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RECENT DEVELOPMENTS IN APTAMER TECHNOLOGY FOR THE TARGETED IDENTIFICATION OF SPECIFIC CANCER BIOMARKERS

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Abstract:

Aptamers are compact single-stranded oligonucleotides that can effectively bind to multiple molecules with high affinity and specificity, establishing themselves as a promising class of molecular recognition elements for the identification of specific cancer biomarkers. The distinctive characteristics of these molecules, such as their high specificity and affinity for target entities, stability in physiological environments and straightforward synthesis, render them excellent options for use in cancer diagnostics and treatment. The smaller dimensions of aptamers in contrast to antibodies, facilitate improved penetration into tissues and enable access to regions with dense cellular structures. Due to their limited immunogenic potential, aptamers are less inclined to trigger allergic reactions or adverse immune responses in individuals. Recent innovations in aptamer technology have emphasized the creation of innovative selection methods, including SELEX (Systematic Evolution of Ligands by Exponential Enrichment). This advancement has facilitated the discovery of aptamers that exhibit improved binding properties to a range of cancer biomarkers. These biomarkers include proteins, nucleic acids, and small molecules associated with tumor progression and metastasis. Furthermore, the association of aptamers with therapeutic agents or imaging probes has opened new pathways for targeted drug delivery and non-invasive imaging in oncology. This review presents recent innovations in aptamer design and their application in targeting specific cancer biomarkers, emphasizing their potential to improve early detection and treatment for cancer patients.

Keywords: *Aptamers, cancer biomarkers, systematic evolution of ligands by exponential enrichment (SELEX), metastasis, oncology*

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INTRODUCTION:

The origin of the term "aptamer" can be traced to the Latin word "aptus," meaning "fit," and the Greek word "meros," which refers to "part" or "region." This designation was adopted to represent the specific lock-and-key dynamic that characterizes the relationship between aptamers and their targets. Aptamers are brief, single-stranded oligonucleotides that can form three-dimensional structures, facilitating their binding to a variety of targets, including proteins, peptides, small molecules, and metal ions as shown in Figure 1. Aptamers are composed of either deoxyribonucleotides or ribonucleotides, typically ranging from 25 to 80 bases in length **[1]**. Their structural flexibility allows them to encircle small molecules or occupy spaces within larger molecular structures. Additionally, aptamers have the capability to bind to proteins, which can result in the disruption of multiprotein complexes or the inhibition of protein activity. Such interactions can produce therapeutic outcomes, including antagonistic effects. For instance, a study conducted by Sullenger et al. **[2]** in 1990 illustrated that an RNA aptamer could block viral replication by attaching to a viral protein, thus preventing its binding to viral RNA. The versatility of aptamers allows for their application in numerous fields, including therapeutics, diagnostics, and target binding. They are effectively utilized in biosensors across diverse disciplines, particularly in the realm of disease detection. During the COVID-19 pandemic, research focused on aptamer-based detection methods to facilitate rapid, point-of-care testing **[3]**. Furthermore, aptamers are instrumental in both imaging and therapeutic strategies. For instance, the Prostate-specific membrane antigen (PSMA) aptamer has been successfully used to target, image, and treat prostate cancer cells that express the PSMA marker **[4]**. The application of aptamers in cancer research has gained momentum due to their potential to target cancer-specific biomarkers with remarkable specificity. This article reviews the recent innovations in aptamer development focused on specific cancer biomarkers, highlighting their roles, applications, and the potential future of cancer treatment strategies.

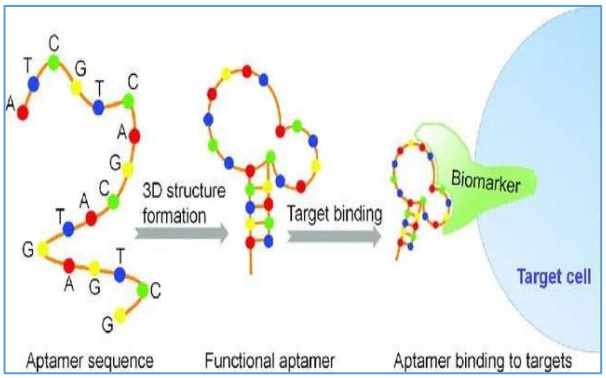

Figure 1 Schematic diagram of aptamer binding to its target

ADVANCED TECHNIQUES FOR THE SYNTHESIS OF APTAMERS

Next-Generation Sequencing (NGS)-Assisted SELEX

Next-Generation Sequencing (NGS)-Assisted SELEX (Systematic Evolution of Ligands by Exponential Enrichment) is an advanced method for generating aptamers, which are short, single-stranded oligonucleotides that can bind specific targets with high affinity and specificity. The integration of NGS into the SELEX process enhances the efficiency and effectiveness of aptamer selection by allowing for the simultaneous sequencing of a vast number of candidate sequences **[5]**. In the standard SELEX approach, a diverse library of nucleic acid sequences is repeatedly selected for its affinity to a target molecule, with subsequent steps including amplification and sequencing of the selected sequences. The process is significantly improved by next-generation sequencing (NGS), which permits the rapid parallel sequencing of millions of enriched sequences. This capability provides a wealth of data concerning the binding affinities and specificities of various aptamers. Consequently, it not only hastens the identification of high-affinity aptamers but also enhances the understanding of sequence diversity and the structural motifs that influence binding.

The application of next-generation sequencing (NGS) within the SELEX framework has brought about notable improvements in a range of fields, including diagnostics, therapeutics, and biosensing technologies. This methodology permits researchers to examine larger libraries and gather more substantial data sets, ultimately enhancing the efficacy of aptamer development.

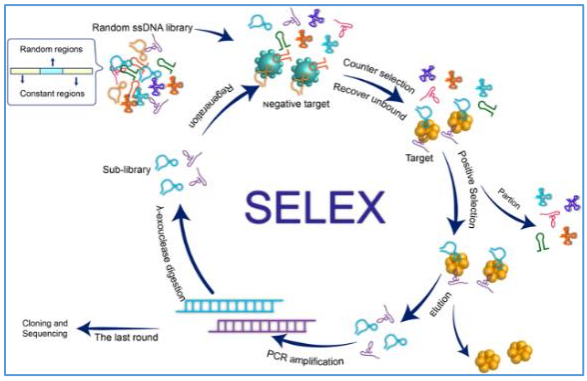

Figure 2 Schematic diagram of SELEX

Microfluidic SELEX

Microfluidic SELEX (Systematic Evolution of Ligands by Exponential Enrichment) is an advanced technique used for the selection and amplification of aptamers, which are short, single-stranded nucleic acids that can bind to specific targets with high affinity and specificity. This method leverages microfluidic technology to enhance the efficiency and speed of the SELEX process. Within the framework of traditional SELEX, an extensive library of nucleic acid sequences is repeatedly selected in rounds targeting a specific molecule. The sequences that emerge from this selection are subsequently amplified using polymerase chain reaction (PCR). Microfluidic SELEX enhances the traditional method by miniaturizing the procedure, which facilitates meticulous control over fluid dynamics. This advancement allows for swift mixing and separation of reagents, leading to decreased reagent usage, expedited selection durations, and the capability to manage multiple targets concurrently **[6]**. The microfluidic platform enables the real-time observation of binding interactions, thereby improving the identification of high-affinity aptamers. Furthermore, it supports the consolidation of multiple stages of the SELEX process within a single device, optimizing workflow and enhancing throughput.

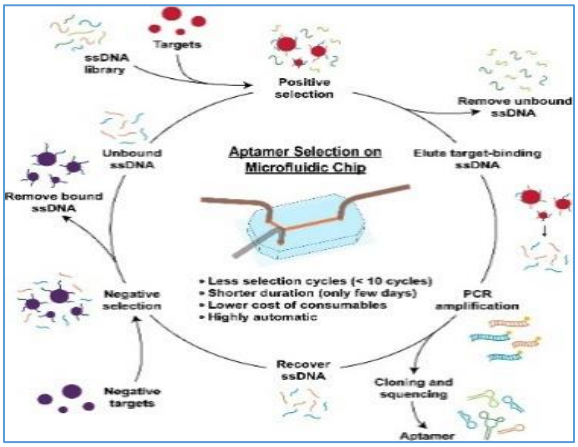

Figure 3 Schematic diagram of Microfluidic SELEX

In Silico Aptamer Design

In silico aptamer design refers to the use of computational approaches to discover and optimize nucleic acid sequences that can specifically bind to target molecules, including proteins and small molecules. This strategy relies on bioinformatics tools and algorithms to predict the secondary and tertiary structures of nucleic acids, evaluate their binding affinities, and simulate interactions with the targets of interest. The utilization of methodologies such as molecular docking, machine learning, and sequence alignment enables researchers to effectively evaluate extensive libraries of potential aptamer candidates prior to their in vitro synthesis **[7]**. This approach markedly decreases the time and resources allocated to experimental SELEX by concentrating on the most promising candidates during the aptamer selection process.

Capillary Electrophoresis-Based SELEX

Capillary Electrophoresis-Based SELEX (Systematic Evolution of Ligands by Exponential Enrichment) is an advanced technique utilized for the selection and amplification of aptamers. These aptamers, which are short, single-stranded oligonucleotides, possess the capacity to bind to specific targets with both high affinity and specificity. This method synthesizes the principles of capillary electrophoresis with the SELEX process to improve the efficiency and speed of aptamer selection. In this context, a library of nucleic acid sequences is exposed to electrophoresis in a capillary system, which permits rapid separation based

on size and charge. The immobilization of the target molecule within the capillary permits the selective binding of aptamers **[8]**. Unbound sequences are subsequently washed away, while the bound aptamers are eluted and amplified through polymerase chain reaction (PCR). This method enhances the purity of the aptamers selected and significantly reduces the time required for the selection process in comparison to standard methods.

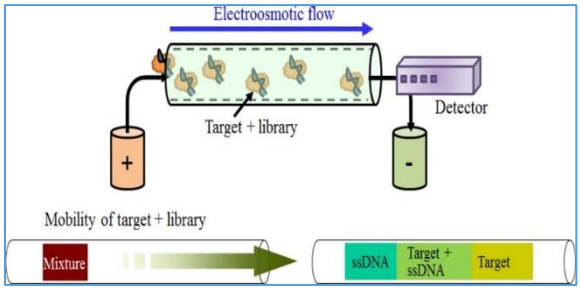

Figure 4 Schematic diagram of Capillary Electrophoresis-Based SELEX

Modified Nucleotide Incorporation

The technique of modified nucleotide incorporation is essential for the preparation of aptamers, which are short, single-stranded oligonucleotides known for their ability to bind specific targets with high affinity and specificity. This method involves the addition of chemically modified nucleotides into the oligonucleotide sequence during the synthesis. Such modifications can contribute to improved stability, binding affinity, and specificity of the resulting aptamers. Commonly employed modifications consist of phosphorothioate linkages, 2'-O-methyl ribonucleotides, and locked nucleic acids (LNAs) **[9]**. By utilizing these modified nucleotides, researchers can enhance the pharmacokinetic profiles of aptamers, making them more viable for therapeutic applications.

Target-Independent Selection Approaches

Target-independent selection approaches for preparing aptamers refer to methodologies that allow for the identification and isolation of aptamers without the need for a specific target molecule during the selection process. These approaches often utilize random oligonucleotide libraries and employ techniques such as SELEX (Systematic Evolution of Ligands by Exponential Enrichment) in a manner that does not rely on predefined targets. Instead, they may focus on general properties such as binding affinity, structural stability, or interactions with a broad range of biomolecules. These approaches are particularly useful in discovering aptamers for novel or poorly characterized targets.

DISTINCTIONS BETWEEN APTAMERS AND ANTIBODIES IN BIOCHEMICAL RESEARCH

In the realm of biochemical research, aptamers and antibodies are vital tools, particularly in diagnostics, therapeutics, and molecular biology. Despite their importance, they differ significantly in ways that affect their application and effectiveness. Below is a detailed discussion of these differences.

Nature and Composition: Aptamers are short, single-stranded oligonucleotides (RNA or DNA) that can fold into specific three-dimensional structures capable of binding to target molecules with high affinity. They are synthesized through a process known as SELEX (Systematic Evolution of Ligands by Exponential Enrichment), which allows for the selection of nucleic acid sequences that bind to specific targets. Antibodies, or immunoglobulins, are large Y-shaped glycoproteins produced by B cells in response to antigens. They consist of four polypeptide chains (two heavy chains and two light chains) and have a complex structure that includes variable regions responsible for antigen recognition **[10]**.

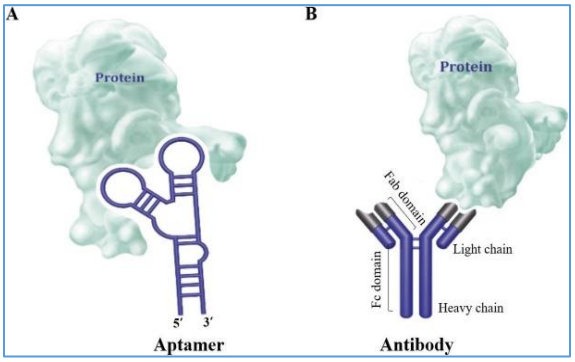

Figure 5 Schematic representation of aptamer (A) and antibody (B) recognizing antigens (proteins)

Binding Mechanism: The binding mechanism of aptamers is primarily based on shape complementarity and electrostatic interactions between the aptamer's folded structure and the target molecule. Their binding sites can be highly specific due to the unique conformations they adopt. Antibodies recognize antigens through their variable regions, which contain hypervariable loops that provide specificity. The interaction involves multiple non-covalent forces such

as hydrogen bonds, ionic interactions, van der Waals forces, and hydrophobic effects **[11]**.

Stability: Aptamers generally exhibit greater thermal stability compared to antibodies due to their smaller size and simpler structure. They can also be chemically modified to enhance stability against nucleases or other degrading agents. While antibodies are relatively stable under physiological conditions, they can be sensitive to extreme pH levels or temperature changes. Their larger size also makes them more susceptible to denaturation **[12]**.

Production Process: The production of aptamers is a synthetic process that does not require living organisms; thus, it can be performed rapidly and at lower costs compared to antibodies. Once an aptamer sequence is identified through SELEX, it can be synthesized in large quantities using chemical methods. The production of antibodies typically involves immunizing animals (e.g., mice or rabbits) with an antigen followed by harvesting serum or producing monoclonal antibodies through hybridoma technology. This process is time-consuming and often expensive **[13]**.

Immunogenicity: Aptamers are generally non-immunogenic since they are derived from nucleic acids rather than proteins; this reduces the risk of eliciting an immune response when used in therapeutic applications. Because antibodies are proteins derived from animal sources, there is a potential for immunogenicity when administered to humans or other species, leading to adverse immune reactions.

Target Range: Aptamers can bind a wide variety of targets including small molecules, proteins, peptides, and even whole cells due to their ability to form diverse structures. Antibodies predominantly target larger biomolecules like proteins but may have limitations when it comes to small molecules due to their size constraints.

Applications in Research and Medicine: Both aptamers and antibodies serve as crucial tools in research for applications such as biosensors, drug delivery systems, imaging agents, and therapeutic agents; however, aptamers offer advantages in terms of ease of modification for targeted delivery systems while antibodies remain the gold standard for many diagnostic assays due to their well-established use.

PROGRESS IN APTAMER DEVELOPMENT FOR TARGETING SPECIFIC CANCER BIOMARKERS

Recent studies have highlighted several novel aptamers targeting cancer-specific biomarkers, which play crucial roles in tumor progression, metastasis, and resistance to therapy. Here some of the key advances in aptamer development targeting specific cancer biomarkers are given below

HER2 (Human Epidermal Growth Factor Receptor 2): HER2 is a well-known biomarker in breast cancer, with overexpression found in approximately 15-20% of breast cancers. Recently, aptamers such as HER2-Aptamer (HB5) have been developed to specifically target HER2-positive cancer cells. HB5, for instance, binds to the extracellular domain of HER2, blocking its activation and downstream signaling pathways involved in cell proliferation and survival. Researchers have also explored conjugating HER2 aptamers with nanoparticles to deliver chemotherapeutic agents directly to HER2-positive tumors, increasing drug accumulation in cancer cells while minimizing systemic toxicity **[14]**.

PD-L1 (Programmed Death-Ligand 1): PD-L1 is a critical immune checkpoint protein that allows cancer cells to evade immune surveillance. The use of aptamers targeting PD-L1 has recently gained significant attention in the field of cancer immunotherapy. For example, the RNA aptamer PD-L1-Apta1 has been developed to bind to PD-L1 on the surface of cancer cells, blocking its interaction with PD-1 receptors on T cells. This blockade effectively reactivates T-cell-mediated immune responses against tumors. Additionally, PD-L1 aptamers can be combined with other immune checkpoint inhibitors or conventional therapies to enhance the overall therapeutic response **[15]**.

EGFR (Epidermal Growth Factor Receptor): EGFR is overexpressed in many solid tumors, including lung, colorectal, and head and neck cancers. Recently, several aptamers have been developed to target EGFR, aiming to block its activation and downstream signaling. One such example is the RNA aptamer CL4, which binds specifically to the extracellular domain of EGFR, preventing ligand binding and receptor dimerization. CL4 has demonstrated promising results in preclinical models, showing reduced tumor growth and enhanced

sensitivity to EGFR-targeted therapies, such as tyrosine kinase inhibitors **[16]**.

PSMA (Prostate-Specific Membrane Antigen): PSMA is a transmembrane protein overexpressed in prostate cancer and is a valuable target for both imaging and therapy. New aptamers targeting PSMA, such as A10-3.2, have been designed to deliver therapeutic agents directly to prostate cancer cells. A10-3.2 has shown excellent binding specificity to PSMA-positive cells and has been successfully used to deliver nanoparticles containing chemotherapeutic drugs, radionuclides, or gene-silencing agents. These aptamer-conjugated delivery systems have demonstrated significant tumor growth inhibition and reduced metastasis in preclinical models **[17]**.

CD133: CD133 is a stem cell marker often associated with cancer stem cells (CSCs) in various malignancies, such as glioblastoma, colon, and pancreatic cancers. Recent studies have developed aptamers that specifically target CD133, aiming to eliminate CSCs and reduce the risk of tumor recurrence and metastasis. The CD133-specific aptamer i.e., Apt-CD133 is loaded with the anticancer drug doxorubicin and can inhibit the self-renewal capacity of liver cancer stem-like cells. This CD133-apt-Dox conjugates binds selectively to CD133-expressing cells, delivering cytotoxic agents or inducing direct cytotoxic effects. Targeting CSCs with aptamers holds promise for overcoming resistance to conventional therapies and preventing cancer relapse **[18]**.

CURRENTLY AVAILABLE APTAMER-BASED MEDICATIONS AND THEIR DIVERSE USES

Several drugs based on aptamer technology have been introduced to the market, primarily targeting diseases such as cancer, age-related macular degeneration, and various infectious diseases. Below is a detailed overview of some aptamer-based drugs available in the market along with their uses.

Macugen (Pegaptanib Sodium): Macugen is an aptamer that targets vascular endothelial growth factor (VEGF), which plays a significant role in angiogenesis and the progression of age-related macular degeneration (AMD). It is used primarily for the treatment of neovascular AMD, helping to reduce vision loss by inhibiting abnormal blood vessel growth in the retina **[19]**.

EYE001: EYE001 is an aptamer designed to inhibit VEGF-A, similar to Macugen but with a different binding mechanism. It has been investigated for its efficacy in treating ocular diseases such as diabetic retinopathy and retinal vein occlusion. Clinical trials have shown promising results regarding its safety and effectiveness **[20]**.

AS1411: AS1411 is a guanine-rich DNA aptamer that targets nucleolin, a protein overexpressed on the surface of cancer cells. This aptamer has been studied for its potential use in cancer therapy, particularly for acute myeloid leukemia (AML) and other malignancies. AS1411 can act as a delivery vehicle for cytotoxic agents directly to cancer cells **[21]**.

NOX-A12: NOX-A12 is an RNA aptamer that inhibits the activity of CXCL12, a chemokine involved in tumor metastasis and immune cell trafficking. It has been explored for use in combination therapies for various cancers, including pancreatic cancer and multiple myeloma, by disrupting the tumor microenvironment **[22]**.

APPLICATIONS OF APTAMERS AS PRECISION TOOLS IN CANCER THERAPY

Targeted Drug Delivery: One of the most significant applications of aptamers in cancer therapy is their use in targeted drug delivery systems. Aptamers can be conjugated with cytotoxic drugs or nanoparticles to deliver therapeutic agents specifically to cancer cells while sparing healthy tissues. This targeted approach minimizes side effects and enhances the efficacy of the treatment. For instance, aptamer-drug conjugates have been developed that selectively bind to tumor markers overexpressed on cancer cells, facilitating localized drug release. Liposomes that have been modified with particular aptamers demonstrate potential in the targeted delivery of drugs to cancer cells. One notable example is a liposome system utilizing the sgc8 aptamer to specifically deliver therapeutic agents to CEM cells.

Imaging and Diagnostics: Aptamers can also serve as imaging agents for cancer diagnosis and monitoring treatment responses. By labeling aptamers with fluorescent dyes or radioisotopes, researchers can visualize tumors in vivo using techniques such as fluorescence imaging or positron emission tomography (PET). This capability allows for early detection of tumors and assessment of tumor progression or regression during therapy. MUC1 is a

glycoprotein commonly overexpressed in breast and ovarian cancers. An aptamer targeting MUC1 has been developed for use in imaging applications. When conjugated with near-infrared fluorescent dyes, this aptamer allows for real-time imaging of tumor margins during surgical procedures, aiding surgeons in distinguishing between healthy and malignant tissues **[23]**.

Therapeutic Agents: Beyond their role in drug delivery, aptamers themselves can function as therapeutic agents. They can inhibit the activity of proteins involved in cancer progression, such as growth factors or receptors that promote angiogenesis and metastasis. For example, PNDA-3 is a specifically engineered aptamer that functions to obstruct the interactions between periostin and the integrins αvβ3 and αvβ5, both of which play critical roles in the processes of cancer development and metastasis **[24]**. Research indicates that PNDA-3 effectively reduces the proliferation of breast cancer cells in both in vitro and in vivo settings.

Combination Therapies: Aptamers can be integrated into combination therapies alongside conventional treatments like chemotherapy or immunotherapy. By enhancing the specificity and reducing toxicity associated with these treatments, aptamers may improve overall patient outcomes. For instance, combining aptamer-based therapies with immune checkpoint inhibitors could enhance anti-tumor immunity while minimizing adverse effects. The A9 aptamer which specifically targets prostate-specific membrane antigen (PSMA), has been employed in combination with gelonin to facilitate targeted drug delivery in the context of prostate cancer treatment **[25]**. This A9- gelonin complex improves the selectivity of gelonin delivery to cancer cells that express PSMA, leading to enhanced therapeutic outcomes while simultaneously reducing systemic toxicity.

Personalized Medicine: The ability to select aptamers based on individual tumor profiles paves the way for personalized medicine approaches in oncology. By tailoring aptamer-based therapies to target specific biomarkers present on a patient's tumor cells, clinicians can optimize treatment regimens for better efficacy and reduced toxicity. An example of a personalized medicine used in the treatment of chronic myelogenous leukemia (CML) is imatinib, commonly known as Gleevec. This drug specifically inhibits the BCR-ABL tyrosine kinase protein, which is a result of a genetic mutation referred to as the Philadelphia chromosome **[26]**. Patients with this genetic alteration experience considerable benefits from imatinib treatment, whereas those lacking the mutation may not achieve the same therapeutic response.

PROBLEMS TO RESOLVE REGARDING APTAMER USE

Stability Issue: The stability of aptamers under physiological conditions presents a major challenge. Nucleic acids are naturally at risk of degradation by nucleases present in biological systems. This instability can limit the feasible applications of aptamers in living organisms. Researchers are investigating various chemical modifications, including 2'-O-methylation and phosphorothioate linkages, to improve the stability of aptamers while maintaining their binding affinity.

Delivery Mechanisms: Effective delivery of aptamers to target sites within the body poses another significant challenge. Unlike small molecules or antibodies that can be delivered via standard routes (e.g., intravenous injection), aptamers may require specialized delivery systems to ensure they reach their intended targets efficiently. Nanoparticle-based delivery systems and conjugation with cell-penetrating peptides are being investigated as potential solutions.

Off-Target Implications: While aptamers are designed for high specificity towards their targets, there remains a risk of off-target binding which could lead to unintended biological effects. This issue necessitates rigorous validation processes during the development phase to ensure that aptamers do not interact with non-target molecules in complex biological systems.

Regulatory Challenges: The regulatory landscape for nucleic acid-based therapeutics is still evolving. Aptamers must undergo extensive testing for safety and efficacy before they can be approved for clinical use. The lack of established guidelines specifically tailored for aptamer-based products can complicate the approval process and slow down their translation from bench to bedside.

Cost-effectiveness: The synthesis and modification of aptamers can be costly compared to traditional antibodies or small molecule drugs. This economic factor may hinder widespread adoption in clinical

settings unless methods for cost reduction are developed without sacrificing quality or performance.

Limited Knowledge on Pharmacokinetics and Pharmacodynamics: There is still limited understanding regarding how aptamers behave in vivo concerning pharmacokinetics (the study of how drugs move through the body) and pharmacodynamics (the study of drug effects). Comprehensive studies are needed to elucidate these parameters fully so that optimal dosing regimens can be established.

Immunogenicity Concerns: Although generally considered less immunogenic than proteins, some aptamers may still elicit immune responses in certain individuals or species due to their foreign nature or structural characteristics. Understanding the immunogenic potential of different aptamer designs is crucial for ensuring patient safety.

Selection Bias During SELEX Process: The Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process used for generating aptamers may introduce biases based on the selection conditions employed during screening phases. This could result in a limited diversity of selected candidates that might not represent optimal binding characteristics across different environments.

CONCLUSION:

Recent advances in the field of aptamer technology have significantly enhanced the ability to target specific cancer biomarkers, offering promising avenues for early detection, diagnosis, and treatment of various malignancies. Aptamers, which are short, single-stranded oligonucleotides that can bind to specific targets with high affinity and specificity, have emerged as powerful tools in cancer research. Their advantages over traditional antibodies include ease of synthesis, low immunogenicity, and the potential for chemical modifications that enhance stability and functionality. The development of aptamer-based assays has shown great potential in identifying tumor markers such as prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), and others. Furthermore, novel strategies combining aptamers with therapeutic agents or imaging modalities are paving the way for targeted therapies and personalized medicine approaches in oncology. As research progresses, it is anticipated that aptamer technology will continue to evolve, leading to more effective cancer diagnostics and therapeutics.

LIST OF ABBREVIATIONS

PSMA - Prostate-specific membrane antigen
SELEX - Systematic Evolution of Ligands by Exponential Enrichment
NGS - Next-Generation Sequencing
LNA - Locked nucleic acids
PCR - Polymerase chain reaction
HER2 - Human Epidermal Growth Factor Receptor 2
PD-L1 - Programmed Death-Ligand 1
EGFR - Epidermal Growth Factor Receptor
PSMA - Prostate-Specific Membrane Antigen
VEGF - Vascular endothelial growth factor
AMD - Age-related macular degeneration
PET - Positron emission tomography
AML - Acute myeloid leukemia
CML - Chronic Myelogenous Leukemia
PSA - Prostate-specific antigen
CEA - Carcinoembryonic antigen

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