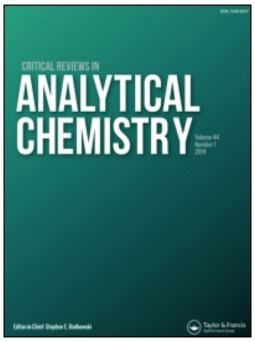

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Gold-Nanohybrid Biosensors for Analyzing Blood Circulating Clinical Biomacromolecules: Current Trend toward Future Remote Digital Monitoring

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ABSTRACT
Mortality level is worsening the situation worldwide thru blood diseases and greatly jeopardizes the human health with poor diagnostics. Due to the lack of successful generation of early diagnosis, the survival rate is currently lower. To overcome the present hurdle, new diagnostic methods have been choreographed for blood disease biomarkers analyses with the conjunction of ultra-small ideal gold nanohybrids. Gold-hybrids hold varieties of unique features, such as high biocompatibility, increased surface-to-volume ratio, less-toxicity, ease in electron transfer and have a greater localized surface plasmon resonance. Gold-nanocomposites can be physically hybrid on the sensor surface and functionalize with the biomolecules using appropriate chemical conjugations. Revolutionizing biosensor platform can be prominently linked for the nanocomposite applications in the current research on medical diagnosis. This review encloses the new developments in diagnosing blood biomarkers by utilizing the gold-nanohybrids. Further, the current state-of-the-art and the future envision with digital monitoring for facile telediagnosis were narrated.

KEYWORDS
Nanocomposites; blood biomarkers; nanobiosensor; gold nanoparticle; telediagnosis

Introduction

Blood circulating biomarker detection has been a considerable attention for the researchers due to the annual mounting-up with mortality and morbidity. Blood disease biomarkers were reported in plenty and their progresses in the human physiological system cause a severe illness. Cardiovascular disease (CVD), malignant tumor, hemophilia and diabetes are the predominant issues and have biomarkers can be defined as the molecules that are circulating in the blood-stream as a sign for the disease progression.[1] The prevalence of CVD is increasing all over the world, categorized in three levels ranging from high-, intermediate-, and low-risks and the diagnosis are planned and implemented consequently. Vast variety of biomarkers related to CVD risks are, Troponin T & I, C-reactive protein, Galectin-3, Neutrophil gelatinase-associated lipocalin, ST-2 and Mid-regional pro-adernomedullin. Generally, biomarkers are grouped based on the disease specificity, acute changes and the pathologic process. In fact, this categorization helps medical department to trace and predict the disease progression.[2] The second predominant disease is malignant tumor, known as cancer, flooding globally and prevalent in women population as breast cancer.[3] Other common biomarkers are human epidermal growth factor receptor 2, alpha-fetoprotein, thyro-globulin, Prostate-specific antigen (PSA), leptin, prolactin, squamous cell carcinoma (SCC) antigen, and Insulin-like growth factor (IGF). On the other hand, Hemophilia is the blood clotting disease due to the defect in the clotting factors, such as factor IX (FIX), a well-known blood circulating biomarker. The above mentioned blood circulating biomarker diseases are mushrooming universally and limited with the effective intervention availability to decline the death rate. An efficient intervention is greatly demanded to prevent and attenuate the disease development at the early progression stage. Therefore, to build an ultimate diagnostic strategy with the implementation of nanotechnology in biosensor has opens the gate for quick and accurate outcome on the disease progression.

Biodetection and nanotechnology

'Biodetection' encompasses with the electrical transduction occurs on a single chip when the biological molecules participate in the binding events.[4,5] This phenomena can be performed on label- and label-free biosensors, individually-integrated analytical devices are comprising biomolecules recognizing elements called 'bioreceptors' (DNA, antibody, enzymes or microorganism) and 'transducer' (Figure 1), they are able to convert the interaction process of ligand-receptor into the electrical measurements.[6,7] Rapid advancing biosensor platform in medical diagnosis has been a

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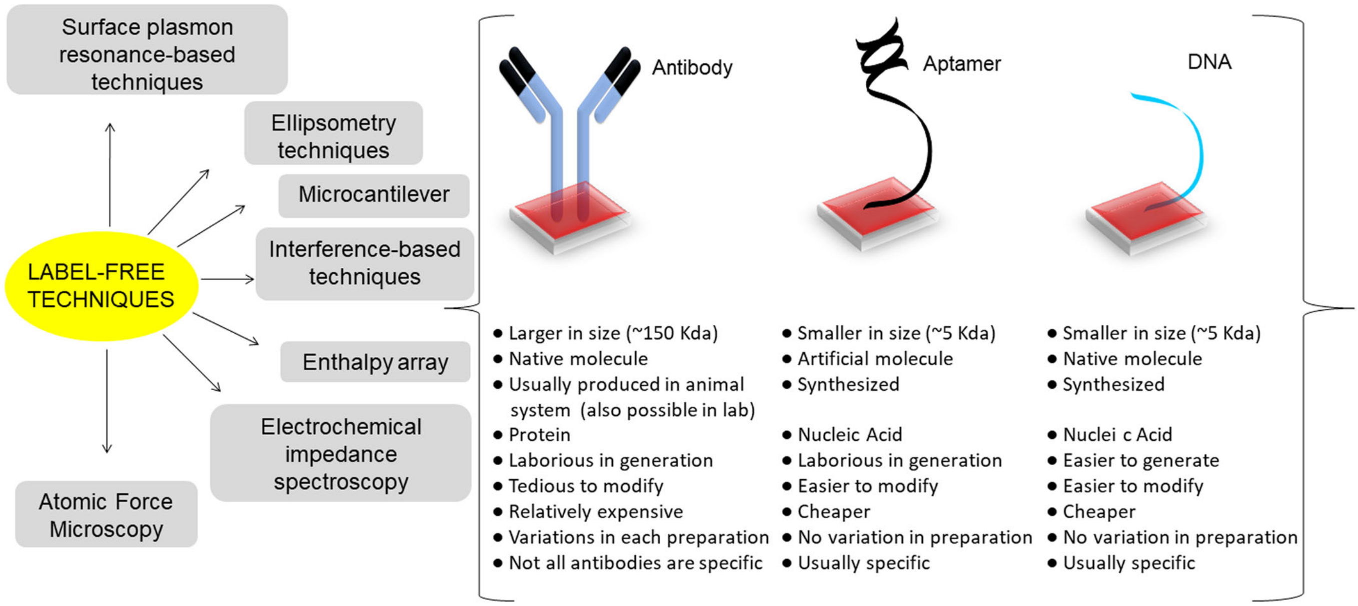

Figure 1. Label-free biodetection systems. Biomolecular-based sensing with the strategies and criteria for immunosensor (antibody-based), aptasensor (aptamer-based) and DNA-sensor (DNA-based) are shown.

hallmark for the blood circulating biomarker disease analysis.[8] Despite, some pitfalls as shown in Figure 2 unable to perform the detection at the maximum accuracy and failed to detect the low amount of samples, have triggered the nanotechnology implementation in sensing applications to overcome these pitfalls.[8] At nanoscale, materials able to assist the manufacturing process of highly sensitive and specific sensor. Furthermore, provides more surface to volume ratio for the biomolecular interaction event led to a higher sensitivity.[9] Despite, nano-sized materials assist in direct flow of electrons between the biomolecules and electrode surface by enhancing the amplification of the electrical signal.[10] These broad characteristics of nanotechnology are resulted in the tremendous transformation in sensing accuracy and able to detect even low sample volumes. Nanohybrids is the subcategory of nanotechnology plays a crucial role in the development of biosensor for the better and quick analysis. Nanohybrids contains a multiple phase of solid materials, where at least one of the phases is designed with one, two- or three-dimensional nanostructures at <100 nm. Generally, gold nanoparticles (AuNPs) are widely applied in nanomedicine because gold carries outstanding key features. AuNPs can be easily prepared with variety of sizes and shapes using the solution-based methods. It has less toxicity compared to other available metals. The fundamental key features with chemical groups on the outer surface of AuNPs, which are readily accessible for the attachment of the relevant biological molecules on the nanosensor. Apart from less toxicity, with easy preparation and easy modification for biomolecular attachments, gold is found to be ideal. AuNPs able to absorb and/or scatter when irradiates by light, which will occur at a specific resonance wavelength, named as localized surface plasmon resonance (LSPR). Apart from AuNPs, several advantages of gold nanohybrids play a significant role in the blood biomarker detection. Researcher found that gold nanohybrids are much better for the detection purpose compared to the spherical AuNPs. In this work, gold nanoplates-based indium tin oxide was utilized to modify the sensor for the detection of dopamine and ascorbic acid. Luckily, proposed nanosensor displays higher electrocatalytic activity and also increases the surface area to volume ratio. These characteristics play important role for the better outcome in this detection system. Moreover, gold nanohybrid can be chemically modified on the sensor surface with much simpler steps and also with appropriate chemical linking agent. Commonly used (3-Aminopropyl) triethoxysilane linker which could ease the binding of AuNPs and biomolecules. In addition, these linkers able to create strong bond with amine functionalized sensor surface. Combination of other nanomaterials with AuNPs to form gold nanohybrids also able to ease the early detection system due to the combined effect of different nanomaterials. For example, utilization of graphene-gold nanohybrids for the detection of troponin biomarker.[11] Whereby, the main pitfall of utilizing gold nanohybrids in detection system is laborious. The preparation of nanohybrids can consume more time with additional steps in turn may delay to proceed with the further steps in sensing system. The *in-situ* reduction method to produce gold nanohybrids may generate difficulties in controlling the size and structure of AuNPs in the resulting nanohybrids. The unusual size and morphology of the AuNPs in developed nanohybrids are able to decline the sensing sensitivity which can generate inaccurate outcome. This is the pioneer reason why gold nanoparticles (AuNPs) own a huge attention in the number of applications and provide a huge impact on the digital monitoring system. With the sensing system gold nanohybrid is widely considered as an ideal part to enhance the performance. As discussed above gold has a wide appealing potential with biosensors, due to its higher compatibility, tailor-made dimensions, suitable with chemical functionalization, these are able to boost the applications with digital

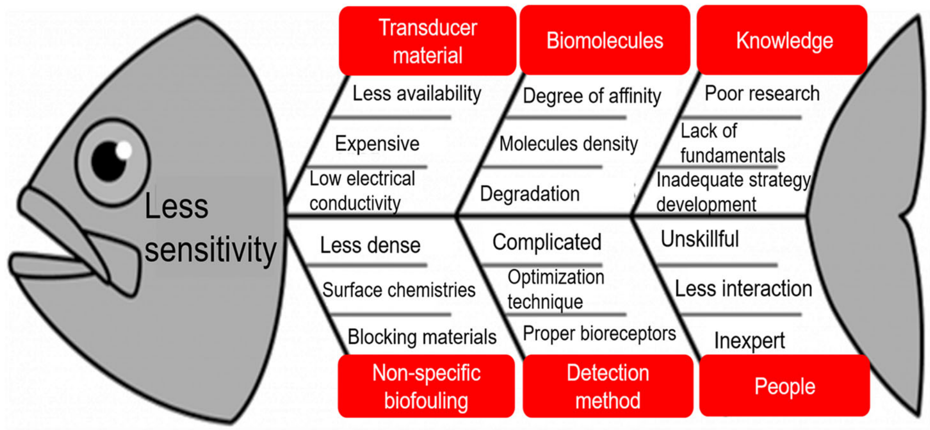

Figure 2. Fish bone diagram. It clearly represents the factors influence the lesser sensitivity of biosensor, which declines the accuracy of the detection. Several factors were stated such as transducer material, the behavior of biomolecules on the solid surface, prior knowledge, characteristics of nonspecific biofouling material, detection method and researchers involved.

monitoring system. Hence, the implementation of gold nanohybrid for the purpose of blood circulating biomarker analysis owes a huge attention for the researchers to plan more advancement future, but unfortunately till today a less development has been reported.

According to the summary above, this context includes a broad discussion about the currently available gold based nanohybrids in nanoscience for the biomedical sensing (Figure 3). The integration of these available gold-based nanocomposites in nanomedicine is revolutionizing the whole medical department into a new rapidly advancing biosensor area compared to the previously accessible diagnostic methods by the electrical transduction. Worth to mention, this review widely covers the synthesization of gold nanomaterial and the configuration of gold nanohybrid for the better attachment of biological molecules.

Configuration of gold-nanohybrids

In rapidly blooming research area, AuNPs are known as the ultimate element in biomedical applications due to their outstanding key features like inert, assist in electron transfer, biocompatibility, easy preparation, and hazard-free substances to the environment.[12] These biocompatible nanoparticles attract the entire attention of research community in the fields of science and technology to build a new development in their respective fields for the better future. To be known as outstanding nanomaterial, surface charges of AuNPs plays the key role. Generally, biosynthesized AuNPs are negatively charged via the enzymatic reduction process (Au^{3+} to Au^{0-}). AuNPs are widely utilized in cellular uptake, electrocatalytic activity, and biosensing technologies in medical diagnosis as the early precautionary system by flipping their negative charge into positive charge.[13] Mentioned flipping method is usually carried out (alkane-thiol/PEG chain/quaternary amine functional group) by the reduction of chloroauric acid.[14] Hence, the positively charged AuNPs interacts with negatively charged biological entities like antibodies, plasmid DNA, cell membranes, and siRNA. The surface charges of AuNPs are highly influence the binding efficiency of biomolecules for the accurate disease detection.[15] Thus, thiol-modification is broadly implemented for the conjugation between AuNPs and biological molecule on the silicon sensing surface.[16] Several polymers are utilized to stabilize the AuNPs like tannic acid and polyvinylpyrrolidone (PVP) as the common capping agents. In biomedicine, bovine serum albumin (BSA), polyethylene glycol (PEG), or many other oligonucleotides, proteins, and peptides are utilized to coat AuNPs for the particle stabilization.[17]

Better detection can be achieved when the binding strategy is highly precise and suitable for the attachment of biomolecules on the particles. Thus, the right combination of linking agents between AuNPs and biological entities is one of the outstanding strategies in order to receive a good outcome in medical diagnosis. Therefore, physical and chemical modifications were proposed to conjugate AuNPs with biomolecules. These modifications are greatly associating with AuNPs surface decoration using the suitable linkers to form a strong biomolecular bonding. Three types of situation have been engaged with the physical modifications: a) hydrophobic attraction between the antibody and the gold surface; b) ionic attraction between negatively charged AuNPs and positively charged antibody; c) dative conjugation by the gold conducting electron and the amino-containing antibody. Chemical conjugation can be achieved between AuNPs and antibody via several phenomena: a) bifunctional linkers; b) chemisorption through thiol-modification; c) adapter molecules such as streptavidin and biotin. Whereby, for the conjugation of antibody to the AuNPs, two different modes, such as covalent and non-covalent bondings were implemented. Covalent mode is the direct binding of AuNPs with thiol-containing biomolecules like antibodies. Dative binding is also categorized as covalent mode, which creates the bond between AuNPs and the free sulfhydryl groups of the antibody. Bifunctional linkers [1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxy-succinimide (NHS)] and adaptive molecules like streptavidin and biotin[18] uses the covalent mode to bind the biomolecules directly on the AuNPs.[19] Commonly, carboxyl modified AuNPs can react with water soluble EDC, while another end to link amine group. In the situation of

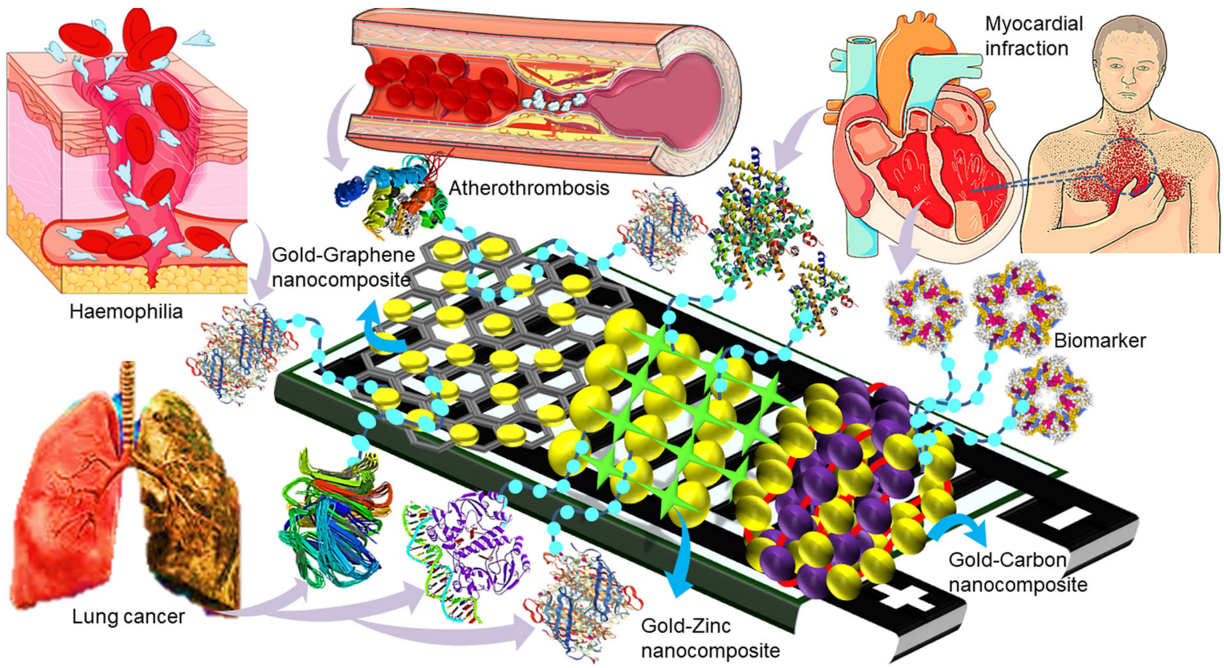

Figure 3. Application of gold nanohybrids in sensing system for blood biomarker diagnostics. Gold-graphene nanocomposites play a vital role in early diagnosis of cardiovascular disease. Likewise, gold-zinc, gold-carbon and gold-titanium dioxide nanocomposites have attracts researcher's attention to develop biosensing platform with the support of multidisciplinary combination of nanotechnology and medicine.

amines on particles surface, active ester compounds NHS can be utilized for the equal formation of amide bonds.[20] Thus, this mechanism creates an effective conjugation event between AuNPs and biomolecules. Adaptive molecules also play an important role in creating covalent modes between nanoparticles and biological molecules. Streptavidin with four biotin binding sites was utilized in this work to create a strong bonding between AuNPs and anti-FIX aptamer.[21] This study validates the multi-anchoring system had revealed an incredible outcome with a high sensitivity detection.[22] Non-covalent modes are strongly connected to the combination of electrostatic and hydrophobic interactions between antibody and AuNPs. Non-covalent modes are concisely described as the spontaneous adsorption of antibodies onto the citrate-stabilized nanoparticles. Therefore, several interactions such as, ionic and hydrophobic interactions may occur. Ionic interaction happens between negatively charged particles and positively charged amino acids and N-terminal on the antibodies. Hydrophobic interaction occurs when the hydrophobic part of antibodies and metal surface interacts to form the non-covalent bond. Some pitfalls have been found like non-covalent mode needs high concentration of antibodies to prepare gold-antibody complex. In addition, the electrostatic attraction is resulting in difficulties to control the biological response.

Dual-metallic nanohybrids: Thin film formation

Currently, nanohybrids contribute huge advantages in the research fields for a new development in science and technology. However, a single nanomaterial performance shows lesser sensitivity and selectivity due to the deficiency of the important physiochemical properties. The combinations of outstanding physical, optical, and electrical properties of AuNPs with unique nanomaterials have been synthesized for a vast variety of purpose. AuNPs are classified as necessary nanomaterials to form composites with other nanomaterials or molecules because AuNPs are easier to modify compared to other nanomaterials. For example, polymer-gold, metal oxide-gold, graphene/graphene oxide-gold, and gold-CNT nanocomposites.

Gold-mediated zinc oxide (ZnO) nanohybrids

As discussed above, gold is an ideal material due to its outstanding physical, electrical, and biological properties. Gold nanohybrids can be easily modified with vast variety of biological molecules and also with different nanomaterials, which welcome a broad opportunity for researchers to design a new development in sensing technologies in order to boost-up the sensitivity and selectivity.[23] Gold/Zinc oxide (Au/ZnO) nanocomposites are the combination of gold and ZnO to enhance the sensing. It is because ZnO possess the superior electrical and optical properties with a broad band gap, less resistivity, and great transparency. The interdigitated electrode was modified with gold doped zinc oxide nanorods for the detection of cervical cancer. This electrochemical detection system utilizes human papilloma virus 16 (HPV-16) as biomarker to diagnose HPV infected cervical cancer. The sensitivity of the proposed sensing system was 1 fM which holds an outstanding potential in medical biosensing applications.[24]

A study was conducted using Au/ZnO nanocomposites to increase the detection capability of Surface Plasmon Resonance (SPR) biosensor.[25] Herein, breast cancer biomarker identification using carbohydrate antigen 15.3 (CA15-3) from blood serum is shown to be ideal. The detection limit shows 4 times lower compared to the previous

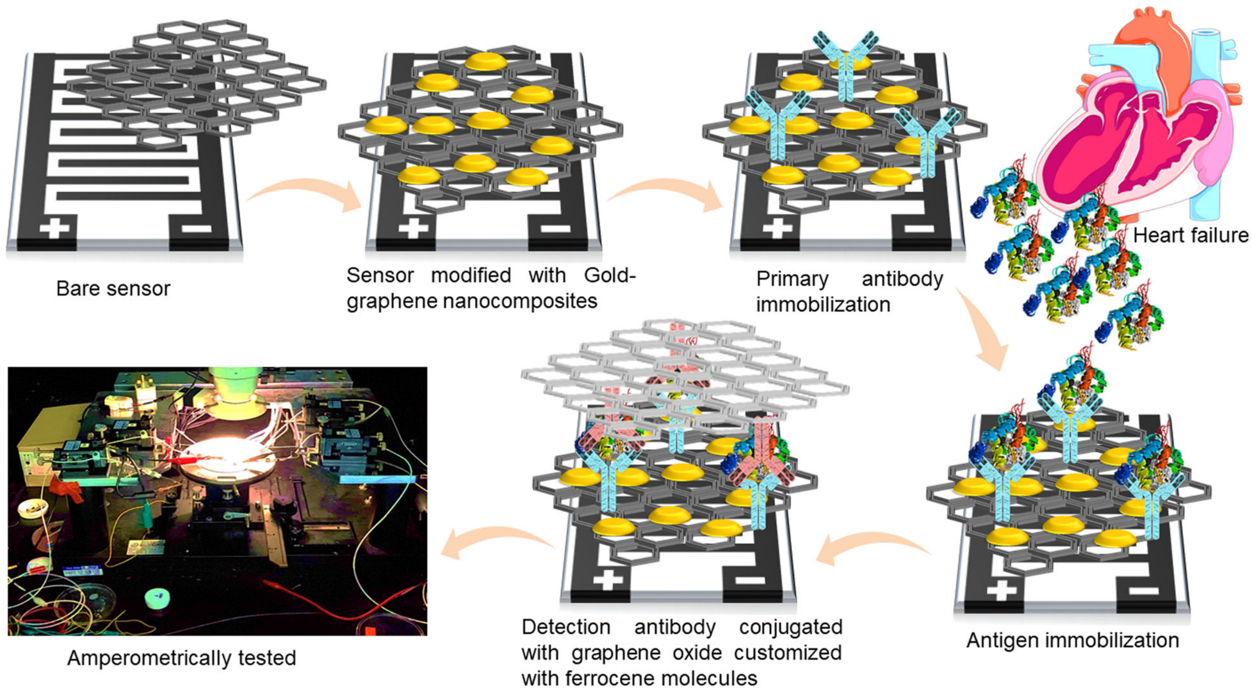

Figure 4. Bare sensor modification with gold-graphene and phenyl group. Two different combos of phenyl groups applied, which are 4-carboxyphenyl and 4-nitrophenyl another 4-carboxyphentl and 4-aminephenyl. The nanocomposite is functionalized on the surface of the sensor. Cardiac troponin I antibody is immobilized on the nanocomposites decorated surface followed by the specific antigen interaction. Detection antibody is prepared by modifying with graphene oxide and ferrocene molecules. After the incubation step, the system is amperometrically tested.

study using Au/Cromium nanocomposites for the similar detection. Proposed study validated that Au/ZnO nanocomposite owns a high capability to enhance the SPR signal and sensitivity level of the detection.

Alpha fetoprotein (AFP) type of yolk sac cancer biomarker circulating in blood was identified using the electrochemical immunosensor with the nanocomposite implementation. This study was conducted by utilizing ZnO nanorods/AuNPs hybridized with the reduced graphene nanosheet (Au/ZnO/RGO) for maximum capturing of antibody followed by horseradish-peroxidase (HRP) enzyme-conjugated secondary antibody (Ab_2) functionalized Au@ZnO composites (Ab2/HRP-Au@ZnO) was interacted to create a strong affinity with AFP biomarker[26] as in Figure 4. Briefly, enzyme-functionalized Au/ZnO nanocomposite was integrated with secondary antibody to maximize the affinity for the better sensitivity and detection. Surprisingly, this sensing development had lowered the limit of detection to 0.01 pg mL^{-1}, thus presented development absolutely can be practiced in the clinical diagnosis using a real clinical sample for AFP tumor marker detection.

Gold-mediated graphene (Au-GP) nanohybrids

To date, gold mediated graphene nanohybrids are widely applied in nanobiotechnology due to the novel properties of these nanomaterials. Currently, varieties of modifications are being done by science and technology research communities in vast applications for the better outcome compared to the last decades. Up to now, gold-mediated graphene with polymer, and gold-mediated graphene with oxide are presently blooming in the medicinal field for the better detection. Numerous researches were conducted and reported in the biosensing application to diagnose blood biomarker detection. For example, 3 D graphene-modified gold nanohybrids was modified on the carbon electrode to diagnose lung cancer using CYFRA21-1 biomarker. The limit of detection was 100 pg mL − 1 which is applicable for clinical diagnosis.[27] Another work was conducted using 3 D graphene-modified gold nanohybrids to detect neuron-specific enolase (NSE) biomarker which associates with small-cell lung carcinoma. Whereby, the detection limit was 10 pg mL^{-1} which is suitable for lung cancer diagnosis.[28]

Gold-mediated graphene oxide nanocomposites were applied for cardiac marker troponin-I detection with a stable label-free electrochemical immunosensor. AuNPs and graphene oxide nanocomposites were prepared and gently implemented on the electrode surface for a rapid electron movement and consequently enhance the sensitivity. Thus, applied nanocomposites create a broad active surface area for the immobilization of anti-cTnI, subsequently increased the effectiveness of detection (Figure 5). Therefore, the integration of gold-mediated graphene oxide nanocomposite to modify the electrode had revealed 100 times lower detection compared to the available conventional techniques.[29] The limit of detection was as lesser as 0.05 ng mL^{-1}, hence, this modification is recommendable for the clinical practice using a real human serum toward the early diagnostic purpose to avoid the mortality rate engaged with myocardial infraction.

Nitric oxide (NO), a type of critical tumor biomarker was detected using graphene-gold (GP-Au) nanocomposites modified glassy carbon electrode (GCE) via sonochemical method.[30] This approach is tremendously bounced out a good impact toward NO marker detection by revealing the

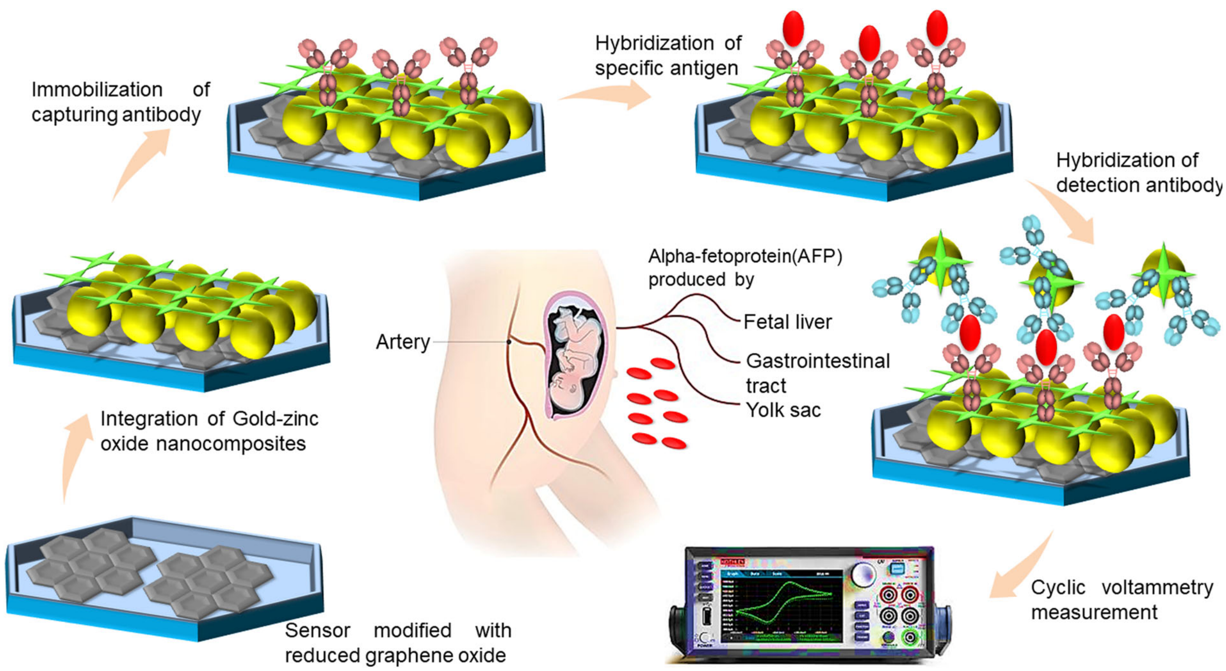

Figure 5. Glassy carbon electrode applied with gold-zinc oxide and reduced graphene oxide nanocomposites. Immobilization of anti-alpha fetoprotein is gently carried out and incubated. Blocking agent is applied by immersing the functionalized electrode in the Bovine serum albumin solution to avoid the nonspecific binding. Later, the titration of different target concentrations are done followed by the immersion in the secondary antibody conjugated horse-radish peroxidase and gold-zinc oxide nanocomposites solution for the immunoreaction. Electrical characterization is carried out using cyclic voltammetry measurements.

detection limit at 0.04 μM. Reason for this is because of the synergistic effect of graphene and gold-assisting rapid electron movement at the active surface area between the biomolecules and GP-Au nanocomposites modified GCE for the better sensitivity with good stability and reproducibility.

Gold-mediated titanium dioxide (Au-TiO_2) nanocomposites

Gold combined Titanium (IV) dioxide (TiO_2) with chitosan nanocomposites is notably viral for progastrin-releasing peptide (ProGRP) biomarker detection, associates with small lung cancer diagnostic mainly at early stages. Mentioned nanocomposites were functionalized on carbon paste electrode (CPE) to exhibit a higher sensing performance compared to the currently available methods for ProGRP detection. This modification has successfully lower the detection limit[31] for ProGRP identification, which can be also practiced in real clinical sample for the cancer diagnostic. Another study was conducted using Au-TiO_2 combined with stannous oxide (SnO_x) nanocomposites in colorimetric immunoassay based biodetection for carcinoembryonic antigen (CEA) identification,[32] also a type blood circulating cancer biomarker. Surprisingly, the detection limit falls down to 5 pg mL^{-1}, is an ideal concentration of CEA to practice the clinical testing for the early cancer diagnosis.

Gold-embedded nanohybrids

The effect of gold nanomaterial integration for blood circulating biomarker detection in biosensor was enormously incredible owing to the outstanding features (good electron transfer, easy to modify, easy production method, eco-friendly and biocompatibility).[33] Hence, research community 'flip' their attention toward nanotechnology from micro-scale technology by incorporating nanoscale advancement into the existing detection system. Nanocomposite is the sub-branch from the head-branch nanotechnology, which can be classified into zero-dimensional (nanoparticles), one-dimensional (nanorods, nanowires, nanotubes, nanocages), two-dimensional (gold nanoplates such as stars, pentagons, squares/rectangles, dimpled nanoplates, hexagons, truncated triangles), and three-dimensional (gold nanotadpoles, gold nanodumbbells, gold nanopods, gold nanostars and gold nanourchin). Yet available nanocomposites have attracted a great deal in clinical diagnosis for the early precautionary assessments.[34]

Zero-dimensional

Zero-dimensional (0-D) gold nanomaterial is an ancestor for other existing nanoscale materials since the first research article based on nanotechnology was published by Eric Drexler on 1981. Generally, 0-D gold nanomaterials are spherical in shape with size the range of 1–50 nm, and classified as AuNPs.[35] Huge number of studies have been conducted by implementing AuNPs to enhance the sensing technologies for the better future view in medical diagnosis.

Gold nanoparticles. "Gold haste" can be seen visibly in a wide variety of science and technology application. The acceleration of gold among research communities is owing to its fascinating features for unique biological and chemical sensors can be authorized by number of publications on the utilization of AuNPs for the novel sensor developments. For example, a study was presented by designing an immunosensor for a cancer detection utilizing AuNPs as a probe for the signaling purpose.[36] In this work, streptavidin-coated magnetic beads were covered with biotinylated anti-human EGFR aptamer, which act as analyte capturing agent. Then, anti-human EGFR antibody was immobilized on AuNPs to serve as a signaling probe. Complex structure of aptamer-EGFR-antibody was formed in the presence of EFGR analyte on the magnetic bead surface. Voltammetric measurements was carried out to study the sensitivity of binding efficiency between the ligand and analyte. This study provides the preliminary results using human serum samples, but the proposed development can be promoted for the future to design more sensitive sensor.[36] Factor IX (FIX) is a blood clotting biomarker was detected using nanogapped dielectric sensor by voltammetric immunoassay. Herein, AuNPs was non-covalently attached to FIX antigen to enhance the detection by anti-FIX antibody. This modification allows more antigens capturing to increase the detection sensitivity. This work is also proved that proposed modification can be utilized in real samples by conducting the detection in human serum. The limit of detection as low as 1 pM was obtained, considered to be lower than the real concentration of FIX in human body (87 nM).[37] Three acute myocardial infraction (AMI) biomarkers[38] were detected using microfluidic paper-based immunodevice simultaneously. AuNPs were functionalized on primary and secondary antibodies to enhance the chemiluminescence (CL) signal for the better outcome. Three biomarkers [cardiac troponin I (cTnI), copeptin, and heart-type fatty acid-binding protein (H-FABP)] were analyzed in a single CL detection via measuring the intensity of the obtained emission peaks. The detection limit falls down to 0.4, 0.3, and 0.06 pg/mL for copeptin, cTnI and H-FABP detection, correspondingly.

One-dimensional

The development of one-dimension (1-D) nanomaterials are primarily emerged when the huge invention like scanning tunneling microscope and cluster science highly pumped-up the nanotechnology industries led to the discovery of fullerenes in 1985. Since after the pioneer of 'carbon nanotubes' was published, yet, this is the platform how 1-D nanomaterials have emerged into nanobiotechnology platform for numerous applications. Therefore, emphasizing 1-D AuNPs have gained immense attention in the fields of biomedical research due to the abundance of novel properties. 1-D AuNPs is made-up of single or numerous layers of atoms strongly linked by the network of chemical structures between them. The superlative performance of 1-D AuNPs was clearly validate in the detection system of blood circulating biomarker. Typically, 1-D AuNPs comprises of gold nanowires, gold nanorods, and gold nanotubes.

Gold nanorods. Gold nanorods (GNRs) are commonly used nanomorphology in biomedical applications.[16] This nanostructure is synthesized by the solution phase (small gold seeds are added in series of growth medium), and seed-mediated method. GNRs with a strong localized surface plasmon resonance (LSPR)-based absorption can be produced by manipulating the production parameters (size of initial gold seeds and the concentration of surfactants and co-surfactants). GNRs plays vital role in enhancing the sensing mechanism for the blood biomarker analysis and several studies were currently overcrowding the journal with keywords "gold nanorod + detection". Notably, myocardial infraction haunting worldwide and early diagnosis is highly needed to increase the survival rate. Different sizes of GNRs were applied in this study to obtain a desired wavelength owing to the LSPR for the multiplexed biosensing.[39] Herein, specific GNR with appropriate LSPR peak was utilized for the detection of myocardial infraction and cardiac troponin I. In this study, the binding of analyte with appropriate antibody was analyzed by monitoring the spectral movement at the particular wavelength. Another study was conducted using GNR to enhance the sensing system by utilizing plasmonic paper devices. Peptide as good recognition molecule used for cardiac biomarker identification, which was modified with GNR to lower the limit of detection for LSPR-based sensing. This study has concluded that smaller sized peptide reveals a higher sensitivity by utilizing bioplasmonic paper devices.[40] Also, a type of LSPR sensing system for the breast cancer detection using GNR was demonstrated. Aptamer-based detection was carried out to increase the specificity and rapid diagnosis. The detection limit was 100 cells mL^{-1} within 30 minutes with a high stability.[41] Recently, hyperglycemia was detected using interdigitated electrode with the integration of GNR. Hyperglycemia is blood-related disease, where the glucose level was monitored using the blood sample from the pregnant women. The observation of glucose level is must during the pregnancy for a good delivery. In this work, 0.06 mg/ml of detection limit was achieved for glucose detection with GNR implementation, suitable for the clinical care diagnosis.[16] Further, early cardiac failure detection was conducted by conjugating GNR with anti-C-reactive protein to increase the surface area for more antigen capturing. Both situations with and without GNR were conducted to study the variations with the detection limit. Ultimately, with the existence of GNR the detection limit was 1 pM, as low as the real concentration of C-reactive protein in human sera.[19]

Gold nanowire. Nanowire falls within nanofibre with a high flexibility like a double helix deoxyribonucleic acid (DNA). Typically, the length to width ratio of nanowires is greater than 1000, but the diameter of wire is limited to tens of nanometer scale with the uncontrollable size in length. Nanowires exhibit lots of novel features which enable the detection system in a superior new ways. Greater flexibility of nanowires contributes several benefits to the scientific world is due to the hollow nanostructures. Nanowires can be easily aligned in the existence of electromagnetic field, which is optically nanostructure. Additionally, it has greater electrical properties because in nanowires the electrons can move freely without any obstacles like collisions with impurities henceforth no loss in energy. According to Young's modulus, gold nanowire is 100 times greater than bulk one which is found to be independent when measured by atomic force microscopy (AFM). Gold nanowire has a promising effect on the medical application for the rapid and accurate diagnosis, which broadly contributes huge amount of unique properties to accomplish the medical task. Aptasensor with silicon nanowire structured electrode was designed for the detection of cell secreted cytokines to monitor tuberculosis (TB), a blood related disease. Designed aptasensor was further modified with gold for a greater sensitivity. Decorated aptasensor with silicon nanowire and gold was further functionalized with thiol-modified aptamer for capturing cytokines. Binding between the cytokines and aptamer-modified silicon nanowire and gold hinder the movement of electron from the redox reporters to the electrode, hence the electrochemical signal declines.[42] Henceforth, the proposed design enhanced the detection system three times faster and two times higher sensitive compared to the standard bare electrodes. Another research community utilizes gold nanowire for the detection of miR-195, which is also one of the blood circulating biomarkers[43] related to Parkinson disease. Screen printed electrode was applied with the exfoliated graphene oxide and gold nanowire to gain a higher sensitivity. Herein, thiol-modified single-stranded probe was designed to hybridize a specific analyte miRNA (miR-195). Electrical characterization was carried out using the cyclic voltammetric method and the limit of detection was 2.9 fM which validates that designed nanosensor, suitable for the least amount of sample.[44] In addition, a real sample experiment has demonstrated no interference in the function of the proposed nanosensor.

Two-dimensional gold materials

Two-dimensional (2-D) nanomaterials are super thin materials due to their thickness and dimensions on nanoscale/macroscale, formed by depositing the specified thickness of specimen on the substrate. 2-D nanomaterial comprises of two unconstrained dimensions while only one is limited to the nanometer scale. Examples of 2-D materials are nanocoating, nanodisks, nanofilms, nanolayers, nanoplating, nanosheets and nanoplates. Despite, 2 D materials have outstanding key features like biocompatibility, optical, mechanical, and chemical properties and better degradability.[45] These features open a path for wide range of applications like biosensor, tissue engineering, drug-delivery, and imaging.

Gold nanosheets. In research market, gold has attracted all the researchers due to mechanical, optical, chemical and electrical properties and as similar for gold nanosheets. Gold nanosheets encompass multiple thin layers of gold but less than ten with more corners and edges to provide huge active sides for target and analyte binding to occur compared to the standard gold nanostructures. Therefore, impedimetric-based biosensor was designed for the detection of human papilloma virus related to cancer, especially with cervical cancer. Gold nanosheets were utilized as a platform to modify the electrode for sensing system. Different concentrations of complementary and non-complementary target DNA sequence were hybridized on gold nanosheets-modified electrode and the standard electrode. Comparative study was conducted using the impedance response toward the binding of target and analyte.[46] Markedly, gold nanosheets-modified nanostructured electrode reveals the good outcome and owes the capability to consider as better electrode in biosensing application.

Gold nanoplates. Recently, gold nanoplates play a crucial role in sensing area due to their properties like ecofriendly, good stability and dispersion, easy to chemically functionalize on the surface and provides a high surface area for the target and analyte binding. Hence, a study was conducted to detect level of uric acid in human serum because the abnormal level of uric acid may trigger various kinds of diseases like cardiovascular disease, gout, Lesch-Nyhan syndrome and hyperuricemia. Herein, triangular shape gold nanoplates have contributes unique benefits for the detection because of strong anisotropy and great LSPR response. The detection limit obtained was 1.3 nM and interference free to the function of biosensor.[47] The early detection for C-reactive protein (CRP) biomarker related to cardiovascular disease is much important in order to know the level of CRP in human serum to proceed with the early diagnostic to avoid the mortality. High level of CRP in human serum may triggers risky with myocardial infraction, a death leading disease. Henceforth, by employing flat gold nanoplates for the CRP detection the limit of detection achieved was at attomolar level. Comparative study was conducted between the immobilization of anti-CRP on gold nanoplate and immobilization of anti-CRP on the standard gold nanostructure.[48] The binding event occurs on gold nanoplate between anti-CRP and CRP. Surface-enhanced Raman scattering (SERS) spectra and Scanning Electron Microscopy (SEM) analyses were carried out in this study to validate the attachment of CRP on gold nanoplate. Surprisingly, an outstanding outcome was obtained by utilizing gold nanoplates because it provides a higher surface to volume ratio for the antigen antibody binding thus more specific binding occurs and the sensitivity increases tremendously.

Multi-dimensional gold nanostructures

Gold nanostructures have gained much attention in medical industries recently for their capability to solve both diagnosis and treatment via their great chemical and physical properties. Universally known that, gold nanostructures are widely mushrooming in biomedical applications through their outstanding optical properties, mainly with scattering and absorption of light under the certain wavelength, when the nanostructures irradiate with light, called 'LSPR'. Additionally, the wavelength may vary depends on the size, geometry and shape of the nanostructures. Despite, implementation of 0-D, 1-D, and 2-D exposes less sensitivity and less effective to LSPR is due to the unusual symmetrical structure and least sensitive plasmonic binding effect between the neighboring nanosheets. This phenomenon obviously led to a small peak shift during the biomolecule's detection, which is normally resolved by using a huge amount of sample. Thus, multi-dimensional gold nanostructures were integrated into medical industries to boost-up the sensitivity followed by the accurate and rapid detection. Multi-dimensional nanomaterials can provide an extremely high volume to surface ratio with superior nanoproperties compared to the existing nanomaterials. Moreover, it able to ease the movement of attached biomolecules in drug-delivery application. Multi-dimensional materials consist of multiple layers of nanomaterials to form nanostars, nanocages, nanourchin, and nanodumbell. Mentioned type of nanomaterials are diversified with unique properties, playing a crucial role with the biosensor application mainly in the detection of blood biomarker related diseases. Recently, 60 nm of gold nanourchin was integrated for the detection of FIX, a so called 'Royal disease' to increase the surface area for the binding of biomolecules. Another key strategy was inserted in this work for the better sensing system, using streptavidin-biotinylated aptamer strategy. Streptavidin is a molecule with four binding sites therefore able to assist for more antigens capturing through biotin. Gold nanourchin was coupled with anti-FIX aptamer and applied on the nanosensor followed by FIX titration on the nanosensor. Amperometric characterization was performed to analyze the binding event between anti-FIX aptamer and FIX. Remarkably, the detection limit was 6 pM as low as the real concentration of FIX in human serum (∼3-5 µg/mL). The performance of gold nanourchin[49] was greatly considerable in this work and have good a potential to perform in the future. Early cardiac treatment for myocardial infraction is highly recommended to increase the living rate. Thus, a triangular icicle-like gold nanostructure was integrated to detect troponin I (TnI) is a novel biomarker for myocardial infraction. Initially, the triangular icicle-like gold nanostructure[50] was deposited on gold substrate to obtain large area of transducer. Then, peptisensor was designed by depositing 13-amino acid affinity peptide on gold nanostructure for the fabrication. A redox marker was applied in the work to identify the binding of TnI on the peptisensor. Later, voltammetric analysis was carried out and the limit of detection attained was 0.9 pg mL^{-1} followed by the human serum was tested. Gold nanoflower[51] was conjugated with DNA to form a novel sensor for microRNA-21(miR21) detection at a low level. The RNA structure was modified in three way junctions; i) one leg was modified with methylene blue (MB) as sensing moiety and ii) remaining two legs are applied with barcode AuNPs as the signal detectors. This fabricated sensor displays a very good outcome and has the capability to perform the diagnosis using the real human serum. A superior work was reported using the gold nanostar for the detection of circulating tumor cell in blood sample. The glassy carbon electrode was covered with gold nanostar followed by the immobilization of the aptamer as the probe for the efficient capture of circulating tumor cells. Gold nanostar[52] plays an important role for the rapid movement of electron from gold nanostar to the external circuit once the LSPR excitation occur. Whereby, the trapped cells on the gold nanostar surface led to the decline in the current response. Despite, ascorbic acid was utilized as electroactive probe to monitor the current responses upon the light irradiation decreases along with the cell concentration. The designed method displays a good outcome that the cell concentration as low as 5 cells mL^{-1} was well-detected. Indeed, the proposed method can be implemented for biological analysis for the better sensitivity in contrast with the available method.

Electrode-conjugated gold nanocomposites

A gold nanocomposite is an eye-catching complex material in medical industries. For the reason of gold nanocomposites have better LSPR response, and highly needed for the biological detection, biocompatibility, fast electron movement and holds better chemical, physical, and electrical key features. Research based on gold nanocomposite in biosensor application are recently overcrowding the market of publication, means sensing system with gold nanocomposites is highly in demand to control the death rate globally. Despite, rapidly advancing biosensor is hallmark for the medical department due to their effective innovation, which includes electrodes modification, surface functionalization and ultimate nanomaterial integration. Generally, electrode modification plays a unique role in biosensing system because it is a conductor utilized in the system to create the interaction with electrolyte captured biomolecules for the detection. Therefore, electrode modification can enhance the system to function effectively by accelerating the movement of electrons through the circuit. High rate of publications are available based on the electrode modification with the biomarker detection. Henceforth, different types of electrodes are widely available like tri-electrode, interdigitated electrode (IDE), and field effect transistor (FET).

Tri-electrode modified gold nanocomposites

Electrochemical biosensor is a sensing system used in medical diagnosis. Electrochemical biosensor encompasses three types of electrodes; i) working electrode; ii) reference electrode; iii) counter electrode, called tri-electrode biosensor. In electrochemical system, the interest is only on working electrode and another two electrodes are to complete the cell. A working electrode that functions solely as a source or sinks for the electrons is called 'an inert electrode' because it plays no chemical role in the electrode reaction. It is important that the material of an electrode is electrochemically inert. Common choices of material for inert electrodes include carbon, gold, platinum and mercury. Usually, working electrode must have useful working potential range and it can be either large or small but $< 0.25\,cm^2$. It must have smooth with a well-defined geometry surface for the current and potential distributions. The role of counter electrode is to provide the current to the working electrode without involvement of optimization steps. This electrode must have a big surface area in contrast with the working electrode and current should flow readily without the need for a large potential. Reference electrode means electrode with a constant voltage throughout the system whether denotes a cathode or an anode with irrespective of current flow. In electrochemical system transducer transforms electrical energy into chemical energy and vice-versa. Hence, the electrochemical transducer can be divided as conductometric, potentiometric, and voltammetric transducers. So, change in conductivity of the medium known as conductometric biosensors. Medium means solutions used to conduct conductometric system. Further, this system mostly involves alteration in solution composition, will normally lead to a change in the electrical conductivity. Usually, conductometric biosensors are nonspecific and have a poor signal-to-noise ratio. Biological membrane receptors can be tracked using interdigitated microelectrodes by ion conductometric sensors. Measurements of voltage in a system at zero current named as potentiometric transducers. The voltage is directly proportional to the log concentration of sample, in addition, difference in pH and ionic concentrations can be measured by the potentiometry system. Despite, voltammetry system can be defined as a deep fluctuation in current will happen and reveals a peak current during the increasing or decreasing potential in a cell until the occurrence of oxidation or reduction of the analyte in the system. The height of the peak current is proportional to the concentration of the electroactive material in the cell. The potential value can be fixed if the suitable oxidation or reduction potential is to monitor the current flow (current at fixed potential), known as amperometry. Numbers of studies have been performed using the electrochemical system for the detection purpose. Cardiac troponin I detection was carried out using the electrochemical biosensor. Herein, working electrode was modified with a gold disk followed by the capture antibody immobilization on the planar gold disk electrode.[53] The counter electrode was modified with platinum wire while silver/silver chloride in 3 M potassium chloride acted as a reference. Cyclometalated iridium (III) complex was used as label for the detection antibody, which readily displays signal that can be easily detected. This complex material is highly implemented in biological detection due to easily modifiable in term of optical, electrochemical and photo-physical. The limit of detection obtained was 10 ag/mL, considered ultra-low than conventional assays. Troponin T detection was carried out[54] using macroporous gold nanostructure modified working electrode. Troponin T biomarker releases into the bloodstream due to the damage of cardiac myocytes. Truly, immediate diagnostic must be carried out to avoid the health risk. Electrochemical system was proposed with the modified working electrode to enhance the detection. Aptamer as the capturing probe was utilized in this work for the better specificity. Furthermore, differential pulse voltammetry measurements were used to monitor the binding of troponin T and aptamer using ferro/ferricyanide as the redox probe. The detection limit was 23 pg/mL^{-1} and the procedure was further applied to analyze real human sample, whereby the sensitivity was greater.[54]

Interdigitated electrode with gold nanocomposites modification

The interdigitated electrode is a device has two main electrode pads with several fingers electrodes array, connected to two main electrodes and forms a comb-like structure. Each finger electrode has a width 'W' (μm or nm), a length 'L' (mm) and distance between two consecutive electrodes 'S' (μm). Normally these sensors are fabricated on top of the Si, glass or SiO_2 substrates. Commonly, used electrode materials are gold, platinum, and aluminum, for conductimetric sensing applications. The biological receptors are immobilized on the top of the active surface area. The biological impedance 'Z' moves through the electrodes was controlled by solution capacitance (Csol) and solution resistance (Rsol), which displays capacity and conductive properties of the solution, respectively. The electrochemical behavior of micro-arrays of interdigitated electrodes was found to be unique different from the conventional electrodes. This unique property of the IDEs compared to other types of electrode has motivated the researchers to utilize this design for the outstanding detection. Carcinoembryonic antigen (CEA) is well known tumor marker associated with breast, colorectal, liver, and colon. A study was conducted using CEA integrated polyaniline-AuNPs (PANi-Au NPs) as a label and gap-based interdigitated electrode for the sensing. The IDE surface was functionalized with adamantine-modified primary antibodies (ADA-Ab_1) followed by carboxymethyl-β-cyclodextrin (CM-β-CD). Detection antibody (Ab_2) was conjugated with PANi-Au NPs-Ab_2, which will be captured and immobilized on the interdigitated electrode surface upon the immune reaction between Ab_1 and CEA. This phenomenon led to decline in resistance value of IDE, therefore, the designed sensor detect CEA as low as 0.007 ng/mL and recommendable to be practiced in clinical diagnosis.[55] Gestational diabetes mellitus normally arises during pregnancy, which affect the transportation of oxygen and nutrients from placenta to the baby in womb. Thus, a study was conducted using IDE-modified with graphene and gold nanocomposite for the detection of glucose. Glucose oxidase was immobilized on the IDE surface for the detection. Graphene and gold nanocomposite enhance the sensitivity from 0.6 mg/mL to 0.3 mg/mL. Furthermore, it also displays high changes in current when tested with all the concentrations of glucose. The limit of detection was between 0.02 and 0.03 mg/mL.[56]

Field effect transistor with gold nanocomposite

Field effect transistor (FET) related sensors are categorized as a semiconductor device encompasses of metal oxide-semiconductor (MOS) structure. Theoretically, the electrical force causes the band bending of the semiconductor channel appropriately when a metal potential (ψm) is changed. This result is in changes of the channel carrier concentration, such as aggregation, degradation and inversion. Usually, in traditional MOSFET gate voltage will be applied to invert the channel (i.e., $V_G > V_{th}$) and switch on the transistor. Likewise, certain considerations, such as solution potentials (e.g., pH values) and charge of biomolecules, may trigger the gate potential. Such factors influence the status of channel carriers and induce a positive or negative changes in the existing current-voltage characteristics and the changes are

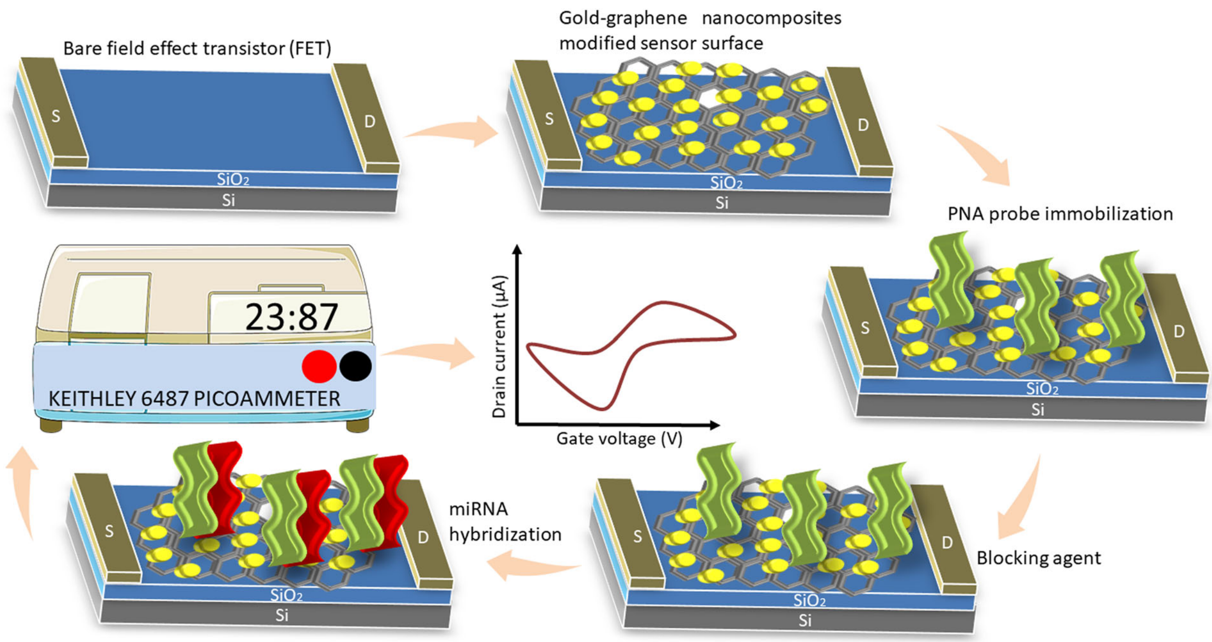

Figure 6. Field-effect transistor for the miRNA detection with gold-graphene nanohybrids. First, the prepared reduced graphene oxide with the chemical reduction method is drop-casted on the sensing area followed by immersing in $HAuCl_4$ for the immediate growth AuNPs. Immobilization of biocatalyst molecules is performed. PNA probe is dropped on the sensor surface and incubated. Specific target, miRNA sequence is injected to hybridize with detection probe. Herein, n-doping is caused by complementary miRNA molecules due to the attachment between miRNA and graphene material. The hybridization between PNA-miRNA molecules is monitored using the left shift of the drain source current and gate voltage curves of the sensor.

displayed by the variations in threshold voltage.[57] Henceforth, the sensitivity of the detection can be calculated by measuring the difference in threshold voltages (ΔV_{th}). In biosensing system, the surface functionalization method is essential to minimize the sensing distance by integrating crosslinking agents like 3-Aminopropyl) triethoxysilane, 3-Aminopropyl) triethoxysilane-glutaraldehyde, and (3-Glycidyloxypropyl) triethoxysilane depending on sensing material. Early detection for cancer disease is mandatory because the disease progression reveals a big impact in terms of health, financial and emotional. Thus, incorporation of FET sensing system for the detection may ease to decide the precautionary steps as early as possible.[58] A study was reported, FET was modified with gold and graphene nanocomposites[59] to detect ideal blood biomarker for cancer is miRNA.[60] However, when the function of miRNA is dysregulated it may result in numerous types of diseases like virus induced disorder and neurodegenerative disease. The FET surface decorated with gold and graphene nanocomposite was functionalized with peptide nucleic acid (PNA) as antigen capturing probe followed by PNA-miRNA immobilization (Figure 6). Hence, designed FET biosensor reveals 10 fM as the limit of detection and was tested using the human serum to validate the proposed method is potential in clinical care.

Gold-nanocomposites in blood biomarker disease analysis

Gold nanocomposites hold variety of fascinating properties and mesmerized scientist to be utilized in nanomedicine and engineering. Gold nanocomposites are known to be unique candidates for effective diagnostics and therapeutics by implementing their properties in nano-scale. Furthermore, preparation of gold nanocomposites is super-easy by solution-based technique with ultralow toxicity. Highly biocompatibility key feature of gold nanocomposites has directed the researchers to implement in biosensor application without any hesitation. Good momentum of electron transfer between the sensor surface and biomolecules is necessary for rapid and accurate detection in nanobiosensing system, which can be offered by gold nanocomposites. In sensing system, high sensitivity outcomes indicate the promising detection by integrating gold nanocomposites to increase the surface-to-volume ratio for more occurrence of coupling event between the biomolecules on the sensor active surface area. Thus, these characteristics promote gold nanocomposites to be utilized widely for the detection of blood biomarker related diseases.

Cardiovascular disease

World Health Organization reported that quarter of mortality happens yearly due to the heart attack, hypertensive heart and ischemic heart diseases. In particular, CVD risks are currently elevating among human populations both in developed and developing countries. Since, there are uncountable possibilities available in order to diagnose the disease yet the mortality rate still increasing. Research says that identification of suitable biomarker for early diagnosis is significant player for biosensor platform to conduct the detection more accurately and also in short period of time.[61] Thus, to enhance the sensing system implementation with gold nanohybrid can be practiced as they hold several outstanding key characteristics. For example, can obtain highly specific outcomes by increasing the biomolecules interaction between the bio-probe and a target (antigen), which may help to diagnose the disease more accurately in minor period of time. This is because gold nanohybrid able to improve the momentum of electrons on the electrode surface in one-way direction between the bio-probe and a target. In addition, gold nanohybrids have the tendency to boost the efficiency of biomolecules immobilization on the sensor surface for the better sensitivity purpose. Therefore, good treatment and diagnostic for such severe diseases have become a routine itinerary for state officials and also the scientific community by finding appropriate procedure and material to perform reasonable and effective treatment. Hence, enormous types of biomarkers are associated with CVD risk, such as C-reactive protein, Galectin, Cardiac troponin I and T, and myeloperoxidase (MPO). Hence, numbers of studies were conducted by implementing the biomarkers and gold nanocomposites for generating the better method.

Cardiac troponin I (cTnI) is a biomarker related to myocardial infraction and early diagnosis, extremely needed to reduce the mortality rate universally. Gold nanocomposite with graphene oxide[29] was applied to modify the sensor surface. Thus, a big active surface area was achieved to load capturing antibody, anti-cTnI. Moreover, gold nanocomposites assist in fast electron movement consequently for a greater sensitivity. The covalent binding between nanocomposites and sensing surface was supplied by aryldiazonium salt coupling functionalization for the super stability. Then, antigen cTnI was immobilized to monitor the binding by voltammetrically. The detection limit was 0.05 ng/mL as low as 100 times in contrast with the traditional method.

An electrochemical detection was proposed for the detection of Galectin-3(Gal-3) biomarker, which is responsible for the heart failure. Herein, glassy carbon electrode was decorated with N-doped graphene nanoribbons immobilized Fe-based-Metal-organic frameworks was deposited with AuNPs (N-GNRs-Fe-MOFs@AuNPs) nanohybrids[62] followed by immobilization of primary antibody (Gal-3-Ab_1). In this work, sandwich type electrochemical nanosensor was designed for the determination of Gal-3. Whereby, to increase the sensitivity of AuPt-Methylene blue (MB) (AuPt-MB) nanocomposites was utilized to enhance the movement of electron in the system. This nanocomposite is able to bind with secondary antibody (Gal-3-Ab_2). A sandwich complex was formed by coupling AuPt-MB-Ab_2 and Gal-3-Ab_1, thus, designed format of nanosensor able to lower the detection limit as 33.33 fg/mL.

An aptasensor was built for the detection of myoglobin via electrochemical method. The sensor was loaded with AuNPs together with boron nitride nanosheets to enhance the sensitivity.[63] The decorated sensor surface with gold nanocomposites was immobilized with thiolated-DNA aptamer against myoglobin. The reported detection limit was 34.6 ng/mL and precisely potential for the clinical diagnostic. An advance sandwich format electrochemical detection[64] for cTnI biomarker have reported. Here, a complex type of nanocomposite was utilized which is toluidine blue- dihydroxylatopillar[5] arene and AuNPs composites Pd/MnO_2 (TB-2HP5@Au-Pd/MnO_2). This nanocomposite was decorated on electrochemical sensor to enhance the specificity, sensitivity and stability of the sensor performance. The detection limit obtained was 2 pg/mL. The proposed design is much suitable of point-of-care diagnostics due to the better performance of the sensor.

Cancer

Cancer is a second leading cause of death worldwide.[65] Even though, extensive methods were proposed to diagnosis this malignancy, remains in challenge mode since 21st century and the survival rates of patients still remain low.[66] Subsequently, a novel early precautionary method and effective treatment are needed in demand. Till now, usual methods with a low sensitivity like biopsy, X-ray, magnetic resonance imaging and ultrasound are still being practiced until the tumor cell overcrowd whole body. Hence, hard work by scientific communities proposed a considerable method by conjugating the early diagnostic of cancer with biosensor application.

Neuron specific enolase (NSE) is a lung cancer associated biomarker was detected using the electrochemical biosensor. Graphene and gold nanocomposites were applied on the sensor surface followed by chitosan as the stabilizing agent.[67] Good sensitivity was obtained via nanocomposites capability of providing a large active surface for more biomolecular attachment. The limit of detection obtained was 0.05 ng/mL.

A great innovation was published by designing H_2O_2 sensor as early precautionary step because normal level of H_2O_2 is vital for cell activities but abnormal level of H_2O_2 directed to the development of diseases like cancer, myocardial infract and Alzheimer's disease. Thus, gold/palladium/platinum nanocomposites was utilized to modify the glassy carbon electrode (GCE).[68] Cyclic voltammetric method was applied to monitor the electrochemical properties of the designed nanosensor. The limit of detection was 2 nM with considerable stability and sensitivity.

Prostate cancer is main leading cause of death in men's population globally. An ideal immunosensor was invented for the detection of prostate-specific antigen (PSA). AuNPs and chitosan nanocomposites was incorporated on the surface of screen printed electrode (SPE) to enhance the detection system.[69] The hybridization of anti-PSA, primary antibody against PSA antigen was done followed by the immobilization of horse radish peroxide (HRP) labeled secondary antibody on the nanocomposites decorated sensor surface. Then, the functionalized sensor was immersed in H_2O_2 as substrate and methylene blue as redox mediator for the signal amplification. The performance of sensor reveals the limit of detection at 0.001 ng/mL.

An electrochemical system using the paper material by screen printing technique was proposed for cancer antigen 125 (CA125), related to the ovarian carcinoma detection. Thus, the working electrode was modified with graphene oxide/thionine/gold (rGO/Thi/AuNPs) nanocomposites[70] followed by anti-CA125 immobilization for the detection. The detection principal is based on the binding between anti-CA125 and antigen, able to reduce the current flow of thionine. The immunosensor reveals a good sensitivity with the detection limit of 0.01 U/mL.

Recent advancement was super outstanding where microfluidic technique was adopted using amino functional

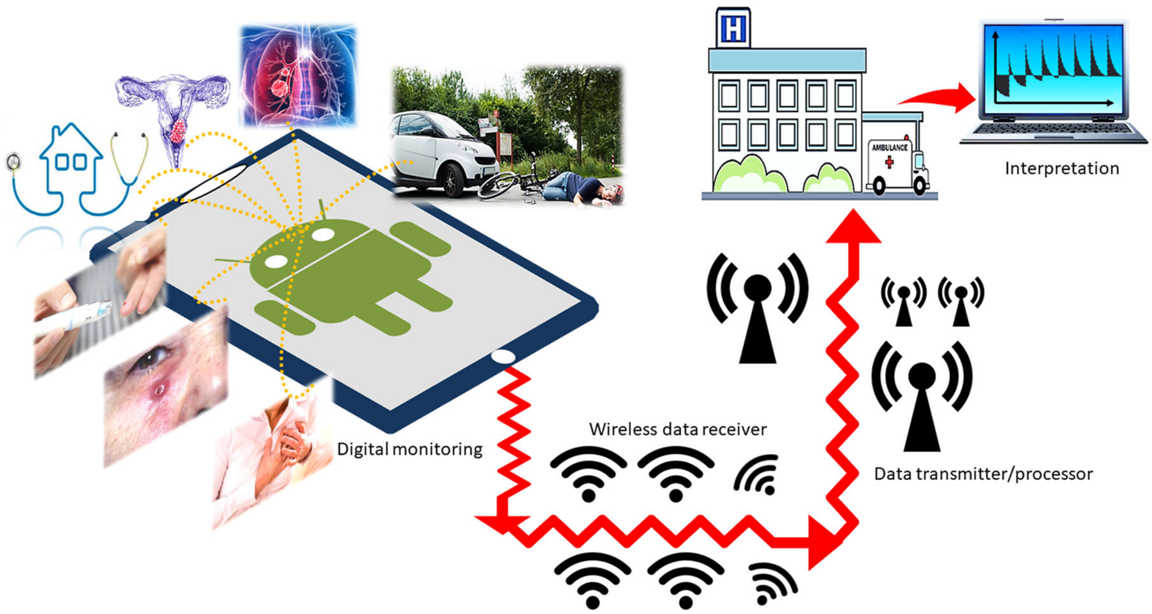

Figure 7. Remote digital monitoring widely applied in current diagnostic. It has been a promising tool after several researches based on the telediagnostic principal, reveals a good outcome. Remote monitoring is applicable for home diagnosis principle means on time diagnosis with a rapid outcome. Data from digital device will be transmitted to wireless network data receiver (WLAN, WSN, PAN, BAN). Then, will be transmitted to data processing system followed by the end terminal either to the computer at the hospital or directly to the medical practitioner's mobile phone, which links the appropriate software.

graphene (NG)-Thionin (THI)- AuNPs and Prussian blue (PB)- poly (3,4- ethylenedioxythiophene) (PEDOT)- AuNPs nanocomposites for the detection of carcinoembryonic antigen and neuron- specific enolase. Here, working electrode was modified with these nanocomposites to increase the antigen antibody capturing event and also to accelerate the rate of electron mobility. Great detection limit was achieved for both carcinoembryonic antigen and neuron- specific enolase which is 2 pg mL^{-1} and 10 pg mL^{-1}, respectively.[71]

Future advancements in digital monitoring: Telediagnosis

Although, wide methods were practiced in and out of the hospitals still the patient survival rate remains unchanged statistically. Thus, a digital monitoring system was a kick-start in healthcare department to cure and identify the status of the disease in a faster way at the early stages of the disease progression.[72] In the current hectic world, patients had undergone a post-surgery, patients with transportation matters, elderly and neonates patients are no need to concern the following-up in hospitals with the existence new technology and services in healthcare system.[73] Remote monitoring system is blooming in medical care department to provide freedom and comfortable environment for the patients rather than being hospitalization. Several advantages are engaged with the remote monitoring system like able to decline the number and cost of the hospitalization, develop effectiveness in healthcare department by utilizing the communication system, provides early and real time diagnostic and continuous disease monitoring technology. Remote monitoring encompasses with data acquisition system, data processing system, end-terminal at the hospital followed by the communication network[74] as illustrated in Figure 7. Typically, the data acquisition system comprises of sensors which is capable to transmit the data in wireless. The most commonly used sensors are wireless sensor network (WSN) and they can be classified into body area networks (BAN), personal area networks (PAN), or wireless body area networks (WBAN). Whereby, receiving and transmitting capability of data are known as data processing system. End terminal can be either computer at the hospital or mobile phone of the medical officers. Simply, communication network is connecting the data acquisition system to the processing system and transmits the processed data and results to the doctor who is linked with the communication network. Based on the fast processing, health care professionals are able to reveal the outcome quickly either for the patient needs to hospitalize or certain first-aid with the medicine that can cure the patient.[75] Research and new invention in this field are yearly increasing due to the diverse outstanding capability of the remote monitoring system, which is as big as an island. The exponential growth in remote monitoring system built a major push for the newer generation in the field. The function between sensor and internet is not only for the data acquisition but also for the real time data processing. Algorithms development based on the data are collected by wearable sensors is the future advancement, which might help users to identify how their daily routine affects the health. Implementation of information from various sources (stress level, food log, and emotion) would further expand the algorithm knowledge to optimize the analysis of past behaviors and practice to predict future activities and health impacts.[76] The accuracy of using machine learning algorithms was reported[77] to predict the outcome of huge database of patients are suffering from the heart failure and successfully recognized four different phenotypes. In addition, an implementation of noninvasive strategy has a potential now being connected to the management of diseases. In this flow, the digital approaches are widely adopted as an ideal system for healthcare systems monitoring. In that way, the professionals from healthcare are ability to consult in order to save the time and drastically minimize the expenses to the poor patients. Further, the noninvasive system with the desired devices can be automated to transmit patient's health issue without intense action by the patient using the wearable device. This system can easily opt for the common diseases such as, hypertension, diabetes, Parkinson and other neurogential diseases, in addition to monitor the oxygen levels, weight and heartbeat. However, with a new growth of remote monitoring system known as 'telediagnosis' in medical area have trigger a huge amend in terms of patient's health, environment and financial.

Conclusions

Blood biomarker disease is the foremost cause of death and worse assaults to the human health universally. The numbers of deaths are associated with the blood biomarker still remain unaffected although variety of novel strategies was implemented for a better diagnostic system. Till now, biosensing platform for blood biomarker disease detection is facing numerous challenges, but concerning about the integration of gold nanohybrid have paid a much interest in developing an ideal biosensor due to the reflection of unique features for an outstanding detection. The function of different gold nanocomposites in blood biomarker detection was clearly presented based on the super current research. The production of AuNPs followed by the configuration of gold nanocomposites with different ideal nanomaterials was evidently narrated. Besides, the integration of nanocomposites in biosensing system may be forward-looking, but there are still several obstacles and 'telediagnosis' technology advancement was discussed to resolve the hindrances. Integration of wireless communication for the early clinical care offers an important place in rapidly developing science and technology. The emergence of remote monitoring system in the healthcare denoted as a huge turning point for the medical professional. This review also comprises the future innovation in remote digital monitoring system to improve the currently available direction for blood biomarker diagnostic and treatment.

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