	Graphene based electrochemical sensors	Biosensor to potentially detect circulating tumor cells and monitor cellular electrical behaviour.	(Joe et al., 2016)

(continued on next page)

Table 1 (continued)

S. No.	Type of nano-biosensor	Target biomolecule	Sample type	Detection system/mechanism	Inference	Reference
20.	Optical biosensor	Circulating tumor DNA	Serum	Gold nanoparticle based surface plasmon biosensor	Sensitive and improved sensor for simultaneous detection of hot-spot mutation and epigenetic CpG methylation on the circulating tumor DNA by measuring shift in the Low Surface Plasmon Resonance peak.	(Nguyen and Sim, 2015)
21.			Serum	Low Surface Plasmon Resonance chip	Rapid detection of cancer biomarkers (human alpha-feto-protein and prostate specific antigen) at picomolar concentration.	(Acimović et al., 2014)
22.			Tumor antigen	Silver nanocrystals	Detection of the prostate-specific antigen as cancer biomarker in whole serum.	(Rodríguez-Lorenzo et al., 2012)
23.			Nucleic acids	Silver nanoparticles	For simultaneous detection of multiplexed cancer-associated nucleic acids	(Guo et al., 2018)
24.		Circulating Tumor-Associated miRNA	Serum	DNA probes conjugated gold nanoparticles	A colorimetric biosensor based on the combination of gold nanoparticle dimers and duplex-specific nuclease-amplified oriented assembly, for ultrasensitive detection of miRNA-21	(Guo et al., 2016)
25.			Urine/serum	Carbon nanotubes	For real-time optical quantification of microRNA	(Harvey et al., 2017)
26.			Serum	PEG-modified capture probes conjugated nanobiosensor	The biosensor can perform ultrasensitive detection of miRNAs at femtomolar concentrations	(Roy et al., 2016)
27.			Telomerase	Fluorescence based optical nano-biosensor	Effective quantitative detection of telomerase and in situ imaging of intracellular telomerase activity.	(L. Zhang et al., 2018)
28.			Serum	Multi-walled carbon nanotube-gold nanocomposites	For ultrasensitive detection of miRNA-155 in human serum samples	(Ma et al., 2018)
29.			DNA	Transition metal dichalcogenide nanosheets	Rapid, sensitive, and multiplexed detection of tumor DNA.	(Zhang et al., 2014)
30.	mRNA		Serum	Graphene oxide and up-conversion nanoparticle conjugated systems	An optical biosensor for detection of disease specific in human blood serum.	(Vilela et al., 2017)
31.	tumor-associated proteins		Blood	Aptamer conjugated surface plasmon resonance based biosensing	Developed a rapid, sensitive, portable and low cost diagnostic platform, which can detect nanomolar range of tumor- proteins.	(Cennamo et al., 2015)
32.			Serum	Dopamine-functionalized CdSe/ZnS quantum dots	The clinical validation of the biosensor was demonstrated by detecting alpha-fetoprotein in serum of hepatocellular carcinoma patients.	(Zhang et al., 2016)
33.			Tumor antigen	Gold nanorod immunosensor	The immunosensor could detect prostate specific antigen in women	(Truong et al., 2011)
34.			Biofluids	Antibody-functionalized carbon nanotube complex	For the rapid detection of Human epididymis protein 4 with nanomolar sensitivity to differentiate malignant disease from benign	(Williams et al., 2018)
35.			Epithelial cellular adhesion molecule (EPCAM) Serum	FRET based silica nanobiosensor	The study demonstrated photostable NPs conjugated-EpCAM as potential biomedical diagnostics tool for point-of-care testing.	(O'Connell et al., 2017)
36.				Gold nanoparticles	For sensing ultralow levels of prostate-specific antigen (PSA) in patient serum samples	(Liu et al., 2013)
37.			Tumor antigens	Ultrasensitive plasmonic nanosensor based on enzyme mimetic gold nanostructures	The nano-biosensors could assist in visual assessment of tumor antigens.	(Zhao et al., 2016)
38.		Circulating tumor cells	Cancer cells	Hybridization chain reaction amplification based DNA tethered biosensors	The study developed DNA nanostructured gold surface biosensor that provide favourable hybridization for the multivalent binding and detection of circulating tumor cells	(Zhou et al., 2014)
39.		Circulating tumor-associated RNA	Blood	Gold nanoparticles	Quantitative detection of RNA through mass-amplifying gold nanoparticles.	(Siross et al., 2012)
40.		Circulating tumor-associated proteins	Blood	Gold nanoparticles-Quantum dots based hybrid nanosensor.	Demonstrated a highly sensitive method for simultaneous detection of EpCAM proteins in circulatory tumor cells.	(X. Li et al., 2017)
41.	Mass based detection	Circulating tumor DNA	KRAS point mutations	Fe-Au nanoparticle based sensors	For early diagnosis and monitoring of diverse malignant tumors.	(Hu et al., 2018b)
42.	Hybrid mechanical and opto-plasmonic nano-biosensor		Tumor antigen	Cantilevers and gold nanoparticles conjugated biosensor	The sensors can be used for the diagnosis, monitoring and prognosis of colon and prostate cancer	(Kosaka et al., 2014)
43.	Colorimetric sensor		Interleukin-6 (IL-6)	Au@Ag bimetallic nanoparticles	Detection of IL-6 in clinical samples with better accuracy than conventional ELISA.	(Yin et al., 2017b)

theranostics. For instance, Jiang et al. (2017) and Azizah et al. (2017) reported the specific detection of cancer cells by aptamer-AuNPs hybrid point-of-care systems. Similar hybrid systems have been utilized for simultaneous *in vitro* imaging and photothermal therapy in non-malignant and malignant oral epithelial cells (D. Yin et al., 2017). Uludag et al., showed the detection of cancer associated biomarkers in serum samples through a plasmonic signal amplification by Surface plasmon resonance, SPR)-based sensor (Uludag and Tothill, 2012). Highly sensitive detection of nano-picomolar concentrations of the prostate cancer specific antigen was evidenced by Kavosi et al., using a poly-amidoamine dendrimer-encapsulated AuNPs based immunosensor (Kavosi et al., 2015).

3.1.3. Magnetic nanoparticles

Over the recent past, magnetic nanostructures have gained significant attention in the field of cancer sensorics (Akbarzadeh et al., 2012). The magnetic nanomaterials possess unique characteristics such as superparamagnetic properties, high mass transference, prompt production of a response, compatibility with biomolecules and unique physicochemical properties. Apart from this, the magnetic nanoparticles can be easily integrated into the transduction systems for efficient detection of the target analytes under the influence of an external magnetic field (Rocha-Santos, 2014). This property of magnetic nanosensor also assists in detection of small amounts of the target with great sensitivity and low noise (Devkota et al., 2014; Tran et al., 2012). The magnetic nanobiosensors have been subsequently modified to improve the performance and applicability of these biosensors in cancer theranostics. The dextran cross-linked superparamagnetic iron oxide nanoparticles, SPIONs) has been developed for multiplexing and highly sensitive molecular profiling of the tumor markers in *in vivo* and *ex vivo* settings (Tassa et al., 2011; Wang, 2015). Accurate detection and differentiation of cancer cells using aptamer-magnetic switches and glycomagnetic nanosensors have been also reported (Bamrungsap et al., 2012; El-Boubbou et al., 2010). Zhou et al. (2009), showed the use of an electro-chemiluminescence based magnetic nanosensor for the detection of telomerase activity in cancer cells. At present, a number of *in-clinic*-point-of-care systems comprising of magnetic nanoparticles such as Feridex I.V.[®] and Combidex[®] are approved by FDA (Hasanzadeh et al., 2013).

3.1.4. Silica based nanomaterials

The silica based nanomaterials mainly silica nanowires contributes as another class of compounds that are widely used for the diagnostic purposes. Amongst the silica-based systems, mesoporous silica/alumino-silica molecular sieves have gathered considerable amount of interest as probes for cancer diagnostics. Studies have also shown that the modified silica based hybrid nanosensors possess the ability to serve as a versatile platform for different biomedical applications (Hasanzadeh et al., 2013; Jo et al., 2015). A silica based hybrid nanobiosensors was developed by Su et al. (2012) for the biosensing and photothermal therapy of cancerous cells. Optical bioimaging using AuNPs conjugated mesoporous silica-graphene oxide nanoconstructs were successfully used for colorimetric cancer cell theranostics (Maji et al., 2014).

3.1.5. Conducting polymer nanoparticles

Polymer based nanoparticles; in particular the CP nanomaterials have recently joined the trend in biosensing as they exhibit remarkable features and provision of commercial-scale economical fabrication. CP nanobiosensors, including field-effect transistor biosensors, aptasensors, immunosensors and DNA chips, have shown significant intrinsic properties to target specific biological moieties. These nanostructures broadly comprises polymers like polypyrrole, polyaniline or poly, 3, 4-ethylenedioxythiophene) (C. Park et al., 2016) that make them an outstanding candidates for electronic and optoelectronic sensing of cancer biomarkers. A number of studies have suggested that the

polymer hybrid nanoconstructs can be efficiently utilized for detection of tumor markers like AFP, CEA, PSA (He et al., 2015; Kumar et al., 2015; Cui et al., 2016; Kumar et al., 2016).

3.1.6. Quantum dots

Another class of nanomaterials that are currently under extensive investigation for bio-analytics are the QDs (Holzinger et al., 2014). QDs are widely used luminescent inorganic nanoparticles that comprise of an atomic core and the shell of wider band-gap semiconductors (Stanisavljevic et al., 2015; Vu et al., 2015). QDs have unique properties like size tunability, narrow symmetric emission and broad absorption spectra, bigger Stokes shift, resistance to photobleaching and high quantum yield that make them potential candidates in analytical chemistry (Vu et al., 2015). QDs may exhibit FRET, Bioluminescence resonance energy transfer, BRET) or Chemiluminescence resonance energy transfer, CRET) signal transduction strategies and possess the ability to perform multiplexed analysis of various biomolecules (Matea et al., 2017; Singh et al., 2018). However, a major problem with QDs is the presence of cadmium in the core which induces toxicity, thus an additional coating of silica shells is required to overcome the issue. Further engineering or manipulation of the shells could improve solubility, sensitivity, specificity and imaging of the target tissue. This potential ability of QDs has been widely assessed in cancer settings. Wang et al., used nuclease-enzyme-based amplification approach for FRET-based detection of femtomolar concentrations of miRNA via QD based nanosensor (Y. Wang et al., 2018). QD-based lab-on-chip, multiplexed sandwiched immunoassay successfully detected the presence of different lung cancer associated biomarkers such CEA, cytokeratin 19 fragments, CYFRA21-1) and neuron-specific enolase, NSE) in the given biological fluid (Liu et al., 2016). A similar paper-chip assay has been used for the multiplexed analysis of cancer associated RNA and miRNA and further demonstrated the point-of-care applicability of QDs (Deng et al., 2017). L.J. Wang et al. (2015) reported the fabrication of a FRET based phosphorylation-directed nano-conjugate comprising of a single QD based nanosensor for the real time detection of cAMP-dependent protein kinases. Similarly, a biocompatible and size tunable emission carbon dots sensor was developed by Zheng et al., for the non-invasive brain cancer glioma imaging (Zheng et al., 2015). Tang et al., utilized the semiconductor QDs for fabrication of aptamer conjugated nanosensors for the determination of EGFR variant III expressed glioma tissues and suggested that the sensor can be used for pre and post-operative examination in glioma tissues (Tang et al., 2017).

All these nanobiosensors assist in simplification of the intricate process of integrating micro-optics and micro-mechanics into point-of-care systems. The QDs, carbon nanodots, MNPs and magnetic nanoparticles have emerged as exceptional tools for the development of diagnostic and theranostic systems. Despite of the unique abilities of the nanomaterials, the applicability of nanosensors are hindered by limitations such as low selectivity, time-consuming response, high detection limit, toxicities of nanoparticles and adverse reactions in patients (Patel et al., 2016). The success of *in vitro* studies have gained significant scientific attention towards developing nanotechnology-based sensors however, the clinical application of these sensors is still in its infancy.

3.2. Bio-modification and conjugation strategies for fabrication of nanobiosensors (Fig. 5)

A number of nano-modelling and surface modification strategies are under investigation to provide control over the site, distribution, conformation and alignment of the biomolecules on the exterior of nanomaterial. These studies suggest a crucial role of the nanomaterial-biomolecule interface in designing early cancer diagnostic strategies. There are two conventional approaches for the conjugation of the biorecognition molecules with the nanomaterial. One is covalent functionalization that involves covalent bonds for surface modification

by means of linker molecules whereas the other uses hydrophilic or hydrophobic surface immobilization of biomolecules for non-covalent functionalization (Mout et al., 2012; Sapsford et al., 2013; Yüce and Kurt, 2017).

3.2.1. Thiol chemistry

This involves a strong interaction between thiol compounds and noble metal surfaces for engineering of self-assembled monolayers on the nanoparticle surfaces. The non-reactive nature of noble metals such as gold permits the surface engineering of the material with various terminally functionalized alkyl groups, such as carboxylic acid) that imparts hydrophilic nature to the nanostructure. A number of compounds such as 11-Mercaptoundecanoic acid, 1,6-hexanedithiol, 4-Aminothiophenol can be used for the thiol modification of the nano-frameworks. This allows the decoration of the sensor molecules at the terminal groups through maleimide hetero-bifunctional coupling reagents such as sulfosuccinimidyl - 4 -, maleimidomethyl cyclohexane - 1 - carboxylate, sulfo - SMCC), (4-(cyanoethynyl) benzoyloxy - 2, 3, 5, 6 - tetrafluorobenzenesulfonate, CBTF) etc. (Werengowska-Ciećwierz et al., 2015). A point-of-care oral chemotherapeutic system was successfully developed using a thiolated chitosan-modified PLA-PCL-TPGS nanoparticles by Jiang and co-workers (Jiang et al., 2013). Similarly, a microfluidic immunosensor using thiolated ligand-exchange approach with AuNPs on a herringbone chip as a point-of-care system was reported for the effective isolation and detection of breast cancer associated circulating tumor cells (Park et al., 2017). Bamrungsap et al., also showed the utility of thiol-conjugation strategy in cancer diagnostics via SERS based detection of protein tyrosine kinase-7 by 4-aminothiophenol, 4-ATP) labelled Au-Ag nanorods in HeLa cells (Bamrungsap et al., 2016).

3.2.2. Avidin–biotin interaction

Avidin-biotin conjugation, the most predominantly used conjugation strategy in various biotechnological techniques is known as one of the strongest bonds involving non-covalent interaction. Avidin generally exists in two forms, i.e., streptavidin, a proteinaceous tetrameric structure comprising four identical biotin binding sites and neutravidin, a de-glycosylated avidin with exclusive binding affinity towards biotin molecules. This robust communication of biotin with avidin has been massively used in the field of nano-biotechnology to allow surface alteration of nanoparticles such as gold, CNTs, QDs, etc. Electrostatic interactions, van der Waals forces, hydrogen bonding or π - π stacking interactions can be employed for streptavidin coupling of nanoparticles (T.-Y. Chen et al., 2017; Macwan et al., 2017; Senapati et al., 2018). A sandwiched electrochemical sensor for EGFR detection was developed by using an end-biotinylated EGFR aptamer immobilized on streptavidin-coated magnetic beads as capture probe and AuNP conjugated detection probe (Ilkhani et al., 2015). The similar sandwiched electrochemical immunosensing for quantitative detection of p53 as a cancer biomarker was also reported using a capture probe of biotinylated antibody conjugated streptavidin (Afsharan et al., 2016).

3.2.3. π - π stacking interactions

π -effects involves strong interaction between π -electrons of two aromatic systems lying in the close proximity. This interaction is highly ubiquitous in various biological processes like nucleobase stacking, amino acid side chains, enzyme-ligand binding, protein-DNA binding, protein-RNA interaction and binding of aromatic structures on the surface of nanoparticles. This chemistry is extremely useful in preparing cost-effective and robust nanobiosensing systems. Of the available nanoparticles, carbon based nanostructures are the most commonly used nanomaterials for the fabrication of nanosensors using π -interactions. Such interaction based structural modification lay the foundation for developing optimal nanosensors for cancer diagnostics (Alibolandi et al., 2015; Cieplak and Kutner, 2016). Using the π chemistry, a novel activable aptamer based approach for detection of cancer cells was

successfully demonstrated by Yan et al. (2014). A fluorescent “on-off” biosensor for in vitro monitoring of ATP and GTP in in situ live breast cancer cell lines was developed through π - π stacking of FAM-labelled ATP and Cy5-modified GTP aptamers on the surface of graphene oxide nanosheets (Wang et al., 2014).

3.2.4. Using EDC–NHS conjugation chemistry

The EDC-NHS carbodiimide chemistry is an advanced technique used for the covalent modification of surface carboxylate groups into amine terminated groups. This chemistry has been extensively employed for the functionalization of nanoparticles to construct cancer nanobiosensors (Werengowska-Ciećwierz et al., 2015; Yüce and Kurt, 2017). In this method, EDC activates the freely available carboxylic acid group of 11-mercaptoundecanoic acid, MUA) on one molecule to allow its binding with the primary amine groups on the other molecule. The water soluble component of NHS reacts with the carboxyl groups and generates *O*-acylisourea, an intermediate moiety of the NHS ester. Stabilization of the intermediate molecule by its conversion into a succinimide ester allows formation of an amide bond with the biorecognition molecules (Erden et al., 2015; Mat Zaid et al., 2017). As there are no residues generated in this conjugate structure, carbodiimide molecules are anticipated as zero-length cross-linkers (Yüce and Kurt, 2017). Applying the chemistry, an anti-PSA polyclonal Ab labelled AuNPs based sensing platform has been reported for the monitoring of prostate cancer (Jazayeri et al., 2016). Bahadır and Sezgintürk demonstrated a novel impedimetric immunosensor to detect human Vascular endothelial growth factor receptor-1, VEGFR-1), a well-known cancer biomarker (Bahadır and Sezgintürk, 2016a).

3.3. Immobilization of biorecognition molecules

Point-of-care real time monitoring of a disease can be achieved through nano-scaled miniaturized sensors. In this regard, the detecting molecules such as enzymes, antibodies, nucleic acids, lectin, amino acids and proteins can be immobilized on the nanomaterial surface. Based on the physical and chemical attributes of both nanomaterials and the biorecognition molecules, different immobilization methods have been proposed. The first category involves physio-sorption wherein the bio-recognizing molecules are adsorbed on the surface, microencapsulated or entrapped in a polymeric shell of the nanomaterial. While the second category includes chemisorption of the biorecognition molecules on the surface of the nanomaterial by means of linker molecules such as SMCC onto functionalized nanoparticles. The third category comprises immobilization of the molecules on functionalized polymeric or inorganic materials such as silica through covalent bonds. Various surface functional groups such as NH_2 , COOH , OH , $\text{C}_6\text{H}_4\text{OH}$ and SH take part in the coupling reaction. This covalent coupling is highly recommended for the fabrication of nanobiosensors as it assures the stability for long term purposes (Yüce and Kurt, 2017).

3.4. Signal conversion and detection methods in nanobiosensors

The nanobiosensors may adopt various methodologies for signal generation, conversion and detection. The electrochemical nanobiosensors involve generation of an electrical signal by transducing nanomaterials in the form of change in current, potential difference or conductivity/resistance. This signal can be later detected by amperometry, voltammetry or conductometric methods (Aparecido Pupim Ferreira et al., 2013; Bahadır and Sezgintürk, 2016b; Tarasov et al., 2016). The electrochemical sensing mechanism based point-of-care systems have been widely reported for the diagnosis of cancer associated biomarkers such as PSA, IL-6, telomerase, glycoproteins or metastatic cancer cells (Pallela et al., 2014; Dai et al., 2016; Diaz-Cartagena et al., 2017; Chowdhury et al., 2018).

Optical nano-biosensing is concerned with the change in the optical properties of the nanomaterials. These changes indicate nanomaterial -

target interaction and can be detected by luminescence-based, SERS-based and/or SPR-based sensing. Luminescence is based on the measurement of change in the intensities or frequencies of the emitted radiation which is directly proportional to the target analyte concentration (Goryacheva et al., 2018). The utility of this sensing methodology for cancer cell detection was clearly evidenced using mannose functionalized DNA-silver nanoclusters (Roda et al., 2016; Zhang et al., 2018a). While in SERS based sensing the analyte sorption on the SERS substrate, metal plasmonic nanomaterials) enhances Raman spectra to several orders of magnitude (Jahn et al., 2016; Markin et al., 2017). The enhanced Raman spectra significantly contribute towards improving the sensor sensitivity. Studies suggest that SERS based monitoring is an effective strategy for detection of cancer biomarkers like Epithelial cell adhesion molecule, EpCAM) and human epidermal growth factor receptor 2, HER2) (Bhamidipati et al., 2018; Tellez-Plancarte et al., 2018). Whereas, in SPR sensing a polarized light at a specific angle falls on a metal surface placed at the interface of two media, usually glass prism and liquid). This leads to generation of surface plasmon and consequent reduction in the intensity of reflected light at a specific resonance angle that is proportional to the mass on the surface. If there are any surface modifications like attachment of the bio-recognition molecule, then the interaction between the target analyte and capture molecules may result in the alteration of reflectivity, angle or wavelengths against time which can be measured via sensorgram. Such nanosensors have been reported for the effective detection and quantification of the cancer-associated miRNA molecules (Liu et al., 2017; Nguyen et al., 2015; Reiner et al., 2018). Another important mode of the optical biosensing is total internal reflection, TIR) that involves generation of signal which is directly proportional to the analyte concentration. These TIR based optical fiber transducers can be further merged with various spectroscopic techniques to effectively detect target analytes (Pidenko et al., 2018).

On the contrary, mass-based nanobiosensors detect alterations in the cantilevers for precise sensing of targets. Studies have shown the use of these nanobiosensors for detection of cancer biomarkers such as microRNA (Johnson and Mutharasan, 2012), prostate specific antigen, PSA) and AFP for point-of-care cancer diagnosis (Su et al., 2013).

3.5. Parameters validating nanobiosensing/nanosensor performance

Nanobiosensor optimisation and validation are two important aspects developing a clinically effective biosensor (Hardik et al., 2015; Zhang and Hu, 2010). After fabrication, the following factors must be taken into consideration for effective optimisation and validation:

- Selectivity:** The specific nanobiosensor response generated by the interaction of bio-recognition system with the specific biomolecules is referred as selectivity. It is the most essential trait of biosensors which is a prerequisite for construction of an effective nanobiosensor.
- Reproducibility:** It defines the ability to produce indistinguishable responses for over a series of experimental arrangements. Precision and accuracy of the signal transduction systems are two key components of reproducibility. Precision defines the ability of a sensor to generate alike results every time and accuracy designates the sensor's capacity to provide a mean value close to the true value. Reproducible responses provide high trustworthiness and durability to the obtained results.
- Stability:** One of the most crucial characteristic of biosensor is stability. It signifies the degree of vulnerability to ambient disturbances in and around the biosensing system which may lead to distortion of the output signals thereby influencing precision and accuracy. Therefore, a biosensor with high affinity towards analyte molecules fortifies its stability.
- Linearity:** This can be associated with the resolution of the biosensor and concentration range of analyte under test. Resolution can

be defined as the slightest change in concentration of the target molecule that could bring significant change in the response. While concentration range can be attributed as amount of analytes that produces responses in a linear fashion.

- Sensitivity:** Sensitivity of a nanobiosensor can be ascribed as the detection of infinitesimal concentration of the target biomolecules effectively and reliably.
- Multiplexing:** Multiplexed analysis involves detection of a manifold of target biomolecules from a single biological sample without any cross-reactivity.

4. Nanobiosensors for in vivo cancer theranostics

The term theranostics is an amalgamation of two words: therapy and diagnostics. This involves combinations of molecular-targeted therapeutics, biosensors, in vitro prognostics and diagnostics, molecular imaging, bioelectronics, image-guided therapy, translational medicines, and system biology. The basic aim of cancer theranostics is to interpret and scrutinize therapy response in real-time and to reduce undesirable toxicities (Choi et al., 2012). Cancer cells are characterized by the formation of permeable vasculatures and metastasize through blood circulation. Therefore, a revolutionary cancer treatment can be achieved through targeted, sustained, and specific “enhanced permeability and retention”, EPR) delivery system (Omidi and Barar, 2014). The rationale behind the development of in-vivo nanobiosensors involves the incorporation of EPR delivery systems with molecules/particles that can be easily detected (Ehlerding et al., 2018). In this regard, a number of diagnostic tools or probes have been amalgamated with different treatment approaches such as chemotherapy, hyperthermia, gene therapy, and radiation. All the diagnostic probes used for imaging are conjugated to the surface agents/delivery cargos that not only offer better imaging but also allow real-time tracking of the trafficking pathway, therapeutic competence and kinetics (Kydd et al., 2017).

Moreover, the multiplexed diagnosis using a single point-of-care approach offer several advantages like multi-functional integration on a single device, reduction of test volumes, rapid analysis, reliability and portability of laboratory processes (Arnaud, 2016; Gubala et al., 2012). This involves approaches such as:

- Paper-based assays:** The paper-based assays like lab-on-chip, lateral flow assays, electrochemical test strips, etc. incorporates multiple laboratory functions on a single chip. These chips are coated with biorecognition molecules and can be used for the detection of cancer associated biomarkers. For example, OncoE6™ and MiSens® are patented paper based technologies.
- Array-based devices:** These devices involve detection of the biomarkers using specific electrodes or fluorescent molecules. Q-POC™ is a novel silicon nanowire-molecular probes conjugated system that is commercially available (Dincer et al., 2017).
- Bead-based systems:** The system utilizes functionalized beads that can specifically bind to the analytes. Thus formed complexes are filtered or separated by size or colour. FDA approved CELLSEARCH® is an example of bead based systems which detects and magnetically separates circulating tumor cells (Arnaud, 2016).

Avantgarde nanotechnological based systems such as QDs, iron oxide nanoparticles, IONPs), CNTs, gold/silica nanoparticles, can significantly assist in designing an early cancer diagnostic strategy. These systems exhibit remarkable surface properties to perform targeting action at the aimed locale and offer effective point-of-care monitoring of the disease. A number of studies have evidenced the multimodal applications of nanostructures for both imaging and therapy. Carbon nanomaterials, including one dimensional CNT and two-dimensional graphene oxide, have often been used to construct fluorescent “turn-on” biosensors. The unique functional properties such as excellent fluorescence quenching by noncovalent π - π stacking interactions with

fluorescently labelled single-stranded DNA and quantitative recovery after exposure to the targets have been utilized to detect disease specific targets in fluid tissue (Li et al., 2015). Mohan et al. (2018) reported the application of analytic hierarchy process by CNT network-based multiplexed biosensors for the real-time detection of DNA hybridization. Moreover, the hybrid structures of iron oxide nanoparticles-SWNT, PEGylated SWCNTs and Cy5.5 conjugated SWCNT offer improved in vivo targeting, imaging and photothermal ablation of the tumor site (Al Faraj et al., 2015; Cisneros et al., 2014; Liang et al., 2014; Liang et al., 2016). Das et al., (Das et al., 2013) fabricated a theranostic prodrug using fluorochrome, (Alexa-fluor, AF488/647), radionuclide, and folic acid-labelled methotrexate loaded multi-walled CNTs. Targeting and imaging of MUC1 tumor marker has been reported using, Cy3-labelled ssDNA probe, P0 aptamer) tethered and doxorubicin-loaded oxide mesoporous carbon nanospheres (C. Li et al., 2017). Apart from CNTs and nanospheres, fullerenes and carbon nano QDs have also gained much attention in the field of cancer theranostics. A facile preparation of carbon-dot-based theranostics nanoplatform was reported by Zhao et al. (2018), that exhibited effective targeting and imaging of tumor-specific TRAIL gene.

Metal based nanostructures, especially AuNPs are considered as attractive tools in the field of biosensorics (Suvama et al., 2017). Cheng et al. (2015) developed gadolinium doped tungsten sulphide nanoflakes for tumor theranostics. Similarly, J. Wang et al. (2018b) evidenced the development of multifunctional polydopamine nanoparticles that offer a combination of photothermal and photodynamic cancer therapy. In addition, gold nanorods combined with CP based nano-frameworks for multiplexed cancer theranostics applications was reported sulphide nanoflakes for concentrations of miRNA via QD based tumor theranostics by J. Wang et al. (2018a). Lv et al. (2017) developed CuS based up-conversion nanoparticles and demonstrated the phenomena of green luminescence - driven hyperthermia. Similarly, an image guided combination of photothermal therapy/photodynamic therapy by means of indocyanine green-loaded silver nanoparticle core/polyaniline shell nano-conjugates was also reported (Tan et al., 2016).

Other than MNPs, studies have also shown the utility of magnetic nanoparticles in cancer theranostics. These nanoparticles are widely assessed as MRI contrasting agents for the image guided drug delivery to cancerous tissues. Shen et al. (2017) showed an additive combination of targeted therapy and imaging by iron oxide nanoparticles. In addition, there have been studies which involve hybrid magnetic nanostructures for image guided delivery of cancer therapeutics (Luong et al., 2017). Detection of various molecular signatures such as microRNAs by means of nanoscaled biosensing devices could probably revolutionize the prediction and pre-determination of cancers. Using this idea, Tian et al. (2017) reported the optomagnetic methods for detection of microRNAs. Bimodal imaging by utilization of the fluorescence/magnetic resonance properties was successfully demonstrated by Xia et al., for detection of cancer cells (Xia et al., 2017).

Along with the other available nanostructures, mesoporous silica nanoparticles and QDs are two widely studied systems for cancer theranostics. The mesoporous silica nanoparticles epitomize promising substitutes for targeted drug delivery as they portray effective delivery and imaging capabilities. Chang et al., (Chang et al., 2018) reported magnetism assisted detection and isolation of circulating tumor cells through mesoporous silica nanoparticles. A combinatorial therapy (Croissant et al., 2016) involving co-delivery of doxorubicin and gemcitabine along with in vivo tumor imaging has been also documented. Detection of cancer related biomolecular signatures have been emerged as the most assuring method for early detection of malignancies. One such study was demonstrated by Treeratrakoon et al. (2017) for the detection of colorectal cancer. Meanwhile, QDs stand out as the most thoroughly and extensively researched systems in the field of theranostics due to their attention grabbing imaging, targeting and novel therapeutic cargo capabilities. A combined theranostic approach for the in-vivo breast cancer targeting has been documented by AbdElhamid

et al. (2018). QD-FRET based strategy was observed to possess the ability to detect various cancer-related epigenetic molecular signatures (Yu et al., 2018). Hypoxia, a condition that initiates tumorigenic signalling, has also been assessed as biomarker for the real-time cancer diagnosis (Shamirian et al., 2016). The in vivo applicability of conventional metal based QDs for theranostic applications is limited due to their toxicity as well as photobleaching properties. Such issues have been resolved with the development of biocompatible and less toxic carbon nanodots. Feng et al. (2016), Li et al. (2018) and Gao et al. (2017) demonstrated the use of QDs for the amalgamated cancer nanotheranostics. All these studies clearly suggest that functionalized nanosensors offer promising tool to develop a point-of-care strategy for cancer theranostics.

5. Advantages of nanotechnology based biosensors

The ever-expanding developments in field of sensorics of nanobiotechnology have generated incredible technology thrust (Dahlin, 2012; Patel et al., 2016), which is mainly due to the following advantages:

1. Integration of the conventional detection techniques into a single platform.
2. Rapid, sensitive and reliable identification of biomarkers and data generation.
3. Simple, user friendly and cost-effective analysis.
4. Reduction of test samples for analysis.
5. Generation of multiplexed information from a single assay.
6. High stability, reproducibility and portability of the constructs.

6. Challenges to development of nanobiosensors as point-of-care systems

Despite of the favourable aspects of the nanobiosensors, a number of challenges exist in their clinical translation (Dahlin, 2012; Dincer et al., 2017; Quesada-Gonzalez and Merkoci, 2018). A few are mentioned below:

1. Integration complexity with decision support services that can be monitored and operated by standalone devices in point-of-care systems.
2. Different subset types of cancer contain different biomarkers thus making it difficult to develop universally applicable diagnostic assay.
3. Additional costs in production of biosensors and diagnostics.
4. Complication in designing and fabrication, assay development and data interpretation due to multiplexing.
5. Requirement of stringent characterization parameters to provide a useful information regarding the storage, functionalization, modification, and use of nanomaterials.
6. Lack of international nanomaterial safety guidelines to address the toxicological aspects.
7. Demonstration of valid correlation with established technologies.

7. Commercially available nanotechnology based point-of-care systems

Nanotechnology based biosensors have revolutionized the field of cancer diagnostics and prognostics. With the rapid innovations in the area of biosensorics, various systems have come in the spotlight as potential point-of-care approaches for the detection of cancer. Out of these a few are either patented and commercialized (Table 2) or are under trails for clinical translation. Combindex, an AMAG Pharmaceuticals Inc product, consisting of ultra-small SPIONs has been approved by FDA as a novel MRI contrasting agent for the detection of metastatic lymph nodes (Grigore, 2017). OraMark™ Test is a simple, non-invasive

Table 2
Table showing list of patents based on the transducer (signal detecting unit) of nano-biosensor.

S.no	Type of nano-biosensor	Patent no.	Assignee	Title	About the invention
1.	Electrochemical nano-biosensor	US6391558B1	Magellan Diagnostics Inc	Electrochemical detection of nucleic acid sequences	Reports the utilization of complementary biological probes like nucleic acid or peptide nucleic acid probes for the selective hybridization and detection of the target analytes. An integrated biosensor system to detect various pathophysiological conditions and provide optimal diagnosis and therapeutics. Voltammetric sequence-selective sensor for detecting the presence of a target polynucleotide sequence in a given physiological sample. Detection of a target sequence in a nucleic acid by conductive oligomers through site-selective modification of nucleic acids with redox active moieties. The system consist of a nucleic acid probe which can detect base-pair mismatches through analyzing electron transfer between donor and acceptor moieties of the hybridization complex. The method can detect a target sequence in a nucleic acid sample through formation of hybridization complex. The invention measures electron transfer of the hybridization complex comprising of a primary single-stranded scissile probe and the target sequence for detection. The sensor can use techniques such as coulometry, amperometry, and potentiometry for determination of analyte concentration in a given biological sample. The detection and isolation of cell free circulating tumor DNA using surface modified conductive polymer based two-dimensional plane structure or three-dimensional nanostructure. A solid-state biosensor for label-free detection of vascular endothelial growth factor (VEGF) through electrochemical sensing. Addresses the simple and sensitive electrochemical method of detecting target nucleic acid sequence or segment using bio-reporter molecules bound working electrodes. Describes a method for development of DNA graphene based electrochemical sensor for detection of survivin gene.
2.		US8346482B2	Fernandez Dennis S	Integrated biosensor and simulation system for diagnosis and therapy	
3.		US5312527A	Concordia University	Voltammetric sequence-selective sensor for target polynucleotide sequences	
4.		US6096273A	Osmetech Technology Inc	Electrodes linked via conductive oligomers to nucleic acids	
5.		US5824473A	California Institute of Technology	Nucleic acid mediated electron transfer	
6.		US6232062B1	Osmetech Technology Inc	AC methods for the detection of nucleic acids	
7.		US6063573A	Osmetech Technology Inc	Cycling probe technology using electron transfer detection	
8.		US6942518B2	Therasense Inc	Small volume in vitro analyte sensor and methods	
9.		KR101701618B1	National Cancer Centre, Korea	Nanostructure for detecting cell-free DNA using conductive polymer and the use thereof	
10.		US8145434B2	Sensor-Kinesis Corp	Method and apparatus for forming a homeostatic loop employing an aptamer biosensor	
11.		US7455975B2	Esa Biosciences Inc	Electrochemical detection of nucleic acid sequences	
12.		CN103063715B	Fujian University of Medicine	Method for detecting survivin gene based on graphene-gold composite material electrochemical DNA (deoxyribose nucleic acid) biosensor	
13.		KR101545160B1	National Cancer Center, Korea	Composition comprising of a conductive polymer for detecting, capturing, releasing, and collecting cell	
14.		US8571805B2	Sensor-Kinesis Corp	Method and apparatus for detecting and regulating vascular endothelial growth factor (VEGF) by forming a homeostatic loop employing a half-antibody biosensor	
15.		US9127304B2	University of California	Probe immobilization and signal amplification for polymer-based biosensor	
16.		US9810661B2	Sensor-Kinesis Corp, Pharmaco Kinesis Corp	Carbon nanotube bioFET with a local amplifier in a system array for analysis of biomarkers and method of analysis of same	
17.		US9645149B2	University of Michigan	System for detecting rare cells.	
18.		CN104939843B	Beijing Yushen Biological Information Technology Co., Ltd.	An implantable cancer recurrence real-time monitoring system.	
19.		US992635B2	University of California	Method for exosomal biomarker detection by electric field-induced release and measurement	
20.		US9395353B2 JP6016792B2	University of Missouri System	Nanopore-facilitated single molecule detection of nucleic acid	

(continued on next page)

Table 2 (continued)

S.no	Type of nano-biosensor	Patent no.	Assignee	Title	About the invention
21.	Optical nano-biosensor	KR101591475B1	Korea University Industry-Academic Cooperation Foundation	Method for simultaneously detecting tumor-specific mutation and epigenetic changes of circulating tumor DNA (ctDNA) using Rayleigh light scattering	A localized surface plasmon resonance and the plasmon coupling based nanosensor are described for simultaneous detection of tumor specific mutation and epigenetic mutations.
22.		KR101812644B1	Korea University Industry-Academic Cooperation Foundation	Method for detecting epigenetic changes of DNA using plasmon coupling dependent surface enhanced Raman spectroscopy	Surface enhanced Raman spectroscopy (SERS) -plasmonic coupling based nanosensor for detection of epigenetic mutations in biological samples.
23.		KR101692052B1	Sogang University Industry-Academia Collaboration Foundation	Methods for detecting circulating tumor cells and stem-like circulating tumor cells using surface-enhanced Raman scattering and systems using thereof	Detection method for circulating tumor stem-like cells and circulating tumor cells using SERS nano-tag.
24.		US9341621B2	Purdue Research Foundation	Ultrasensitive detection of biomolecules using immune-separation and diffractometry	The given invention depicts rapid and ultrasensitive detection of very low amounts of target biomolecules in a sample by means of immune-separation and diffractometry based biosensors.
25.		US9914955B2	Instytut Biologii Doswiadczalnej Im Marcelego Nenckiego Polska Akademia Nauk	Genetically encoded FRET-based MMP-9 activity biosensor and use thereof	A genetically encoded FRET-based biosensor for ratiometric analysis of matrix metalloproteinase 9 (MMP-9) activity.
26.		KR101459311B1	Korea Research Institute of Standards and Science Korea Research Institute of Science and Technology	Surface plasmon bio sensor using optical fiber and detecting means using optical fiber	An optical fibre based biosensor for the detection of target analytes by specific binding to the antibodies that causes changes in the frequency of surface plasmons.
27.		CN103713130B	Third Affiliated Hospital of the Third Military Medical University of the Chinese People's Liberation Army	The aptamer-based biosensor for rapid detection of circulating tumor cells	A piezoelectric aptamer-based biosensor for rapid detection of circulating tumor cells, and early diagnosis of cancer metastasis.
28.		KR101525299B1	Yonsei University Wonju Industry-Academia Collaboration Foundation	Carbon nanotube biosensor with aptamers as molecule recognition elements and method for sensing target material using the same.	An aptamer-conjugated carbon nanotubes based biosensor for detection of a target substance.
29.	Mechanical based nano-biosensor	US7105301B2	Intel Corp	Detecting molecular binding by monitoring feedback controlled cantilever deflections	A probe labelled cantilever biosensor that upon binding with the analyte causes deflection in the cantilever which is detected.
30.		US8940663B2	University of Texas System	Nano-scale biosensors	Recyclable devices and methods for detecting protein-nucleic acid and cell-nucleic acid hybridization, using surface-tethered aptamer probes.
31.		US9144883B2	University of Arkansas	Device and method for in vivo non-invasive magnetic manipulation of circulating objects in bioflows	Flow cytometry based in vivo method for manipulation and detection of a magnetic target within a circulating biofluid.
32.		US6471968B1 CA2408535C	Michigan University of Regents	Multifunctional nano-device platform	Dendrimer based multifunctional compositions and systems for disease diagnosis and therapy.

easy-to-administer oral rinse procedure for the accurate detection of oral cancers. Similarly, Cxbladder offers another non-invasive, precise, urine-based laboratory test for bladder cancer detection. Two blood-based liquid biopsy tests as Epi proLung[®] and Epi proColon[®] are commercially available lung and colorectal cancer detection systems. Furthermore, Videssa[®] Breast, a product line based on Provista's proprietary ProteoMark[®] Technology is a protein-based blood test for the detection of breast cancer that analyses several tumor blood-borne protein biomarkers. NuView Life Sciences is currently in the developmental stage of NV-VPAC1 technology as an in vitro diagnostic kit which contains a fluorophore attached to NV-VPAC1 peptide for the detection of shed cancer cells in voided urine. There are many on-site diagnostic approaches or tools that are under developmental stage and are expected to increase as profoundly used point-of-care approaches in the coming years.

8. Summary and conclusion

In the recent times, biosensors have emerged as the key players in the field of cancer theranostics. Nanotechnology has provided an exceptional opportunity for the development of advanced nanoscaled biosensors that can be integrated in lab-on-chip platforms. The combination of nanotechnology with disease-specific molecular signatures opens the possibilities of detailed visualization and treatment. Incorporation of nanomaterials in the biosensing frameworks significantly improves sensitivity, stability, shelf-life, better signal-to-noise ratio, prompt response, and multiplexed detection, which could remarkably enhance the performance of the biosensor. Simultaneously, nanobiosensors offers cost-effective and patient-friendly portable sensing devices. Despite of the aforementioned advantages, the application of nanobiosensors in clinical diagnostics is limited due to the issues related to the safety, toxicity compliance, and complexity in detection. Therefore, much work is now focussed towards constructing simple, reliable and inexpensive nanosensors with increased sensitivity and reproducibility to establish their potential clinical applicability. These nanobiosensors would lead to overcome the barriers of current molecular techniques and holds promise to facilitate the progression in developing personalized medicine as the point-of-care diagnostic devices.

9. Future perspectives

Cancer theranostics marks the most important area of nanobiosensing application. The conventional modalities are time-consuming and often leads to delay in the initiation of the treatment. On the contrary the ultrasensitive nanobiosensors could effectively detect minute concentrations and aberrantly expressed biomarkers for early prediction and staging of cancer. In addition, significant advancements in the area of microfluidics and detection technologies have permitted multiplexed detection with high sensitivity, reduced analytical time consumption and minimal user-intervention. Moreover, the gross commercialization of these nano-tools will assist patients to get prompt disease information that will help them to initiate the treatment on time. This will certainly contribute towards increasing their life-expectancy and reducing disease related mortality. Future trends will proceed with the further nanonization of the biochips for developing minuscule devices capable of simultaneous detection and treatment. For instance, a nanotheranostic device could be surgically placed as a prophylactic tool and operated through remote sensors for disease monitoring. However, successful translation of these promising nanobiosensor strategies as point-of-care technologies may require robust clinical analysis, simultaneously addressing issues like standardization, further miniaturization of the sensor components and their facile and smart integration for signal readout.

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Author contributions

RS, AB and NB performed comprehensive review of literature. RS, AB and IYG wrote the manuscript. RS, NB and RT helped in formulation of tables and figures. PKM and IYG designed the concept of the manuscript and revised the article for important intellectual.

Declaration of interests

None.

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