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## Review

## Aptamer based nanobiosensors: Promising healthcare devices

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## ABSTRACT

Nanobiosensors based on aptamer are extensively being studied as potent analytical tools in clinical analysis. These biosensors provide high sensitivity, fast response, specificity and desired portability in addition to simplicity and decreased cost compared to conventional methods. The purpose of this manuscript is to provide readers with an overview of current advances about electrochemical, electrochemiluminescent and photoelectrochemical aptasensors from the sea of available literature. These are mainly used for determination of protein-based biomarkers, especially for cancer diagnosis. Here in we have given special emphasis on nanosize-based aptasensors which have been reported to show considerable improvement in the analytical performance.

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## 1. Introduction

The DNA/RNA oligonucleotides which possess high affinity towards certain molecules are called aptamers. Aptamers, discovered in 1990, is derived from a Latin word ‘aptus’ meaning to fit (Cooper, 2002; Jayasena, 1999; Yeom et al., 2011). These nucleotides can be DNA, RNA or even small peptide molecules. After the discovery of DNA aptamer (Ellington and Szostak, 1992), in both scientific and industrial research, the aptamer technology has received attention. DNA-based aptasensors have promising potential for clinical applications due to their various important characteristics including high affinity towards target molecules, high specificity, secondary shape change upon target binding and high detection sensitivity. Moreover, these aptasensors have flexibility due to their small size besides ease in designing their special structure (Keefe et al., 2010). These target molecules for these aptasensors include proteins, amino drugs, toxins and other small molecules (O’Sullivan, 2002). Aptamers dissociation constants (Kd) range from picomolar (pM) to nanomolar (nM) concentration after binding to their targets (Jenison et al., 1994). Modification of aptamers via chemical or enzymatic synthesis causes incorporation of reporters or linkers into them. Aptamers are attached to ribozymes (catalyst RNA molecules) which are self-cleaving RNA molecules when target molecules are present. They show high reproducibility and purity. The extensive range of targets and combinations with different materials available for aptamers makes them fit to be used as innovative bioassay tools in the fields of diagnostics, anti-bioterrorism, and environmental and food analysis (Tombelli et al., 2007).

Aptamers are short DNA/RNA oligonucleotide sequences which attain distinct 3-dimensional conformations which are able to identify and interact with a wide array of complementary sequences of target molecules. Aptamers mimic antibodies but show advantages over them. They are chemically stable under a wide range of buffer conditions, show reversibility after thermal denaturation, retains bioactivity in harsh conditions, high specificity and high affinity towards various targets such as enzymes

and several types of proteins eg, immunoglobulins, cytokines, proteins of membranes, viral membrane proteins, growth factors, drugs, metal ions, small molecules and intact cells (Keefe et al., 2010). Newly discovered nanomaterials in combination with aptamers have enhanced the performance of aptamer-based biosensors. Aptamer-based biosensors have huge potential to be used for diagnosis of various disease (Du et al., 2011; Ma et al., 2011). The nucleotides whether RNA or DNA aptamers are selected *in-vitro* by Systematic Evolution of Ligands by Exponential enrichment (SELEX process) from immense populations of random sequences for which the basic knowledge of aptamer biochemistry and other requirements are important.

## 2. Aptamers as biosensors

Aptamers are known as biological recognition elements and can be used as biosensors due to their important characteristics like small size, high specificity, high affinity, high sensitivity, and efficient immobilization. Aptasensors are aptamer-based biosensors and the first optical biosensor was discovered in 1996 which uses fluorescently labeled aptamers (Davis et al., 1996). Aptamer-based biosensors are designed and developed to detect different targets such as adenosine, thrombin, ATP, cocaine, thrombin, VEGF, IgE, etc (Du et al., 2011; Ma et al., 2011; Tombelli et al., 2007). Biosensors are mainly used for precise and fast detection for pathogens, various biomarkers for diseases, pollutant (Yeom et al., 2011; Zelada-Guillén et al., 2009). Aptamers were used as an anticoagulant agent due to their high specificity, affinity, and bioavailability (Kuliczowski et al., 2010). Due to the presence of RNases in cell, RNA aptamers were designed using amino or fluoro groups or RNA inhibitors (Biesecker et al., 1999; Jellinek et al., 1995; Liu et al., 2011; Ruckman et al., 1998). The aptamer-protein binding occurs by electrostatic, stacking interactions, or complementary shape hydrogen bonding. Sandwich biosensor based on glucose dehydrogenase-labeled signaling was first electrochemical aptasensor that was discovered in 2004 (Ikebukuro et al., 2004). Due to more binding sites for target proteins, in sandwich-assay based biosensors, one aptamer is attached to sensor which binds via epitope to target protein and second one which binds to different epitope of target protein is labeled one, which brings the reporter and sensor closer to readout a positive signal (Ikebukuro et al., 2005).

Nucleic acid aptamers can be synthesized by *in-vitro* selection or SELEX method as shown in Fig. 1. This method helps to identify and select aptamers which possess high binding affinity towards their target molecules (Huang et al., 2009). Aptamer-based biosensors have been classified into different categories discussed below.

### 2.1. Electrochemical aptasensors

These types of biosensors use electrochemical transduction and include various methods e.g faradic impedance spectroscopy (FIS), potentiometry, differential pulse voltammetry (DPV), alternating current voltammetry (ACV), square wave voltammetry (SWV). Upon binding of target to aptamers, either positive or negative readout signal is detected (Sharon et al., 2009). The simultaneous monitoring of the signal due to ligand-analyte interactions done by an electrochemical impedance spectroscopy (Xu et al., 2005) was first used for the immunoglobulin-E (IgE) recognition, where the sensors compare DNA based aptamer with antihuman IgE antibody, and reduce background noise as well as non specific adsorption (Wang et al., 2011). Another example of electrochemical aptasensors is for thrombin detection which has application in prevention of thrombosis.

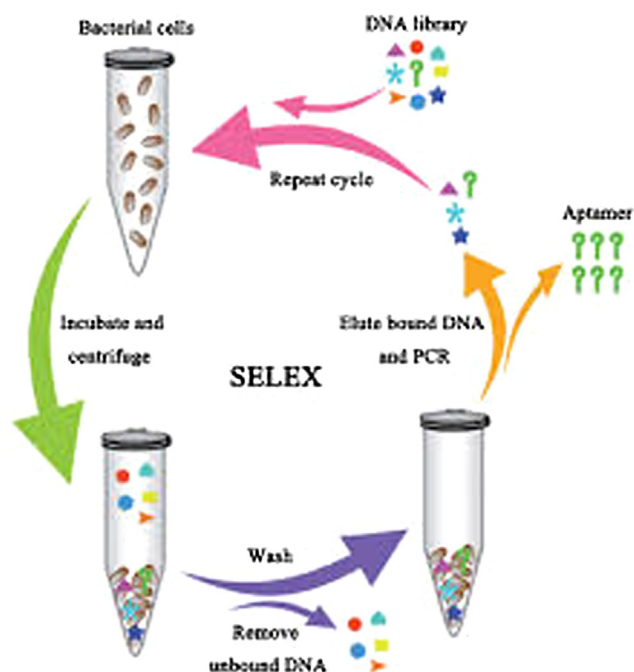


Fig. 1. SELEX method used for the isolation of aptamers. (Source: Zhang et al., 2015).

A nanometer gap-sized impedance biosensor was used in which RNA aptamer was compared with an antibody for thrombin detection (Schlecht et al., 2006). The real time reading of five sensor elements in its multiplexer-approach was enabled so the detection of different targets by immobilizing their specific ligands on separate electrodes. Reference sensors are used for the removal of background noise (Schlecht et al., 2006). Complementary DNA (cDNA) aptamer oligonucleotides were used as probes for electrochemical aptamer aptasensors technique. In this method, the labeled cDNA is synthesized and made to hybridize to their specific aptamers to form double-stranded DNA (ds-DNA) which self-assemble ds-labeled DNA onto electrodes. Aptamers on binding to the target confine to the surface of electrode which separates itself from their complementary cDNA oligonucleotides into the solution and in addition the single-stranded cDNA forms a hairpin structure. This change in conformation causes alteration in voltammetric signal of the redox moiety on labelled cDNA. Based on this technique, many electrochemical aptasensors are designed which uses ferrocene gold electrodes as redox moieties like that of Adenosine Triphosphate and thrombin-binding aptamers. Yet another application of these aptamers is in lysozyme detection. Lysozyme is an antimicrobial enzyme produced by the cells as an innate immune response (Ragland and Criss, 2017). This enzyme works by lysing the peptidoglycan cell wall of especially gram positive bacteria (Cunningham et al., 1991). The detection of levels of lysozyme form an important diagnostic technique for bronchopulmonary dysplasia (Revenis and Kaliner, 1992). Besides other applications include in formulation of lysozyme rich growth promoting feeds for some animal species including swine (Oliver and Wells, 2015) For lysozyme detection, DNA aptamer was immobilized on gold surfaces via  $[\text{Ru}(\text{NH}_3)_6]^{3+}$  which uses electrostatic interactions for binding to the aptamer. Upon binding to lysozyme, release of  $[\text{Ru}(\text{NH}_3)_6]^{3+}$  cations occurs which leads to decrease in the integrated charge of the reduction peak (Cheng et al., 2007). Thence, measurement of  $[\text{Ru}(\text{NH}_3)_6]^{3+}$  reduction peak height gives the surface density of aptamers in cyclic voltammogram.

In an electrochemical aptasensors, aptamers both sides can be labeled. Upon protein binding, change in shape occurs which leads to either a smaller or larger distance of the reporter from the electrode thus causes an increase or decrease in an electron transfer (Mir and Katakis, 2007; Xiao et al., 2005). In this method, intercalators like methylene blue (MB) are used as reporters, which combines with the ds DNA aptamer. As upon target binding various conformational changes occurs and intercalator is released thus producing a negative response (Xiao et al., 2005) For endotoxin lipopolysaccharide detection, an electrochemical gold nanoparticle

based aptasensor was reported by Kim et al. (2012), which possesses high sensitivity along with a detection range of 0.01–1 ng/ml. While maintaining a comparable detection with traditional limulus amoebocyte lysate this gold nanoparticle based aptasensor had advantages of lower detection time, negligible cross binding reactivity to various biomolecules viz pDNA, RNA, proteins and saccharides which are also found along with endotoxin LSL in liquor bioprocessing. For the detection of tetracyclines, a RNA based aptamer (cb28) was screened which shows resemblance with the small ribosomal subunit (Berens et al., 2001) Recently ss DNA aptasensor with high specificity was developed for tetracycline detection (Kim et al., 2012; Zhang et al., 2010) In 2010, glassy carbon electrodes were used as electrochemical aptasensor for tetracycline detection, which was having high sensitivity (in ngs) so was able to detect tetracycline in milk (~1 ng/ml) and is used specifically for chloramphenicol detection (Pilehvar et al., 2012; Zhang et al., 2010). Aptamer based tetracycline detection is advantages of being fast inexpensive highly specific and precise than most of the other methods (Zhang et al., 2010). Various methods and techniques for mobilization and labeling for the construction of electrochemical aptasensors are being used. One of them is shown in Fig. 2.

## 2.2. Optical aptasensors

Optical aptasensors exploit optical phenomenon of fluorescence, colorimetry, chemiluminescence, surface plasmon resonance (SPR), surface-enhanced raman scattering, methods for transduction (Feng et al., 2014). The modification of optical parameters like alteration in the refractive index upon binding to the targets can be detected and quantified without use of any labeled molecules. In SPR biosensor detection method, surface plasmons are produced on a high refractive index gold layer which is immobilized on a glass surface. As the aptamer and target combines together, alteration of the refractive index of the gold layer and SPR angle occurs which can be used for measurement of various biological interactions with aptamers with good sensitivity of nanomolar (nM) range and a range of linear detection from 8.4 to 84 nM like SPR sensing and fixed-angle imaging method (Pollet et al., 2009; Polonschii et al., 2010; Wang et al., 2011; Xia et al., 2010). The usual colorimetric methods, have lower sensitivity in millimolar [mM] to micromolar [ $\mu\text{M}$ ] range (Liu and Lu, 2006; Wang et al., 2011; Xia et al., 2010; Zhang et al., 2011b) Other techniques which includes quartz crystal microbalance (QCM), acoustic wave, micro-cantilever have also been reported (Gronewold et al., 2009; Savran et al., 2004).

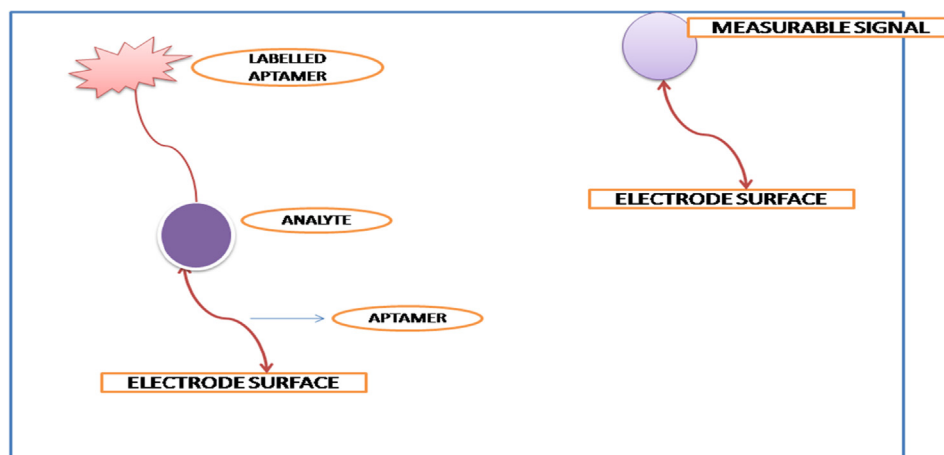


Fig. 2. Representative diagram of aptamer-analyte-labeled aptamer sandwich for electrochemical aptasensor construction.

### 2.3. Fiber-optic biosensors (FOBS)

These are special class of optical biosensors in which aptamers or enzymes are deposited on the surface of optical-fibers to measure biological molecules. For measurement of biological molecules, optical field is used in this method. Tapered fiber-optic biosensors (TFOBS) possess a special shape to depict the momentary field to bind with the samples. Alteration in refractive index, absorption, fluorescence, SPR are among various methods used in TFOBS to increase the specificity and sensitivity. A detailed account working principle and mechanism of this category of biosensors is beyond the scope of this review as it focusses majorly on the application area. The FOBS have a variety of applications including detection of pathogens, environmental pollutants medical and detection of DNA hybridization. Zibaii et al reported the use of simple tapered fiber optic biosensor for measuring real time growth of bacteria *Escherichia coli* (E. coli) in water (Zibaii et al., 2010). Monitoring of halogenated compounds commonly found as trace pollutants in environment has been reported using purified haloalkane dehalogenase LinB and the fluorescent pH indicator CF immobilized on the optical fiber with a poly(methyl methacrylate) core (Bidmanova et al., 2010). The FOB showed a detection limit of 0.014 mM and range of 0–0.8 mM detection for 3-chloro-2-(chloro methyl)-1-propene (Bidmanova et al., 2010). A high selectivity and sensitivity FOB was reported by Kudo et al for monitoring gaseous ethanol (Kudo et al., 2010). The bio-sniffer used alcohol dehydrogenase to detect the ethanol in the range of 0.3–300 ppm ethanol. Due to specific enzyme activity of alcohol dehydrogenase high selectivity towards ethanol was observed which highlights the potential of this biosensor in breath analyzers. More recently a lot of fiber optic biosensors have been reported for a varied sensing applications such as detection of thrombin (Albert et al., 2013) bisphenol A (Long et al., 2014) acetone (Renganathan and Ganesan, 2015; Ye et al., 2015) proteins on surface of E. coli (Brzozowska et al., 2015) tumor marker prostate specific antigens (Jeong et al., 2013), Crimean-Congo hemorrhagic fever (CCHF) IgG antibodies (Algaar et al., 2015) and other clinically significant triacetylglyceraldehydes (Baliyan et al., 2013).

### 2.4. Fluorescently labeled aptamers or signaling aptamers

Aptamers linked with fluorescent probes are fluorescently labeled aptamers. These are sensitive and inexpensive. Aptamers are used for this purpose to form fluorescently labeled aptamers (Yamamoto and Kumar, 2000). Aptamer (DNA/RNA) sequence is placed in a molecular beacon, labeled with fluorophore and a quencher. As the target interacts with an aptamer, it separates fluorophore and a quencher which will lead to emit fluorescent signals (Fig. 3). In yet other method, aptamer is linked with

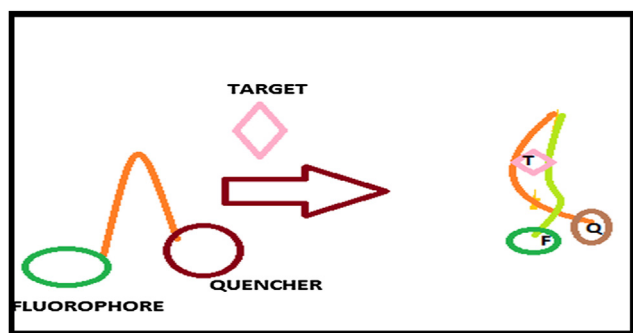


Fig. 3. Fluorescently labeled aptamers in which fluorophore and Quencher comes close as the target binds.

a fluorophore with cDNA sequence and labeled quencher. As target binds, dissociation of the corresponding strand from the aptamer occurs, results in an amplification in intensity of fluorescence (Nutiu and Li, 2004, 2003) This technique is used in various important techniques like from cell-based research to regenerative medicine (Terazono et al., 2010).

### 2.5. Quantum dots (QDs)

The Quantum dots is an improvised form of fluorescently-labeled aptamers (Choi et al., 2006; Levy et al., 2005) which is used for drug delivery detection in cells (Bagalkot et al., 2007). This shows sensitivity in nanomolar (nM). ATP and cocaine limits of detection were of 30 nM and 50 nM range using QDs (Zhang et al., 2011a). For this, GBI-10 (ss DNA) aptamer to the QD surface for tenascin-C on the surface of glioma cells was used to form QD-Aptamer nanoprobe and is helpful for the development of *in-vitro* diagnostic assays for glioma as this conjugate possess features like increased fluorescence, stability, homogeneity and monodispersity (Wu et al., 2011a,b). QD based aptamers were used to detect changes in potassium ions ( $K^+$ ) by the fluorescence intensity of the molecular beacon. Dissociation constant ( $K_d$ 's) of the aptamer probes against  $K^+$  are also obtained (Ikanovic et al., 2007; Wu et al., 2011a,b). For Prostate specific membrane antigen (PSMA) detection, Quantum dot-A10 RNA aptamer (QD-Apt) is used in combination with drug anticancer Doxorubicin (Dox) for optical imaging of the delivery of Dox against PSMA-specific agent. QDs with carbon nanotubes (CNTs) are used to identify spores of *Bacillus thuringiensis* (Ikanovic et al., 2007) and the sensitivity was 103 CFU/ml. QD's were also used to differentiate *Bacillus thuringiensis* from *Bacillus Globigiiat* concentrations when higher than 105 CFU/ml.

### 2.6. Fluorescence resonance energy transfer (FRET)

This technique exploits relocation of energy between two fluorescent molecules – donor and acceptor. One side of aptamer is linked to a fluorophore and other by a quencher which is used to quench its signal through FRET. Graphene is commonly used as a quencher as it is an energy acceptor. Graphene oxide is known to have strong non covalent adsorptive interactions with nucleic acid bases and nucleosides (Lu et al., 2009; Varghese et al., 2009). As aptamer and target interacts, the intensity in the fluorescence signal changes which can be used for recognition and measurement of the concentration of the target. However, FRET probes has limitation as it shows a lot of background noise so directly target analyzing is difficult (Bagalkot et al., 2007).

For detection of trace metal bisphenol A (BPA), the lanthanide-doped K GdF4 nanoparticles (KGdF4:Tb<sup>3+</sup> NPs) were tailored in such a way that an aptamer recognizes BPA, and gold nanoparticles (AuNPs) with cDNA of the aptamer. Binding of BPA with aptamer forms KGdF4:Tb<sup>3+</sup> NP-aptamer-BPA complexes, FRET is disrupted, and the fluorescence is restored and the change in intensity is equivalent to the concentration of BPA, with sensitivity even less than 0.16 ng ml<sup>-1</sup> (Duan et al., 2016).

For detection of thrombin via FRET technique, aptamers with two distinct epitopes labeled with a different fluorophore were used which were linked via alkyl linkers (Heyduk and Heyduk, 2005). Thrombin links two aptamers in close proximity for FRET. The fluorescence signal was initially quenched by graphene but the signal increases upon thrombin binding. This helps the detection of thrombin in pM range as well as good specificity in serum (Chang et al., 2010). For adenosine detection, aptamers at 5' end were immobilized on a magnetic microparticle and modified with fluorescein while as its 3' end is attached to a quencher. When adenosine binds, it causes spatial change of the aptamer so leads

to the displacement of quencher and recovery of the fluorescence signal. The FRET technology has also been used for the detection of low levels 17 $\beta$ -estradiol (E2) in water samples (Yildirim et al., 2012).

### 2.7. Field-effect transistor (FET)

This technique exploits the electrical properties of an aptamer when binds with a target and this helps in the detection of target in femtomolar (fM) range. An aptamer is made to be attached to surface, its one end is attached with carbon nanotube and a gate voltage is applied between aptamer and nanotubes. As the target binds and aptamer interacts, the electrical properties due to charge transfer to the nanotube between the source and electrode occurs. A study by Rahim Ruslinda et al. (2013) observed the properties of charge density on the surface of HIV-1 tat protein using RNA aptamers on a diamond FET. Combination of target molecule and aptamer leads to gate potential change of 91.6 mV (Rahim Ruslinda et al., 2013). For detection of lead, graphene based FET aptasensor was developed, with high selectivity and specificity than metal cations like Sodium (Na<sup>+</sup>), Potassium (K<sup>+</sup>), Magnesium (Mg<sup>2+</sup>), and Calcium (Ca<sup>2+</sup>), so can be used in a complex sample matrix (Wang et al., 2016). A single walled carbon nanotube FET (SWCNTFET) arrays aptasensors were customized to detect E. coli DH5 $\alpha$  and E2 (Zheng et al., 2015). As the E-Coli cells and aptamer binds, change in conductance is observed in FET aptasensors. These FET based aptamers shows high specificity and specificity assays were conducted with Salmonella typhimurium. For the detection of Bacillus anthracis- a gram positive bacteria, a causative agent of Anthrax, a single stranded DNA based aptamer linked to SWCNFET, with sensitivity ( $\sim$ 1 nM) has been developed by Cella et al. (2010). Due to high sensitivity of FET biosensors, ATP detection has also been done where these aptasensors showed an increase in the drain current with ATP addition (Mukherjee et al., 2015). Similarly, for Interferon  $\gamma$  (IFN- $\gamma$ ) detection, graphene is attached to IFN- $\gamma$  aptamer and is integrated on a Polydimethyl-siloxane (PDMS) substrate. As IFN- $\gamma$  is added, change in current occurs due to alteration in charge distribution with detection limit of 83 pM. For the adsorption of aptamer on gra-

phene surface unique structural approach by Atomic Force Microscopy technique was exploited (Farid et al., 2015).

### 2.8. Enzyme-linked immunosorbent assay (ELISA) with aptamers

It works on the principle of sandwich based ELISA, but has higher sensitivity due to the more binding sites of aptamer-conjugated nanoparticles (Fig. 4). It uses green fluorescent ferritin nanoparticles which were bound to platelet-derived growth factor B-chain (PDGF-BB) homodimer (Kim et al., 2011). This aptamer-ELISA detects PDGF-BB as low as 100 fM. The uses of aptamers in ELISA are called as enzyme-linked apta-sorbent assay (ELASA) (Toh et al., 2015) Lipocalin-2 (LCN2), is a molecular biomarker of hepatocellular carcinoma (HCC) with sensitivity of 2.5–500 ng mL<sup>-1</sup> and a detection limit of 0.6 ng mL<sup>-1</sup> was detected by using this technique (ELASA) (Lee et al., 2015). To detect MPT64 protein among early stage tuberculosis patients in both sputum smear positive and sputum smear negative patients, MPT64 antibody aptamer were developed with the help of SELEX and then ELASA technique was used (Zhu et al., 2012). A competitive enzyme-linked aptamer assay (ELAA) was used to diagnose tetracycline in milk. It shows better sensitivity and specificity. This technique uses two different aptamers, DNA and RNA (Jeong and Rhee Paeng, 2012).

### 2.9. Electrochemiluminescence or electrogenerated chemiluminescence (ECL)

Electrogenerated chemiluminescence (ECL) exploits the principles of electrochemistry i.e. during transitions of electrons from higher excited level to a lower energy level state, dissipation of radiations occur in the form of as photons in the UV, visible, and close infrared (IR) region. The light emission in a reaction occurs in different ways like the intensity of light is proportional to the quantity i.e. concentration of the reactants (Bard, 1988) chemiluminescence, photoluminescence, electrogenerated luminescence and bioluminescence. The aptasensors based on ECL was thrombin and was first reported in 1992 (Bock et al., 1992). DNA aptamer with thrombin leads to a stable intramolecular G-quadruplex

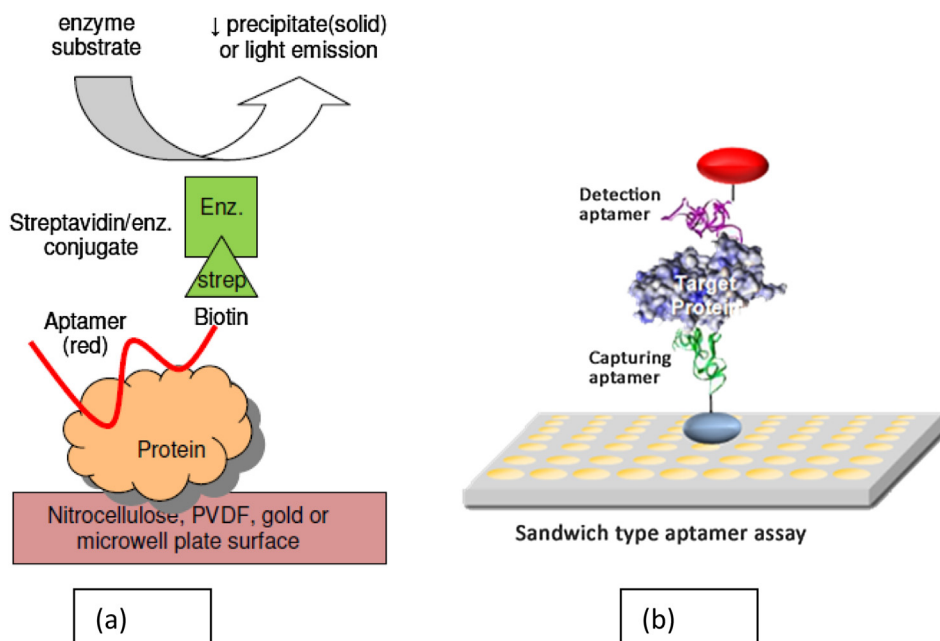


Fig. 4. (a) Direct "aptamer ELISA" or "ELASA" (Source: Base Pair Biotechnologies, Inc.). (b) Sandwich ELASA (Source: Aptamer Sciences, Inc.).

structure formation (Xiao et al., 2005) DNA thrombin binding aptamer binds with higher affinity to heparin-binding site of thrombin affinity. Aptamers do not interfere with other binding sites they interact with two different binding sites of thrombin, giving them high advantages in development of biosensors. The aptamers for thrombin are treated as important bioreceptors (Mascini et al., 2012). ECL-AB biosensors have been used for the detection of cocaine and ruthenium complex. For the detection of cocaine, ECL aptamers are used in which when cocaine binds to an aptamer, an ECL signal increases as change in conformation took place from random coil to three-way junction structure, in close proximity to the sensor interface. With the change in ECL signal intensity, the concentration of cocaine was found. These types of aptasensors were also used for the detection of platelet-derived growth factor B chain (PDGF-BB) assay with an aptamer N-(aminobutyl)-N-ethylisoluminol functionalized gold nanoparticles (ABEI-AuNPs) as nanopobes.

### 2.10. Photoelectrochemical aptasensors (PEC)

PEC exploits the principle of photochemistry which uses photoactive material (organic, inorganic or hybrid semiconductors), using light as a source of excitation and then the production of photocurrent. Excitation source causes excitation of molecule that reacts with an electron acceptor or donor molecule, producing either anodic or cathodic photocurrents, respectively. Inorganic semiconductors are modified by using manifold nanomaterials like stannic oxide (SnO<sub>2</sub>), titanium Oxide (TiO<sub>2</sub>), NPs as well as cadmium sulfide (CdS) and cadmium selenide (CdSe), QDs to make them conductive. Gold nanoparticles (AuNPs) are highly used in combination with semiconductors like AuNPs/TiO<sub>2</sub> hybrid materials, graphene/CdSe, and porphyrin/fullerene/AuNPs (Zhao et al., 2014). A photoelectrochemical aptasensor based on graphene and cadmium selenide nanoparticles has been reported as a highly sensitive biosensor for detection of thrombin. The normal detection range for this aptasensor was in between 10<sup>-12</sup> and 10<sup>-10</sup> M with the ultimate limit of the order of 10<sup>-13</sup> M (Zhang et al., 2011b). Another PEC based aptasensor based on nitrogen doped graphene quantum dots has been reported for chloramphenicol detection which is a potential carcinogenic agent. This PEC showed high sensitivity than HPLC, electrophoresis, chemiluminescent and electrochemical sensors (Liu et al., 2015).

PEC shows many advantages over ECL detection i.e., less cost, simple, compact instrumentation, high sensitivity due to reduced background noise associated with it (Liu et al., 2015; Zhang et al., 2011b; Zhao et al., 2014).

### 3. Comparison with conventional biosensors

Aptamers have some distinctive advantages, over traditional monoclonal antibodies used in biosensors. The aptamers can be isolated and have a wide choice of target molecules from simple small molecules to whole microorganisms (Feng et al., 2014; Ikebukuro et al., 2004; Kudo et al., 2010; Ye et al., 2015; Zibai et al., 2010). Other advantages include enhanced pH and temperature stability, high target affinity and specificity besides comparable ease of synthetic mass production (Goldman et al., 2000; Liu et al., 2012). Given to these advantages the application scope of the aptasensors is very broad encompassing environmental monitoring, food analysis, medical diagnosis etc. Despite several advantages aptasensors have their own pitfalls which include limited detection of small molecules, problematic multiple analyte detection, cross reactivity among some molecules leading to faux results and cumbersome immobilization procedures leading to loss of precision (Arugula and Simonian, 2014).

### 4. Conclusion and future prospectus

In the past decade, there has been a dramatic increase in research for aptamers due to their various advantages in biosensor field. Nonmaterials used in the development of aptamer-based biosensors have greatly helped in the discovery of important and versatile diagnostic devices. Owing to their small size, portability, easy to use, cost efficiency, non toxicity and disposability. These aptamer based biosensors more interesting for application in clinical analysis. In this review article, the types of aptasensors, their applications in the field of mainly in the field of medical diagnosis a nanomedicine and biotechnology have been reviewed. Aptamers are manufactured in large number and modification by the use of different materials makes them versatile compounds to be used in variety of clinical applications. With the continued progress in the field of aptasensors instrumentation of biosensors is becoming cost effective, easy to operate and fast. But there are still many challenges as discussed in the review which remain to be addressed leading to widespread applicability along with better precision.

### Conflicts of interest

The authors declare no conflict of interest.

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