Recent Advances in Aptamer-based Detection and Therapeutics: Applications in Disease Detection, Biosensing and Targeted Drug Delivery

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

Aptamers, with their high specificity and affinity, represent a promising avenue for drug delivery and therapeutic applications in both cardiovascular and neurodegenerative diseases. Unlike traditional antibodies, aptamers are chemically synthesized, avoiding immunogenic responses and offering a more versatile platform for targeting molecular disease markers. In cardiovascular diseases,

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aptamers address limitations of existing therapies by offering targeted and precise treatment options, such as anti-platelet therapies and stent coatings. For neurodegenerative diseases, aptamers can bind to misfolded proteins, potentially preventing disease progression. Additionally, aptamers have been developed for the diagnosis and treatment of prionopathies and other animal diseases, providing rapid, sensitive, and cost-effective solutions. Their application in detecting viral and bacterial infections, toxins, and drug residues further showcases their diagnostic potential. Recent advancements in aptamer technology, including refined selection methods and chemical modifications, have positioned aptamers as versatile and powerful tools in modern diagnostics and therapeutics, offering a compelling alternative to antibodies in proteomics and beyond.

1. INTRODUCTION

Aptamers, introduced in 1990 by Ellington and Szostak as well as Tuerk and Gold, are short synthetic single-stranded nucleic acid sequences capable of binding to a wide array of targets such as metal ions, chemical compounds, proteins, cells, and microorganisms. These affinity ligands offer several advantages over traditional antibodies, including longer shelf life, consistent batch quality, low immunogenicity, and the ability to incorporate chemical modifications for enhanced stability and targeting affinity. Consequently, aptamers have found applications in therapy, drug delivery, diagnostics, functional genomics, and biosensing over the past few decades (AlShamaileh et al., 2017; Tapsin et al., 2018).

Aptamers are typically developed in vitro through a procedure known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX) (Tuerk and Gold, 1990). The original SELEX procedure is labor-intensive and time-consuming. Over the past three decades, advancements in material sciences and analytical techniques have led to various SELEX adaptations aimed at reducing processing time and improving efficiency. Despite these advancements, developing highly specific and high-affinity aptamers remains a significant challenge.

2. SELEX PROCESS

SELEX is a multidisciplinary technique involving molecular biology, nucleic acid chemistry, material science, and bioinformatics to develop affinity ligands for diverse targets (Blind and Blank, 2015). A universal SELEX protocol suitable for all experimental settings does not exist (Wang et al., 2018). Designing a SELEX protocol requires consideration of factors such as time and cost efficiency, initial library type and modifications, and instrument accessibility.

3. SELEX LIBRARY DESIGN

The initial nucleic acid (NA) library is critical for SELEX. Important aspects of NA library design include the type of library, primer binding sites, chemical modifications, fixed sequences, and randomization strategies.

4. DNA OR RNA?

Both DNA and RNA libraries have been used in SELEX, with early protocols favoring RNA due to its perceived ability to form more functional motifs and higher affinity binders (Kohlberger et al., 2022). However, recent evidence suggests that single-stranded DNA (ssDNA) can form complex tertiary structures comparable to RNA. DNA aptamers offer several advantages over RNA, including greater chemical and biological stability, easier selection and application, cost and time efficiency (due to the absence of a reverse transcription step), and better commercialization prospects (Lakhin et al., 2013). Consequently, DNA libraries have become more prevalent, representing almost all products from commercial aptamer developers by 2013 (Darmostuk et al., 2015).

5. GENOMIC SELEX

Genomic SELEX, which uses genomic DNA, genome-encoded RNA, and transcriptomic total RNA as starting libraries, differs from common SELEX. It aims to identify regulatory domains in a genome, such as sequences recognized by transcription factors and components of the gene expression machinery (Vorobyeva et al., 2018). Despite its lower sequence diversity, genomic SELEX benefits from endogenous binding sequences, facilitating the identification of targets.

6. WHAT IS AN APTAMER?

The term "Aptamer" was coined by Andy Ellington, derived from the Latin words "aptus" (to fit) and "meros" (part) (Ellington 1992, Roxo et al., 2019). Aptamers are short single-stranded DNA or RNA molecules that selectively bind to specific targets, including proteins, peptides, carbohydrates, small molecules, toxins, and cells. Their binding is determined by their tertiary structure, involving shape-dependent interactions, hydrophobic interactions, base-stacking, and intercalation (Ku et al., 2015).

7. SELEX PROCESS OVERVIEW

The SELEX process involves iterative cycles of *in vitro* selection and enzymatic amplification, mimicking Darwinian evolution to select high-affinity binding sequences (Jijakli et al., 2016). A typical SELEX process starts with a chemically synthesized random DNA oligonucleotide library. For RNA SELEX, this DNA library is converted into RNA. The library is incubated with the target, and unbound sequences are washed away (Boussebayle et al., 2019). Bound sequences are eluted, amplified by PCR (or RT-PCR for RNA), and used in subsequent rounds of selection. The process continues until target-specific oligonucleotides are enriched. Selected aptamers are cloned, sequenced, and characterized for binding affinity and specificity (DeRosa et al., 2023).

8. CHIMERIC APTAMERS

Recent advancements include chimeric aptamers, which combine aptamers with other molecules like siRNA, proteins, enzymes, drugs, or imaging agents for enhanced stability and functionality (Zhang et. al., 2019). Chimeric aptamers are highly stable, efficient, and capable of drug delivery, showing potential in targeting tumor cells and enhancing antitumor immunity (Han et. al., 2020).

9. APPLICATIONS IN CANCER

Aptamers screened by using biomarkers closely related to the development of cancer as targets can be used as drugs themselves, and can also act as a targeted drug delivery system by conjugating with drugs, siRNA, nanoparticles, etc. to form a targeted drug delivery system which can target specific tumor cells, thus minimizing the toxicity to normal cells, reducing the dose needed for treatment and enhancing

therapeutic efficacy. Aptamers offer a promising alternative to traditional anti-tumor drugs, which often have severe side effects. Aptamers targeting tumor biomarkers can serve as therapeutic agents or targeted drug delivery systems, reducing toxicity and improving therapeutic efficacy. Examples include aptamers targeting PSMA, nucleolin, EpCAM, PTK7, and MUC1. (Wei et. al., 2022; Venkatesan et al., 2023).

10. THERAPEUTIC USE OF APTAMERS

The first SELEX experiment identified an RNA aptamer against bacteriophage T4 DNA polymerase (Tuerk and Gold, 1990). Despite the discovery of many aptamers since then, only one, Macugen (Pegaptanib sodium), has received FDA approval (Kaur et al., 2018). Challenges include susceptibility to nucleases, rapid renal excretion, and insufficient *in vivo* binding affinity. Chemical modifications, such as 2'-fluoro, 2'-amino, 2'-O-methyl substitutions, locked nucleic acids (LNA), phosphorothioate linkages, and 3'-end capping, enhance stability.Spiegelmers, mirror-image aptamers, resist nuclease degradation. Conjugation with polyethylene glycol (PEG) or proteins extends aptamer half-life and improves pharmacokinetics. Aptamers have also been developed for targeted drug delivery and as antagonists or agonists of their targets (Chandola et al., 2020).

11. APTAMERS AS DIAGNOSTIC REAGENTS

The aptamer market is rapidly expanding and poised to make significant contributions to the diagnostic industry. Over the past decade, aptamers have been integrated into various point-of-care diagnostic platforms (Kaur et al., 2018).

These include Aptamer-Linked Immobilized Sorbent Assay (ALISA), Dot-blot (Citartan, 2021), electrochemiluminescence (ECL) assays (Climent, E. & Rurack., 2021), nanoparticle-based assays (Matteoli et al., 2023), lateral flow test strips (Zhang et al., 2021), upconverting fluorophore-based assays (Lostao et al., 2023), electrochemical sensors and glucometer-based assays (Nur et al., 2021) for detecting a range of analytes from small molecules to complex antigens and whole cells. Many of these aptamer-based diagnostic assays align with the WHO's "ASSURED" criteria for point-of-care

diagnostics, being affordable, sensitive, specific, user-friendly, robust, and suitable for use by unskilled labor outside of laboratory settings (Everitt, 2021). Additionally, aptamer technology is versatile, applicable to various diseases, sample types, and environmental pollutants like pesticides and heavy metals (e.g., arsenic, lead, mercury) (McConnell, et al., 2020).

Aptamers have also garnered interest for preclinical molecular imaging across all imaging modalities, including Positron Emission Tomography (PET) (Li et al., 2023), Fluorescence Imaging (Su et al., 2022), Magnetic Resonance Imaging (MRI) (Lin et al., 2023), Ultrasound (US) Imaging (Kim et al., 2022), X-Ray Computed Tomography (X-Ray CT) and multimodal imaging applications (Gao et al., 2022). Molecular imaging probes typically comprise three components: a reporter molecule that generates a detectable signal, a targeting moiety that interacts selectively with a molecule of interest, and a spacer connecting the targeting ligand and reporter (Robinson et al., 2022). This spacer may also possess additional functionalities, such as redox- or pH-sensitive cleavage or pharmacokinetic property alterations (Bohrmann et al., 2022). In nanomedicine, the lines defining imaging probes blur further, with nanomaterials sometimes serving as the reporter (e.g., quantum dots) or as carriers for reporter and therapeutic molecules (Pavelic et al., 2023). Nanomaterials also have the ability to accumulate in tumors via the Enhanced Permeability and Retention (EPR) effect, a property due to increased vascular permeability in cancerous tissues (Zhu et al., 2021).

12. APTAMER-BASED ANTIBACTERIAL AND ANTIVIRAL THERAPY

Nucleic acid aptamers, single-stranded DNA or RNA molecules selected *in vitro*, can bind to a wide range of targets with high affinity and specificity (Kim et al., 2022). They are emerging as promising alternatives to conventional anti-infective agents for combating infectious diseases (Afrasiabi et al., 2020). Aptamers targeting pathogen components or entire pathogenic cells have demonstrated notable inhibitory effects on pathogenic invasion, enzymatic activities, and viral replication, including for highly drug-resistant strains and biofilms (Gan et al., 2022). Aptamer-mediated drug delivery and controlled release strategies are also being explored. However, there are technical barriers to the therapeutic application of

aptamers, including production costs, binding condition variability, and the tendency for non-specific binding due to the negative charge of oligonucleotides (Doherty et al., 2024). Further research is needed to optimize aptamer selection and functionality in diverse environments, such as human plasma, and to improve commercial viability (Agha et al., 2024).

13. APTAMER-MEDIATED DRUG DELIVERY SYSTEM FOR CARDIOVASCULAR DISEASES

Aptamers are particular molecules capable of binding to targets relevant to cardiovascular diseases, many of which have progressed to clinical trials (Di Mauro et al., 2024). Current therapeutic agents often suffer from limitations such as non-selectivity, inconsistent pharmacodynamic effects, narrow efficacy-safety profiles, and the lack of a reliable platform for precise titration or active reversibility based on patient-specific, disease-specific, and clinical conditions (Ramchandani et al., 2023). Aptamers, resembling "chemical antibodies," offer high specificity and affinity without the risk of immunogenic responses, making them promising candidates for applications ranging from anti-platelet therapies to intracoronary stent coatings (Chen et al., 2022). To translate aptamers into clinical practice, more efficient selection methods and easier conjugation strategies are required. Researchers have already identified high-affinity aptamers for a wide range of targets, highlighting their potential for therapeutic applications. However, challenges such as unpredictable pharmacokinetics, toxicity, and off-target effects need thorough investigation (Kovacevic et al., 2018). As more academic and commercial entities engage in aptamer research, the development of aptamer-based therapeutics is expected to accelerate, finding niche applications in cardiovascular disease treatment and significantly impacting clinical patient management.

14. APTAMER APPLICATIONS IN NEURODEGENERATIVE DISEASES

Neurodegenerative disorders, characterized by the accumulation of misfolded proteins in the central nervous system, pose a significant challenge as populations age (Lamptey, et. al., 2022). Aptamers offer new avenues in this field by binding to target proteins, potentially interrupting their accumulation and thus preventing or slowing disease progression

(Shraim et al., 2022). Recent advances in aptamer generation and their applications in diseases with the global population aging, the incidence of neurodegenerative diseases such as alzheimer's, parkinson's, transmissible spongiform encephalopathy, huntington's disease, and multiple sclerosis are expected to rise, emphasizing the need for effective diagnostics and treatments (Qu et al., 2017). Aptamers, with their high specificity and low production costs compared to antibodies, provide a promising alternative for diagnosing and treating these conditions. Although aptamers are relatively new compared to antibodies, their development is progressing, and they are expected to offer numerous opportunities in neuroscience diagnostics and therapeutics (Zhou, J., & Rossi, J. (2017).

15. APTAMERS FOR PRIONOPATHIES

Aptamers have been developed for prionopathies, or transmissible spongiform encephalopathies (TSEs), which affect both animals and humans (Niederlender et al., 2021). These diseases involve the conversion of normal prion proteins into abnormal, insoluble forms. Aptamers offer fast and precise diagnostic and therapeutic options

for these conditions, which is crucial for effective clinical management (Macedo, B., & Cordeiro, Y. 2017). Current diagnostic methods for TSEs and other animal diseases need improvements in specificity, sensitivity, and cost-effectiveness (Chandola, C., & Neerathilingam, M. (2020).Aptamers have shown promise in developing biosensors for detecting pathogens, drug residues, toxins, and cancerous cells (Devi et al., 2021).While *in vivo* applications of aptamer-mediated biosensing and therapy in animals are limited, advancements in aptamer technology are paving the way for their use in diagnostics and therapeutics.

16. APPLICATIONS OF APTAMERS IN DISEASE DIAGNOSIS AND TREATMENT

Aptamers have been used to detect viral and bacterial diseases, toxins, and drug residues in animal health (Devi et al., 2021). For instance, they have been developed to detect foot-and-mouth disease (FMD) and SARS-CoV-2, among others. Aptamer-based diagnostic tools offer quick and accurate detection, essential for timely intervention and treatment. Many toxins such as Shiga toxins have two antigenically distinct forms, which could not be identified by
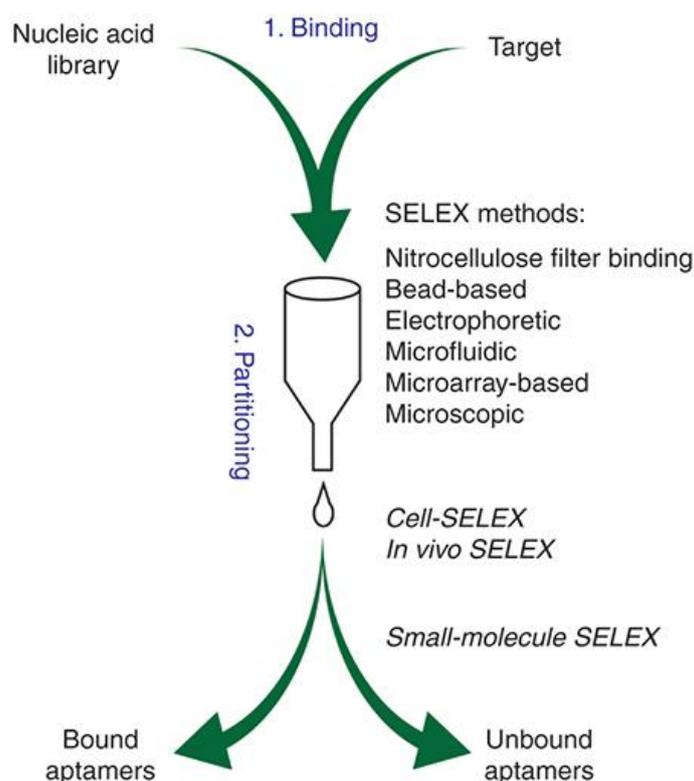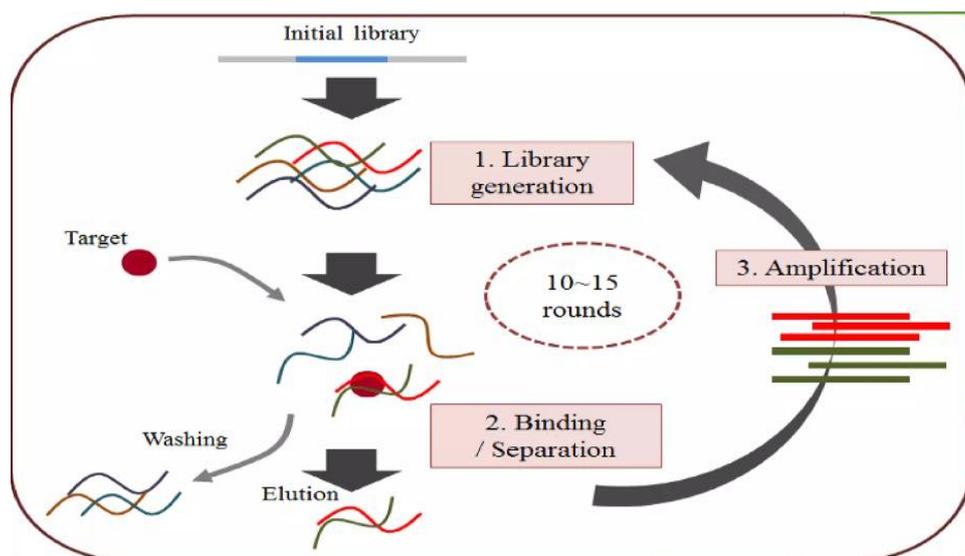

Fig. 1. A schematic representation depicting the selection process of SELEX technology

Fig. 2. A diagram illustrating the selection process of SELEX technology

a single aptamer (Kaur et al., 2020). Colibacillosis in poultry adversely affects egg production and chicken growth, increases bird mortality, and results in significant economic losses. DNA aptamers have been developed to detect *E. coli* strains K88 by binding to the fimbriae protein of enteropathogenic *E. coli* (Vidic et al., 2017). In therapeutic applications, aptamers provide targeted delivery of drugs, addressing challenges such as antibiotic resistance (Kim et al., 2018). They are also being explored as alternatives to antibodies in proteomics due to their high specificity, ability to detect multiple proteins simultaneously, and adaptability through chemical modifications (Cohen and Walt, 2019). This versatility makes aptamers promising tools for both diagnostic and therapeutic applications in veterinary and human medicine.

17. APTAMERS AS DIAGNOSTIC REAGENTS

Affinity selection of threomers against protein's receptor binding domain revealed binding affinities comparable to conventional SELEX-derived aptamers (Lozoya-Colinas et al., 2023). Cheng et al. (2016) developed aptamer-coated magnetic beads and antibiotic-capped gold nanoclusters for the detection of bacteria for early diagnosis of mastitis. sDNA aptamers were selected against P48 protein of *M. bovis* with high affinity and specificity (Fu et al., 2014). Aptamers are emerging as effective alternatives to monoclonal antibodies in diagnostic applications due to their high sensitivity,

specificity, and ability to be chemically modified. They can detect a wide range of proteins simultaneously in multiplex platforms, overcoming the cross-reactivity issues often encountered with antibodies. Recent developments in aptamer technology, including new selection methods, enhance their potential in proteomics and other diagnostic applications.

18. CONCLUSION

Aptamers, single-stranded nucleic acid sequences with high specificity and affinity for molecular targets, have emerged as powerful tools in diagnostics, therapeutics, and drug delivery. Aptamers represent a groundbreaking advancement in molecular diagnostics and targeted therapy, offering numerous advantages over traditional antibodies, such as high specificity, low immunogenicity, and ease of chemical synthesis. Their applications span diverse fields, including cardiology, oncology, neurology, and infectious disease management, where they facilitate precise drug delivery, early disease detection, and novel treatment strategies. Despite challenges like susceptibility to degradation and rapid clearance, ongoing innovations in chemical modifications and conjugation techniques continue to enhance their stability and clinical viability. As research progresses, aptamers are expected to play a crucial role in the future of precision medicine, providing safer, more effective, and highly specific solutions for disease diagnosis and treatment.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The authors of this work hereby declare that no generative AI tools, such as text-to-image generators or large language models were utilized in its authoring or editing.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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