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Multidimensional (0D-3D) nanostructures for lung cancer biomarker analysis: Comprehensive assessment on current diagnostics

Santheraleka Ramanathan[a], Subash C.B. Gopinath[a,b,*], M.K. Md. Arshad[a,c], Prabakaran Poopalan[c]

[a] Institute of Nano Electronic Engineering, Universiti Malaysia Perlis, 01000, Kangar, Perlis, Malaysia
[b] School of Bioprocess Engineering, Universiti Malaysia Perlis, 02600, Arau, Perlis, Malaysia
[c] School of Microelectronic Engineering, Universiti Malaysia Perlis, Pauh Putra, 02600, Arau, Perlis, Malaysia

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ABSTRACT

The pragmatic outcome of a lung cancer diagnosis is closely interrelated in reducing the number of fatal death caused by the world's top cancerous disease. Regardless of the advancement made in understanding lung tumor, and its multimodal treatment, in general the percentage of survival remain low. Late diagnosis of a cancerous cell in patients is the major hurdle for the above circumstances. In the new era of a lung cancer diagnosis with low cost, portable and non-invasive clinical sampling, nanotechnology is at its inflection point where current researches focus on the implementation of biosensor conjugated nanomaterials for the generation of the ideal sensing. The present review encloses the superiority of nanomaterials from zero to three-dimensional nanostructures in its discrete and nanocomposites nanotopography on sensing lung cancer biomarkers. Recent researches conducted on definitive nanomaterials and nanocomposites at multiple dimension with distinctive physiochemical property were focused to subside the cases associated with lung cancer through the development of novel biosensors. The hurdles encountered in the recent research and future preference with prognostic clinical lung cancer diagnosis using multidimensional nanomaterials and its composites are presented.

1. Introduction

Cancer has never lost its impasse as the most death-dealing disease in the world. According to the statistical analysis conducted by the International Agency for Research on Cancer using GLOBOCAN 2018 estimates 18.1 million new malignancy cases and almost half of it (9.6 million) ended in cancer death (Bray et al., 2018). The uncontrolled fatal deaths caused by the non-communicable cancerous disease have been a tough hindrance in the effort of elevating human life expectancy at every corner of the world. Among both man and women, lung cancer is the most leading cause of mortality and statistics prove 18.4% of the total deaths cases were due to lung cancer (Boloker et al., 2018; Siegel et al., 2019). The statistics revealed that the lung cancer incidence rate over the past decade fluctuates about 2% annually and the death rate follows a similar trend resulting in the unexpected tumor deaths (Bray et al., 2018). The survival rate of diagnosed lung cancer patients for 5 years is only about 10% from the overall incidence rate, yet about half of the diagnosed patients die within a year of diagnosis (Cryer and Thorley, 2019; Zappa and Mousa, 2016). The countless number of deaths from infants to elderly people regardless of the genetic inheritance and black-white disparities around the world.

There are numerous diagnostic strategies were recognized and clinically implemented to detect lung cancer. Invasive histological examination of tumor malignant was clinically practiced and acts as preliminary studies on the diagnosis of lung cancer. Over the decade, the emergence of recent technology in identifying lung cancer biomarkers, such as gene mutation and DNA hybridization towards recognizing the subtypes of lung cancer prompts high accuracy lung cancer treatments. Epidermal growth factor receptor (EGFR) mutations and circulating tumor biomarkers such as microRNA and cytokeratin-19 fragment acts an activating agent for the diagnosis of lung cancer. Polymerase chain reaction (PCR) based detection on lung cancer primers is implemented to date on the recognition of genome mutation and screening of lung cancer biomarkers (Chen et al., 2016; Han et al., 2012; Shoja et al., 2018). The samples are acquired by various biopsy techniques to obtain detailed tumor-markers information or its carrier. To date, the evolution of lung cancer in term of its causes has been presented by researches and clinical studies, however, the effective diagnostic method for different subtypes of lung cancer is yet to be recognized. The fundamental reasons for this situation is the failure in recognition of lung cancer tumor-marker at an early stage and thus fail to transmit therapeutics to the tumor at adequate focuses without

* Corresponding author. Institute of Nano Electronic Engineering, Universiti Malaysia Perlis, 01000, Kangar, Perlis, Malaysia.
E-mail address: subash@unimap.edu.my (S.C.B. Gopinath).

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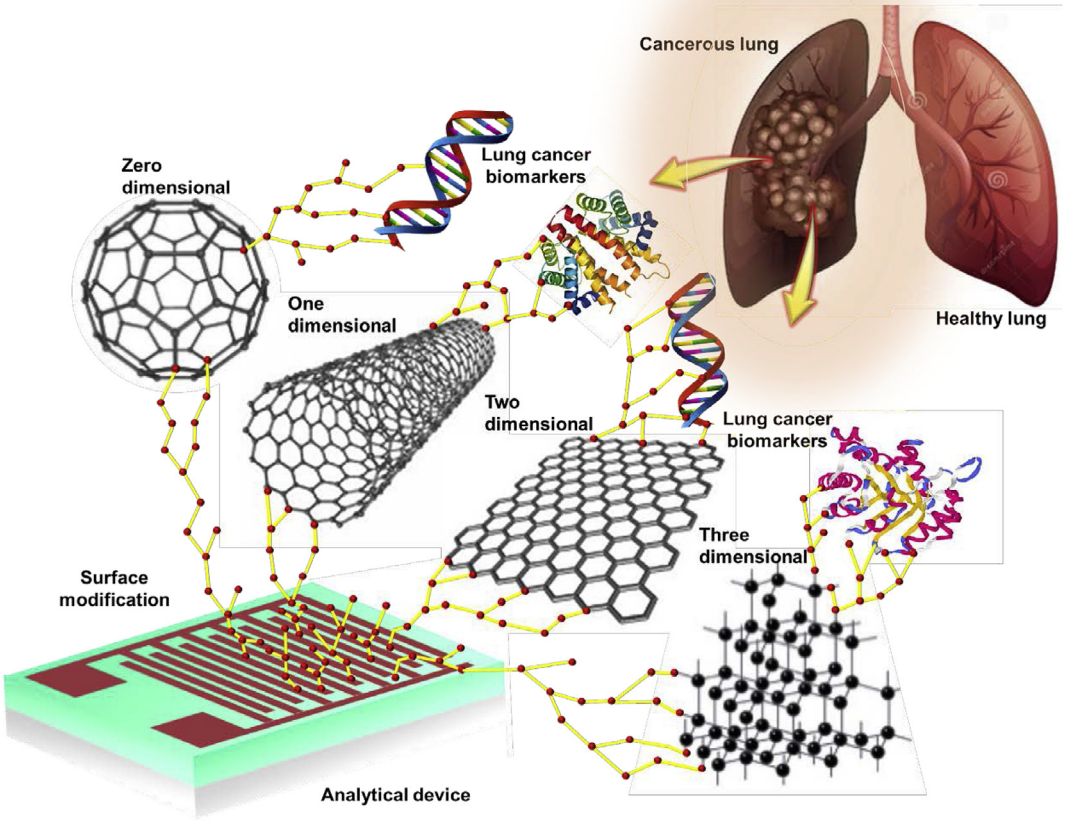

Fig. 1. Overall concept of lung cancer diagnostics applicable to multiple types of biosensor. Surface functionalization was performed on the sensing platform of the biosensor to immobilize various dimensions of nanomaterials and nanocomposites, which are modified with antigen, RNA/DNA targeting the lung cancer biomarker.

damaging healthy lung cells (Liu et al., 2015b; Peng et al., 2009; Wang et al., 2019; H. Zhao et al., 2018b). An ideal lung cancer diagnosis empowers the quick and high selective capturing of tumor biomarkers at the early stage of the growth. The potentiality in achieving the ideal diagnostic strategy, the emerging nanotechnology plays the key role.

Biosensors comprise the physio-chemical transducer and biological origins have been highly recommended in the diagnostic of lung cancer (Chen et al., 2018b; Farka et al., 2017). In the last decade, biosensors are widely applied in the detection of lung cancer, yet it is non-ideal due to the inability in capturing tumor cells in low analyte concentration with an immediate response, as it is highly welcomed in point of care diagnostic and treatment. In response to that, nanotechnology has been broadly expended in the application of biosensor as the fabrication of 1–100 nm size nanomaterials critically influences the performance of biosensors. Nanomaterials with a high surface area to volume ratio encounter the high stability against biological molecules compared to macromolecules and act as nanoprecursors on the sensing platform to effectively transform electron potential into the measurable current (Cryer and Thorley, 2019; Farka et al., 2017; Pohanka, 2019; Taylor et al., 2016). Although the multifaced nanomaterials have been augmented as a promising nanoprecursor for biosensors, it is yet to be established in the clinical application. The ability on reproducibility, and the hazards associated with the nanomaterials due to its toxicity has been classified as the barriers for clinical implementation.

Based on the above context, the present review comprises the current diagnostic of lung cancer with the aid of advanced multidimensional nanomaterials and its composites on biosensors. The present concept of multidimensional nanomaterials can be applied to diagnose other tumor cell or biocarriers to identify diseases since its nanoscience and technology has a broad spectrum of pharmaceutical and medical applications. We also look into the real-time application of biosensors in the diagnosis of lung cancer in relation to the current and future advances of lung cancer diagnostics.

2. Nanomaterials in diagnostic tools

Oxygen biosensor developed by Led and Clark in 1962 is the first analytical device invented in human therapeutics which induced the interest of biosensor for medical applications. Since then, biosensors has shown intense potential in medical diagnostics and pharmaceutical industries. Over the past decades, numerous sensing concepts and related analytical devices has been developed. The conventional concept of biosensors involve the direct conversion of biological event to electric signal which is amplified in multiple formations. Among many non-communicable diseases, cancer is one of the targeted tumor diseases that has given much attention for the development of biosensor its early diagnosis. In the early 20th century, the detection of tumor markers with biosensors developed in conjunction with other diagnostic techniques where transducers were inter-related in the system as the biological signals are transformed into electrical signal (Patel et al., 2016). As the barriers associated with the effective techniques of cancer diagnostics, nanotechnology has been highly recognized as a productive alternative growing technology with the augment of biosensors, resulting in high-performance nanobiosensors. As stated briefly above, nanomaterials have numerous fascinating potentials in its physio-chemical properties sanction itself to be highly involved in conjugation with biomolecules and biomarkers in the pharmaceutical and medicinal applications (Letchumanan et al., 2019b, 2019a). The intense area of

Table 1
Comparison between researches established in recent literature from zero-to three-dimensional nanostructures based biosensors for lung cancer diagnosis.

Device	Nanomaterial	Biomarker	Detection strategy	Detection Limit	Reference
Zero-Dimensional Nanomaterials					
Fluorescence biosensor	Nanosphere quantum dots	EFGR type 2 in A549 lung cancer cells	Fluorescence microimaging	SPR peak was evaluated	Zhao et al. (2016)
Fluorescence microscopic biosensor	Single quantum dots	Cy5-dGTP	Fluorescence microimaging	5.3 aM (32 copies)	Tang et al. (2015)
Fluorescence immunoassay biosensor	Multicolor quantum dots	CYRFA 21-1, CEA, and NSE	Fluorescent signal through SPR spectrum at 525, 585 and 625 nm	1.0 ng/mL	Jing et al. (2016)
One Dimensional Nanomaterial					
Interdigitated electrode	Carbon nanotube	CA-125	Electrochemical signal through microfluidic PDMS channel	560 μg/ml	Mandal et al. (2018)
Dielectric immunosensor	Multi-walled carbon nanotube	Arginase 1	Dielectrophoresis signal	< 30 ng/ml	Baldo et al. (2016)
Cotton thread immunoassay device	Multi-walled carbon nanotube	Ferritin antigen	Chromatographic technique	50 ng/mL	Meng et al. (2017)
Field effect transistor (FET)	Silicon nanowire	Breathprint from a lung cancer patient	Electrical signal	> 80% accuracy wit 374 subjects	Haick et al. (2016)
FET devices	Silicon nanowire	microRNA − 126 and CEA	Electrical signal	0.1 fM	Zhou et al. (2017)
Disposable breath sensor	Silver nanowire	2-propyl-1-pentanol (2-PP) lung cancer biomarkers	Moisture variation through dynamic stimulation	2-PP concentration exceeding 100 ppb	Wu et al. (2016)
Electrochemical biosensor	Gold nanorods	CEA	Chemiluminescence immunoassay	1.5 pg/mL	Huang et al. (2016)
Two Dimensional Nanomaterials					
Breath sensor	Hydrogen vacant silicane nanosheets	Exhaled human breath biomarkers	Absorption phonon band	Absorption energy between −0.778 to −1.274 eV	Nagarajan and Chandiramouli (2018)
Breath gas sensor	Titatnium oxide nanosheets	1-nonanal gas	Electrical resistance	0.055 ppm	Masuda et al. (2015)
Colorimetric sensor	Ni/Fe layered double hydroxide nanosheets	micro RNA, *let-7b*	SPR spectrum	0.36 fM	(Chen et al., 2018a)
Infrared absorbance sensor	Gold nanoplates	Peptide P75 (EGFR target)	Photothermal infrared conversion	5.1 fold target cell expression	(Y. Zhao et al., 2018)
Fluorescence sensor	Graphene oxide nanoplate	miRNA of single lung cancer cell	Fluorescence response and gel electrophoresis	25 μg/mL cultured cell	Zhang et al. (2016)
Microfluidic sensor	Graphene nanoplate	Circulating tumor cells	Electrical impedance	500 fold cell enrichment and 94% detecting rate in peripheral blood	Han and Han (2015)
Three Dimensional Nanomaterials					
Plasmonic biosensor	Gold nanosquares	Live lung cancer A549 cell	SPR absorbance peaks	5×10^3 cells/ml	(Zhu et al., 2018a)
Electrochemical biosensor	Hierarchical flower-like gold nanostructures	miRNA-21	Electrochemical signal amplification	1.0 × 10–13 M target miRNA	Su et al. (2016)
Plasmonic biosensor	Quasi gold nanostructure	Live lung cancer A549 cell	SPR absorbance peaks	0.08 cells mm^{-2}	Zhu et al. (2016)
One Dimensional Nanocomposite					
Immunosensor	Amine functionalized graphene-gold nanocomposite	NSE	Electrochemical signal	10 pg mL^{-1}	Xu et al. (2017)
Immunosensor	Gold nanocomposites with microscales titanium oxide	Progastrin-releasing peptide	Electrical resistance	0.98 ng/mL	Wei et al. (2019)
Plasmonic biosensor	Gold nanorod with silver shells	CEA	SERS scattering	4.75 fg/mL	Rong et al. (2016)
Plasmonic biosensor	Ferum (III) oxide/gold/silver nanocomposites	Trace level of adenosine in urine of lung cancer patient	SERS signal transduction	10^{-10} M	(Yang et al., 2014b)
Electrochemical immunosensor	Carbon nanotube-chitosan nanocomposite	anti-MAGE A2 anti-MAGE A11	Electrochemical signal	5 fg mL^{-1} to 50 ng mL^{-1}	Choudhary et al. (2014)
Electrochemical immunosensor	Gold coated single-walled carbon nanotube	miRNA-21	Electrochemical signal	1.95fM	(Liu et al., 2015a)
Electrochemical immunosensor	Graphene-carbon nanotube composite	CEA	Electrochemical signal	60 pg mL^{-1}	Feng et al. (2013)
Two Dimensional Nanocomposites					
Electrochemical genosensor	Dendritic gold graphene nanocomposite	Long noncoding RNA	Electrochemical signal	0.25 fM	Li et al. (2018)
Electrochemical genosensor	Titatium oxide-graphene nanoplates	ANXA2 antigen ENO1 antigen VEGF antibody	Electrical resistivity	100 fg/ml	Li et al. (2015)

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research on nanomaterials has to lead the revolutionary diagnostic techniques in the detection of non-communicable diseases, mainly cancer (Holzinger et al., 2014; Quesada-González and Merkoçi, 2018; Vieira and Gamarra, 2016; Viswambari Devi et al., 2015).

The main challenge in the achievement of successful lung cancer diagnostic is the ability of nanobiosensor to capture an extremely low limit of detection and to enhance the amorphous electrical signal generated from the physiological signal of biomarkers with the reaction of tumor cells to the conductive electrode. To overcome the above hurdles in the fabrication of high-performance nanobiosensor with the aid of nanomaterials, the affinity, specificity and its sensitivity play a significant role in the factors to be considered (Goryacheva et al., 2019; Li et al., 2012; Pasinszki et al., 2017; H. Zhao et al., 2018a). With increase interest in topographical structures of nanomaterials, multidimensional nanomaterials are much welcomed in the recent development of biosensors. A single nanoscale atom or microsize bulk material owns certain limitations in the conjugation with biomolecules and unable to satisfy the expected detection limit of a sensor in tumor cell recognition due to its small surface area/volume ratio. Particularly, the multidimensional nanomaterials are characterized in accordance to its physical property and the field of biomarker interest depending on whether it is a DNA sequence, microRNA or target proteins (Chueng et al., 2016). The present review demonstrates the application of multidimensional nanomaterials which acts as nanoprecursor on the biosensing platform for the current diagnostics on lung cancer biomarker. Fig. 1 illustrates the overall concept of this review where multidimensional nanomaterials functionalized on various biosensors to detect lung cancer biomarkers.

3. Transition of zero to three dimensional nanostructures for lung cancer diagnosis

The influence of distinctive nanomaterials at various dimensions on the performance of biosensor for effective lung cancer diagnosis was well-presented. Table 1 summarizes the recent literature reported by using multidimensional nanostructures as effective nanoprecursor to generate prospective sensor for lung cancer diagnosis.

3.1. Zero dimensional nanostructures

Zero-dimensional nanomaterials are defined as the pioneer product of nanotechnology since 1974 when Norio Taniguchi proposed the term ‘nano’, where the micro-building blocks were narrowed down to the technology of nanoscale block buildings (Suominen et al., 2016). When nanoparticles were discovered with zero direction, the nanoscale materials are developed in a well-controlled dimension in all direction. Over time, the zero-dimensional nanomaterials have met its own significant properties depending on the size and shape of the zero-dimensional nanoparticle (Tiwari et al., 2012).

3.1.1. Quantum dot nanospheres

In recent technology, quantum dot (QD) nanospheres are well-recognized as a zero-dimensional nanomaterial. Nanosphere exhibits a large surface area and high mechanical strength in nature due to its hollow spheres in container pattern (Dai, 2015; M. Zhao et al., 2018). QDs nanospheres hold a broad excitation range coupled with a narrow and symmetric emission spectrum which enables QDs to get excited with a single wavelength and function in a multicolor mode for disease imaging and mapping (Singh et al., 2018a,b). Due to the super magnetic fluorescent property, zero-dimensional QDs nanospheres are found to be promising nanomaterials for the biosensors and medical imaging. Fig. 2A(i) demonstrates the presence of QDs on the sensing surface of an electronic device Fig. 2A(ii) shows the morphological image of QDs under a transmission electron microscope whereas Fig. 2A (iii) shows the fluorescence optical image of QDs. Despite numerous techniques in the early diagnosis of lung cancer, the zero-dimensional QDs

Table 1 (*continued*)

Device	Nanomaterial	Biomarker	Detection strategy	Detection Limit	Reference
Electrochemical genobiosensor	Reduced graphene oxide- mesoporous carbon nanocomposite	EGFR point mutation	Differential pulse voltammetry	120 nM	Shoja et al. (2018)
Three Dimensional Nanocomposites					
Electrochemical immunosensor	Graphene gold nanocomposite	CYFRA 21-1	Electrochemical signal	100 pg mL^{-1}	Zeng et al. (2018)
Electrochemical immunosensor	Reduced graphene oxide/polyaniline nanocomposite	Neuron specific enolase	Electrochemical signal	0.1 pg mL^{-1}	Zhang et al. (2018)
Electrochemical biosensor	3D graphene functionalized with silver nanocomposites	CYFRA21-1	Electrical impedance	1.0×10^{-14} M	(Chen et al., 2018c)
SERS based immunosensor	Gold-silver encapsulated in ARANP shell nanoparticles	Exosomal microRNA	SERS signal reporter	5.0 μL	Ma et al. (2018)
Electrochemical immunosensor	GNP/reduced graphene oxide composite	NSE	Electrochemical signal amplification	0.05 ng/mL	Wei et al. (2017)
Electrochemical cytosensor	Carbon nanosphere-gold nanocomposite	Lung cancer cell line A549	Voltammetry signal	14 cells mL^{-1}	Zhang et al. (2019)

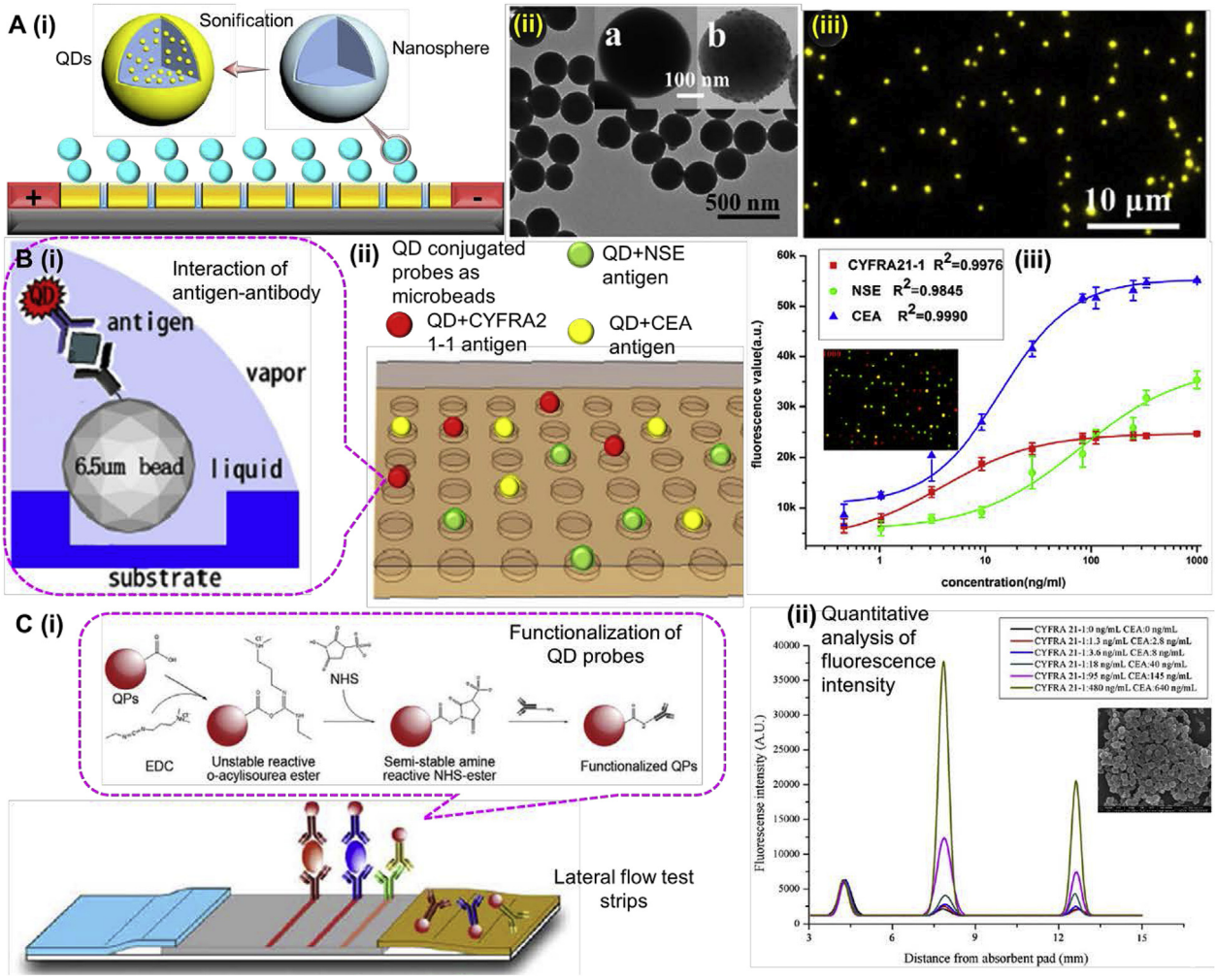

Fig. 2. A (i) Schematic illustration of zero-dimensional quantum dot nanosphere on conductive sensing surface and the cross-sectional view of nanosphere show the microscopic fluorescence quantum dots. A (ii) Morphology of QDs under transmission electroscope. A (iii) Fluorescence optical image of QDs nanospheres. Reproduced with permission from Hu et al. (2016) Copyright 2016 ACS pubs. B (i) Illustration of antigen-antibody interaction using 6.5 µm bead-based multiplex sandwich assay. B (ii) Three different colors of QD beads conjugated with antibodies which were used as labels to remark the detection of specific targets acts as the detection principle of the assay. B (iii) The graph shows fitted logarithmic curves based on fluorescence intensity reflected by QDs as labels for the detection of different lung cancer targets at different concentration investigated in the bead-based multiplexed assays. Reproduced with permission from (Liu et al., 2016) Copyright 2016 Elsevier B.V. C (i) Schematic representation of QD conjugated probe and target interaction on lateral flow test strips. The QD was functionalized with polystyrene nanoparticles to improve the repeatability and recovery of the assay. C (ii) The curves represent fluorescence intensity induced by QDs in the presence of CEA and CYFRA-21 targets at different concentrations. The prominent peak reflects the presence of target at highest concentration of both targets. Reproduced with permission from (Singh et al., 2018a,b) Copyright 2018 Elsevier B.V. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

nanospheres hold the excellent optical property and real-time detection in lung cancer diagnosis. The absence of additional modifications of QDs in this approach results in a simpler generation of QDs without complicated chemical functionalization (Zhao et al., 2016). In a study, Cy5-DNA-QD complex based biosensor was generated to detect genomic DNA mutant target in human lung cancer cell. The immobilization strategy was designed as the Cy5-labeled biotinylated probes were conjugated with QDs nanospheres, and the bonding were strengthen by fluorescence resonance energy transfer (FRET) generated between the biomolecules and QDs. The study acclaimed that the QDs based biosensor exhibits high sensitivity with detection limit of 5.3 aM of mutant target for the genomic diagnosis of lung cancer cell (Tang et al., 2015). Further, Liu et al. (2016) reported that QD based on-chip multiplexing immunoassay system was developed by constructing sandwich structured magnetic beads with zero-dimensional QDs modified with probes to study the interaction of antigen-antibody (Fig. 2B (i)). Microarray system were implemented where single microbead-QD complex were trapped in a planar array, resulting in bead-based on-chip immunoassay to detect three lung cancer biomarkers (cytokeratin 19 (CYFRA21-1), (carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE)), simultaneously. The role of QD here were significant in enhancing single excitation wavelength in single microarray as the detection signal, which eliminates the complicated processing in signal amplification for single bead-based assay system. Fig. 2B (ii) shows the structure of chip with three different color of QD beads resemble the different lung cancer biomarkers. The sensitivity of QD bead microarray on multiplex immunoassay system was demonstrated with 10 µl of human serum and the system was justified as a highly sensitive with attained low detection limits (CYFRA21-1: 0.97 ng/ml; CEA: 0.19 ng/ml; NSE: 0.37 ng/ml; S/N = 3) and expected to be implemented in early screening of lung cancer cells. The sensitivity also justified by the regression value obtained from fitted logarithmic curves as shown in Fig. 2B (iii) (Liu et al., 2016). Later on, the zero direction QDs nanoparticles were doped with polystyrene to develop lateral flow test strips to detect CYFRA21-1 and CEA in human serum of lung cancer infected patients. The excellent light properties were shown by QDs gave

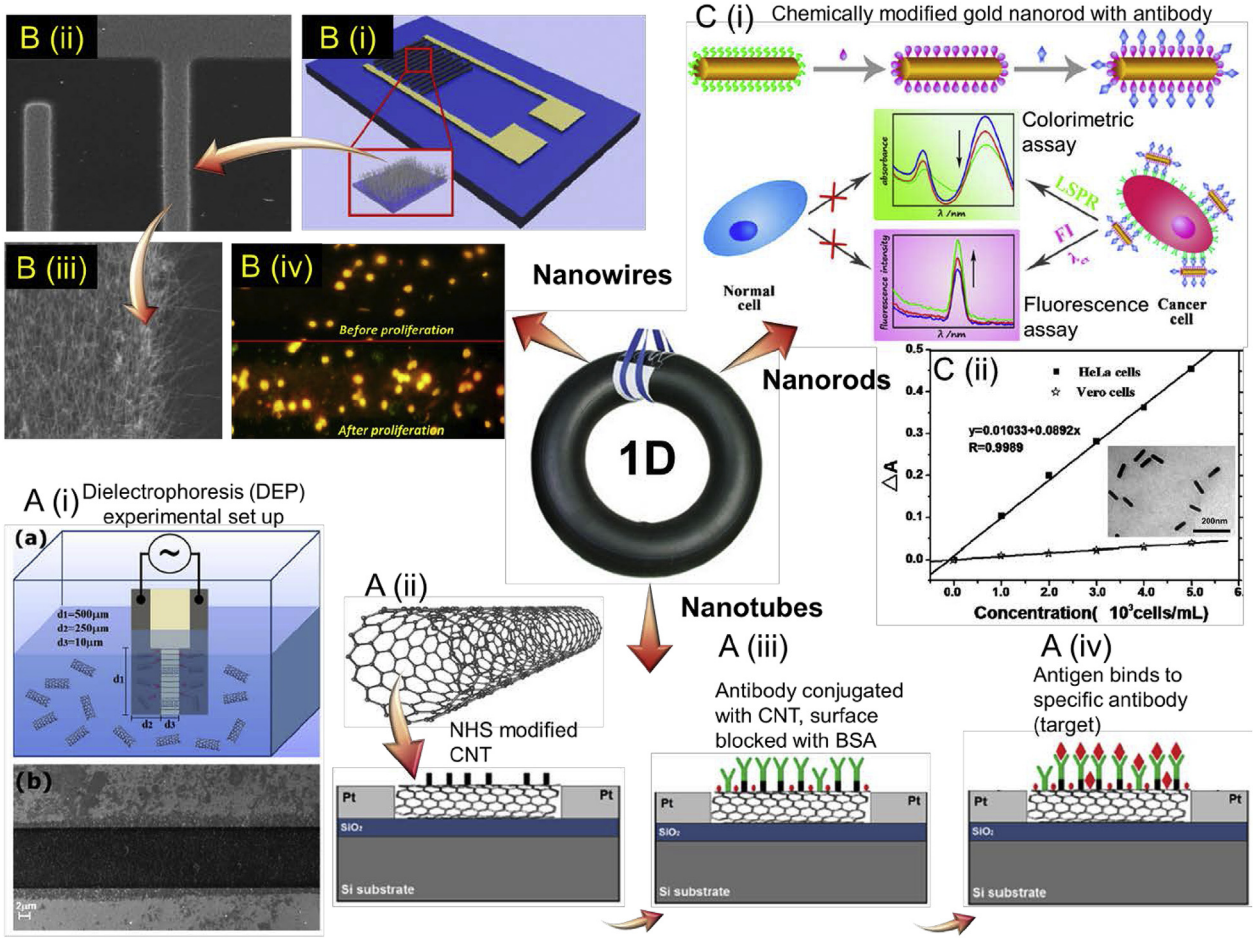

Fig. 3. 1D nanostructures functionalized on biosensor for lung cancer diagnosis were shown. (A) Detection of AGR-1 protein of lung tumor using DEP technique using multi-walled CNT on silicon substrate. (i) a. the experimental set up of DEP to deposit multi-walled CNT between electrodes. b. the optical image of electrode observed under SEM. (ii) 2D CNT were modified with NHS for probe conjugation. (iii) The surface of electrode were blocked with BSA to avoid non-specific binding. (iv) Antigen binds to antibody and the electric signal amplified reveals the detection of ARG-1 protein. Reproduced with permission from (Baldo et al., 2016) Copyright 2016 Elsevier B.V. (B) (i) – (iii) Silicon NW grown on space between the electrodes and optical image observed under SEM reveals the morphology of silicon NW. (iv) Florescent images of silicon NW before and after proliferation stage of QUDB cells seeded on the electrode surface which amplifies the electrical impedance for lung cancer detection. Reproduced with permission from (Azimi et al., 2015) Copyright 2015 Elsevier B.V. C (i) Schematic illustration on the preparation of probes and assay for detection of cancer cell using dual detection strategy; fluorescence and colorimetric assay. 1D gold nanorod were chemically modified with antibody and allowed to react with cancer cells. (ii) Due to excellent plasmonic characteristics of gold nanorod, a linear relation between fluorescence signal and concentration of cancer cells were observed with high sensitive detection strategy, R^2 = 0.9989. Reproduced with permission from (Yang et al., 2014a) Copyright 2014 Elsevier B.V.

efficient analysis based on the fluorescent peak height obtained by using a fluorescent strip reader. Fig. 2C shows the schematic representation of the assay and the fluorescence signal amplified by the QDs in the presence of biomarkers. The detection limit attained in the diagnosis of lung cancer using CEA and CYFRA21-1 were 0.35 and 0.16 ng/ml, respectively. It implies the novelty of the research conducted in early screening of lung cancer by utilizing the zero-dimensional QDs nanospheres for advanced diagnosis techniques (Chen et al., 2017; He et al., 2016; Jing et al., 2016). In spite of that, researches do acclaimed on the drawbacks of QDs in biological application as the zero dimensional nanostructure pressures the diffusion of QDs across cell membrane which may cause constraints and disrupts the delivery process. In many cases, researched are keen into the method of synthesizing nanoscale QDs to resolve the issues associated with large QDs and ensure smooth delivery process in QD-based biological applications (Wang et al., 2016).

3.2. One dimensional nanomaterials

The interest in one dimensional (1D) nanomaterials emerged when Sumio Iijima discovered carbon nanotube (CNT) in 1991 when a tubular structure of carbon atoms was observed under the electron microscope. Since then, 1D nanomaterials have received more attention as the nanomaterial with less than 100 nm size reflect numerous novel functional properties. 1D nanomaterials often appear in an elongated circular structure, made up of single or multiple layers of atoms connected by a network of chemical structure. As the structure of 1D nanomaterials is interconnected, it has a key role in the fabrication of electronic devices and as well as biosensors. The effectiveness carried by 1D nanomaterial was significantly proven in the detection of malignancy cells. The most common type of 1D nanomaterials stands from nanotubes, nanowires and nanorods.

3.2.1. Nanotubes

Carbon nanotube (CNT) is the intermediate nanostructure of fullerenes and graphite. However, it has unique physiochemical properties, which are not carried from graphite and fullerenes. CNT has a large surface area/volume ratio and high mechanical and electrochemical strength. It has high electronic sensation towards any molecules absorbed on its surface, enables it to behave as starting nanomaterial for

the generation of electronic sensors (Zaporotskova et al., 2017). Moreover, surface functionalization on the CNT is proven to be extremely feasible as it shows a better interaction with biomolecules, analyzed by its sensitivity (Sireesha et al., 2018). Biosensors made up with CNT as starting material are considered as a highly stable, because it gives a low-fouling effect and a lower redox potential. The sensors are also expected to reveal quick and rapid response due to its high kinetic in electron transfer reactions (Su et al., 2012). With this regard, CNT based sensors are widely applied in current diagnostic on lung cancer biomarkers. CNTs were implemented in a novel immunochromatographic assay using cotton thread to detect human ferritin antigen, a protein-based lung cancer biomarker. Previously, Meng et al. (2017) has worked on gold nanoparticle (GNP) conjugated probe on cotton thread assay since GNP are able perform dual label amplification. Then, the team concentrated on CNT conjugated probe on cotton thread immunochromatographic assay. The research findings justified that the 2D CNT with spectacular tubular characteristics is an ideal nanomaterial for cotton thread assay. Since CNT behaves as reporter probe and colored reagent for visual and rapid detection of human ferritin antigen, it is accepted for dual label amplification and able to substitute GNP for cotton thread assay. The research emphasized the potentiality of cotton thread assay in developing rapid, and simple device in the growing future of clinical diagnosis of diseases using biosensors and not forgetting the significant role of CNT as an efficient nanomaterial in improving device performance (Meng et al., 2017). In another study, multi-walled CNT was reported for the detection of ARG-1 protein biomarker of lung cancer using immunosensor. In this work, dielectrophoresis (DEP) techniques were applied to deposit solution-dispersed CNTs on silicon substrate between platinum electrodes. Although chemical vapor deposition is the usual method handled for growing CNTs, the study proclaimed that, DEP is much straightforward and more cost-effective methods for appropriate surface functionalization of CNT in the effort of developing high efficient immunosensor. Fig. 3A(i)shows the experimental set up for DEP based detection. Moreover, high sensitive and reproducible multi-walled CNT on immunosensor was reported to detect ARG-1 protein biomarker, in the range between of 30 ng/ml and 100 ng/ml of protein concentration, highlight the reliability of CNT modified immunosensor using DEP method for detection of biomarker related to various hematological malignancies. The surface functionalization method performed were reported as low-cost and feasible for a large scale production of point-of-care lung cancer diagnosis. Fig. 3A (ii) – (iv) shows the detection strategy implemented to evaluate the interaction between antibody and ARG-1 antigen (Baldo et al., 2016). Mandal et al. (2018) acclaimed the improved detection of lung cancer based on cost-effective, small-spaced and simplified surface modification on CNT for the sensitive interdigitated electrode transducer and efficient signal transduction in the microfluidic channel generated by PDMS. The of sensor were coated with Self Assembled Monoloayer (SAM) before adding the carboxylic modified CNTs. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS) were added to active CNTs which enables it to bind with antibodies as it is immobilized on the sensor surface. The simple, proper and efficient surface modification were affirmed through the results on detecting CA-125 antigen at micro-volume fluid sample via CNT modified interdigitated electrodes (Mandal et al., 2018). Besides fluidic sample, human breath was examined for lung cancer diagnosis based organic material functionalized single-walled CNTs which empowers a high sensitivity towards the volatile organic compounds (VOC). Zhang et al. (2011) investigated selectivity of single-walled CNT in relation to two different organic materials (tricosane ($C_{23}H_{48}$) and pentadecane ($C_{15}H_{32}$) with polar dioctyphthalate ($C_{24}H_{38}O_4$)) used for its effective surface functionalization on biosensor, moreover controls the swellability of thin organic layer coated on CNTs in contact with VOCs. Direct coating techniques were used to coat single-walled CNT modified with organic materials on the sensing surface. The finding of the research evolved that the $C_{23}H_{48}$ functionalized CNTs show pronounced sensitivity toward polar VOCs molecules, which were evaluated through the changes in resistance of biosensor when tested with polar and nonpolar VOCs, the biomarkers for lung cancers via breath analysis (Sanginario et al., 2017; Zhang et al., 2011).

3.2.2. Nanowires

1D nanowire (NW) has evolved after nanotube which empowers much simpler synthesizing techniques with specific nanostructures. NWs exhibit similar structure as nanotube, however, it varies in the nanoscale dimension and it possesses higher flexibility due to its non-hollow nanostructure. NWs are classified as a semiconductor with a large surface to volume ratio and high stability against external materials. It holds a simple synthesizing method with high accuracy in electrical properties ensures it to be a promising tool in the conductive ultrasensing platform. Among various semiconducting metals, silicon is one of the appealing metals used in the synthesis of NW. Silicon nanowire can be easily synthesized and fabricated on sensors via simple lab-based protocols for highly sensitive detection in the diagnosis of cancer cells. As such, silicon NW based biosensors are widely applied in the detection of lung cancer biomarkers due to its high biocompatibility with enzymes and tumor markers. Azimi et al. (2015) conducted a study in monitoring the spreading stage of lung metastatic cells (QUDB) from normal ones (MRC-5) evaluated from the current amplified through electric cell-substrate impendence sensor (ECIS), a microfabricated biosensor for clinical diagnosis. Due to its electrically active elongated and flexible nanostructure, silicon NW were grown on the biosensor using chemical vapor deposition method to amplify electrical interaction in relation to the proliferation of cancerous cells generated by the extension and penetration of cell in comparison with normal cells. Fig. 3B (i) shows the design of electrode of impedance sensor with the image of silicon NW grown in between the electrodes, whereas Fig. 3B (ii), and (iii) reveals the enlarged image of silicon NW. Fig. 3B (iv) show the florescent images of QUDB cells multiplied in the electrode space before and after proliferation stage. Morphology and architecture of doped Si nanowires covered microelectrodes observably enhance the contact area between cells and electrodes which support accurate signal recording from stretched cells (Azimi et al., 2015). Then, silicon NW was incorporated with field effect transistor (FET) where high sensitive and selective multiplexed sensor were generated to detect microRNA (miRNA) − 126 and CEA, lung cancer biomarkers readily expressed in blood serum of lung cancer patient. To enhance the rapid responses of the sensor, polydimethylsiloxane (PDMS) was integrated on the sensing platform and ideal sensor for lung cancer detection was reported by identifying lung cancer biomarkers from the clinical samples. The study has focused on the fabrication of silicon NW using low-cost 'top-down' method. The conventional 'top-down' method such as e-beam lithography requires expensive and complicated step of process in developing thin film of silicon NW. In spite of that, the team succeeded in the fabrication of silicon NW on multiplexed sensor using low-cost 'top-down' method aided by PDMS, creating a smooth fluid-exchange system that rapidly transfer the biomolecules (Zhou et al., 2017). Moreover, FET with silicon NW was reported in the detection of lung cancer through non-invasive breath samples. The results were justified to discriminate and detect the infected lung cancer diseases based on the sensitive and selective examination on volatile organic compounds in the sample. In this work, CVD reactor were used to grow silicon NW at controlled pressure and temperature using vapor-liquid-solid (VLS) principle. The generated NW were deposited on the substrate with spray-coating process resulted in well-aligned NW array. (Haick et al., 2016). Moreover, Wu et al. (2016) developed single titanium oxide and silver NW on the disposable breath sensing tube for simple, non-invasive, point-of-care detection of lung cancer biomarkers in the exhaled breath. Dynamic experiments and simulations were performed to design optimal sensing tube and simultaneously detects the lung cancer biomarker without the influence from temperature and

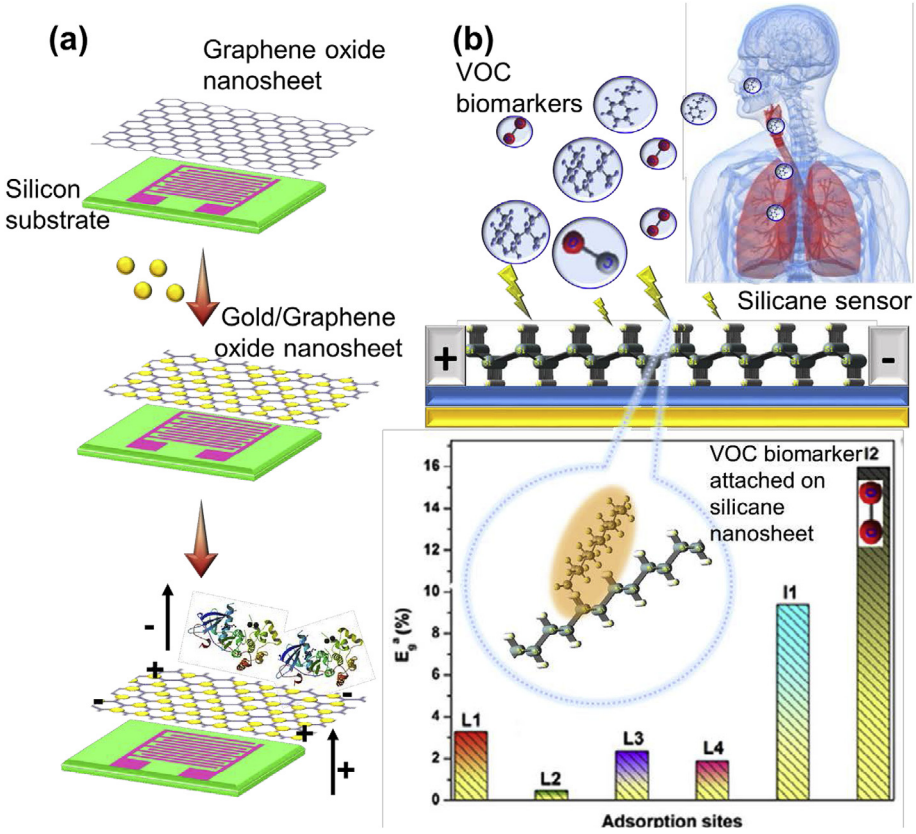

Fig. 4. (a) Schematic illustration below shows the common graphene oxide nanosheet on lung cancer diagnostic biosensor, further coated with GNP for cancer cell protein biomarkers. (b) Detection of VOC biomarkers from breath samples of lung cancer patients using silicane sensor modified with silicon nanosheet. The research were evaluated using bare, hydrogenated silicane and hydrogen vacant silicane nanosheets on sensing surface to determine the excellent VOC absorbing nanosheet for early detection of lung cancer. The graph shows the obtained electrical signal for different VOC biomarkers using hydrogen vacant silicane nanosheets, and it was affirmed that hydrogen vacant silicane nanosheets shows the prominent absorption energy change and significant for early detection of lung cancer. Reproduced with permission from (Nagarajan and Chandiramouli, 2018) Copyright 2018 Elsevier B.V. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

humidity of the flowing gas. Silver NWs are significantly known for its flexible pressure controlling in protein sensing. However, silver NW alone encounters instability when there are conducting current with the presence of high density biomolecules. To resolve that, titanium oxide able to conduct current throughout the entire area of nanowire electrodes. Thus, the study generated gas-sensing tube using titanium oxide and silver NW integrated on the sensing surface via DEP method for the detection of 2-propyl-1-pentanol in exhaled breath of lung cancer patient (Wu et al., 2016).

3.2.3. Nanorods

Nanorods are also known as a remarkable 1D nanomaterial with well-controlled rod-shaped structure in the enhancement of electronic sensing devices. In the midst of many metal nanorods, the gold nanorod is highly recognized as a signal enhancer in nanobiosensing due to the distinctive physical and chemical properties of gold with the 1D structured nanorod. Gold nanorods evidence high compatibility in SPR, which enables it to be precisely synthesized in the desirable SPR band, where efficient biomolecules absorption is achieved (Hayajneh et al., 2018). Further, gold nanorods disclose a high sensitive dielectric platform due to its longitudinal and transverse localized SPR with regard to the biomolecules absorption (Huang et al., 2016). A recent study reported that the efficient fluorescence and absorption properties of gold nanorods were significantly implemented in the detection of cancer cell (HeLa cells) in contrast with normal cells (Vero cells) based on localized SPR fluorescence property at different concentration of cancer cell, normal cells and the mixture of cancerous and normal cells which validates the discrimination shown in fluorescence intensity. The gold nanorod was conjugated with folic acid and further functionalized with a multifunctional optical probe for the imaging of cancer cell through dual detection strategy, fluorescence and colorimetric assay. In this work, gold nanorods were prepared using gold/cetyl trimethylammonium bromide (CTAB) solution, however CTAB coating on gold nanorods induce toxicity and it is non-ideal for in vivo and in vitro diagnosis. Thus, follic acid were conjugated to replace CTAB on gold nanorod and eventually improve the biocompatibility in the detection of malignancy cells (Figure C (i)). The sensitivity of the sensor were affirmed through the linear relation between fluorescence signal and concentration of cancer cells as shown in Figure C (ii) (Yang et al., 2014a). Then, highly selective and as well as sensitive electrochemical biosensor was developed to detect the (CEA) by using gold nanorod as the signal enhancer, which functionalized with a hairpin-shaped oligonucleotide (HO) together with avidin-streptavidin interaction. Aptamer was used as the recognition element in the detection strategy whereas HO functionalized with gold nanorod play role in enhancing the electrochemical signal generated when biotin conjugated aptamer fills the loop portions of streptavidin. The ability of sensor in detecting (CEA) in a human serum sample from lung cancer patients at low detection limit of 1.5 pg/mL justified the accuracy of the chemiluminescenceimmunoassay and the proposed strategy was encouraged for implementing in other DNA-based diseases detection (Huang et al., 2016). Although 1D nanomaterials proven to improve the sensitivity of biosensor based on the referenced work, the 1D longitudinal structure has also claimed to exhibit low and inefficient biomolecule attachment directly on its surface. To resolve such situation and in fact, improve the biomolecule immobilization efficiency, 1D nanostructures are integrated with other nanomaterials, and charged metals to generate 1D nanocomposite with excellent biocompatibility (Shi et al., 2011).

3.3. Two dimensional nanomaterials

Two dimensional (2D) nanomaterials are classified as the great success in the technology of nanoscience and nanomaterials, where layered atomic sheets were discovered with the extraordinary physiochemical properties, which have raised a huge interest in various application and industries. The dual large surface of 2D nanomaterials not only increase the surface area but also creates an uniform platform for biomolecule integrations. 2D nanomaterials appear as layers which are

named as nanosheets, nanoplates, nanoprisms, and nanodisks. Fig. 4a illustrates graphene oxide nanosheet coated with GNP on lung cancer diagnostic biosensor for cancer cell protein biomarkers. 2D nanostructures materials own its characteristics depends on the shape it exhibits and also the component involved in the development of nanolayers (Tiwari et al., 2012). In general, 2D nanostructures are well established as a flexible, versatile and functionalized nanomaterial. The thickness of nanolayer structured in the development of 2D nanomaterial, varies from microscale to nanoscale determines the electronic and structural characteristics of the nanomaterial (Wen et al., 2018). Single or multilayer 2D nanostructures have given a huge interest in the application of sensors, electronic devices, and catalysts, due to its excellent compatibility with biomolecules and organic substances, where the least modification on its nanosurface was required (Zhu et al., 2018a,b.).

3.3.1. Nanosheets

Nanosheets are widely recognized as 2D nanomaterials as the emergence of 2D graphene nanosheet has shown a massive success in sensors and electronic devices. Besides graphene, carbon and metal nanosheets are widely used in the fabrication of sensing platform. The application of 2D nanosheets in lung cancer diagnostics is proven with plenty of research conducted on lung cancer biomarkers. A recent report indicated that $Ti_{0.8}O_2$ nanosheets were capable of suppressing lung cancer stem cell. Titanium oxide (TiO_2) nanosheet empowers semiconducting and dielectric properties in nature, thus chemical functionalization can be easily performed on the surface of negatively charged nanosheets and it is able to be done at microscale or even large scale colloids. A superoxide anion in cancer stem cell is engulfed on the TiO_2 nanosheets which differentiate the cancer cell from the normal lung cell based on electrical induction. TiO_2 nanosheets were synthesized through a series of reaction consist of solid state mixing, proton exchange and exfoliation which was simple and convenient for lab scale production, yet it is also suggested for large scale synthesis of nanoseets (Soonnarong et al., 2019). In another case, tin oxide nanosheets were fabricated on fluorine-doped tin oxide substrate in order to manipulate the hydrophobic and hydrophilic property and the chemical modification of functionalized molecules. A system of photoelectric conversion effect and biomolecule identification strategy were implemented to detect lung cancer cells (Masuda et al., 2012). Further, Masuda et al. (2015) reported that tin oxide (SnO_2) nanosheet was developed by using tin oxide nanoparticles and metal catalyst and introduced non-invasive detection of the lung by taking human breath sampling. The concentration of 1-nonanal gas present in breath were detected by the resistance shown by the sensor enhanced by the crystal SnO_2 nanosheets which accelerates the oxidation rate of non-anal molecules. It has recognized as an effective and simple approach of early diagnosis of lung cancer. (Masuda et al., 2015). Later on, Masuda developed SnO_2 nanosheet based sensor to reveal higher resistance towards human breath in the presence of non-anal gas as lung cancer biomarkers such as ammonia, nitrogen dioxide, formaldehyde, hydrogen sulphide, acetone, or carbon monoxide. However, in this work, Masuda synthesized SnO_2 nanosheet without using SnO_2 nanoparticles, instead the substrate were directly immersed in an aqueous solution containing SnF_2 at 5 mM to generate thin film of SnO_2 nanosheets on the biosensor (Masuda et al., 2019). Based on the researches conducted by team, the prominent evaluation were conducted on the electrical resistance shown by the SnO_2 nanosheets based sensor when it is fabricated with and without the consumption SnO_2 nanoparticles. The results concluded that both devices with SnO_2 nanosheets implies significant sensitivity in the detection of non-anal gas of lung cancer biomarker, just has made differences in the simplicity of method for synthesizing SnO_2 nanosheet coated device. Meanwhile, exhaled breath samples were used for lung cancer biomarkers, volatile organic compounds (VOC) identification via hydrogenated silicone and hydrogen vacant silicane nanosheets. The novel method was acclaimed the early detection of lung cancer with significant parameters such as energy gap, absorption energy and Bader charge transfer. Fig. 4b shows the schematic representation of detecting VOC biomarkers using silicane sensor which was modified with silicon nanosheet. The researcher claimed that 2D nanosheets are much preferred compared to 1D nanomaterial, although both give notable electronic property, yet 2D nanosheets can be easily modified with hydrogen and fluorine through surface passivation technique to improve the absorptions of lung cancer biomarkers (Nagarajan and Chandiramouli, 2018). Recently, double layered magnetic nanosheet was developed using nickel/ferrum (Ni/Fe) hydroxides to detection microRNA present in lung cancer cells. DNA hairpins were generated through the hybridization chain reaction method, which was then separated and immobilized on the surface of Ni/Fe nanosheet to be catalyzed by TMB reaction. A low detection limit at 0.36 fM was attained through the method justifies the simple and inexpensive approach for the efficient lung cancer diagnosis using clinical samples (Chen et al., 2018a).

3.3.2. Nanoplates

Nanoplates is also regarded as a significant signal enhancer in sensing systems, where the colloidal metal nanoparticles are aligned to create a bed-shaped 2D nanostructured with sharp edges. Gold with excellent SPR properties are used in the development of 2D gold nanoplates, which disclose the exceptional dielectric characteristics in sensing element and it could be adjusted by modeling the shape and size of nanoplate through the modification in synthesizing methods, mainly involving SPR based energy sources (Wijaya et al., 2017). Sharp end featured nanoplate is unstable for plasmonic properties, thus reshaping of nanoplates and conjugation of nanoplates with nanostructured metals are mostly preferred to be done to generate highly stable nanoplates against electrical and plasmonic signals (Morsin et al., 2017). In general, nanoplates induce two types of absorption, longitudinal SPR and transverse SPR. The two absorption bands were optimized in the investigation of biosensing with regard to a variety of nanoplates shapes such as, hexagonal, triangular and flat rods for diagnosis of fatal diseases (Lee et al., 2016). Few novel types of research have been reported in recent for lung cancer diagnosis using 2D nanoplates. Triangular gold nanoplate (TGN) was developed by conjugating with P-75 gene sequence, EGFR targeting peptide biomarker to detect NSCLC. In the research, TGN is selected as the signal enhancer due to its effective photothermal conversion and the excellent biocompatibility, because the expression of EGFR mutations in NSCLC was investigation through the near-infrared absorbance band-aided with photoacoustic imaging and computed tomography. TGN were synthesized through direct method of modified seedless process using potassium iodide and cetyltrimethylammonium chloride (CTAC) as cationic surfactants due it its simplicity in generating purified gold nanoplates using CTAB solutions as cationic detergent (Y. Zhao et al., 2018). Besides gold, graphene oxide nanoplates based sensors are significantly recognized in cancer cell diagnosis. Zhang et al. (2016) developed graphene oxide nanoplate functionalized with triple-helix DNA probe for identifying target DNA based on rolling circulation amplification of genetic information. The graphene oxide were prepared through Hummers and Hoffman method, known method for quantities synthesis of graphene oxide with little modification as it fits the biocompatibility for DNA immobilization. The system was reported to detect and visualize the low concentration microRNA present in the targeted cell via fluorescence bright spots in a single tumor cell (Zhang et al., 2016). In another way, the circulation tumor lung cells were also detected through microfluidic device generated by using graphene nanoplates without in its oxide state. The detection strategy works based on the electrical impedance shown by graphene nanoplates spiked with circulation tumor cell in peripheral blood in comparison with normal cells where is it modified to enhance the signal through impedance cytometry indicating the presence of targets in circulating tumor cells (Han and Han, 2015). Apart all the precedence shown by 2D

nanomaterials, there are also few drawbacks revealed by researchers in 2D nanomaterials based biosensors for biomarkers analysis. The major disadvantage is the aggregation of 2D nanosheets/nanoplates during the fabrication of electrode which prominently reducing its cycling stability. One effective way to overcome it is to conjugate 2D nanomaterial with another type of nanomaterial to form hierarchical hybrid and stable nanostructures (Zhang, 2015).

3.4. Three dimensional nanomaterials

To generate a system with extremely large surface area/volume ratio and supreme nanoproperties in contrast to other nanomaterials, the momentous evolution and contribution of three dimensional (3D) nanomaterials in multiple applications are not negligible in the thriving field of nanotechnology. As emphasized earlier, controlled morphology such as shape, size and surface roughness play a key role in the exceptional property of nanomaterials. As such, 3D nanomaterials have shown a great interest in a wide range of application due to the higher surface area which enhances its physiochemical, magnetic, electronic and plasmonic properties according to its morphological structure. In addition, it also facilitates and accelerates the transport of attached biomolecules, which reveal its better performance in drug delivery and diagnosis in pharmaceutical and medicinal applications. With this regard, 3D nanomaterials in the development of biosensor especially in the diagnosis of non-communicable cancer diseases are mostly welcomed due to its extensive absorption, immobilization or area of reaction catalysis for biomolecules and biomarkers. Consequently, the application of 3D nanomaterials based biosensor in the current diagnosis of lung cancer is reviewed. 3D nanomaterials usually appear as nanocluster, nanoflower, nanopillars, nanocone and many other types as long as it exposes three directions nanostructure. Fig. 5A shows the electrical characterization of biosensor functionalized with 3D nanoflower modified with DNA probe for DNA based lung cancer diagnosis.

3.4.1. 3D gold

The most common types of nanomaterial used for the development of 3D nanostructure in the biosensing of lung cancer biomarkers are the mesoporous GNP, as it holds the excellent optical and electrical properties. The implementation of 1D or 2D gold nanostructures reveals less sensitivity and moderately ineffective to SPR because of the asymmetric structure and low sensitive plasmonic coupling effect between the adjacent nanoplates. This will direct apparently small peak shift in the examination of biomolecules which is usually solved by using a large amount of sample. With 3D gold nanostructures, the above limitation could be swamped, in fact it empowers the plasmonic property of metallic gold. In a recent study, quasi 3D gold nanostructure was developed via nanoimprint lithography technique, where it was developed in between gold nanosquares and SU-8 nanopillars at the top and bottom, respectively. The reason behind the nanoimprint techniques is to generate high uniform plasmonic 3D gold nanostructures, which are able to reveal the apparent peak shift in SPR visible spectrum in comparison to 1D and 2D gold nanomaterials, in order to detect the level of A 549 lung cancer cells. The research conducted was justified the high sensitive lung cancer cell detection with large plasmon peak shift at 51 nm for as little as 0.08 cells mm^{-2} of RPE cells for high sensitivity cell detection, indicating the novelty of the research conducted (Zhu et al., 2016). Later on, the research were developed by varying the offset of 3D multilayer gold nanostructure, which has established a low amount lung cancer cell detection at 5E3 cells/ml with only 2 µl of sample volume with the aid of multilayered plasmonic microfluidic sensing system. In relation to the previous study, the 3D plasmonic biosensor modified with 3D gold detects the complementary DNA target at 10^{-14} to 10^{-7} M, giving a significant peak shift in the SPR spectrum without additional signal amplification. (Zhu et al., 2018a). Su et al. (2016) have evolved hierarchical flower-like gold nanostructures, acclaimed as gold nanoflower for the detection of miRNA-21, biomarker from human NSCLC. The system was successfully established with developing the label-free electrochemical modified with 3D gold nanoflower bounded

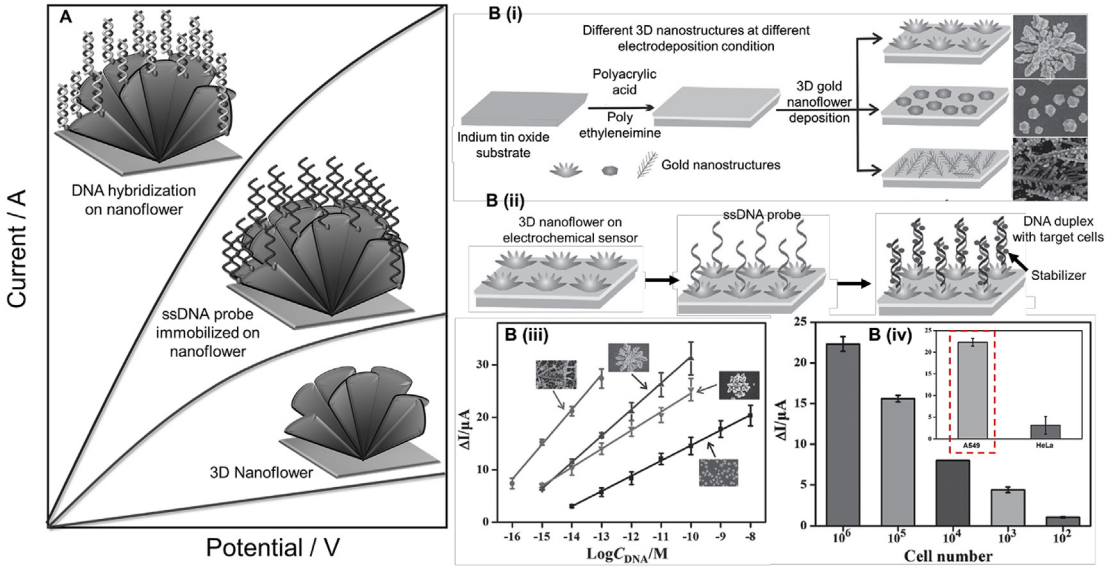

Fig. 5. A. Electrical characterization of biosensor functionalized with 3D nanoflower modified with DNA probe for DNA based lung cancer diagnosis. The reduction in negative charge due to the enclosure of phosphate in single-strand DNA generates significant electron shift which may be transmitted to the conductive electrode through high sensitive 3D nanoflower. The electrochemical signal amplified indicates the detection of the target gene and empowers the diagnostics of high specific cancerous genomes. B. (i) Synthesis of gold nanostructures on indium tin oxide substrate which were coated with polyacrylic acid and polyethyleneimine through electrodeposition techniques where the deposition time, deposition potential, concentration and compositions of electrolyte were varied to generate different structures of 3D gold on electrochemical biosensor. (ii) The detection strategy of A549 lung cancer cell through miRNA-21. ssDNA strand were immobilized on 3D gold nanostructures modified electrochemical biosensor and target DNA strands were immobilized to identify the intensity of DNA duplex formation using electric potential. (iii) Electric potential amplified by four typical gold nanostructures with different morphologies. (iv) Electrochemical signal of 3D gold nanostructured-based electrochemical biosensor for detection of miRNA-21 extracted from A549 cell at different concentrations. Reproduced with permission from (Su et al., 2016) Copyright 2016 WILEY-VCH. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

miRNA/DNA strands that track and detects the target miRNA-21 with a low detection limit of 1 fM. Fig. 5B shows the detection strategy implemented to detect lung cancer targets using 3D gold nanostructures at shapes generated at various electrodeposition condition using an electrochemical biosensor. The study implemented electrochemical deposition method for the fabrication of hierarchical flower-like gold nanostructures by controlling different parameters such as deposition time, deposition potential, concentration and compositions of electrolyte (Su et al., 2016).

3.4.2. 3D graphene

Structured by carbon atoms, which exposes the largest surface among all the existing nanomaterials. However, 2D graphene has exclaimed the low thermodynamic stability in the contact of different materials, influenced by its charge carried in its electronic band structure. In that case, graphene was meant to be conjugated with various nanomaterials to generate 3D graphene, which is highly useful in the engineering of nanobiosensors (Suvarnaphaet and Pechprasarn, 2017). Hence, graphene on biosensors is generally existed in the state of nanocomposites for advanced sensitivity of sensing surface.

4. Nanocomposites in multi-dimension on biosensors for lung cancer diagnosis

As it is well known, nanomaterials at multiple dimension with very specific physiochemical properties are widely used in the invention of biosensors especially for cancer diagnosis. However, independent nanomaterials intermittently show low sensitivity, and selectivity with certain intermediates due to the surface poisoning, and distinction of physiochemical properties. Thus, nanocomposites made up of more than one material, was acknowledged where at least one of it is in nanoscale structure. The dimension of nanocomposites purely depends on the type of discrete nanomaterials used to create the nanocomposites. In the current technology of lung cancer diagnosis, nanocomposites based biosensors are significantly used with respect to the type of biomarkers and the extent of biocompatibility, consequently eliminate the limitation inherited from non-nanocomposites (Shrivastava et al., 2016).

4.1. Graphene-gold nanocomposites

Usually graphene with many defects at its discrete state is a hurdle in enhancing the efficiency of the biosensor. Intensive efforts have been taken into the application of graphene and its composition in conjunction with other metals/elements to improve the sensing performance. In this regard, nanoporous gold particles with its excellent properties have always been a highly recognized metal to be conjugated with graphene to generate graphene-gold nanocomposites. It is widely reported in the application of biosensor to diagnosis lung cancer. Zeng et al. (2018) reported that 3D graphene-modified gold nanocomposites were immobilized on the carbon electrode to enhance the electrochemical detection of immunosensor to diagnose CYFRA21-1. The cross-linking of anti-CYFRA21-1 on the nanocomposites was strengthened using chitosan and glutaraldehyde. Graphene oxide were prepared using conventional Hummer's method, then it was mixed with chloroauric acid where the mixture were ultrasonicated to generate graphene gold nanocomposite in gel form. It was then drop casted on carbon electrode and proceeded for immunosensing. Graphene gold nanocomposite-modified immunosensor neglects the interferences aroused from a complex mixture of CEA, bovine serum albumin, ascorbic acid, dopamine and uric acid and giving a low detection limit at 100 pg mL^{-1} (Zeng et al., 2018). When the attention in diagnosing small-cell lung carcinoma was evoked, a wireless point of care system with multiple analyzers was generated to detect NSE biomarker. The immunosensor was modified with 3D graphene-gold nanocomposites and thionine was added to enhance the cross-linking. Graphene plates was chosen due to its good electrical conductivity and ability in accelerating electron transfer whereas GNP were chosen due to its biocompatibility, high tolerance in biological environment and ability in amplifying electrical signal. Thionine was used electroactive activator and strengthen the chemical interaction between the nanocomposite and substrate. The finding of the work resulted that the wireless immunosensing device attained significant limit of detection of 10 pg mL^{-1} which emphasizes the potential for on-site lung cancer diagnosis (Xu et al., 2017). Additionally, graphene disulfide where modified with dendritic GNP to improve the signal enhancement on the double determination of two different genomes inferred from long non-coding RNA using electrochemical genosensor. The selectivity of genosensor has been justified through the low limit of detection of different sequences using the real samples encourages the application of the genosensor in the clinical diagnosis of lung cancer (Li et al., 2018).

4.2. Graphene-mediated nanocomposite

Apart from gold, conducting metals and polymers has performed its significant role in conjunction with graphene to develop a high sensitive biosensor for lung cancer diagnosis. Label-free biosensor for the detection of NSE for NSCLC was developed by a 3D macroporous film of reduced graphene oxide and polyaniline (PANI) on silica-gold sensing plate. The tendency of pure graphene oxide in self-agglomeration on the sensing surface is one of the major problem to be resolved. On the other hand, PANI as semiconductive polymer acts as an electroactive probe in the sensing of NSE, in addition increase the distribution of graphene-PANI nanocomposite to facilitate the immobilization of biomolecules and amplify electrical signal. With reduced graphene oxide, the nanocomposites were found to improve the selectivity and stability of immunosensor (Zhang et al., 2018). Moreover, graphene nanocomposites with polymer and metal oxide were studied due to the ability to control the morphology and induce tuning effect on the nanomaterials, respectively (Taniselass et al., 2019). With this regard, in recent study, 3D graphene nanoplates with titanium oxide and shrink polymer were generated through self-assemble technique to control the components and morphology, respectively. The implementation of the tuning effect after the deposition of nanocomposites on biosensors has improved the efficiency of the sensor and fosters its application in diagnosis of cancerous diseases. Fig. 6A shows the process of developing shrink induced layered graphene incorporated with titanium oxide nanoparticle in between the graphene layer and the sensitivity of biosensor with each modifications of nanocomposites (Li et al., 2015). Moreover, Chen et al., 2018a,b,c developed 3D electrochemical DNA biosensor for the detection of CYFRA21-1 using 3D graphene-modified with silver nanoparticles (AgNPs). The research claimed that 2D graphene sheets suffer from low conductivity due to its high junction contact resistance and poor quality. Conversely, 3D graphene generated using CVD technique shows no or least junction resistance which empowers its electrical conductivity. AgNPs, owning its exceptional property were integrated with 3D graphene to improve biocompatibility of DNA hybridization and facilitate electron transfer. The improved biocompatibility and electron transfer were justified due to the graphene-AgNP nanocomposites, where attained the low detection limit of 1.0×10^{-14} M of target DNA (Chen et al., 2018c). In a recent study, Shoja et al. (2018) demonstrated the electropolymerized sensing platform for the detection of EGFR exon 21 point mutation using the reduced graphene oxide functionalized with mesoporous carbon and Ni (II)-oxytetracycline, a conducting metallopolymer nanoparticles on pencil graphite electrode. Nanocomposite made up of reduced graphene oxide, carbon and Ni(II)-oxytetracycline were prepared through a series of chemical reactions and it was drop casted on graphite electrode of electrochemical biosensor. Excellent thermal and electrical conductivity were exhibited from the detection strategy due to the polymerized graphene nanocomposite (Shoja et al., 2018).

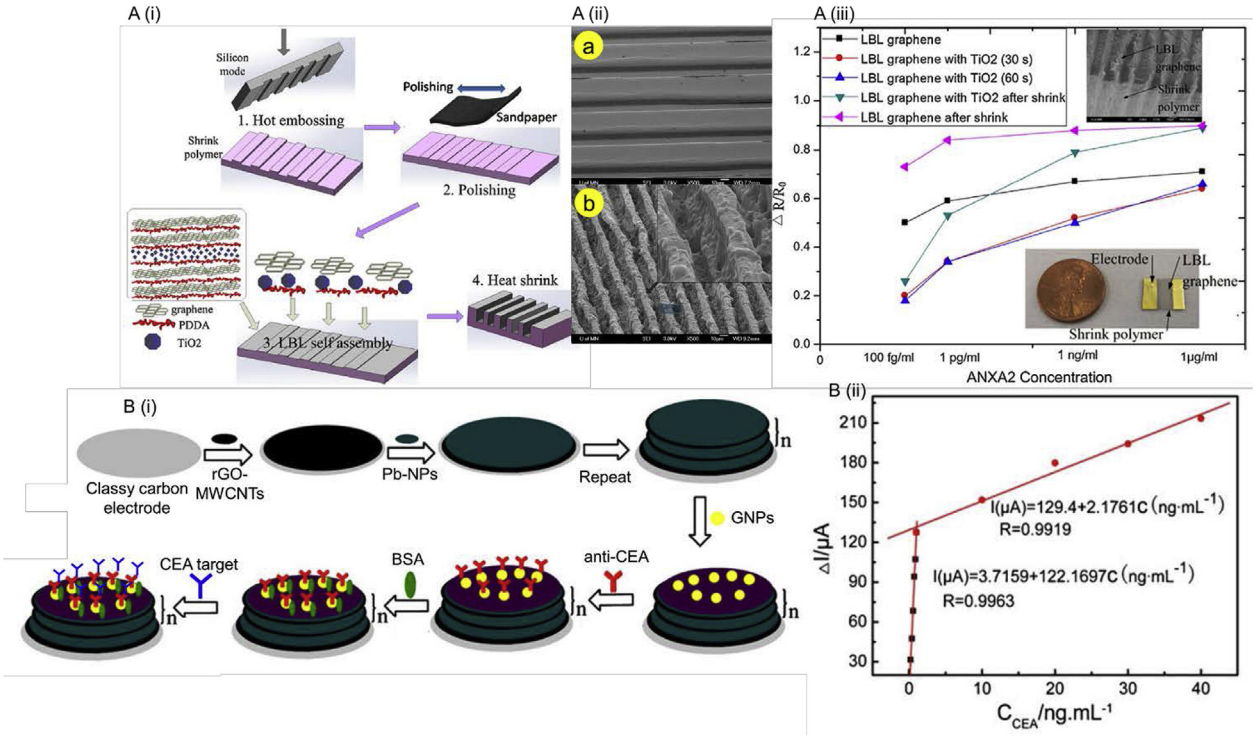

Fig. 6. A (i) The schematic diagram shows the process of developing shrink layered graphene biosensor where layered graphene assembled with titanium oxide nanoparticles were deposited on silicon substrate modified with polymer which was then allowed to shrink through heat energy. A (ii) SEM image of microchannel array on biosensor a. before and b. after heat shrink. (iii) The graph shows the sensitivity of biosensor as the resistance ($\Delta R/R_0$) increases and the titanium oxide nanoparticle stabilizes the biosensor for lung cancer detection at different concentration and with repeatability experimentations. Reproduced with permission from (Li et al., 2015) Copyright 2015 Elsevier B.V. B (i) The schematic representation shows the development of electrochemical immunosensor and the detection strategy to investigate the interaction between CEA antigen and antibody. Reduced graphene oxide-multi-walled CNT (rGO-MWCNT) were assembled on glassy carbon electrode in multiple layers whereas Pb nanoparticles were deposited in between the rGO-MWCNT layers. GNP were conjugated on the surface of nanocomposite for the immobilization of anti-CEA. The surface were vlocked with BSA to prevent non-specific binding and investigated for CEA target detection. (ii) The graph shows calibration plots of the peak current (ΔI) at different antigen concentration, measured through the differential voltammograms potential. Reproduced with permission from (Feng et al., 2013) Copyright 2013 RSC pubs. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4.3. Gold-mediated nanocomposites

Gold nanocomposites are commonly made of gold with metal nanoparticles. Surface-enhanced Raman scattering (SERS) is the most recognized detection strategy for lung cancer diagnosis using gold nanocomposites based biosensors. Rong et al. (2016) conducted research on gold nanorods modified with thin-shelled AgNPs functionalized on the SERS substrate to detect CEA lung cancer biomarker. The integration of gold nanorods and AgNPs creates a 3D nanostar structure of the composite which enhances the surface of sensor with near-infrared plasmon. The detection strategy demonstrates the sandwich immune complexes and plasmonic coupling between the functionalized nanocomposites, which amplifies the signal on the SERS substrate (Rong et al., 2016). Then, Ma et al. (2018) have evidenced the detection of exosomal miRNA, NSCLC biomarker using SERS signal amplification through gold-silver nanocomposites on silicon microbead substrate. The GNP were encapsulated in silver shells, conjugated with target DNA immobilized on the probe and immobilized on silicon microbeads. The researcher explained that the main reason for selecting gold-silver-silicon combination for the study is to generate a stable and efficient platform for SERS intensity and amplifying the signal, consequently improves the sensitivity of sensor. 5 fM detection limit attained from the study justified the high sensitivity of the sensor (Ma et al., 2018). In another study, adenosine, a possible biomarker for lung cancer diagnosis was detected through urine samples of lung cancer patients and healthy patients. SERS sensing array was developed and enhanced with the iron oxide/gold/silver nanocomposites to examine the trace state of adenosine in urine samples using a portable Raman. Chemical co-precipitation technique was used to synthesis the nanocomposite and stabilized by IP6, where a series of chemical mixing, precipitation and purification processes were done to obtain crystalline nanocomposite (Yang et al., 2014b). Moreover, the NSCLC was detected through progastrin-releasing peptide (ProGRP) as it is recognized as the treasured substitute for NSE. ProGRP was detected electrochemical immunosensor modified with titanium (IV) oxide-gold nanocomposite. The nanocomposite was prepared with the use of chitosan as eco-friendly stabilizing and reducing agent. The research reported a highly sensitive immunosensor were achieved due to the plenty of potential site on the large surface area of nanocomposite (Wei et al., 2017).

4.4. Carbon-mediated nanocomposites

Last but not least, carbon nanocomposites has shown an attractive approach in improving the biosensor performance for lung cancer diagnosis. The common carbon nanocomposites stand from zero-dimensional carbon nanosphere and 2D CNTs with single and multi-walled nanostructures incorporated with a variety of metals/nanoelements. A glassy carbon electrode sensing surface was modified with carbon nanotube with Prussian blue (PB) and graphene appeared in multilayer thin films. Further, GNP were allowed to be absorbed on the nanocomposite thin film, where the antibody for CEA was immobilized. PB is an excellent candidate as redox mediator and widely used in electrochemical sensor. However, it poses few limitations such as leaking of PB on electrode surface which decreases the stability of PB film and thus,

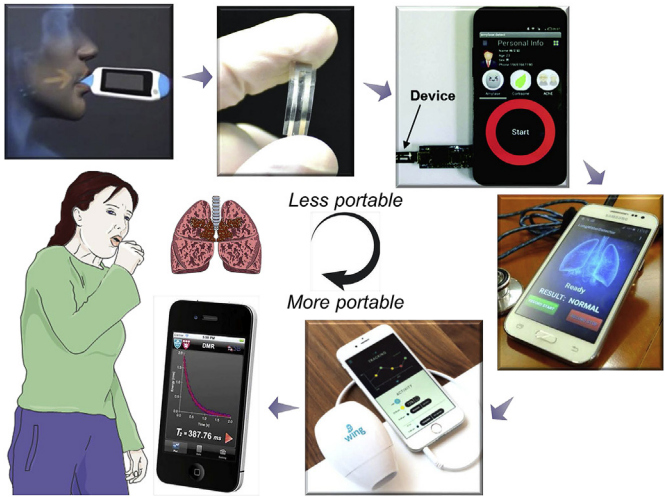

Fig. 7. Modern diagnostic tools from less portable to more portable with the aid of advanced digital smartphones for instantaneous lung cancer diagnostics through non-invasive clinical sampling. Less portable diagnostic tools require effort for sampling through portable devices which are in need of appropriate handling and packaging and then undergoes analysis for cancer diagnosis. However, more portable toolkits omit the sampling procedure using devices and highly competent to perform advanced analysis through a smartphone or other readout gadgets resulting in a rapid diagnosis of lung cancer.

reduces the sensor's efficiency. Feng and co-workers resolve the limitation with the use of assembly of reduced graphene and CNT with PB nanoparticle through the method of electrodeposition, as the possible leakage was reduced with the appropriate framework of nanocomposite and thus maintains the sensor's stability. GNPs were used only to immobilize CEA antibody and increase SPR intensity. Fig. 6B indicates the development of electrochemical immunosensor and the detection strategy to investigate the interaction between CEA antigen and antibody. The constructed biosensor modified with nanocomposites resulted with a detection limit of 60 pg mL^{-1} of CEA antigen. The electrochemical immunosensor were tested with clinical samples which have shown a great agreement with the analyzed clinical data. (Feng et al., 2013). Then, single-walled CNTs were modified with chitosan and it deposited on graphite electrodes to detect anti-MAGE A2 and anti-MAGE A11 lung cancer biomarkers. Chitosan modified CNT was prepared from the process of ultrasonication and agitation and it was deposited on immunoelectrode through drop casting method. Chemical modifications were performed on biomarker with amine-carboxyl interaction aided by EDC-NHS chemical activator, to enhance immobilization of antibody on electrode surface. Differential pulse voltammetry (DPV) was used to detect the simultaneous detection of two antigens with high specificity and sensitivity (Choudhary et al., 2014). Liu et al. (2015a,b) generated layer by layer oxidized single-walled CNT modified with GNPs to detect miRNA of lung cancer cells. Then, probes were immobilized on the GNPs. The electrochemical signal generated was recorded with DPV measurements, and researcher claimed that the GNPs attached on CNT play the significant role and chosen to improve acquirement of DPV readings. The electrochemical signal was amplified from the hybridization reaction, where low detection limit with 1.95 fM was attained (Liu et al., 2015a). In a recent study, Zhang et al. (2019) developed an electrochemical cytosensor for detection of A549 cell line, NSCLC biomarker. 3D nanostructured carbon nanosphere-gold nanocomposite was synthesized and placed on chitosan thin film, then functionalized on the glassy carbon electrode. In this work, the monodisperse carbon nanosphere was synthesized using microwave hydrothermal method and then assembled with GNPs, results in 3D structure of nanocomposite. The synergic effect of the nanocomposites was perceived through the voltammetry signal transduced from the electrode and the significant sensitivity in recognizing target cells (Zhang et al., 2019).

5. Clinical preference for lung cancer diagnosis

Advantages from the recent nanobiotechnology, therapeutics of lung cancer has greatly improved. It has proven by the patient's survival period after the first diagnosis. However, the recognition of lung cancer in human is still inefficient in contrast with the advanced therapeutics of lung cancer treatments. Moreover, poor diagnosis with the point-of-care clinical sampling is highly in need of service and commercial application especially at rural areas is extremely disappointing. Nanomaterials-based biosensors for lung cancer detection hasn't commercialized to date due to several unsolved challenges, mainly in giving the best production and quality of nanomaterial or nanocomposites synthesis, excellent surface functionalization of nanomaterial on the biosensor, the best electronic device for clinical and point-of-care lung cancer diagnosis. It is indeed disappointing in knowing the inability to solve the challenges and sadly the extreme benefits of nanomaterials and its composites is yet to be utilized for commercial lung cancer diagnostics.

In the recent diagnostics of cancerous cells, there are few demands in the approach to developing the commercial biosensor including point-of-care diagnosis, exclusive of invasive clinical sampling, quick read-out sensor, light and portable and interconnected digital telecommunications. Nanomaterials and nanocomposites with multidimensional nanostructures are extremely correlated in accomplishing the above demands. Nanomaterials with numerous synthesizing methods are introduced in accordance with its relevant field of application such as electronic, medical or food industries. Thus, to develop a biosensor for non-invasive clinical sampling in the new era of lung cancer screening, nanomaterials are recommended to be applied in transforming the electrical signal from the sensor to a portable digital analyzer. As shown in Fig. 7, non-invasive clinical lung cancer diagnosis using sensors originated by using lab-on-chip, where the exhaled breath of lung cancer patients was collected and analyzed using an adapter connected to smart-phones. To improve the accuracy without the influence of external factors, clinical sampling analysis connected to the digital software without an adapter is in demand. The system is expected to be implemented in real-time application connected to quick read-out software installed in a smart-phone. The new era of lung cancer screening excludes the lengthy diagnostics procedures and a longer time is taken to interpret the sample, but develops a cost-effective, simple diagnostic procedure and immediate real-time results displaying system as it directs the path to the instantaneous point of care diagnostics and therapeutics.

6. Conclusion

Lung cancer is the most dreadful non-communicable disease which kills the highest number of human on earth. Although significant diagnostic strategies have been advanced in the detection and therapeutics of lung cancer, an insight inquisition is required since the statistics of lung cancer death has never reduced. Addressing the current circumstances in the development of cancer diagnosing biosensor, nanomaterials with various dimensions in their discrete and composite nanostructures have a huge interest in the lung cancer imaging due to the specific novelty reflected by its each differential dimension. The transition of zero to 3D nanomaterials in the technology of lung cancer diagnostics are well-presented based on the recent researches conducted to develop an ideal biosensor. Besides discrete, biocompatibility of nanocomposites comprises in various dimensions on the biosensing surface were reported. Based on the literature and its unsolved obstacles, future preference on the clinical lung cancer diagnosis through non-invasive sampling and real-time displaying with the advanced technology of digital telecommunication were discussed. Integrating nanomaterials and biosensors might be advanced, however, the effort

to generate a clinical non-invasive point of care and instantaneous biosensor with excellent specificity and sensitivity is still hasn't met the ideal application. This review revealed the interpretation of multi-dimensional nanomaterials on a biosensor in term of recognizing biomarkers and improving its electrical property which has specified a designated direction in the current and future technology of lung cancer diagnosis.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Azimi, S., Gharooni, M., Ali Hosseini, S., Janmaleki, M., Hosseini, M., Mohajerzadeh, S., Abdolahad, M., Abiri, H., 2015. Monitoring the spreading stage of lung cells by silicon nanowire electrical cell impedance sensor for cancer detection purposes. Biosens. Bioelectron. 68, 577–585. https://doi.org/10.1016/j.bios.2015.01.057.

Baldo, S., Buccheri, S., Ballo, A., Camarda, M., La Magna, A., Castagna, M.E., Romano, A., Iannazzo, D., Di Raimondo, F., Neri, G., Scalese, S., 2016. Carbon nanotube-based sensing devices for human Arginase-1 detection. Sens. Bio-Sens. Res. 7, 168–173. https://doi.org/10.1016/j.sbsr.2015.11.011.

Boloker, G., Wang, C., Zhang, J., 2018. Updated statistics of lung and bronchus cancer in United States (2018). J. Thorac. Dis. 10, 1158–1161. https://doi.org/10.21037/jtd.2018.03.15.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Canc. J. Clin. 68, 394–424. https://doi.org/10.3322/caac.21492.

Chen, K.-Z., Lou, F., Yang, F., Zhang, J.-B., Ye, H., Chen, W., Guan, T., Zhao, M.-Y., Su, X.-X., Shi, R., Jones, L., Huang, X.F., Chen, S.-Y., Wang, J., 2016. Circulating tumor DNA detection in early-stage non-small cell lung cancer patients by targeted sequencing. Sci. Rep. 6, 31985. https://doi.org/10.1038/srep31985.

Chen, Z., Liang, R., Guo, X., Liang, J., Deng, Q., Li, M., 2017. Simultaneous quantitation of cytokeratin-19 fragment and carcinoembryonic antigen in human serum via quantum dot-doped nanoparticles. Biosens. Bioelectron. 91, 60–65. https://doi.org/10.1016/j.bios.2016.12.036.

Chen, Chengbo, Yang, T., Xia, D., Tang, S., Sun, J., Chen, L., Shen, W., Mao, W., Qi, T., Li, Y., 2018a. Magnetic Ni/Fe layered double hydroxide nanosheets as enhancer for DNA hairpin sensitive detection of miRNA. Talanta 187, 265–271. https://doi.org/10.1016/j.talanta.2018.05.037.

Chen, Chao, Zhang, M., Li, C., Xie, Y., Fei, J., 2018b. Switched voltammetric determination of ractopamine by using a temperature-responsive sensing film. Microchimica Acta 2, 185.

Chen, M., Wang, Y., Su, H., Mao, L., Jiang, X., Zhang, T., Dai, X., 2018c. Three-dimensional electrochemical DNA biosensor based on 3D graphene-Ag nanoparticles for sensitive detection of CYFRA21-1 in non-small cell lung cancer. Sensor. Actuator. B Chem. 255, 2910–2918. https://doi.org/10.1016/j.snb.2017.09.111.

Choudhary, M., Singh, A., Kaur, S., Arora, K., 2014. Enhancing lung cancer diagnosis: electrochemical simultaneous bianalyte immunosensing using carbon nanotubes–chitosan nanocomposite. Appl. Biochem. Biotechnol. 174, 1188–1200. https://doi.org/10.1007/s12010-014-1020-1.

Chueng, S.-T.D., Yang, L., Zhang, Y., Lee, K.-B., 2016. Multidimensional nanomaterials for the control of stem cell fate. Nano Converg. 3. https://doi.org/10.1186/s40580-016-0083-9.

Cryer, A.M., Thorley, A.J., 2019. Nanotechnology in the diagnosis and treatment of lung cancer. Pharmacol. Therapeut. 198, 189–205. https://doi.org/10.1016/j.pharmthera.2019.02.010.

Dai, Q., 2015. CaCO 3/CaIP 6 composite nanoparticles effectively deliver AKT1 small interfering RNA to inhibit human breast cancer growth. Int. J. Nanomed. 10, 4255–4266.

Farka, Z., Juřík, T., Kovář, D., Trnková, L., Skládal, P., 2017. Nanoparticle-based immunochemical biosensors and assays: recent advances and challenges. Chem. Rev. 117, 9973–10042. https://doi.org/10.1021/acs.chemrev.7b00037.

Feng, D., Lu, X., Dong, X., Ling, Y., Zhang, Y., 2013. Label-free electrochemical immunosensor for the carcinoembryonic antigen using a glassy carbon electrode modified with electrodeposited Prussian Blue, a graphene and carbon nanotube assembly and an antibody immobilized on gold nanoparticles. Microchimica Acta 180, 767–774. https://doi.org/10.1007/s00604-013-0985-8.

Goryacheva, I.Y., Mishra, P.K., Bhargava, A., Shandilya, R., Tiwari, R., Bunkar, N., 2019. Nanobiosensors: point-of-care approaches for cancer diagnostics. Biosens. Bioelectron. 130, 147–165. https://doi.org/10.1016/j.bios.2019.01.034.

Haick, H., Davies, M.P.A., Leja, M., Shehada, N., Johnson, D.W., Cancilla, J.C., Brönstrup, G., Pariente, E.S., Christiansen, S., Liran, O., Peled, N., Torrecilla, J.S., 2016. Silicon nanowire sensors enable diagnosis of patients via exhaled breath. ACS Nano 10, 7047–7057. https://doi.org/10.1021/acsnano.6b03127.

Han, S.I., Han, K.H., 2015. Electrical detection method for circulating tumor cells using graphene nanoplates. Anal. Chem. 87, 10585–10592. https://doi.org/10.1021/acs.analchem.5b03147.

Han, H.S., Lim, S.N., An, J.Y., Lee, K.M., Choe, K.H., Lee, K.H., Kim, S.T., Son, S.M., Choi, S.Y., Lee, H.C., Lee, O.J., 2012. Detection of EGFR mutation status in lung adenocarcinoma specimens with different proportions of tumor cells using two methods of differential sensitivity. J. Thorac. Oncol. 7, 355–364. https://doi.org/10.1097/JTO.0b013e31823c4c1b.

Hayajneh, R.H., Al-Rawi, O.F., Alhamdan, I.R., Oweis, R.J., Alabed, R.A., Al-Fandi, M.G., Alshraiedeh, N.H., 2018. Direct electrochemical bacterial sensor using ZnO nanorods disposable electrode. Sens. Rev. 38, 326–334. https://doi.org/10.1108/sr-06-2017-0117.

He, D., Wang, D., Quan, W., Yu, C., 2016. Functional quantum dots for promising cancer diagnosis and therapy. Int. J. Nanomed. Nanosurg. 1, 1–6. https://doi.org/10.16966/2470-3206.103.

Holzinger, M., Le Goff, A., Cosnier, S., 2014. Nanomaterials for biosensing applications: a review. Front. Chem. 2, 1–10. https://doi.org/10.3389/fchem.2014.00063.

Hu, J., Zhang, Z., Wen, C., Tang, M., Wu, L., Liu, C., Zhu, L., Pang, D., Hu, J., Zhang, Z., Wen, C., Tang, M., Wu, L., Liu, C., Zhu, L., 2016. Sensitive and quantitative detection of C-reaction protein based on immunofluorescent nanospheres coupled with lateral flow test strip. Anal. Chem. 88, 6577–6584. https://doi.org/10.1021/acs.analchem.6b01427.

Huang, J.-Y., Zhao, Y.-D., Wang, S.-F., Bao, T., Zhou, J., Xia, H.-X., Zhang, X.-H., Wen, W., 2016. Increased electrocatalyzed performance through hairpin oligonucleotide aptamer-functionalized gold nanorods labels and graphene-streptavidin nanomatrix: highly selective and sensitive electrochemical biosensor of carcinoembryonic antigen. Biosens. Bioelectron. 83, 142–148. https://doi.org/10.1016/j.bios.2016.04.039.

Jing, F., Jin, Q., Zhai, W., Mao, H., Wu, S., Liu, L., Zhao, J., Zhang, H., Jia, C., Li, G., 2016. Multiplexed detection of lung cancer biomarkers based on quantum dots and microbeads. Talanta 156–157, 48–54. https://doi.org/10.1016/j.talanta.2016.05.005.

Lee, Y., Park, I.-K., Nurunnabi, M., Nafiujjaman, M., Lee, S.-J., Huh, K.M., 2016. Preparation of ultra-thin hexagonal boron nitride nanoplates for cancer cell imaging and neurotransmitter sensing. Chem. Commun. 52, 6146–6149. https://doi.org/10.1039/c5cc10650h.

Letchumanan, I., Gopinath, C.B., Arshad, S., Anbu, M.K.M., Anbu, P., Lakshmipriyae, T., 2019a. Gold nano-urchin integrated label-free amperometric aptasensing human blood clotting factor IX: a prognosticative approach for “Royal disease.”. Biosens. Bioelectron. 131, 128–135.

Letchumanan, I., Md Arshad, M.K., Balakrishnan, S.R., Gopinath, S.C.B., 2019b. Gold-nanorod enhances dielectric voltammetry detection of c-reactive protein: a predictive strategy for cardiac failure. Biosens. Bioelectron. 130, 40–47. https://doi.org/10.1016/j.bios.2019.01.042.

Li, J., Li, S., Yang, F., 2012. Electrochemical biosensors for cancer biomarker detection. Electroanalysis 24, 2213–2229. https://doi.org/10.1002/elan.201200447.

Li, P., Zhang, B., Cui, T., 2015. TiO2 and shrink induced tunable nano self-assembled graphene composites for label free biosensors. Sensor. Actuator. B Chem. 216, 337–342. https://doi.org/10.1016/j.snb.2015.03.111.

Li, X., Peng, G., Cui, F., Qiu, Q., Chen, X., Huang, H., 2018. Double determination of long noncoding RNAs from lung cancer via multi-amplified electrochemical genosensor at sub-femtomole level. Biosens. Bioelectron. 113, 116–123. https://doi.org/10.1016/j.bios.2018.04.062.

Liu, L., Song, C., Zhang, Z., Yang, J., Zhou, L., Zhang, X., Xie, G., 2015a. Ultrasensitive electrochemical detection of microRNA-21 combining layered nanostructure of oxidized single-walled carbon nanotubes and nanodiamonds by hybridization chain reaction. Biosens. Bioelectron. 70, 351–357. https://doi.org/10.1016/j.bios.2015.03.051.

Liu, Q., Yin, S., Soo, R.A., Kyoung, M., Shin, Y., 2015b. A rapid MZI-IDA sensor system for EGFR mutation testing in non-small cell lung cancer (NSCLC). Biosens. Bioelectron. 74, 865–871. https://doi.org/10.1016/j.bios.2015.07.055.

Liu, L., Wu, S., Jing, F., Zhou, H., Jia, C., Li, G., 2016. Bead-based microarray immunoassay for lung cancer biomarkers using quantum dots as labels. Biosens. Bioelectron. 80, 300–306. https://doi.org/10.1016/j.bios.2016.01.084.

Ma, D., Huang, C., Zheng, J., Tang, J., Li, J., Yang, J., Yang, R., 2018. Quantitative detection of exosomal microRNA extracted from human blood based on surface-enhanced Raman scattering. Biosens. Bioelectron. 101, 167–173. https://doi.org/10.1016/j.bios.2017.08.062.

Mandal, D., Nunna, B.B., Zhuang, S., Rakshit, S., Lee, E.S., 2018. Carbon nanotubes based biosensor for detection of cancer antigens (CA-125) under shear flow condition. Nano-Struc. Nano-Obj. 15, 180–185. https://doi.org/10.1016/j.nanoso.2017.09.013.

Masuda, Y., Ohji, T., Kato, K., 2012. Tin oxide nanosheet assembly for hydrophobic/hydrophilic coating and cancer sensing. ACS Appl. Mater. Interfaces 4, 1666–1674. https://doi.org/10.1021/am201811x.

Masuda, Y., Itoh, T., Shin, W., Kato, K., 2015. SnO2 nanosheet/nanoparticle detector for the sensing of 1-nonanal gas produced by lung cancer. Sci. Rep. 5, 1–7. https://doi.org/10.1038/srep10122.

Masuda, Y., Kato, K., Kida, M., Otsuka, J., 2019. Selective nonanal molecular recognition with SnO2 nanosheets for lung cancer sensor. Int. J. Appl. Ceram. Technol. 3, 0–2. https://doi.org/10.1111/ijac.13154.

Meng, L.L., Song, T.T., Mao, X., 2017. Novel immunochromatographic assay on cotton thread based on carbon nanotubes reporter probe. Talanta 167, 379–384. https://doi.org/10.1016/j.talanta.2017.02.023.

Morsin, M., Salleh, M.M., Umar, A.A., Sahdan, M.Z., 2017. Gold nanoplates for a localized surface plasmon resonance-based boric acid sensor. Sensors 17, 1–9. https://doi.org/10.3390/s17050947.
Nagarajan, V., Chandiramouli, R., 2018. Novel method to detect the lung cancer biomarker volatiles using hydrogen vacant silicane nanosheets: a DFT investigation. Comput. Theor. Chem. 1138, 107–116. https://doi.org/10.1016/j.comptc.2018.06.008.
Pasinszki, T., Krebsz, M., Tung, T.T., Losic, D., 2017. Carbon nanomaterial based biosensors for non-invasive detection of cancer and disease biomarkers for clinical diagnosis. Sensors (Switzerland) 17, 1–32. https://doi.org/10.3390/s17081919.
Patel, S., Nanda, R., Sahoo, S., Mohapatra, E., 2016. Biosensors in health care: the milestones achieved in their development towards lab-on-chip-analysis. Biochem. Res. Int. 1–12 2016. https://doi.org/10.1155/2016/3130469.
Peng, G., Tisch, U., Adams, O., Hakim, M., Shehada, N., Broza, Y.Y., Billan, S., Abdah-Bortnyak, R., Kuten, A., Haick, H., 2009. Diagnosing lung cancer in exhaled breath using gold nanoparticles. Nat. Nanotechnol. 4, 669–673. https://doi.org/10.1038/nnano.2009.235.
Pohanka, M., 2019. Biosensors and bioassays based on lipases, principles and applications, a review. Molecules 24, 616. https://doi.org/10.3390/molecules24030616.
Quesada-González, D., Merkoçi, A., 2018. Nanomaterial-based devices for point-of-care diagnostic applications. Chem. Soc. Rev. 47, 4697–4709. https://doi.org/10.1039/c7cs00837f.
Rong, Z., Wang, C., Wang, J., Wang, D., Xiao, R., Wang, S., 2016. Magnetic immunoassay for cancer biomarker detection based on surface-enhanced resonance Raman scattering from coupled plasmonic nanostructures. Biosens. Bioelectron. 84, 15–21. https://doi.org/10.1016/j.bios.2016.04.006.
Sanginario, A., Miccoli, B., Demarchi, D., 2017. Carbon nanotubes as an effective opportunity for cancer diagnosis and treatment. Biosensors 7, 1–23. https://doi.org/10.3390/bios7010009.
Shi, Y., Lawford, P., Hose, R., 2011. Review of zero-D and 1-D models of blood flow in the cardiovascular system. Biomed. Eng. Online 10. https://doi.org/10.1186/1475-925X-10-33.
Shoja, Y., Kermanpur, A., Karimzadeh, F., 2018. Diagnosis of EGFR exon21 L858R point mutation as lung cancer biomarker by electrochemical DNA biosensor based on reduced graphene oxide/functionalized ordered mesoporous carbon/Ni-oxytetracycline metallopolymer nanoparticles modified pencil graphite elec. Biosens. Bioelectron. 113, 108–115. https://doi.org/10.1016/j.bios.2018.04.013.
Shrivastava, S., Jadon, N., Jain, R., 2016. Next-generation polymer nanocomposite-based electrochemical sensors and biosensors: a review. Trends Anal. Chem. 82, 55–67. https://doi.org/10.1016/j.trac.2016.04.005.
Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. Canc. J. Clin. 69, 7–34. https://doi.org/10.3322/caac.21551.
Singh, Radha D., Shandilya, R., Bhargava, A., Kumar, R., 2018a. Quantum dot based nano-biosensors for detection of circulating cell free miRNAs in lung Carcinogenesis . Biol. Clin. Transl. 9, 1–23. https://doi.org/10.3389/fgene.2018.00616.
Singh, Radha D., Shandilya, R., Bhargava, A., Kumar, R., Tiwari, R., Chaudhury, K., Srivastava, R.K., Goryacheva, I.Y., Mishra, P.K., 2018b. Quantum dot based nano-biosensors for detection of circulating cell free miRNAs in lung carcinogenesis: from biology to clinical translation. Front. Genet. 9, 1–23. https://doi.org/10.3389/fgene.2018.00616.
Sireesha, M., Jagadeesh Babu, V., Kranthi Kiran, A.S., Ramakrishna, S., 2018. A review on carbon nanotubes in biosensor devices and their applications in medicine. Nanocomposites 4, 36–57. https://doi.org/10.1080/20550324.2018.1478765.
Soonnarong, R., Maluangnont, T., Pongrakhananon, V., Petpiroon, N., Chantarawong, W., Chanvorachote, P., Bhummaphan, N., 2019. Ti0.8O2 nanosheets inhibit lung cancer stem cells by inducing production of superoxide anion. Mol. Pharmacol. Mol. 118, 114447. https://doi.org/10.1124/mol.118.114447.
Su, L., Jia, W., Lei, Y., 2012. Carbon nanotube-based biosensors. Sensor. Actuator. B Chem. 207, 355–414. https://doi.org/10.1201/b11989.
Su, S., Wu, Y., Zhu, D., Chao, J., Liu, X., Wan, Y., Su, Y., Zuo, X., Fan, C., Wang, L., 2016. On-electrode synthesis of shape-controlled hierarchical flower-like gold nanostructures for efficient interfacial DNA assembly and sensitive electrochemical sensing of MicroRNA. Small (Weinheim an der Bergstrasse, Germany) 12, 3794–3801. https://doi.org/10.1002/smll.201601066.
Suominen, A., Li, Y., Youtie, J., Shapira, P., 2016. A bibliometric analysis of the development of next generation active nanotechnologies. J. Nanoparticle Res. 18, 270. https://doi.org/10.1007/s11051-016-3578-8.
Suvarnaphaet, P., Pechprasarn, S., 2017. Graphene-based materials for biosensors: a review. Sensors (Switzerland) 17. https://doi.org/10.3390/s17102161.
Tang, W., Zhu, G., Liang, L., Zhang, C.Y., 2015. A single quantum dot-based biosensor for DNA point mutation assay. Analyst 140, 5936–5943. https://doi.org/10.1039/c5an01270h.
Taniselass, S., Arshad, M.K.M., Gopinath, S.C.B., 2019. Graphene-based electrochemical biosensors for monitoring noncommunicable disease biomarkers. Biosens. Bioelectron 130, 276–292. https://doi.org/10.1016/j.bios.2019.01.047.
Taylor, J., Huefner, A., Li, L., Wingfield, J., Mahajan, S., 2016. Nanoparticles and intracellular applications of surface-enhanced Raman spectroscopy. Analyst 141, 5037–5055. https://doi.org/10.1039/c6an01003b.
Tiwari, J.N., Tiwari, R.N., Kim, K.S., 2012. Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. Prog. Mater. Sci. 57, 724–803. https://doi.org/10.1016/j.pmatsci.2011.08.003.
Vieira, D.B., Gamarra, L.F., 2016. Advances in the use of nanocarriers for cancer diagnosis and treatment. Einstein (São Paulo) 14, 99–103. https://doi.org/10.1590/s1679-45082016rb3475.
Viswambari Devi, R., Doble, M., Verma, R.S., 2015. Nanomaterials for early detection of cancer biomarker with special emphasis on gold nanoparticles in immunoassays/sensors. Biosens. Bioelectron. 68, 688–698. https://doi.org/10.1016/j.bios.2015.01.066.
Wang, H., Wang, X., Wang, J., Fu, W., Yao, C., 2016. A SPR biosensor based on signal amplification using antibody-QD conjugates for quantitative determination of multiple tumor markers. Nat. Publ. Group 1–9. https://doi.org/10.1038/srep33140.
Wang, L.X.F.J., Song, Z.Y.S.A., Dong, W.X.Z.S.H., Zhang, H.S.Y.Y., 2019. Clinical significance of serum EGFR gene mutation and serum tumor markers in predicting tyrosine kinase inhibitor efficacy in lung adenocarcinoma. Clin. Transl. Oncol. https://doi.org/10.1007/s12094-018-02014-6.
Wei, Z., Zhang, J., Zhang, A., Wang, Y., Cai, X., 2017. Electrochemical detecting lung cancer-associated antigen based on graphene-gold nanocomposite. Molecules 22, 1–9. https://doi.org/10.3390/molecules22030392.
Wei, Z., Cai, X., Zhang, J., Fan, J., Xu, J., Xu, L., 2019. High sensitive immunoelectrochemical measurement of lung cancer tumor marker ProGRP based on TiO2-Au nanocomposite. Molecules 24, 656. https://doi.org/10.3390/molecules24040656.
Wen, W., Song, Y., Yan, X., Zhu, C., Du, D., Wang, S., Asiri, A.M., Lin, Y., 2018. Recent advances in emerging 2D nanomaterials for biosensing and bioimaging applications. Mater. Today 21, 164–177. https://doi.org/10.1016/j.mattod.2017.09.001.
Wijaya, Y.N., Kim, J., Choi, W.M., Park, S.H., Kim, M.H., 2017. A systematic study of triangular silver nanoplates: one-pot green synthesis, chemical stability, and sensing application. Nanoscale 9, 11705–11712. https://doi.org/10.1039/c7nr03077k.
Wu, C.H., Wang, W.H., Hong, C.C., Hwang, K.C., 2016. A disposable breath sensing tube with on-tube single-nanowire sensor array for on-site detection of exhaled breath biomarkers. Lab Chip 16, 4395–4405. https://doi.org/10.1039/c6lc01157h.
Xu, S., Cai, X., Liu, J., Wang, Y., Luo, J., Fan, Y., Xu, H., 2017. A wireless point-of-care testing system for the detection of neuron-specific enolase with microfluidic paper-based analytical devices. Biosens. Bioelectron. 95, 60–66. https://doi.org/10.1016/j.bios.2017.04.003.
Yang, P.-H., Zhang, L., Luo, J.-J., Guo, Y.-J., Sun, G.-M., Tang, Y.-J., 2014a. Multifunctional optical probe based on gold nanorods for detection and identification of cancer cells. Sensor. Actuator. B Chem. 191, 741–749. https://doi.org/10.1016/j.snb.2013.10.027.
Yang, T., Guo, X., Wu, Y., Wang, H., Fu, S., Wen, Y., Yang, H., 2014b. Facile and label-free detection of lung cancer biomarker in urine by magnetically assisted surface-enhanced Raman scattering. ACS Appl. Mater. Interfaces 6, 20985–20993. https://doi.org/10.1021/am5057536.
Zaporotskova, I.V., Boroznina, N.P., Parkhomenko, Y.N., Kozhitov, L.V., 2017. Carbon nanotubes: sensor properties. A review. Mod. Electron. Mater. 2, 95–105. https://doi.org/10.1016/j.moem.2017.02.002.
Zappa, C., Mousa, S.A., 2016. Non-small cell lung cancer: current treatment and future advances. Transl. Lung Cancer Res. 5, 288–300. https://doi.org/10.21037/tlcr.2016.06.07.
Zeng, Y., Bao, J., Zhao, Y., Huo, D., Chen, M., Yang, M., Fa, H., Hou, C., 2018. A sensitive label-free electrochemical immunosensor for detection of cytokeratin 19 fragment antigen 21-1 based on 3D graphene with gold nanopaticle modified electrode. Talanta 178, 122–128. https://doi.org/10.1016/j.talanta.2017.09.020.
Zhang, H., 2015. Ultrathin two-dimensional nanomaterials. ACS Nano 9, 9451–9469. https://doi.org/10.1021/acsnano.5b05040.
Zhang, Y.H., Qiao, L., Liu, F.L., Fang, H.L., Xiao, P., Dai, H.F., 2011. Single-walled carbon nanotube-based biosensors for the detection of volatile organic compounds of lung cancer. Phys. E Low-dimens. Syst. Nanostruct. 44, 367–372. https://doi.org/10.1016/j.physe.2011.08.033.
Zhang, Z., Wang, Y., Zhang, N., Zhang, S., 2016. Self-assembly of nucleic acid molecular aggregates catalyzed by a triple-helix probe for miRNA detection and single cell imaging. Chem. Sci. 7, 4184–4189. https://doi.org/10.1039/c6sc00694a.
Zhang, Q., Li, X., Qian, C., Dou, L., Cui, F., Chen, X., 2018. Label-free electrochemical immunoassay for neuron specific enolase based on 3D macroporous reduced graphene oxide/polyaniline film. Anal. Biochem. 540–541, 1–8. https://doi.org/10.1016/j.ab.2017.10.009.
Zhang, H., Ke, H., Wang, Y., Li, P., Huang, C., Jia, N., 2019. 3D carbon nanosphere and gold nanoparticle-based voltammetric cytosensor for cell line A549 and for early diagnosis of non-small cell lung cancer cells. Microchimica Acta 186, 2–8. https://doi.org/10.1007/s00604-018-3160-4.
Zhao, N., Liu, S., Jiang, Q., Lan, T., Cheng, Z., Liu, H., 2016. Small-protein-stabilized semiconductor nanoprobe for targeted imaging of cancer cells. Chembiochem 94040, 1202–1206. https://doi.org/10.1002/cbic.201600219.
Zhao, Y., Liu, W., Tian, Y., Yang, Z., Wang, X., Zhang, Y., Tang, Y., Zhao, S., Wang, C., Liu, Y., Sun, J., Teng, Z., Wang, S., Lu, G., 2018. Anti-EGFR peptide-conjugated triangular gold nanoplates for computed tomography/photoacoustic imaging-guided photothermal therapy of non-small cell lung cancer. ACS Appl. Mater. Interfaces 10, 16992–17003. https://doi.org/10.1021/acsami.7b19013.
Zhao, H., Chen, K.-Z., Hui, B.-G., Zhang, K., Yang, F., Wang, J., 2018a. Role of circulating tumor DNA in the management of early-stage lung cancer. Thoracic Cancer 9, 509–515. https://doi.org/10.1111/1759-7714.12622.
Zhao, H., Chen, K., Hui, B., Zhang, K., Yang, F., Wang, J., 2018b. Role of circulating tumor DNA in the management of early-stage lung cancer. Thoracic Cancer 9, 509–515. https://doi.org/10.1111/1759-7714.12622.
Zhao, M., Chen, F., Ding, S., Li, X., Zhou, X., Ling, J., Tang, H., 2018. An enzyme-free electrochemiluminescence biosensor for ultrasensitive assay of Group B Streptococci based on self-enhanced luminol complex functionalized CuMn-CeO2 nanospheres. Biosens. Bioelectron. 127, 167–173. https://doi.org/10.1016/j.bios.2018.12.012.
Zhou, L., Zhao, J., Li, T., Wang, Y., Mao, H., Gao, A., Yang, X., Tong, J., 2017. Multiplexed detection of lung cancer biomarkers in patients serum with CMOS-compatible silicon nanowire arrays. Biosens. Bioelectron. 91, 482–488. https://doi.org/10.1016/j.bios.

2016.12.072.
Zhu, S., Li, H., Yang, M., Pang, S.W., 2016. High sensitivity plasmonic biosensor based on nanoimprinted quasi 3D nanosquares for cell detection. Nanotechnology 27. https://doi.org/10.1088/0957-4484/27/29/295101.
Zhu, Shuyan, Li, Hualin, Yang, Mengsu, P, S.W., 2018a. Label-free detection of live cancer cells and DNA hybridization using 3D multilayered plasmonic biosensor. Nanotechnology 36, 1–17.
Zhu, J., Hou, J., Uliana, A., Zhang, Y., Tian, M., Van Der Bruggen, B., 2018b. The rapid emergence of two-dimensional nanomaterials for high-performance separation membranes. J. Mater. Chem. 6, 3773–3792. https://doi.org/10.1039/c7ta10814a.