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Bioinspired biomaterials and enzyme-based biosensors for point-of-care applications with reference to cancer and bio-imaging

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ABSTRACT

Over the years, significant research efforts have been made to engineer numerous types of bio-sensing prototypes for various applications. For instance, bio-sensing prototypes have been configured to yield requisite single measurements to meet specific requirements for a variety of concerns including uses in the biomedical research, drug discovery, the environment, pharmaceutical, nutraceutical and process industries, etc. As compared to, in practice, traditional analytical approaches, biomaterials, and enzyme-based biosensors have notable advantages, e.g., (1) high sensitivity, (2) specificity, (3) portability, (4) cost-effectiveness, (5) possibilities for miniaturization and (6) mass production among others. However, the selection of biomaterial and enzyme for designing a bio-sensing prototype is an important issue. The current research progress and development in biosensor arena have gained special interests and thus inevitably focused on the bioinspired biomaterials and enzymes that offer new potentialities to solve the problems such as efficacy, sensitivity, biocompatibility, and biofouling, etc. for point-of-care diagnostic testing and/or in-vivo and in-vitro diagnostics. Moreover, bioinspired biomaterials and enzyme-based biosensors have applications for rapid, specific, sensitive, inexpensive, in-field, online and/or real-time detection. Among different biomaterials, chitosan, collagen, graphene, carbon nanotubes, metallic nanoparticles, and various polymer composites comprising quantum dots have been exploited in biosensors. This review covers recent advancements in the development of biomaterials and enzyme-based biosensors. A particular focus has been given to design characteristics, performance evaluation, and point-of-care applications with specific reference to cancer and bio-imaging.

1. Introduction

The development of new types of bio-sensing/bio-imaging technology has been a point of discussion among the scientific and biotechnological community, especially because of the great impact that these instrumental tools as biosensors have had in recent years. According to IUPAC (International Union of Pure and Applied Chemistry) gold book, biosensor is defined as “a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals” (IUPAC, 1997). In a biosensor device, the recognition processes rely on utilization of biochemical mechanisms. Biosensors are high precision detector devices that translate specific biological activity into a quantifiable signal (Hernandez-Vargas et al., 2018; Rasheed et al., 2018a, 2018b). The whole detection process comprises on a series of components that include, a specific receptor and analyte bind, a configuration that raises a signal, a transductor that translates the signal to an electrical quantity, a system to convert it to a parameter and the interface for its presentation. The output signal from a biosensor strongly depends on the type of transducer which may be a conventional electrochemical biosensor or others (Rasheed et al., 2018a). The information acquired reflects the system condition. The study of complex biological systems often requires data acquisition to understand, control and improve several characteristics. Thus, a multidisciplinary approach is of high interest to combine, execute and understand different conditions at the same time by combining material science, biology, physics, electrochemistry, and biochemistry among others (Mehrotra, 2016).

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To have a better understanding of biosensors, it is fundamental to present a brief history of these noteworthy devices. It all began with the ideas and innovation of Leland C. Clark, Jr., who is well known as the founding father of biosensors (Heineman et al., 2006). His unique and brilliant contributions to this field like the oxygen sensor (Also known as Clark electrode) allowed to monitor the level of oxygen in the blood of patients during cardiopulmonary bypass surgery (Heineman et al., 2006). Later, Clark presented the world another impressive invention, a very simple device that was used to measure glucose quickly and inexpensively, the first biosensor, and with it, he opened a new world which has been in constant growth ever since (Heineman et al., 2006). In 1962 Clark presented the concept of the enzyme-based device in the New York Academy of Sciences Symposium and in 1975 a new product came out as a commercial clinical analyzer by "Yellow Springs Instruments" (Wilson and Hu, 2000). It is also important to remark that there have been significant medical advances in the field of biosensors regarding the multiple applications for in-vivo measurements (Wilson and Hu, 2000). The most common and widely used for practical applications in the biomedical field include the glucose, lactate, urea, and glutamate/glutamine biosensors (Wilson and Hu, 2000; Ghica et al., 2009; Wu et al., 2009; Susanto et al., 2013; Nguyen and Yoon, 2016). In the last few years, biosensors have been used in the clinical sector for diagnosis and prevention (e.g., in-vivo glucose sensors for diabetes treatment and lactate sensors in sports medicine) (Wilson and Hu, 2000).

Research is underway around the globe to engineer numerous types of bio-sensing prototypes for various applications. Depending on the application, the choice to use bio-sensing or bio-imaging can be requisite and suitable to achieve better results. Fluorescence imaging is a sensitive technique that can identify the spatial spreading of an analyte within living cells with high confidence (Sharma et al., 2017). Quick response is witnessed for metal ions and biological species using in-vivo and in-vitro fluorescent sensors with certainty and sensitivity (Tsien, 1993). Major milestones and/or noteworthy achievements in fluorescence science for the development of different biosensor types are shown in Fig. 1 (Rasheed et al., 2018b). So far, different types of biosensors have been widely used for different applications including in biomedical research, drug discovery, defense sector, forensic science, the environment, pharmaceutical, food and beverage industries, nutraceutical, and process industries, etc. (Chen and Rosen, 2014; Justino et al., 2015; Mehrotra, 2016; Hernandez-Vargas et al., 2018; Rasheed et al., 2018a, 2018b). Biosensors can be incorporated into different applications depending mostly on the capability to produce high stability in the system's conditions, in addition to the receptor-analyte bind into the architecture that raises a signal. In order to achieve a stable device for a specific application, the correct supporting material selection is crucial for its manufacture.

Herein, an effort has been made to highlight recent advancements in the development of biomaterials and enzyme-based biosensors. The first half describes different biomaterials-based biosensors and enzyme-based biosensors. Following that the working mechanism of biosensors and bio-imaging is discussed. In the later part of the review, a particular focus has been given to point-of-care applications with specific reference to cancer and bio-imaging. Towards the end, information is also given on concluding remarks and future perspectives.

2. Biomaterials-based biosensors

A tendency to use biomaterials that are environmentally friendly, very specific and sensitive is getting huge attention. In this context, the current research progress and development in biosensor arena have gained special interests and inevitably focused on the bioinspired biomaterials (Ghica et al., 2009; Wu et al., 2009; Susanto et al., 2013; Nguyen and Yoon, 2016). In most biosensors for different applications, the base material is silicon, or petroleum-derived plastics and electrodes are made of several metals. It is important to address issues such as saturation, non-specific binding, strong affinities, and complex selections. As compared to synthetic counterparts, bio-based materials offer new potentialities with higher efficacy, sensitivity, selectivity, and biocompatibility, etc. for point-of-care diagnostic testing and/or in-vivo and in-vitro diagnostics. Moreover, bioinspired biomaterials-based biosensors have applications for rapid, specific, sensitive, inexpensive, in-field, online and/or real-time detection. Among different biomaterials, chitosan, collagen, graphene, carbon nanotubes, metallic nanoparticles, and various polymer composites comprising quantum dots have been exploited in biosensors (Wilson and Hu, 2000; Ghica et al., 2009; Wu et al., 2009; Zhou et al., 2010; Susanto et al., 2013; Fang and Ramasamy, 2015; Nguyen and Yoon, 2016; Wang et al., 2016). Table 1 summarizes various biomaterials-based biosensors along with their considerable detection limits and potential application. From the

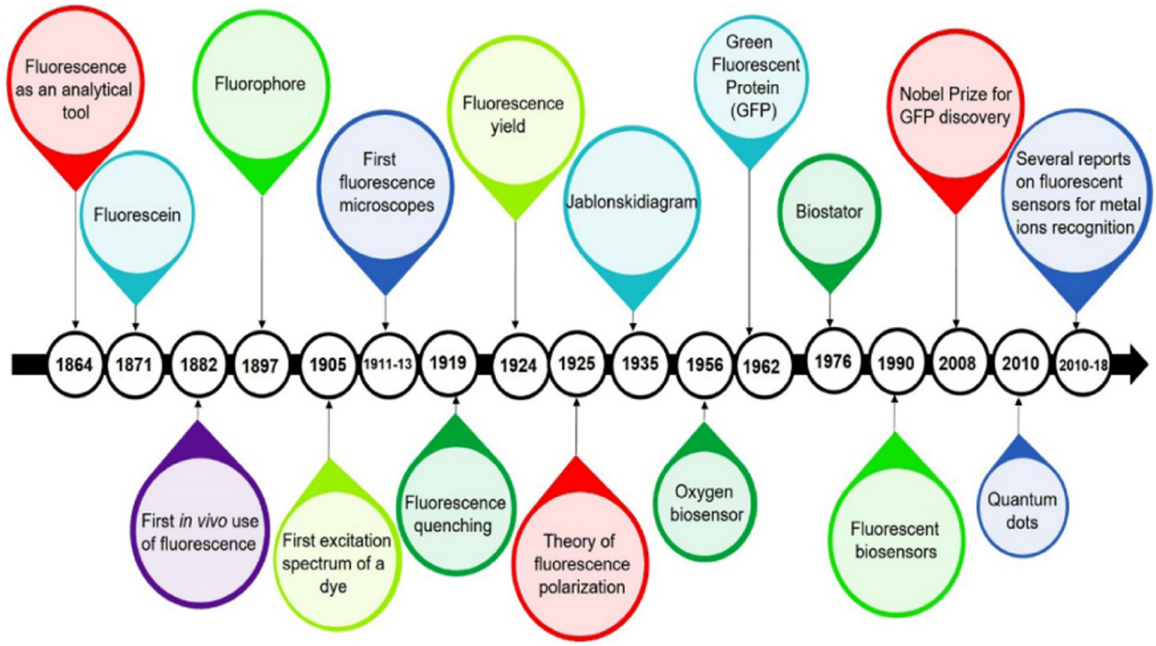

Fig. 1. Major milestones and/or noteworthy achievements in fluorescence science. Reproduced from Rasheed et al. (2018b), with permission from Elsevier.

Table 1
Biomaterials-based biosensors.

Biomaterials	Detection limit	Application	Reference
Chitosan-Au	1.7×10^{-6} M	Hydrogen peroxide	(Zhou et al., 2010)
Chitosan-glucose oxidase carbon nanotubes	NR	Glucose	(Susanto et al., 2013)
Chitosan-nickel oxide nanoparticles	10 mg/dL	Triglyceride	(Narang et al., 2013)
Chitosan-carbon nanotubes	22.6×10^{-6} M	Lactate	(Hernández-Ibáñez et al., 2016)
Chitosan-glucose oxidase multiwall carbon nanotubes	21×10^{-6} M	Glucose	(Wu et al., 2009)
Chitosan-carbon nanotubes	16×10^{-6} M	Glucose	(Ghica, 2009)
Chitosan-folic acid	430 cells/mL	Cancer cells	(Zhang et al., 2014)
Chitosan-acetylcholinesterase	7.5×10^{-9} M	Paraxon (pesticide)	(Warner et al., 2016)
Esterase-Chitosan/Gold Nanoparticles-Graphene Nanosheet	0.19×10^{-9} M	Parathion	(Bao et al., 2015)
	1.51×10^{-9} M	Malathion (Pesticides)	
Chitosan polyaniline-Au	37.89 mg/dL	Cholesterol	(Srivastava et al., 2014)
Cellulose-Graphene	0.085×10^{-6} M	Catechol	(Palanisamy et al., 2017)
Tosylated-cellulose	$0.01–0.1 \times 10^{-6}$ M	Pathogenic DNA	(Saikrishnan et al., 2014)
Cellulose-ZnO	$1–12 \times 10^{-3}$ M	Glucose	(Mun et al., 2015)
Cellulose- poly(oligoethylene glycol methacrylate)	0.1–1 μg/mL	DNA	(Deng et al., 2014)
Ferrocene functionalized hydroxypropyl cellulose	0.1×10^{-6} M	Hydrogen peroxide	(Li et al., 2016)
Cellulose-carbon nanotubes nickel oxide	7×10^{-6} M	Urea	(Nguyen and Yoon, 2016)
Graphene-modified cellulose	NR	HIV − 1	(Safavieh et al., 2015)
Cellulose-phenanthroline	2.6 ppb	Fe^{2+}	(Nawaz et al., 2018)
Carboxymethylcellulose/ZnCdS	NR	Human osteosarcoma cancer cells	(Mansur et al., 2017)
Cellulose-*graft*-poly(p-diox-anone)	75 μg/mL	Cancer cells	(Zhong et al., 2017)
Carbon nanotubes	1.0×10^{-5} M	Choline	(Wang et al., 2006)
Carbon nanotubes-Au nanoparticles gelsolin	28 p.M.	beta-amyloid	(Yu et al., 2015)
Carbon quantum dots	0.05 μg/L	Paraxon	(Wu et al., 2017)

materials' shape and surface viewpoint, the most common used geometries include micro and nanoparticles, nanotubes, nano-layers, nanorods, nano-pores, mesoporous, screen printed layers, hydrogels, sol-gels, lipid bilayers, and surface coating. The mentioned geometries are manufactured with materials that provide characteristics in a wide spectrum for its radiant, catalytic, electrical, mechanical and thermal properties (Wang et al., 2016). Biomaterials provide stable conditions to achieve catalytic recognition at a high level for its specific binding or interaction with the biological or chemical species. Moreover, a good supporting material must not interfere with the actual biological signal meaning that it does not interact with any biological molecule. Also, other physical-chemical interactions must be very low or non-existent. Some biological interactions to avoid are non-specific binding with the supporting materials and receptors, which happen very often, also natural ion transport or electric charge sources, pH variations, etc.

Carbon is one of the most used biomaterials for biosensors. Its physicochemical properties give a good base for its electrochemical activity, electrical conductivity, ease functionalization and biocompatibility (Wang and Dai, 2015). Chitosan is one of the most studied for its structural and functional properties. Chitosan is the synthetic product of deacetylated chitin, a long chain polymer that constitutes fungal cell walls, insects and crustacean exoskeletons, mollusk radulas and cephalopod beaks. Chitosan can be found in applications as films, gels, suspensions, microscopic, threads, fibers, and spheres (Suginta et al., 2013). The major cellular support protein in mammals is collagen, and it helps with many cellular processes as differentiation, maintenance, and remodeling tissue. Also, it is a very attractive biomaterial with high biocompatibility, biodegradation, capacity to form complexes with biomacromolecules as proteins and nucleic acids. Especially, the complex with DNA is the most attractive to biosensors type to use collagen (Ning et al., 2013). To produce biosensors with lower ecological footprint, the cellulose substrate is one of the most widely used material. It provides a good support material with the particularities to be economical, lightweight, renewable, easily disposable, high surface area, intrinsic capillary fluidic, bending and dry storage among others. Cellulose is compatible with several other linking molecules to functionalize specific areas. Also, it has an insulation property, and it can be doped with metals to generate electrodes or conducting structures. Printing on cellulose paper is the common method to produce the biosensors, which makes the processes easy to transfer into industrial production. This kind of biosensors is reaching the target of health care systems in developing countries due to all the advantages mentioned (Kim et al., 2014).

Gold, silver, platinum, and palladium are some of the pure, noble metals widely used in biomedical, environmental, and energy applications. Also, noble metals oxides used for biosensors include cerium, copper, nickel, iron, cobalt, manganese, zinc, titanium, tin, cadmium among others. The principal geometries used with noble metals are nanostructures, such as nanoparticles, nanorods, and other nanoporous thin films. Noble metals provide advantages with its properties of stability, conductivity, biocompatibility, and low cytotoxicity in addition to its electric, magnetic and optical characteristics (Syshchyk et al., 2015; Chen et al., 2016; Maduraiveeran et al., 2018).

The materials mentioned above have been used in biosensors with different strategies. For instance, cellulose and chitosan as a support structure for the whole device or electrode fabrication with enhanced sensitivity, contrast, surface area, conductivity. In most cases, a composite is produced involving several polymers and materials to fulfill the mentioned biosensors components. Novel materials research has focused on composites as a consequence of the technological viability to control material deposition precisely. Composites are materials integrated by two or more materials with different properties leading to a new set of properties in the composite. The trending approach is to use biomaterials that include properties of biocompatibility, biodegradability, encapsulation, flexibility, disposability, bio-recognition, electromagnetic, optical, fluorescence, dielectric, etc. Polymers composites are some of the preferred types of composites for sensors and biosensors applications. The main characteristics are a high integration with other materials and the possibility to use different geometries (Grieshaber et al., 2008).

Quantum dots are nanoparticles with special optical and electrical properties. This type of nanoparticles can emit light with a proper energy excitation. Moreover, quantum dots have semiconductor properties and are the smallest possible semiconductor piece produced. The last thirteen years advances in technology allowed its accurate manufacture that is in the quantum length scale (Vukmirović et al., 2011). Synthesizing technique is also a way to classify different types of quantum dots. The main methods are electrostatic, self-assembled and colloidal. Each fabrication can lead to a specific size range, for electrostatic quantum dots the typical sizes are in the order of 100

nanometers. For self-assembled quantum dots typically achieve between 15 and 30 nanometers and in a higher precision between 3 and 7 nanometers. Colloidal quantum dots, also called nanocrystals, with diameters as low in the range of 2–4 nanometers (Vukmirović et al., 2011). Applications of quantum dots have an impact on basic and applied fields. One of the sound themes is artificial atom creation with a controlled number of electrons for fundamental physical phenomena, namely fermions, single electron transport, Coulomb blockade effect, and Kondo. Another topic is the prospect for quantum information processing using the state of the dot as a qubit. Practical applications are related to high efficient photovoltaic cells, nanocrystal-based LEDs, lasers, optical amplifiers, single photon sources, photodetectors and fluorescent bio-imaging (Vukmirović et al., 2011).

3. Enzyme-based biosensors

Enzymes are biological catalysts for particular reactions and can bind themselves to the specific substrate. This catalytic action is made use of in the biosensor (Eggins, 2013). It is fundamental to know the role of the enzyme in bio-sensing technology to understand the main characteristics and applications of enzyme-based biosensors. Enzymes as biological elements provide the major selective element in biosensors. These biological elements must be substances that can attach themselves to one particular substrate but not to others. The four main groups of materials that can do this are enzymes, antibodies, nucleic acids, and receptors. For enzymes used in biosensors, the mode of action involves oxidation or reduction which can be detected electrochemically (Eggins, 2013). Schematic illustration of enzymatic biosensor based on (A) mediated electron transfer and (B) direct electron transfer (DET) is shown in Fig. 2 (Fang and Ramasamy, 2015). Enzymes overcome some problems; a good enzyme stabilization can be achieved to prevent non-specific binding and avoid saturation (Kobos, 1987; Wilson and Hu, 2000).

The most common type of enzymes used to engineer enzyme-based biosensors are peroxidases, oxidoreductases, amino oxidases and polyphenol oxidases (Mehrotra, 2016). Nevertheless, according to Wilson and Hu (2000), there are two subclasses that are most frequently encountered, the oxidases and dehydrogenases. Eqs. (1) and (2) shown the enzyme-substrate based reaction sequence. Whereas, the Eqs. (3) and (4) are more specific with reference to the glucose oxidase (GOx).

$$S_{red} + E_{ox} \rightarrow S_{ox} + E_{red} \quad (1)$$

$$S'_{ox} + E_{red} \rightarrow S'_{red} + E_{ox} \quad (2)$$

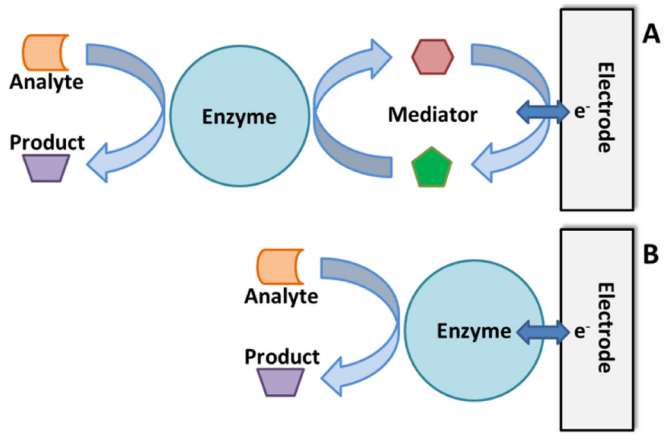

Fig. 2. Schematic illustration of enzymatic biosensor based on (A) mediated electron transfer and (B) direct electron transfer (DET). Adapted from Fang and Ramasamy (2015), an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

Herein, S_{red}, E_{ox}, S_{ox} and E_{red} correspond to substrate reduced, enzyme oxidized, substrate oxidized, and enzyme reduced, respectively.

$$G + GOx \rightarrow GA + GOr \quad (3)$$

$$O + GOr \rightarrow HP + GOx \quad (4)$$

Where $G(S_{red})$,$GOx(E_{ox})$,$GOr(E_{red})$,$GA(S_{ox})$,$O(S'_{ox})$ and $HP(S'_{red})$ correspond to glucose, glucose oxidase, glucose oxidase reduced, gluconic acid, oxygen and hydrogen peroxide respectively (Wilson and Hu, 2000).

Primarily, there are two well-known types of enzyme-based biosensors, optical and electrochemical sensors for in-vivo detection (Wilson and Johnson, 2008; Ispas et al., 2012). The electrochemical have multiple applications in clinical monitoring (e.g., self-monitoring of blood glucose levels for diabetes treatment) and their usage, due to its ease of operation, simplicity and sensitivity is perfect for hormone determination (Ispas et al., 2012; Bahadir et al., 2015). The optical biosensors have applications in biomedical research, healthcare, and pharmaceuticals (Fan et al., 2008).

4. The working mechanism of biosensors

Sensors and biosensors can be developed in a large number of variations, depending on the possibility to detect the parameter to measure. Some of the most common sensor types are related to direct physical or chemical properties. Sensors for physical properties include magnetic, radioactivity, optical, pressure, light, flow, etc. Sensors for chemicals include pH, oxygen, mass, CO_2, and many other chemical species. The principles that dictate electrochemical biosensors are working mechanisms to provide a detectable change in a system require the following ideas. The main quantifiable parameters used to register a change are related to electric signals and imaging. Most common electric properties used are current, voltage and impedance. For imaging, it is the capability to produce enough contrast with the surroundings and provide accurate localization of the objective with the proper intensity (Rasheed et al., 2018a).

A biosensor detects biological or chemical species though transducers that are capable of interacting with them. The transducer can be made of pure electrical interfaces or bio-receptors. The transduction process usually requires three electrode types, a reference, auxiliary or counter, and a working electrode held in an isolating material. The functions of each electrode are important to keep a good measurement. The reference electrode sustains a stable potential to make a comparison with the working electrode. The working electrode is responsible for transducing the electrochemical reaction. The auxiliary or counting electrode makes a connection to an electrolytic solution and allows establishing a current to the working electrode. Once the three electrodes are assembled in the electrochemical cell, they enable different types of measurements to understand how the electrical parameters (current, voltage and impedance) are measured. Current or amperometric devices measure the electron flow resulting from oxidations or reduction of electroactive species in a reaction. In the case of biosensors, a biomolecule is responsible for the electrochemical reaction with the sensible species. Typically, the current is measured at a constant potential (Grieshaber et al., 2008).

Voltage or potentiometric devices measure the accumulation of charge or potential at the working electrode. The potential difference between working and reference electrodes held by the electrochemical reaction is measured when the current is zero or near zero. Potentiometric sensors provide good measurements at low concentrations and can work with small sample volume (Fisher, 2010; Ronkainen et al., 2010). Impedimetric measurements are related to the properties of resistive and capacitive properties of materials. This is based on the response to a perturbation of a system in equilibrium by a sinusoidal excitation signal at a small amplitude. Impedance can be scanned in a very wide range of frequency of alternating current which is highly

valued in characterization, analysis, and study of the system. Also, capacitive and resistive properties can be measured separately again as biosensor mechanisms (Chang and Park, 2010). More details for each technique to measure electrochemical reactions have been reported in earlier reports (IUPAC, 1997; Grieshaber et al., 2008).

5. The working mechanism of bio-imaging

Bio-imaging is a medical field to study or investigate the light interactions with biological organisms, tissues, cells, and molecules to produce images. It includes all methods that allow the visualization of biological processes without invasion of organisms and has low interaction with the phenomena. The aim is to achieve two and three dimensions' images. The methods developed uses light, fluorescence, electrons, ultrasound, X-rays, magnetic resonance and positrons. Bio-imaging, specifically molecular imaging is getting progress in the successful in-vivo monitoring and recording of spatiotemporal distributions of molecules and cells. Moreover, it is based mainly on fluorescent nanoparticles and near-infrared fluorescence imaging (Yao et al., 2014). The reason is that a window of the infrared spectrum has a very low interaction with tissue, deoxyhemoglobin, oxyhemoglobin, lipids, and water. This region is called the "diagnostic window" and the wavelength is between 650 and 900 nanometers (Stefflova et al., 2007).

Nowadays, bio-imaging technology growth thanks to the understanding of the phenomena of fluorescence, fluorescent resonant energy transfer (FRET), fluorescent lifetime measurement, and multiphoton microscopy (Gopich and Szabo, 2012). The development of fluorescent labels has been intense regarding its applicability, characteristics and high detection (Waggoner, 2006). Photoluminescence or fluorescence labels are molecules that interact with biomolecules and light. For light interaction process, the molecules gain energy by excitation with particular wavelength radiation and lose energy by emitting light in a longer wavelength that is collected as an image (Combs and Shroff, 2017). Interactions with biomolecules take place on free amino groups. Also, fluorescent labeling has the characteristics of fast acquisition, multicolor labels, sensitivity, localized signal, low interaction, robust and labeling process is straightforward when functional groups are present (Waggoner, 2006).

Novel materials use the same working principles to integrate bio-imaging progress. The development of nanoparticles, quantum dots and composites are now some of the more suitable labels for fluorescent bio-imaging (Resch-Genger et al., 2008). Several techniques and methods for fluorescence microscopy include, from basic to complex, wide-field, total internal reflection, laser-scanning confocal, multi-point/slit confocal, two-photon, structured light microscopy, super-resolution structured light microscopy, simulated emission depletion, single molecule, light sheet, and lattice light sheet with structured light microscopy (Combs and Shroff, 2017).

6. Point-of-care applications

Biosensors have been fundamental in point-of-care applications for multiple areas such as biomedical research, health-care, pharmaceuticals and environmental monitoring for its use as an analysis and research tool (Fan et al., 2008). Among different sectors, the medical field is in constant development and evolution as many recent discoveries and advances have been made for effective disease treatments. Regarding sensing technology, biosensors have been extremely helpful in the detection process of a substance and, in recent years, emerged as an opportunity to address research gaps for in-vivo measurements. Biosensors are making its way through the field of clinical monitoring due to multiple factors such as the low cost of production, the possibility of mass production and advantages such as precise detection and high sensitivity (Ispas et al., 2012). Different biosensors with notable point-of-care applications with specific reference to cancer and bio-imaging are summarized in Table 2.

6.1. Biosensors for cancer diagnosis

Cancer continues to be the most feared global disease and the second leading cause of death in the United States. Cancer can take over 200 distinct forms, including breast, lung, prostate, ovarian, hematologic, skin, and colon cancer (Bohunicky and Mousa, 2011). Worldwide there has been a serious health concern for women, breast cancer. Based on scientific literature evidence, around 23% of all the cases, breast cancer is the second largest number of death cases in women (Singh and Nalwa, 2011). Despite the existence of several types of breast imaging technologies, such as ultrasound, optical, tomography, mammography, sonography, molecular breast imaging, thermography, nuclear, infrared and thermal imaging techniques, none of them is well established to capture an image breast cancer with hundred percent certainty. There exist many developing countries that do not even have access to clinical facilities mentioned above. In this context, the development of new imaging tools with better contrast for biological imaging for breast and other types of cancer can play a momentous role in early breast cancer detection by screening, diagnosis, and prevention (Singh and Nalwa, 2011). It is also necessary to have efficient and low-cost detection and treatment techniques (Mittal et al., 2017). Scientist discovered that it existed some limitations and the situations of false positive or negative results of the previous diagnosis techniques (Mittal et al., 2017). Because of the limitations and misleading results mentioned before, it is necessary to develop detection methods with some characteristics, e.g., highly sensitive, non-invasive, specific and cost-effective devises. The parts of a biosensor for breast cancer diagnosis consist of a biomarker (target molecule), bio-receptors (recognition element) and a compatible transducer. All of the previous components are important and decide the technical role and decide the technical specifications of the biosensor device (Mittal et al., 2017). There exist various researchers that have made attempts to develop biosensors for early diagnosis of breast cancer using electrochemical transducers and overexpressed biomarkers such as a mutated BRCA1 gene, VEGF, EGFR, MUC1, CEA, HER-2, CA15-3, and miR-21 (Mittal et al., 2017).

The surface functionalization, optical properties, in-vitro and in-vivo imaging, and photothermal effects of gold nanorods have been described in an earlier study (Tong et al., 2009). In an earlier study, Zhu et al. (2006) developed biocompatible nano-template engineered nanoparticles containing gadolinium (Gd) as a potential Magnetic Resonance Imaging (MRI) contrast agent. Nanoparticles with a diameter of 130 nm having surface chelating functions were made. The uniform distribution of $Gd3+$ on the surface of the nanoparticles was characterized and confirmed using inductively coupled plasma atomic emission spectroscopy and Scanning Transmission Electron Microscopy (STEM). Nanoparticles were found to be hemocompatible and enzymatically metabolized containing accessible Gd ions on their surface, which induced relativities in the bulk water signal showing their usefulness as next-generation MRI tumor contrast enhancement agents. The sensing prototypes/probes enable two-point characterization of cells and allow for discrimination of premalignant cells from differentiated epithelial cells and normal cells under an in vitro setting (Kannan et al., 2018). Fig. 3 illustrates the identification of breast cancer cells using Fluorescence-based GLUT5 with fluorescent 1-AM-coumarin conjugates ManCou1 and ManCou2 (Kannan et al., 2018).

Among cancer-related deaths, lung cancer is another most common cause which is typically divided into two broad categories, i.e., (1) non-small cell lung cancer (NSCLC), and (2) small cell lung cancer (SCLC) (Hatzakis et al., 2002; Cheng et al., 2015). For a clear differentiation between both, above-mentioned, lung cancer types, Cytokeratin fragment 21–1 (CYFRA 21–1) and neuron-specific enolase (NSE) are useful tumor markers (Hatzakis et al., 2002). Several, in practice, sensor-based detection methods i.e., enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and chemiluminescence immunoassay (CLIA) have a number of disadvantages such as lengthy steps and complex handling in ELISA based detections, specialized equipment and long

Table 2
Point-of-care applications with specific reference to bio-imaging.

Biosensor type	Remarks	Bio-imaging or detection	Reference
Quartz crystal microbalance	Reusable	Cancer cells	(Zhang et al., 2014)
Two-photon fluorescent	*In vivo* pneumonia diagnose	LTA4H marker	(Wang et al., 2018)
Transmission electron microscope	RGB light emissions conjugated polymers	Tumor cell and diagnosis	(Zhong et al., 2017)
Photoacoustic imaging	High spatial resolution	Tumor profiling	(Sun et al., 2017)
Near Infrared Fluorescence	In vivo and surface functionalization	Tumor targeting	(E.M. Kim et al., 2017)
Fluorescence, TEM	Blue/green/yellow carbon nanoparticles folic acid, riboflavin, and lactose	HepG2 cells	(Ali et al., 2018)
Two-photon microscopy	Dual-color emission	Ion-channel activation	(Kim et al., 2017b)
Two-photon fluorescence	Activatable	Tumor cells	(Liu et al., 2018)
Photothermal imaging	Cancer therapy	Tumor cells	(Zhang et al., 2017)
NIR photothermal heater	Multifunctional nanoplatform (drug delivery and cancer therapy)	Tumor cells	(Zhang et al., 2018)
DNA-graphene-polypyrrole (DGP) based biosensor	This research additionally permits an early detection of colorectal cancer and the mapping and expertise of the method related to the area of the mismatch repair.	Colorectal cancer (CRC)	(Hemmanur et al., 2018)
Electrochemical biosensor	A promising platform for early stage diagnosis of cancer	Human breast carcinoma cells (MCF−7), human lung adenocarcinoma cells (A549) and human umbilical vein endothelial cells (HUVEC)	(An et al., 2018)
Graphene field effect transistor (GFET) immunosensor	The GFET biosensor could find applications in a broad range of medical diagnostics in addition to cancer, such as neurodegenerative (Alzheimer's and Parkinson's) and cardiovascular disorders	Human Chorionic Gonadotropin (hCG)	(Haslam et al., 2018)

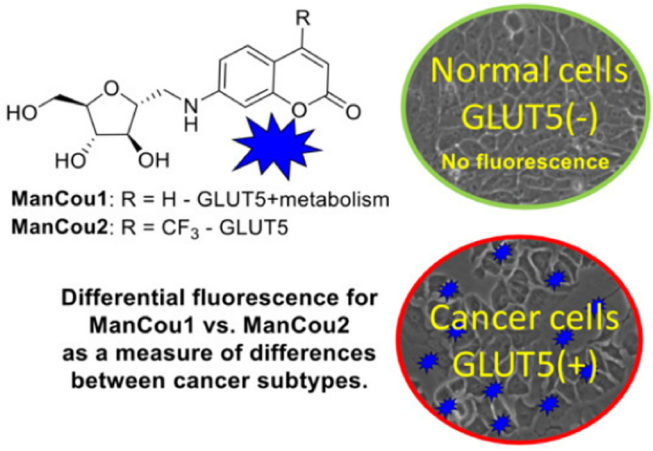

Fig. 3. Fluorescence-based identification of breast cancer cells and discrimination of cancer phenotypes through GLUT5 with fluorescent 1-AM-coumarin conjugates ManCou1 and ManCou2. Adapted from Kannan et al. (2018), an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

analytical time requirements in RIA based detections, and expensive instrumentation and handling issues in CLIA based detections (Cunningham et al., 1990; Pujol et al., 1993; Takada et al., 1995; Orlino et al., 1997; Zhang et al., 2011; Fu et al., 2012; He et al., 2013; Luo et al., 2013). In this context, a biosensor allowing rapid and multiplexed detection of CYFRA 21–1 and NSE is in demand. Recently, Cheng et al. (2015) developed a field effect transistor (FET) based biosensor for label-free, sensitive, real-time, and multifunctional bio-sensing of CYFRA 21–1 and NSE. The developed biosensor was fully capable of quantitatively detecting these tumor markers in both phosphate-buffered saline and human serum (Cheng et al., 2015). Aiming to recognize a specific cancer biomarker, the optimal recognition materials should be executed as the receptor particle while designing a biosensor. This is because the sensitivity, selectivity, and specificity of the recognition/sensing materials play a critical role in the overall success rate of the device. Synthetic (artificial) molecular recognition elements have also been fabricated as affinity materials and used for analyte detection and analysis and reported elsewhere (Tothill, 2009). Very recently, Alvau et al. (2018) developed an enzymatic biosensor based on acetylcholine esterase (AChE) and choline oxidase (ChOx) for therapeutic drug monitoring of anticancer drug Irinotecan (a most widely used drug in the treatment of colorectal cancer). In another study, a novel electrochemical microRNA (miRNA) detection method based on enzyme amplified bio-sensing of mir21 from breast cancer cell lysates of total RNA was demonstrated (Kilic et al., 2012). From the detection limit and specific perspectives, the newly developed alkaline phosphatase based amplified bio-sensing method was detailed and comparable with the conventional guanine oxidation based assay (Kilic et al., 2012).

6.2. Biosensors for bio-imaging

Owing to several characteristics such as a tunable emission wavelength, a narrow and symmetrical emission band, excellent biocompatibility, biodegradability, low cost and eco-friendliness, high selectivity and sensitivity, etc. quantum dots based materials are one among the most extensively used and exploited in biosensors for several bio-imaging applications (Zhou et al., 2006; Moussodia et al., 2010; Yuan et al., 2010; Zhu et al., 2016). For example, tracing live cells, and real-time monitoring of target tissues, etc. (Yang et al., 2009; Gao et al., 2010; Liu et al., 2011).

Recently many progress in the synthesis, modifications, and applications of carbon dots have been made with their particular involvement in the biomedical field for cell bio-imaging and as biosensors agent (Ding et al., 2013; Zhu et al., 2013; Wang et al., 2015; Guo et al., 2017; Zou et al., 2017; Mehdi et al., 2018). The development of high-performance photoluminescent carbon dots for multicolor patterning, sensors, and in-vitro and in-vivo bio-imaging have been reported (Zhu et al., 2013; Wang et al., 2015). Very recently, Mehdi et al. (2018) reported a notable performance of newly developed multifunctional core-shell silica microspheres with a small particle size in self-carrier decomposition and fluorescent bioimaging. A carbon dots based on the biocompatible photo-luminescent material was prepared and inserted in a silica shell around the Ptx-SiO_2 core by aiming to achieve the fluorescents properties of the synthesized material.

Besides other optical properties, the long-term chemical and photostability features of quantum dots make them ideal materials for in-vivo

targeting and imaging applications (Michalet et al., 2005). Ruan et al. (2007) prepared Tat peptide-conjugated quantum dots (Tat-QDs) and exploited to study the complex behavior of nanoparticle probes in live cells. Kumawat et al. (2017) fabricated graphene quantum dots (GQDs) using leaves from *Mangifera indica* (mango) as its carbon precursor, hence addressing them as mGQDs. The developed mGQDs were used as fluorescence bio-imaging probe and intracellular nanothermometry, attached at the cell cytoplasm, allowing it to be used in-vivo. Likewise, several other studies have also demonstrated the use of various natural sources such as honey, milk, ground coffee, and water chestnut for the synthesis of natural carbon-based quantum dots and used for bio-imaging and/or in other sensing applications (Zhu et al., 2012; Yang et al., 2014; Wang et al., 2016; Hu et al., 2017). Sahu et al. (2012) developed carbon-based quantum dots from the juice of *Citrus nobilis deliciosa,* which were used for cellular imaging.

7. Conclusion and future recommendations

In conclusion, the exploitation of diverse concepts from engineering, physics, chemistry, materials science, biology, medicine, and medical sciences has made great contributions to nanotechnology-based novel materials and devices. The last few decades have witnessed breakthroughs in nanotechnology-based novel diagnostic techniques, detections systems for diagnosis and treatment of various types of disease, including cancer. The major advances in biosensors have come through the needs of medical care. In this particular review, the medical applications of biomaterials and enzyme-based biosensors were discussed along with the importance of sensing technology in the clinical sector. Biosensors have been a useful, accurate and cheap tool that has helped to prevent, diagnose and treat some diseases like Diabetes and Breast Cancer. In the medical field, there is a great opportunity for further research and improvement of bio-sensing technology for early-stage breast cancer detection. Some other applications of biosensors that prove constant development in the clinical analytical sector are the urea, ethanol and lactate biosensors. In addition, the inclusion of biomarkers pattern software along with microfluidics can make bio-sensing systems and/or devices highly efficient, sensitive, selective and more appropriate for point-of-care applications (Ahmed et al., 2018; Sosa-Hernández et al., 2018). With the development of more cost-effective tools such as enzyme-based biosensors, the clinical field can be in constant growth and improvement for the well-being of its patients.

Despite the key developments in the biosensor arena, there is still a challenge to construct improved and highly reliable devices to avoid instrumental drift and other crucial challenges, such as multiplex analysis of several biomarkers where arrays of sensors need to be developed. In this context, an in-depth study is needed to present the future trends in the biosensor field and other related areas that will ultimately have a marked influence on the development of new bio-sensing strategies in the future. In summary, the advent of “smart” and user-friendly electrochemical biosensors augers well for the future. It is clear from the data discussed above that the future of electrochemical biosensors will rely on the success of emerging sophisticated technologies, both at micro and nano level, along with in-depth contributions from electronics and/or bioelectronics, bionanotechnology, materials science, biology, medicine, biochemistry, and physics.

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Conflicts of interest

The authors declare no conflict of interest.

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