Point of care (POC) medical biosensors for cancer detection

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8.1 Introduction

Point of care (POC) medical devices could be defined as medical/clinical analysis at or near the location of patient care (Kost et al., 2006; Nichols, 2002). One of the first POC tests reported in the literature was documented in 1550 BCE, wherein an Egyptian researcher used ants to evaluate glycosuria (excretion of glucose into the urine) in patients suspected of having diabetes mellitus (DuBois and Clarke, 2014). Hence, the goal of POC devices is to provide fast, convenient and easy-to-use diagnostic testing that shortens the therapeutic turnaround time when compared with testing at a core laboratory. These devices can provide rapid diagnosis in a hospital or in resource-poor countries that lack a core laboratory infrastructure, thus permitting immediate or remote clinical management decisions to improve patient medication, cure or direct any changes in medical procedure. These POC biosensor devices can be classified by their biorecognition and transducer systems, as depicted in Fig. 8.1.

One of the major challenges in the medical application of POC biosensors is to make possible the use of these devices to diagnose and monitor severe diseases like cancer. Hence, at the start of the chapter, it is important to define cancer and its types to show how each cancer can be detected using POC biosensors with some approaches in the development of medical biosensors for cancer detection.

8.2 Definition of cancer

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells, and results in death if its spread is not controlled. Damage to a gene or specific molecule could disrupt communication amongst cells, ultimately leading to the termination of all biological functions that sustain a living organism. Cancer is caused by external factors, such as tobacco, infectious organisms and an unhealthy diet, and by internal factors, such as inherited genetic mutations, hormones and immune conditions. These factors may act together or in sequence to cause cancer, and manifestation of the disease may occur at variable periods between the exposure to external carcinogenic factors and detection of cancer markers (American Cancer Society, 2015a; Simon, 2010) or after changes in the genetic code and the formation of cancer cells (Fig. 8.2). Proto-oncogenes will be discussed in Section 8.3.

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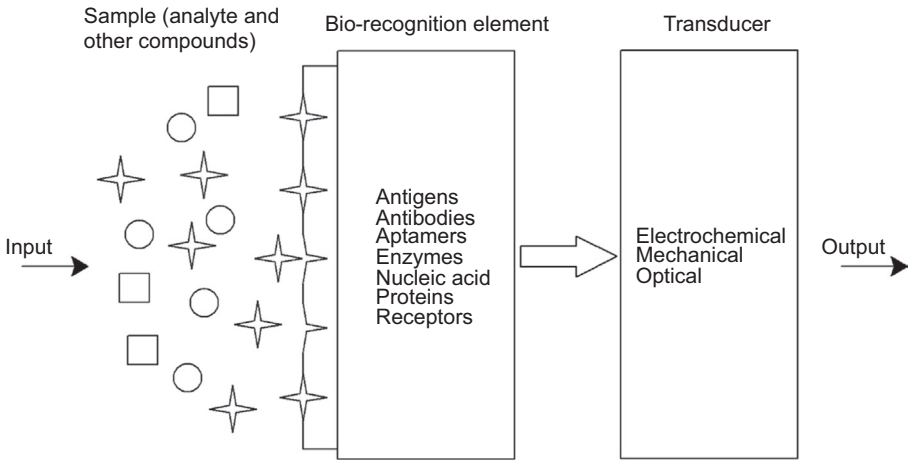

Figure 8.1 Schematic diagram of POC biosensor device.

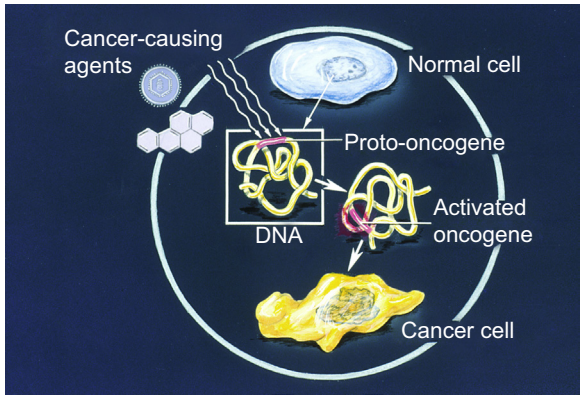

Figure 8.2 Conversion of a normal cell to a cancer cell, when an oncogene is activated. This image (with the ID 2351) was released by the National Cancer Institute, an agency that is a part of the National Institutes of Health. The image is in the public domain and can be freely reused.

8.3 Cancer biomarkers

Biomarkers are defined by the National Cancer Institute at the National Institutes of Health (http://www.cancer.gov/) as 'biological molecules found in body fluids or tissues that can sign a normal or abnormal process, or of a condition or disease'. They can also be used to check how well the body responds to a treatment for a disease or condition. There is tremendous variety in biomarkers, which can include proteins (eg, an enzyme or receptor), nucleic acids [eg, a microRNA or other noncoding ribonucleic acid (RNA)], antibodies and peptides, amongst other categories. A biomarker can also be a collection of alterations, such as gene expression, proteomic and metabolomic signatures. Genetic biomarkers may be inherited and detected as sequence variations

in germ line deoxyribonucleic acid (DNA) isolated from whole blood, sputum or buccal cells, or they may be somatic and can be identified as mutations in DNA derived from tumour tissue (Henry and Hayes, 2012).

Besides being found in body fluids and tissues, some markers are associated with the smell of breath and skin. The correlation between breath smell and disease has been reported in literature (Matsumura et al., 2010; Horvath et al., 2009; Silveira-Moriyama et al., 2008), and these signature molecules are volatile organic compounds found at concentrations lower than the ppb range. These markers are formed as metabolic products generating a 'fingerprint' of the diseased state (Simon, 2010).

The choice for a correct candidate as a biomarker to be monitored or detected will reflect various pathophysiological conditions of the biological system and enable better disease diagnosis and/or treatment outcomes, because it can indicate the disease stage of the patient the best treatment option (Chen et al., 2015). A unique marker can signalize different diseases or different stages of the same disease. Table 8.1 summarizes some of the important biomarkers that can be used to detect different cancer types, and they can be employed for different clinical purposes: prognosis, diagnosis, staging, monitoring, screening and selection of therapy (Ludwig and Weinstein, 2005).

8.4 Types of cancer

In this section, the most common types of cancer according to the National Cancer Institute and American Cancer Society are listed (National Cancer Institute, 2015b) (Table 8.2). They were chosen because of their high incidence and mortality, and due to the potential application of POC sensors to monitor these types of cancers. Based on our literature search, we found that POC devices have not been developed for some of the cancers listed in Table 8.2.

8.4.1 Breast cancer and point of care devices

Breast cancer is a type of cancer that affects mostly women (only 1% of men are affected) and is the most diagnosed cancer worldwide, with more than 230,000 estimated new cases in 2015 in the United States alone (National Cancer Institute, 2015b). However, the chances of cure for breast cancer are above 80%, in contrast to lung cancer, in which approximately 30% of the cases can be cured (American Cancer Society, 2015a). Although the number of breast cancer cases has decreased in the last few years, breast cancer is still a cause for concern, as it is the second largest cancer with a high mortality rate in women; lung cancer tops the list, with the highest mortality. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue.

Because cancer progression results in modification of nucleic acids, as illustrated by Fig. 8.2, these large molecules are commonly used as main targets to detect cancer.

Table 8.1 Biomarkers used to detect different cancer types and their clinical use

Biomarker	Cancer type	Clinical use
Chromosomes 3, 7, 9 and 17	Bladder	Screening and monitoring
NMP22	Bladder	Screening and monitoring
Fibrin/FDP	Bladder	Monitoring
BTA	Bladder	Monitoring
High molecular weight CEA and mucin	Bladder	Monitoring
CA 15-3	Breast	Monitoring
CA 27-29	Breast	Monitoring
Cytokeratins	Breast	Prognosis
Oestrogen receptor and progesterone receptor	Breast	Selection for hormonal therapy
HER2/NEU	Breast	Prognosis, selection of therapy and monitoring
21 gene recurrence score	Breast	Prognosis
BRCA1 germline mutation	Breast and ovarian	Estimated risk of developing cancer
Pap smear	Cervical	Screening
CEA	Colon	Monitoring
Epidermal growth fat or receptor	Colon	Selection of therapy
KRAS mutation and anti-EGFR antibody	Colon	Selection of therapy
KIT	GIST	Diagnosis and selection of therapy
CA 125	Ovarian	Monitoring
CA 19-9	Pancreatic	Monitoring
PSA (total)	Prostate	Screening and monitoring
PSA (complex)	Prostate	Screening and monitoring
PSA (free PSA %)	Prostate	Benign prostatic hyperplasia versus cancer diagnosis
α-Fetoprotein	Testicular	Staging
Human chorionic gonadotropin-β	Testicular	Staging
Thyroglobulin	Thyroid	Monitoring

BRCA, breast cancer biomarker; *BTA*, bladder tumour-associated antigen; *CA*, cancer antigen; *CEA*, carcinoembryonic antigen; *EGFR*, epidermal growth factor receptor; *FDP*, fibrin degradation protein; *KIT*, proto-oncogene c-Kit; *KRAS*, colorectal cancer mutation biomarker; *NEU*, human epidermal growth factor receptor 2; *NMP22*, nuclear matrix protein 22; *PSA*, prostate-specific antigen.
Data extracted from Ludwig, J.A., Weinstein, J.N., 2005. Biomarkers in cancer staging, prognosis and treatment selection. Nature Reviews Cancer 5, 845–856 and Henry, N.L., Hayes, D.F., 2012. Cancer biomarkers. Molecular Oncology 6, 140–146.

Briefly, these biosensors or nucleic acid sensors exploit the interaction of the analysed target with immobilized complementary nucleic acid (biorecognition layer) at the surface of the sensor/transducer, as shown in Fig. 8.3. As the complementary nucleic acid has a specific sequence, the recognition is very specific, conferring this sensor a higher specificity. Hence, after recognition by the biorecognition element, the signal

Table 8.2 Number of deaths for each common cancer type (26 January 2015)

Cancer type	Estimated deaths
Thyroid	1950
Melanoma	9940
Endometrial	10,170
Kidney (renal cell and renal pelvis) cancer	14,080
Bladder	16,000
Non-Hodgkin lymphoma	19,790
Leukaemia (all types)	24,450
Prostate	27,540
Breast (female–male)	40,440
Pancreatic	40,560
Colon and rectal (combined)	49,700
Lung (including bronchus)	158,040

Retrieved from National Cancer Institute at the National Institutes of Health, 2015b. http://www.cancer.gov/cancertopics/types/commoncancers.

can be transduced by different types of optical, mechanical (Quartz Crystal Microbalance and acoustic sensors) and electrochemical techniques (Tothill, 2009; Soper et al., 2006). Fig. 8.3 shows an example of an electrochemical readout, based on guanine oxidation mediated by a ruthenium complex in solution. If the number of guanine molecules increases in the recognition layer, the signal increases, and if the nucleic acid recognized is expressed in cancer, this sensor can be used a good candidate for rapid screening of cancer.

Being an aggressive disease, breast cancer should be detected and treated early in a simpler and faster way, if possible, to achieve better results. With this view, some research groups have worked on nucleic acid sensors with the possibility of miniaturization to make the diagnostic process easy for doctors and patients. A combination of electrochemical and optical approaches was used as a readout to create an ultrasensitive method for detection of messenger RNA (mRNA) for the proto-oncogene (a normal gene that, with slight alteration by mutation, becomes a gene that has cancer-causing potential; Fig. 8.2) c-Myc in Michigan Cancer Foundation-7 (MCF-7) cells (breast cancer cell line). In the device, the authors modified the anodic pole with antisense DNA to be used as recognition element and detected nucleic acid from tumour cells on an indium tin oxide bipolar electrode in a poly(dimethylsiloxane) microchannel (Wu et al., 2012). The electrochemiluminescence biosensor was able to detect 2203 copies of the nucleic acid in MCF-7 cells compared with 13 copies in an immortal hepatic cell line control, indicating that the miniaturized device can be used as a good POC device for breast cancer.

Other genes can also be used as targets for breast cancer detection. BRCA1 and BRCA2 (breast cancer 1 and 2) are genes that produce tumour suppressor proteins that help repair damaged DNA and, therefore, play a role in guaranteeing the stability of the genetic material in the cell. Mutations in BRCA1 and BRCA2 genes are associated

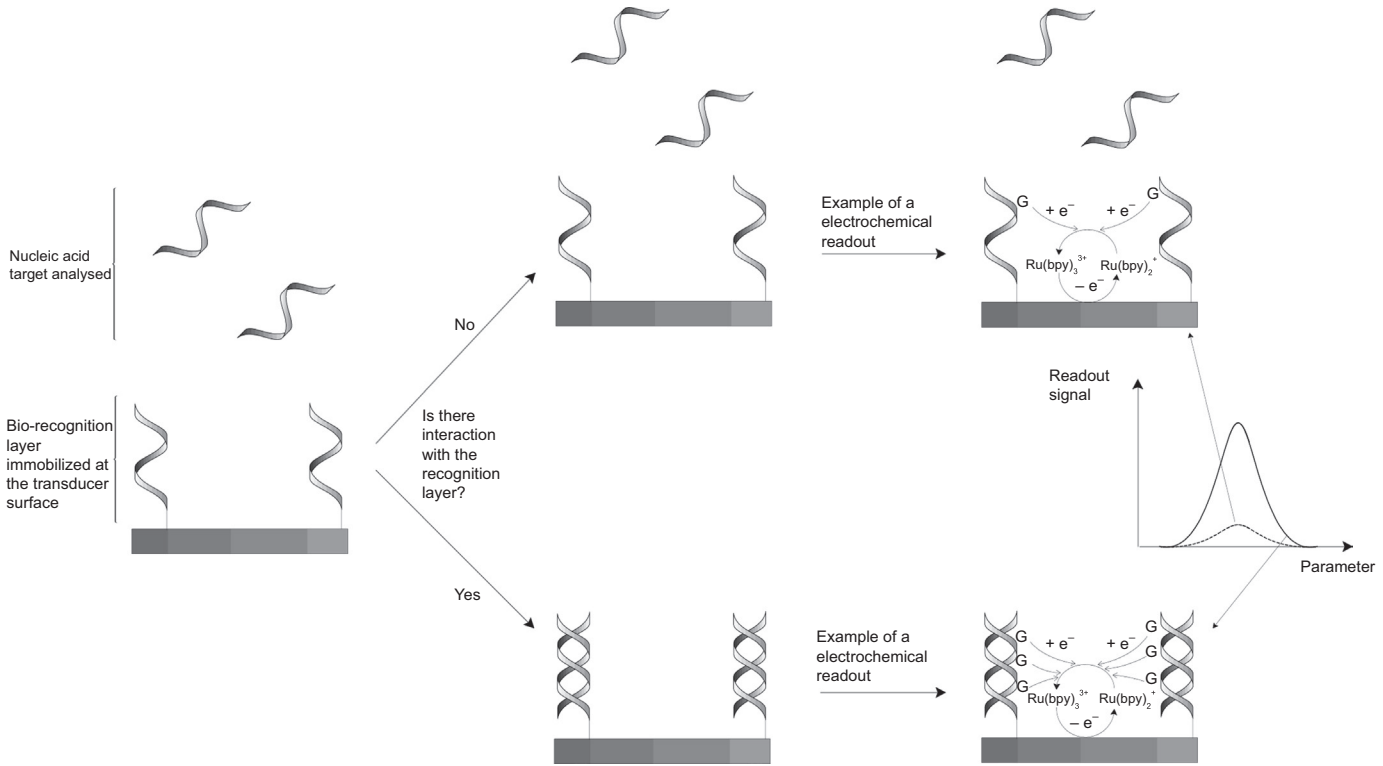

Figure 8.3 Schematic representation of nucleic acid sensor design to detect cancer. An example of an electrochemical readout using a ruthenium complex to mediate the guanine oxidation is shown.

with breast cancer syndromes, and some researchers have already identified a large number of mutations in the BRCA genes, which are associated with a risk of cancer. Based on this finding, the detection of BRCA gene mutant can lead to an interesting POC biosensor. An electrochemical nucleic acid sensor that is able to detect BRCA1 mutant using zinc oxide nanowires to immobilize oligonucleotide probe/biorecognition element has been developed (Mansor et al., 2014). A detection limit of 3.32 μM was obtained after employing differential pulse voltammetry techniques to recognize the target molecule. Other approaches in the literature exploit similar ideas of using nucleic acid sensors for BRCA1 detection (Rasheed and Sandhyarani, 2014; Li et al., 2012). This type of approach is important not only to diagnose cancer but also to monitor its development.

Human epidermal growth factor receptor 2 (HER2) is a marker associated with aggressive breast cancer, and its monitoring is important to choose the best treatment option. HER2 is a receptor tyrosine kinase protein that controls growth factors and hormones. Alterations in HER2 are related to abnormal processes in the cell, indicating their use as biomarkers for some types of cancer, such as breast and ovarian cancer (Zwick et al., 2001). A proposed biosensor by Gohring et al. (2010) to detect HER2 in human serum combines optical ring resonator architecture with microfluidics. Antibodies were attached to the sensor surface and the device was able to measure concentrations of HER2 ranging from 13 to 100 ng/mL, reported by the authors as medically relevant concentrations for real cases.

Another optical sensor has been used by Jokerst et al. (2009) to simultaneously quantify three important cancer markers, namely carcinoembryonic antigen (CEA), cancer antigen 125 (CA125) and HER2. In this approach, the authors integrate semiconductor nanoparticle quantum dots (QDs) into a microfluidic biosensor, which is able to quantify the markers in both saliva and serum. QDs have some advantages compared to organic fluorophores in POC devices due to their unique spectroscopic properties, because their narrow emission peaks enable multiplexed analysis and increase in signal-to-noise ratio (Soper et al., 2006). However, some drawbacks reported by Soper et al. (2006) stress the need to improve the stability of the QDs in biological medium, by capping to prevent aggregation and by development and optimization of the conditions to realize stable and active QD bioconjugates as challenges for successful use of QDs in cancer diagnostics. According to some researchers (Harris et al., 2007), the simultaneous detection of multiple biomarkers can help ensure the best diagnosis and suitable treatment for each patient. It is important to highlight that CEA and CA125 are nonspecific antigens for some types of cancer, but they are used as markers because their levels are elevated in the presence of tumours.

8.4.2 Colon and rectal cancer and point of care devices

Cancers of the colon and the rectum are often associated and are mostly referred to as colorectal cancer. Colorectal cancer is the most lethal cancer in the United States after lung cancer and can be avoided with screening. The procedures for detecting abnormal growths in the colon or rectum are quite simple; such masses can be removed before turning cancerous or at early stages, curing the disease in most of the cases (Prevention, 2015).

In cases in which the number of deaths is very high, the development of an analytical method wherein the targets indicating the cancers can be detected in a small amount is an urgent requirement. Biosensors can operate on a very low density of cells, which is a very attractive feature in the diagnostic area, especially to detect and study rare and uncommon cells hidden in a large heterogeneous cell population (Zhang et al., 2014b). It is also interesting that these sensors can be portable, fast and easy to operate so that patients and health professionals can understand and apply the results of the measurements obtained to help in treatments. An electrochemical device based on the biosensing approach with a great potential to be used as a 'point of care' sensor was tested in mice; this device could discriminate between normal and cancerous epithelial tissues (Vernick et al., 2011). The device was developed to measure the enzymatic activity of intestinal alkaline phosphatase (ALP), an enzyme known to be downregulated in cancerous cells. In colorectal cancer cells, its activity was shown to be as low as <0.0001 unit/mg of protein, whereas a healthy differentiated intestinal epithelial cell could exhibit an activity of >0.7 unit/mg protein (Gum et al., 1987). The activity of this enzyme was measured in slices of a biopsy using a carbon-counter electrode, gold working electrode and Ag/AgCl reference electrode screen-printed on ceramic within a few minutes on a cheap device.

A relatively common electrochemical type of sensor is a DNA-based biosensor reported earlier. In a specific case (Wang et al., 2008), the K-ras gene (which is highly associated with colorectal cancer) was detected by a sensor based on a horseradish peroxidase (HRP)-labelled probe modified with a sulfhydryl group (–SH) group and chemically adsorbed on the gold electrode through self-assembly. The target DNA containing the complementary sequence to the probe DNA was captured by a hybridization process, as depicted in Figure 8.3. The HRP-labelled oligonucleotide (detection DNA), which is complementary with another part of target DNA, was hybridized in the form of a sandwich. Then, H_2O_2 electroreduction current catalysed by HRP was measured amperometrically in the presence of hydroquinone as the mediator. In another case (Feng et al., 2006), a modified glassy carbon (GC) electrode with a nanoporous CeO_2/Chitosan composite film was used to immobilize a DNA probe, hybridized and its signal was recorded using methylene blue as an indicator and by the differential pulse voltammetry technique. The detection of the target sequence associated with colorectal cancer gene has a relatively wide linear range, low detection limit, high sensitivity and satisfactory reproducibility.

Cancer research includes several optical sensors, including works with microwave, fluorescence (Tao et al., 2012) and magnetic-based assays. The basic principle of these sensors is to analyse the electromagnetic properties of the targets. Zhang et al. (2014b) showed, in an interesting study, that it is possible to find electromagnetic signatures between benign and malignant cells and to estimate the phase of the tumour, because cancer diagnosis is based on staging of the tumours. As the stage increases (from zero to four), the malignant cells are more aggressive and obtain the propensity to proliferate and produce metastases in remote tissues. In the study, five colorectal cell lines in different stages were selected; data were obtained using 15 passive sensors and four tunable frequency sensors. This study demonstrated the potential of intracellular dielectric permittivity analysis at microwave frequencies to evaluate the degree of

aggressiveness of malignant cells. This technology is indeed promising for targeting uncommon or rare cells and providing an early prognosis with the objective to assess and prevent tumour spread and metastasis development.

A magnetic bead-based assay showed that it is possible to detect the enzyme telomerase in presence of colon and bladder cancer (Rothacker et al., 2007). Telomerase, also called telomere terminal transferase, is a ribonucleoprotein enzyme that catalyses the addition of repeated DNA sequences TTAGGG or telomeres at the end of chromosomal DNA. In cancer cells, cell division can occur indefinitely and telomere lengths are maintained by expressing telomerase. In contrast, in normal cells, telomerase expression is repressed and telomeres shorten progressively with each cell division (Greider, 1996). Telomerase has been identified in over 80% of tissue samples derived from bladder carcinomas, regardless of the tumour stage or degree of differentiation (Muller, 2002), and is being considered as a biomarker in cancer. In a previously published study (Rothacker et al., 2007), colon and bladder cancer cells were captured using antibody-coated magnetic beads. Telomerase activity was detected using a biosensor connected to an oligonucleotide containing the telomerase recognition sequence, also covalently coupled to magnetic beads. Magnetic beads are an effective tool for extracting and concentrating biomarkers. Using this dispersed solid-phase approach, magnetic beads are mixed with large volumes of patient sample to capture biomarkers. These magnetic beads are then recollected magnetically, and the captured biomarkers are released from the bead surface into a more amenable reaction buffer (Bordelon et al., 2013). This approach helped distinguish between cancer patients and normal healthy volunteers, indicating a high sensitivity and specificity for this method.

8.4.3 Bladder cancer and point of care devices

Squamous cell carcinomas and adenocarcinomas develop in the inner lining of the bladder as a result of chronic irritation and inflammation (National Cancer Institute, 2015a). According to National Health Services in the United Kingdom, bladder cancer mostly affects the elderly and cannot always be prevented; however, some lifestyle modifications such as smoking cessation and dietary changes can reduce its risks. An early diagnosis is essential to ensure minimal suffering in cancer patients. Some that focus on this purpose have been reported in the literature. Some Chinese researchers have suggested a method to detect specific DNA sequences of bladder cancer (Zhang et al., 2014a). In this study, an electrochemical biosensor was developed by the modification of GC surfaces with CdTe QDs—semiconductors that help to improve the electrode area—for subsequent immobilization of a DNA probe. In the next step, target DNA sequences were hybridized, and in the final stage, methylene blue was used to obtain electrochemical signals using differential pulse voltammetry. Some factors such as ease of operation, good selectivity and sensitivity, rapid response and low cost render this sensor useful to achieve good results in the medical field.

Another approach, a label-free technique, was used to detect telomerase activity in human urine (Kim et al., 2013). The device is a silicon-based micro-ring resonator biosensor using telomerase extracted from two bladder cancer cell lines, J-82 and HT-1376, in a buffer solution as well as spiked urine. This chip-based sensor is fast,

cost-effective and can function as a POC device in contrast to the Polymerase Chain Reaction (PCR)-based telomeric repeat amplification protocol (TRAP) method, which is the standard test for telomerase activity (Hou et al., 2001). The TRAP assay is time-consuming, requires expensive equipment and reagents and does not provide precise quantitative information, besides other problems related to other conventional PCR methods (Sharon et al., 2010).

Field-effect transistors (FETs) biosensors have attracted attention, because they present the advantages of miniaturization and superior sensitivity besides offering rapid, inexpensive, label-free detection and high selectivity achieved by immobilization of biomolecules to bind to targets. Chen et al. have reported the first FET biochip to diagnose bladder cancer from urine specimens (Chen et al., 2015). In this study, graphene sheets were used to improve the conductivity and nanowires were employed to increase the superficial area to obtain a better immobilization of anti-APOA2, the antibody for apolipoprotein A-II (APOA2) recognition, which was recently identified as a new biomarker that showed elevated rates in pooled bladder cancer (Chen et al., 2010, 2012).

8.4.4 Kidney cancer and point of care devices

Renal cell carcinoma, also known as *renal cell cancer*, is the most common type of kidney cancer. About 9 out of 10 kidney cancers are renal cell carcinomas (American Cancer Society, 2015c). This cancer forms in the lining of very small tubes in the kidney that filter the blood and remove waste products. Transitional cell cancer of the renal pelvis is kidney cancer that forms in the centre of the kidney in which urine is collected. Wilms' tumour is a type of kidney cancer that usually develops in children under the age of 5 (based on information of the National Cancer Institute). An estimated 61,560 new cases of kidney (renal) cancer are expected to be diagnosed in 2015 in the United States. This estimate largely reflects renal cell carcinomas, but also includes cancers of the renal pelvis (5%), which behave more like bladder cancer, and Wilms' tumour (1%) (American Cancer Society, 2015a).

Unfortunately, there are no blood or urine tests that directly detect the presence of kidney tumours. A combination of imaging studies [ultrasound and computer tomography (CT) scan] is usually required to completely evaluate a suspected tumour (Urology Care Foundation, 2014). Very few studies on biosensors for kidney cancer have been reported. However, an American patent offers an approach for early diagnosis of renal cancer with a label-free technique. The process is based on surface-enhanced Raman spectroscopy (SERS) and/or localized surface plasmon resonance (LSPR) as transducer platforms; these methods read the fingerprint of the proteins and allow the measurement of the exact amount of these proteins in the urine. Two proteins, aquaporin-1 (AQP1) and adipophilin (ADFP) were used as markers, using imprinted artificial receptors for noninvasive and rapid screening of kidney cancer with surface-enhanced Raman scattering (SERS) and/or localized surface plasmon resonance (LSPR) in a biosensor based on metal nanostructures (Singamaneni et al., 2012). The authors suggest some ways to create the invention and obtain the proposed results. One of these methods is a paper-based plasmonic biosensor for sensitive and specific detection of

target proteins in urine for rapid screening of kidney cancer, which has been proposed in an article by the same research group (Tian et al., 2012). As a result, the created biochip offers numerous advantages such as low cost, easy storage and POC diagnosis. Besides this, paper-based LSPR substrates transformed into printable microfluidic devices to enable the detection of multiple bioanalytes in complex physiological fluids are considered one of the challenges for the future application of POC biosensors for cancer treatment.

8.4.5 Leukaemia and point of care devices

Leukaemia is one of the most known, studied and aggressive types of cancer. It starts in blood-forming tissues such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and entered into the bloodstream (National Cancer Institute, 2014). Leukaemia can be divided into four main groups according to the cell type and rate of growth: acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML). Majority (91%) of the leukaemia patients are 20 years and older (American Cancer Society, 2015a; Abdulhalim et al., 2008). A sensitive and accurate diagnosis is essential for effective treatment of this disease. Methods currently used for the detection of leukaemia cells include flow cytometry, polymerase chain reaction and fluorescence measurement (Shan et al., 2014). Accordingly, a sensitive and quantitative biosensor that can be applied in diagnostics and treatment with POC properties has been proposed (Liu et al., 2009). The device combines optical properties of gold nanoparticles and the advantages of aptamers (single-stranded oligonucleotides that bind to a specific target molecule) in comparison with conventional molecular probes that include stability, ease of production and high specificity amongst others (Jayasena, 1999). Ramos cells (lymphoma cells) interacted with aptamers conjugated with gold nanoparticles, allowing the rapid qualitative and quantitative detection of cancer cells in bloodstream at low cost; in addition, it is possible to use different aptamers to detect several types of cancer cells in the near future.

Optical transducers are common in the cancer biosensor research area. In the literature, we can find studies on fluorescence, field-effect transistors and nanoparticles amongst others (Soper et al., 2006). Surface plasmon resonance (SPR) is an optical technique that enables the characterization of biomolecular interactions on the surface in real-time without labelling, because it is sensitive to the changes in the refractive index of biomaterials at the interface between a thin gold film and an ambient medium (Abdulhalim et al., 2008). An SPR biosensor that combines the cited technique and spectral imaging has been used (Fang et al., 2011) to measure a type of specific myeloid antigen, CD33. This antigen acted as a cell surface marker for the clinical diagnosis of and to determine the preferred treatment for myeloid leukaemia. The obtained results were compared with the standard flow cytometry test, and they corroborate statistically. Additionally, this method is easy to reproduce, less time-consuming, enables direct analysis and is cheaper than the conventional methods.

DNA-based biosensors, as reported previously, are common types of biosensors for cancer detection (in any stage) and are mainly used in combination with an

electrochemical readout. An example of this combination is the work reported by Lin and collaborators (Lin et al., 2007), wherein an 18-base DNA sequence relating to Chronic Myelogenous Leukaemia (CML, Type b3a2) was used along with methylene blue (MB) as the hybridization indicator. The DNA probe was attached to a GC surface and the interaction between MB and the CML gene generated a voltammetric signal similar to the signal shown in Figure 3 in the absence or presence of the CML gene. The proposed method is very simple and sensitive and could be applied for real testing for clinical diagnostics.

Piezoelectric sensors are rarely used as transducer readouts; however, some studies have been reported, in which the authors suggest using *p*-aminophenylboronic acid conjugated gold nanoparticles (AuNPs) (Shan et al., 2014). AuNPs were used as catalysts for silver ion reduction in the presence of the reducing agent hydroquinone. A specific aptamer for human acute lymphoblastic leukaemia was immobilized on the gold quartz crystal microbalance electrode and this interaction enabled the defined cancer cells to be captured. The leukaemia cells were indirectly monitored in real time through the resonant frequency change of the quartz crystal microbalance caused by the deposition of silver metal. A good relationship between frequency response and number of cancer cells with a detection limit of 1160 cells/mL shows the promise of this method for future applications.

8.4.6 Melanoma and point of care devices

According to the National Cancer Institute (NCI) and American Cancer Society (National Cancer Institute, 2015b), melanoma is the most dangerous form of skin cancer, a malignancy of the melanocyte, the cell that produces pigments in the skin. Melanoma is most common in individuals with fair skin, but can occur in people with all skin colours. Most melanomas present as a dark, mole-like spot that spreads and, unlike a mole, has an irregular border. The tendency of developing melanoma may be inherited, and the risk increases with overexposure to the sun and sunburn.

Melanoma can be diagnosed through the monitoring of tyrosinase, a cytoplasmic melanocyte differentiation protein, which is a key enzyme in melanin synthesis and has been listed as important melanoma biomarker. Mossberg et al. (2014) developed an electrochemical biosensor platform with an amperometric detection mode to detect the enzymatic activity of tyrosinase in fresh biopsy samples without pretreatment of the samples. The combination of this method with modern portable devices can provide interesting POC sensors in the future.

An interesting approach was developed by D'Amico et al. (2008), in which they used an electronic nose sensor with a good sensitivity towards volatile organic compounds emitted by skin lesions from melanoma patients, and the method seems to be effective for identification of malignant lesions. The gas sensor used gas chromatography mass spectrometry detection and shows satisfactory accuracy. This approach does not use a biosensor but combines chemometric tools with a sensor that can be a favourable approach to detect a pattern in POC biomedical devices.

8.4.7 Lymphoma and point of care devices

The NCI defines lymphoma as a cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One is Hodgkin's lymphoma, which is marked by the presence of a type of cell called the Reed–Sternberg cell. The other is non-Hodgkin's lymphoma, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin's lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course.

Mansur et al. (2014) have shown the potential applications for in vitro diagnosis of non-Hodgkin's lymphoma (NHL) tumours using novel multifunctional immunoconjugates composed of QDs as the fluorescent inorganic core and antibody-modified polysaccharide as the organic shell. The QDs/immunoconjugates have shown binding affinity to antigen CD20 (aCD20) expressed by malignant B-lymphocytes.

8.4.8 Lung cancer and point of care devices

Lung cancers usually form in the cells lining the air passages of the lung. The two main types of lung cancer are small-cell lung cancer and nonsmall-cell lung cancer, based on how the cells appear under a microscope (National Cancer Institute, 2015b).

The main biomarkers for lung cancer are thymidine kinase 1 (TK1) and CEA, an acidic glycoprotein of which CEA is a non-specific marker that could be elevated in breast, ovarian, lung and liver cancers. It is used to monitor cancer recurrence after surgery and to follow patients during therapy. Serum CEA levels are typically below 5 ng/mL in healthy individuals (Ronkainen and Okon, 2014). CEA studies have revealed an association between highly elevated marker levels, metastases and poor prognosis (Ronkainen and Okon, 2014). Li et al. (2010) developed a rapid and sensitive detection of nitrated ceruloplasmin, a significant biomarker for cardiovascular disease, lung cancer and stress response to smoking. The authors created a portable fluorescence biosensor based on QDs and a lateral-flow test strip, and the results hold great promise for POC and in-field analysis of protein biomarkers. Drawing on the same biomarker, Gao et al. (2011) constructed an amperometric immunosensor for detection of CEA, utilizing uniform carbon nanotubes (CNTs)-based film with gold nanoclusters and anti-CEA immobilized antibodies. This immunosensor had a detection limit of 0.06 ng/mL and good stability, showing potential for screening of CEA levels. On the other hand, Alegre et al. (2014) developed a traditional Enzyme-Linked Immunosorbent Assay (ELISA) to detect TK1 in serum.

8.4.9 Pancreatic cancer and point of care devices

In pancreatic cancer, also called exocrine cancer, malignant (cancer) cells are found in the pancreatic tissues. The exocrine cells and endocrine cells of the pancreas form different types of tumours. It is very important to distinguish between exocrine and endocrine cancers of the pancreas, because they have distinct risk factors and causes, different signs and symptoms and tests for diagnosis (American Cancer Society, 2015b).

Measurement of serum carbohydrate antigen (CHA) 19-9 has shown satisfactory sensitivity and predictive potential in pancreatic cancer patients (Kim et al., 2004). Zhang et al. (2014c) demonstrated a sandwich-type electrochemical immunosensor for the detection of CHA 19-9 antigen based on the immobilization of primary antibody (Ab1) on a three-dimensional ordered macroporous magnetic (3DOMM) electrode. The 3DOMM electrode was fabricated by introducing core–shell Au–SiO_2@Fe_3O_4 nanospheres onto the surface of a three-dimensional ordered macroporous Au electrode.

Chang et al. (2013) developed a high-throughput biosensor based on metal-enhanced fluorescence technique for detection of a pancreatic cancer marker, UL16-binding protein 2 (ULBP2), in diluted human serum. The authors describe this biosensor as a cost-effective high-throughput sandwich immunoassay; compared with the limit of detection (LOD) of the conventional ELISA method, the LOD of the proposed biosensor for ULBP2 is significantly improved 100-fold under the same conditions.

8.4.10 Prostate cancer and point of care devices

Prostate cancer affects the prostate gland, which is a part of the male reproductive system and is located below the bladder and in front of the rectum. One of the most commonly used biomarkers for prostate cancer is prostate-specific antigen (PSA), which is found at elevated levels in cancer patients (Jolly et al., 2015). PSA is a serine protease that is synthesized specifically in the epithelial cells of the prostate gland and its expression therein is regulated by the androgen receptor. The normal reference range for PSA is 0–4 ng/mL and its cancer sensitivity as well as its tissue specificity makes PSA the most useful tumour marker available for screening and managing prostate cancer (Ronkainen and Okon, 2014).

Damborsky et al. (2015) used SPR for measuring real-time quantitative binding affinities and kinetics of the interactions of specific antibodies with different epitopes of free and complexed prostate-specific antigen (PSA) to be used in microfluidic immunoassay-based platforms for POC devices. The authors describe a selective, sensitive and reliable biosensor for prostate cancer diagnosis as a lab-on-chip device.

Wan et al. (2011) describe a CNT-based, multiplexing, electrochemical immunosensor utilizing a sandwich-immunoassay type on a disposable screen-printed carbon electrode for sensitive and simultaneous determination of PSA and interleukin 8 (IL-8), another cancer biomarker.

Azmi et al. (2014) created a handheld, POC system, in which a silicon nanowire biosensor (SiNW) chip is wire-bonded to a ‘bio-smartcard’ and subsequently slotted into an electronic readout device. This sensor detects an oxidative stress biomarker, 8-hydroxydeoxyguanosine (8-OHdG), which has been related to prostate cancer risk.

8.4.11 Thyroid cancer and point of care devices

The thyroid gland is an organ at the base of the throat that produces hormones that help control heart rate, blood pressure, body temperature and weight. The four main types of thyroid cancer are papillary, follicular, medullary and anaplastic thyroid cancers, based on how the cancer cells appear under a microscope (National Cancer Institute, 2015b).

Thyroglobulin (Tg) is used as a tumour marker for thyroid cancer, and is used post-surgically to monitor disease recurrence (Krahn and Dembinski, 2009). Burne et al. (2005) describe POC assays for autoantibodies to thyroid peroxidase (TPO) and to thyroglobulin. Both assays are based on the ability of autoantibodies in test samples (whole blood, plasma or sera) to inhibit the binding of monoclonal antibodies to TPO or to Tg. These assays require no special equipment and yield results in 10 min.

Choi and Chae (2009) created a microfluidic sensing platform for the detection of Tg using competitive protein adsorption. The authors engineered two surfaces covered by two known proteins, immunoglobulin G (IgG) and fibrinogen, with different affinities. This microfluidic device offers selective protein sensing by being displaced by a target protein, Tg, on only one of the surfaces. The adsorption and exchange are evaluated by fluorescent labelling of these proteins.

Thus, POC biosensors could be used to detect cancer with the help of different biomarkers. Further research in this area is warranted for this method to be applicable and accessible to the public. Additionally, the field of laboratory medicine also needs some modifications (DuBois and Clarke, 2014). Keeping the future in perspective, Soper et al. (2006) made a list with 11 points that should be considered for the future development of POC biosensors. In two of these points, they mention the necessity of (1) developing POC biosensors based on a molecular signature or a panel of signatures, like a fingerprint for cancer. In this regard, we believe that it is important to include the necessity of (2) combined POC biosensors with chemometrical approaches such as pattern recognition tools to evaluate this complex signature. These approaches could include, for example, Principal Components Analysis (PCA), Artificial Neural Networks (ANN), K-nearest neighbours (KNN) and Soft Independent Modelling of Class Analogy (SIMCA). The other nine points are important to (3) increase the selectivity of biosensors due to the complexity of sample media, (4) work in tissue samples, (5) process small amounts of sample, (6) decrease detection limits and costs. In addition, (7) develop sensors set apart for screening, (8) decrease the number of false positives and false negatives, (9) make devices for real-time monitoring, (10) integrate POC with sample handling and processing and (11) develop companion devices for research. For the two last points, we believe that the incorporation of multivariable calibration and detection is important to make devices for simultaneous detection of different types of cancers.

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