International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 1, January 2025 ijppr.humanjournals.com ISSN: 2349-7203

Aptamers: A Diagnostic and Therapeutic Tool for Clinical Applications

Deepthi D*, Ramesh Kumar K, Praveen Kumar N, Sowmiya P, Theyaneshwaran P.

*Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai – 600 003 India.

Received: 2025-1-07 Revised: 2025-1-19 Accepted: 2025-1-25

ABSTRACT

Aptamers are oligonucleotides, such as peptide molecules or single-strand deoxyribonucleic acid (ssDNA) or ribonucleic acid (RNA), that have particular three-dimensional shapes that allow them to bind to their targets with great affinity and specificity. Many studies have examined aptamers as a biomaterial for use as a biosensing probe, diagnostic and therapeutic tool, and in the creation of novel medications, drug delivery systems, etc. There have been efforts to look for aptamers that are unique to targets linked to a number of illnesses, including viral infections and cancer. In this review article, Aptasensor design configurations, different detection techniques, and Systematic Evolution of Ligands by Exponential Enrichment (SELEX) are discussed. Aptasensor offers a importance in the detection of heavy metal ions because to its good specificity, high sensitivity, and ease of preparation for small molecule detection.

Keywords: Aptasensor, Detection, SELEX, Electrochemical aptamer sensors, Heavy metals ion.

1.INTRODUCTION

Biosensors offer real-time detection, inexpensive analysis, and quick results. A biosensor is a device that connects a transducer and a biological recognition element to provide qualitative and/or quantitative information on biomolecular interactions. (see Fig. 1). A bioreceptor and a transducer are the two primary parts of a biosensor. A biomolecule known as a bioreceptor attaches itself selectively to the target analyte. The converter converts the binding event into signals that are measured and observable. A reporter and a detector are the two other sub-components that make up the transducer. Between the bioreceptor, the detector, and the authors to whom correspondence should be sent, the reporter serves as a signaling interface. Nevertheless, the reporter may not be used in the transducer parts of some biosensors.[1]

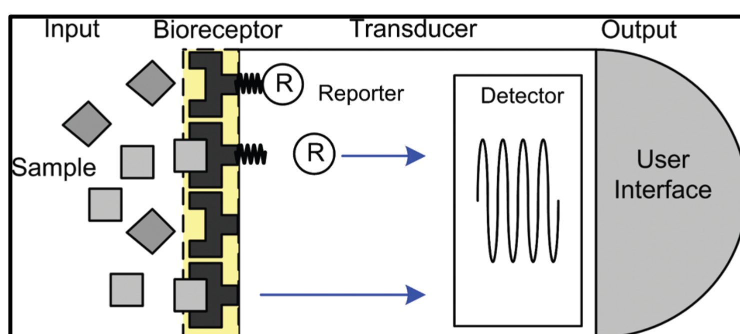

Fig 1. Diagrammatic illustration of a biosensor. Transducers and bioreceptors make up the two basic parts of a biosensor. Certain biosensors require reporters in order to communicate with the detection module, however other biosensors don't.[1]

As biorecognition components in biosensors, aptamers—short oligonucleotides produced in vitro from randomized libraries—offer a variety of benefits over antibodies. They can attach to certain molecules with high affinity.[2] Encoding, transmitting, and expressing genetic information are all made possible in large part by nucleic acids [3, 4]. Highly binding affinities between specific sequences of nucleic acids, often known as aptamers, and their targets form an intriguing class situated between small, biological molecules.

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Systematic Evolution of Ligands by Exponential Enrichment (SELEX), an in vitro process, is widely used for aptamer selection and synthesis, offering greater purities, aptamer quantities, and increased reproducibility. Aptamers are chemically manufactured single-stranded RNA or DNA molecules that have the ability to bind to a variety of targets. These targets are chosen in vitro from vast populations of random sequences. They have multiple uses of different kinds due to their capacity to target targets effectively. The complete viruses or cells, as well as peptides, proteins, medications, metal ions, and other target molecules, have all been selected by researchers as high-affinity aptamers thus far [5-9]. Finally, after being denaturated at high temperatures, aptamers have great stability and can revert to their active conformation [10].

Aptamers have more affinity, specificity, stability, and benefits from chemical synthesis than ordinary molecules, making them particularly appealing for applications ranging from chemical biology to medicine [11-13]. Therefore, they have many advantages over anti-bodies, such as high selectivity, chemical stability, and ease of modification. For researchers looking to create and develop aptasensors, this page offers an overview of aptasensors. It provides a summary of popular surface immobilization strategies and current approaches for converting the aptamer-binding event into a signal that can be physically detected [14,15].

2.SELEX METHOD

The fundamental steps in the SELEX method of aptamer screening include binding, partitioning, elution, amplification, and regeneration [16]. In the binding step, a library of oligonucleotides (DNA or RNA) with a central core that either entirely random sequences or pre-defined biased sequences surrounded by consistent priming sections is incubated with the target analyte [17]. The partitioning step then removes low-affinity or non-binding oligonucleotides from the binding oligonucleotides. The polymerase chain reaction (PCR) method is used to further elute the binders, or binding oligonucleotides, which are subsequently amplified (enriched) (RNA oligonucleotides are reverse transcribed to DNA prior to PCR). Finally, for the following SELEX round, dsDNA is transcribed back to RNA (for RNA aptamer selection) or regenerated to ssDNA (for DNA aptamer selection). The next iteration of SELEX begins with this newly enhanced library. A complicated library of oligonucleotides is reduced to a small number of oligonucleotides with high affinity for the target analyte by repeating the SELEX cycle [18]. Fig. 2 shows a schematic representation of the steps that make up SELEX.

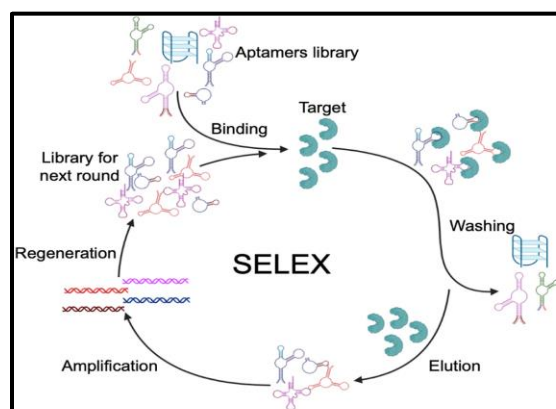

Figure 2 shows a diagram of the SELEX process's phases. made with BioRender.com.

2.1.Filtration Using Nitrocellulose Membrane SELEX

Because of its non-specific affinity for amino acids, nitrocellulose membranes are frequently employed to immobilize proteins in Western blots and atomic force microscopy (AFM), offering simple and quick protein immobilization. Kramlova's group used nitrocellulose membranes in 1968 to swiftly and simply extract RNA molecules from proteins.[19]

*2.2.*Magnetic Bead-Based Technology and Affinity Chromatography SELEX

One technique for distinguishing the constituents of a biological combination is affinity chromatography. It is principally employed in the purification of recombinant proteins, which are derived from highly specific biological interactions, including those involving an antigen and an antibody or a receptor and a ligand. Usually made up of agarose-based beads, the immobile phase is composed of these beads packed onto a column for the purposes of washing and elution. By immobilizing target molecules on the beads during the binding and separation stages of SELEX, affinity chromatography helps to select only the library components that have an affinity for the target (Figure 3(a)) [20-22] One particularly effective method for quickly and easily isolating target-immobilized beads using a magnet is to utilize magnetic beads (Figure 3(b, c)) [23-25].

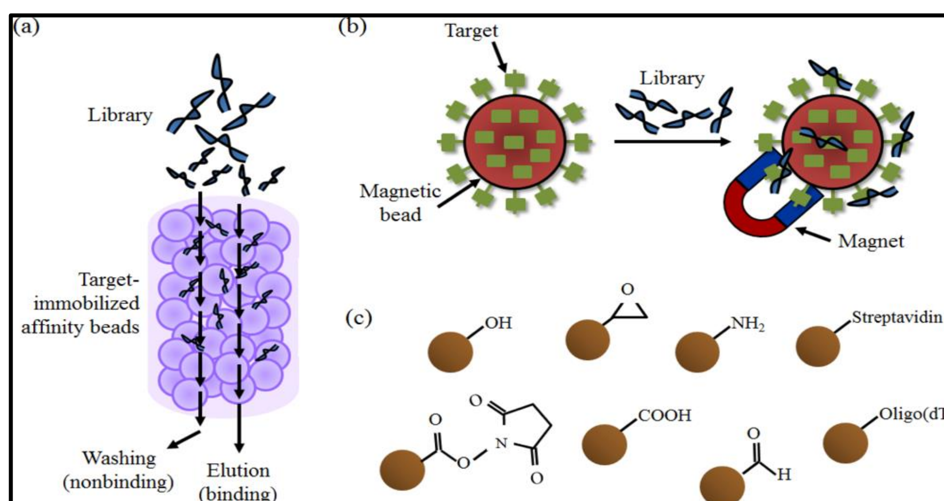

Figure 3: (a) a schematic representation of the affinity column-based library selection phase; (b) the magnetic bead selection stage; and (c) a variety of functional group-activated beads, including epoxy- and tosyl-activated beads.

2.3 Capillary Electrophoresis-Based SELEX

Capillary electrophoresis (CE) possesses several appealing advantages over the other analytical separation methods in the aspects of speed, resolution, capacity, and minimal sample dilution. This method can separate ionic species by their charge, frictional forces, and hydrodynamic radius under the influence of an electric field [26]. With this method, an aptamer can be selected by a mobility shift among the mixture of a target, the library, and the target-library complex (Figure 4) [27,28].

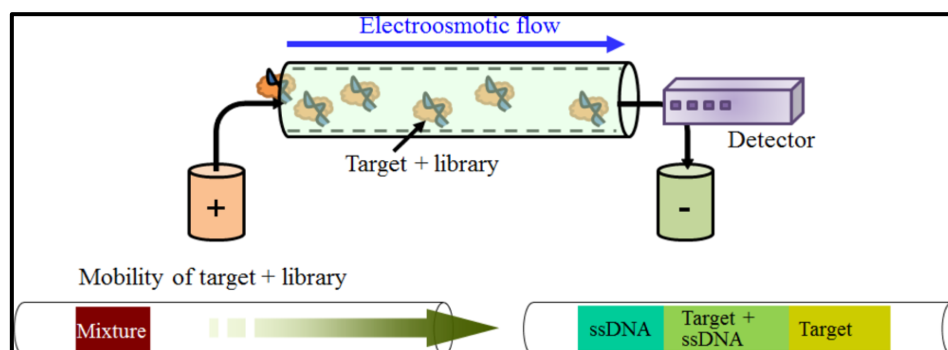

Figure 4: The basic idea behind the CE selection process. The differential in mobility resulting from mass and charge is used to choose aptamers.

2.4. SELEX Based on Microfluidics

SELEX, which uses a microfluidic or chip device, was created to more efficiently choose an aptamer. [29] This approach can improve selection efficiency on a small scale because it is mostly chip-processed. For instance, utilizing Soh's group's Continuous-flow Magnetic Activated Chip-based Separation (CMACS) apparatus, a single selection round produced the DNA aptamer-specific bound to neurotoxic type B [30].

2.5.TheCell-Selex

While single, highly-purified proteins are the main targets of other SELEX techniques, Cell-SELEX looks for an aptamer against an entire cell. In other words, the targets of Cell-SELEX are extracellular proteins on the cell surface or unique structures of the cell. In the majority of cases, Cell-SELEX processes have washing (for adhesive cells) or centrifugation (for suspension cells) steps during the separation of aptamers, because target immobilization is not practicable in the solid phase.[31]

2.6. Other Method-Based SELEX

Regarding SELEX, a number of techniques have been used, including surface plasmon resonance (SPR), AFM, and electrophoretic mobility shift assays (EMSA). The efficiency of these procedures in selecting the aptamer has not been proved, despite the fact that they have the advantage of fewer selection rounds [32-35].

3.TYPES OF APTA-SENSORS (Transducers)

3.1 OPTICAL

When an aptamer binds to a target, its conformation changes.
An aptamer can be made to detect the target binding event by adding reporter molecules or signaling molecules to it. In optical detection, a common technique is the molecular beacon, which is a hairpin-shaped molecule with a fluorophore-quencher attached. Ozaki et al. (2021) employ a fluorescent detection aptasensor utilizing fluorophore-quencher pairs as a molecular beacon to identify L-argininamide). The structure generated by DNA aptamer was random in the absence of L-argininamide. By stabilizing the stem-loop structure and binding the target to the aptamer domain, the fluorescence will be quenched. The aptamer structure's conformational change upon target binding is the basis for the majority of published work utilizing molecular beacons.[36]

Colorimetric or fluorometric optical transduction was first described by Ho et al., and it used a cationic, water-soluble polythiophene derivative as the reporting element in identifying the target of human thrombin. The probes or analytes are not tagged in any way during this transduction process. When anionic single-stranded oligonucleotides and a target protein are mixed with the conjugated backbone of a cationic poly (3-alkoxy-4-methylthiophene) derivative, it makes use of various electrostatic interactions and conformational changes (see Fig. 5(a)).[37]

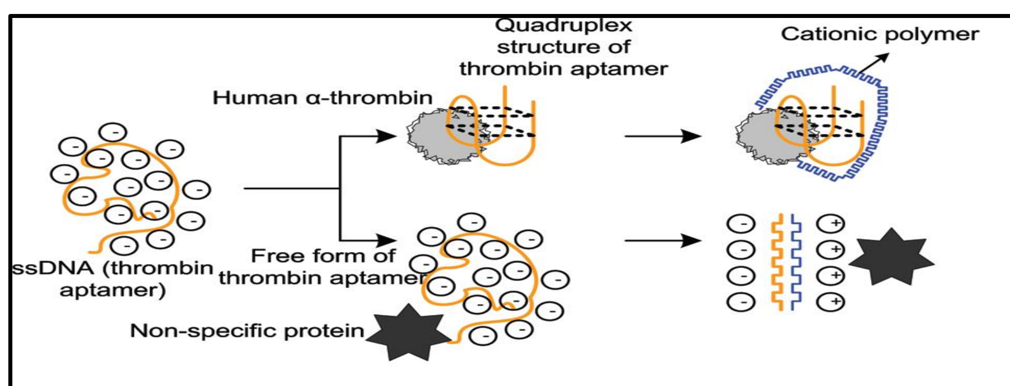

Figure 5. (a) Diagrams showing how to employ a cationic polymer and a ss-DNA thrombin aptamer to specifically detect human thrombin 1. Without target labeling, Cationic Polymer 1 converts the newly formed complex formation into an optical signal. Permission to reprint from J. Amer. Chem. Soc. 126, 1384 (2004), H.-A. Ho and M. Leclerc. Copyright 2004 by American Chemical Society.

3.2. Electrical

3.2.1. Electrochemical

Owing to its simplicity in construction and ability to be integrated with lab-on-a-chip technologies, electrochemical detection is becoming more and more common in biosensors. Along with simultaneous multi-analyte detection, it provides a straightforward, quick, and affordable sensing platform. Two working electrodes, one auxiliary electrode, and one reference electrode make up a typical electrochemical detection configuration. Current flow or the potential for detection will alter as a result of biomolecular interactions at the electrode interface. [38-40]

An aptamer's conformational shift upon target engagement is the basis for the majority of electro actively labeled electrochemical detections. Electroactive labels are placed far from the electrode surface in the signal "on" design (see Fig. 6) to limit electron transport in the absence of a target. An increase in current results from the binding process, which brings the electroactive label closer to the electrode surface and enhances electron transfer. The signal "off" design (see Fig. 7) operates in the opposite way, producing electrochemical signals when the redox-tag connected to the aptamer is brought close to the electrode surface in the absence of a target. A target's addition disassembles the redox-tag that is attached, which lowers the signal.[41]

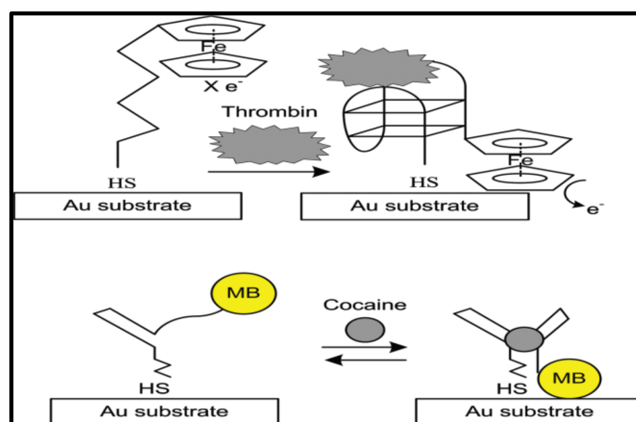

Figure 6: Diagram showing the signal "on" design of an electronic aptamer-based sensor (a) Co-immobilized micro peroxidase uses ferrocene-labeled aptamer as a redox partner. In order to measure variations in distance-dependent voltage-amperometric behaviour caused by a 3-D conformational change upon target contact, the redox-labeled aptamer self-assembles on the gold electrode. Published by permission of M. N. Mir and I. Katakis, Molecular BioSystems 3, 620 (2007), [31]. A 2007 Royal Society of Chemistry publication. (b) Using an alkanethiol group, an aptamer labeled with methylene blue is rendered immobile on a 1 mm2 gold electrode. The aptamer folds into a three-way junction that binds cocaine when the target is present. B. R. Baker et al., J. Amer. Chem. Soc. 128, 3138 (2006), is reprinted with permission from [32]. Copyright 2006, American Chemical Society.

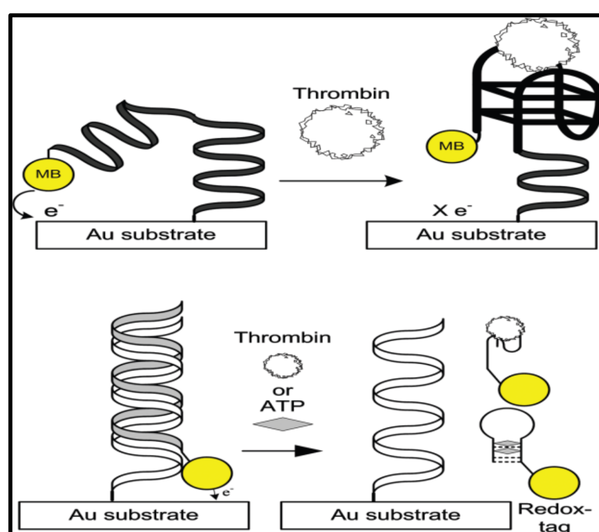

Figure 7: Diagram of an electrical sensor utilizing an aptamer based on signal "off" architecture (a) Aptamer is extremely dynamic when it is unbound, allowing the MB redox tag and electrode to collide quickly. Efficient electron transfer results from this. When the aptamer binds to its target, it generates a stable, hard structure that prevents electron transmission. Reprinted with permission from Angewandte Chemie 117, 5592 (2005), by Y. Xiao et al. Wiley Interscience, copyright 2005. (b) The target-induced strand released of a redox modified aptamer from the aptamer-capture DNA duplex bound on electrode powers the electronic aptamer-based biosensor. Reprinted with permission from The Analyst 133, 323 (2008), J. Yoshizumi et al. [34]. The Royal Society of Chemistry, 2008.

4.Aptasensors: An Detection Tool for a Range of Applications

Many applications, such as environmental monitoring (e.g., toxins, heavy metals), food safety (e.g., antibiotics and additives), law enforcement (e.g., illegal drugs), and medical diagnostics (e.g., metabolites, neurotransmitters), depend on the sensitive and accurate detection of small-molecule targets. Chromatography and mass spectroscopy-based techniques provide for precise and quantitative detection, but they are mostly limited to laboratory environments and call for highly skilled workers and costly, sophisticated equipment. From point-of-care disease biomarker screens to on-site drug tests and personal glucose meters, biosensors have become

a viable substitute for straightforward and portable detection applications. Due to its ability to combine high sensitivity and specificity with affordability, ease of use, and quick turnaround times, biosensors have become widely used.

4.1. Heavy metal ions:

Through electrostatic interaction, aptamers, a type of polyanion, can draw metal ions to them.[42]A variety of three-dimensional structures with affinities for particular metal ions can be formed by aptamer sequences.[43] The aptamers lack efficient recognition sites due to their basic structure and solitary binding site for heavy metal ions.[44] Additionally, similar structures of distinct metal ions make it challenging for aptamers to identify metal ions within a group. Furthermore, choosing heavy metal ion aptamers presents difficulties. Because of their low molecular weight and minimal steric barrier upon binding to nucleotide sequences, heavy metal ions will significantly impact the screening process's ability to separate them. Highly specialized aptamers are difficult to separate using most SELEX procedures. The current standard selection method for heavy metal ions involves fixing the library to the matrix, which comprises graphene oxide-SELEX and affinity chromatography-SELEX. [45]

4.2. Prostate specific antigen:

Globally, cancer is the leading cause of death, and among men, prostate cancer, which attacks the prostate gland, is the third most common cause of cancer death. In order to diagnose prostate cancer, prostate specific antigen (PSA) is a commonly utilized marker. The development of quick assays utilizing biosensing technologies has drawn more interest recently. PSA is detected electrochemically using a label-free, microfluidic paper-based analytical instrument. In order to create hydrophobic and hydrophilic layers for the microfluidic channel, the paper device was made via wax printing. Three electrodes—the working, counter, and reference electrodes—were then screen-printed. After being created and described, gold nanoparticles (AuNPs)/reduced graphene oxide (rGO)/thionine (THI) nano composites were applied to working electrodes to immobilize DNA aptamer probes.[46]

4.3. Pathogens:

Due to the serious hazards that food-borne viruses pose to public health and food safety, quick, sensitive, and multifunctional detection methods must be developed. One crucial instrument for highly sensitive analyte detection is a biosensor. A significant benefit of the multiplex aptasensor is its ability to identify several food-borne viruses on a single platform, which also lowers the detection cost and exhibits good selectivity because the multiplex platform and aptamer are integrated.[47]

4.4. Tumour Necrosis factor:

A major indicator of inflammation, tumor necrosis factor-a (TNF-a) is engaged in a variety of physiological and pathological reactions. The target analyte's binding event is thought to alter the distance between electrodes and redox reporters, producing electrochemical signals that may be detected. Significantly, aptamer electrodes are regenerable and reusable.[48]

4.5. Tetracycline:

Tetracycline is detected with an electrochemical aptasensor that uses a ssDNA aptamer that binds to it specifically as a recognition element. In order to differentiate small structural alterations in other tetracycline derivatives, the aptamer was extremely selective for tetracycline. Tetracycline's binding to the biotinylated ssDNA aptamer was examined using square wave and cyclic voltammetry after the aptamer was mounted on a streptavidin-modified screen-printed gold electrode.[49]

4.6. Proteins:

Protein is one of the fundamental components that make up all of the human body's cells and tissues. Since proteins play a crucial role in the body's vital organs, it is very important to detect proteins accurately and promptly when diagnosing illnesses, especially since medical precision has increased. An electro-chemical apta-sensor to identify the α-synuclein oligomer was described by Taghdisi and associates. Methylene blue, terminal de-oxynucleotidyl transferase, and exonuclease I served as the foundation for the sensing platform. Because Apta-sensor employs a label-free aptamer, terminal deoxynucleotidyl transferase, and exonuclease I, it has a higher sensitivity.

A significant current signal is produced when terminal deoxynucleotidyl transferase lengthens the aptamer and complementary strand in the absence of α-synuclein oligomer. This enhances the accumulating methylene blue as a redox agent on the electrode surface. Conversely, in the presence of an α-synuclein oligomer, exonuclease I breaks down complimentary strands on the electrode surface, resulting in a weaker current signal and less methylene blue buildup. Higher accuracy and iterability were demonstrated by the sensor in detecting the α-synuclein oligomer in serum samples. Sulfur and nitrogen codoped reduced graphene oxide (SN-rGO)

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was created by Chen et al. as the electrode that supports the substrate using a practical and effective reflux method. Following the electrodeposition of gold nanoparticles (AuNPs), an Au-S bond was used to modify the tetrahedral DNA (TDNA) probe on the electrode. Fig. 8 displayed the biosensor's developed mechanism.[2]

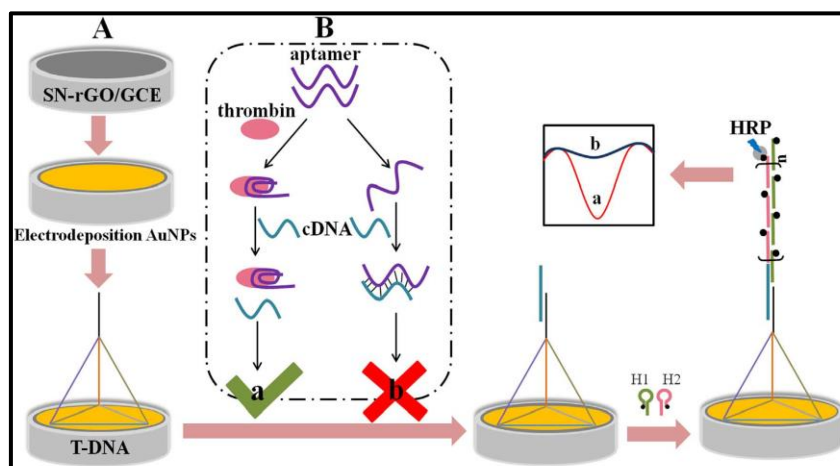

Fig. 8. Schematic diagram of the competitive apta-sensor for thrombin detection.

5.Conclusion:

A lot of recent research has been done on apta-sensors specifically for clinical diagnostic detection and monitoring of environmental and food toxins, according to the results of the current review papers. The detection of pathogenic factors is highly probable with electrical and optical apta-sensors because of their great sensitivity, real-time monitoring, and high frequency. Since they show a greater binding affinity for the target analyte, the aptamers can be useful as bio-recognition agents. It may be possible to create new structure-switching aptamers in the future to identify hazardous chemical substances and various clinical biomarkers. Combining lab-on-chip platforms with functional nanostructures and aptamers can create a viable avenue for the advancement of necessary and advantageous instruments for clinical diagnostic detection, food analysis, and biomonitoring.

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How to cite this article:
Deepthi D et al. Ijppr.Human, 2025; Vol. 31 (1): 188-196.

Conflict of Interest Statement: All authors have nothing else to disclose.

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