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Review

Computational Frontiers in Aptamer-Based Nanomedicine for Precision Therapeutics: A Comprehensive Review

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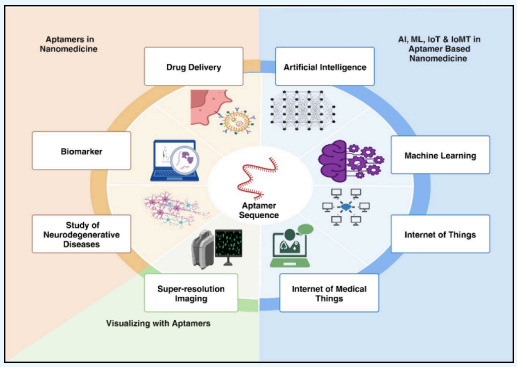
ABSTRACT: In the rapidly evolving landscape of nanomedicine, aptamers have emerged as powerful molecular tools, demonstrating immense potential in targeted therapeutics, diagnostics, and drug delivery systems. This paper explores the computational features of aptamers in nanomedicine, highlighting their advantages over antibodies, including selectivity, low immunogenicity, and a simple production process. A comprehensive overview of the aptamer development process, specifically the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process, sheds light on the intricate methodologies behind aptamer selection. The historical evolution of aptamers and their diverse applications in nanomedicine are discussed, emphasizing their pivotal role in targeted drug delivery, precision medicine and therapeutics. Furthermore, we explore the integration of artificial intelligence (AI), machine learning (ML), Internet of Things (IoT), Internet of Medical Things (IoMT), and nanotechnology in aptameric development, illustrating how these cutting-edge technologies are revolutionizing the selection and optimization of aptamers for tailored biomedical applications. This paper also discusses challenges in computational methods for advancing aptamers, including reliable prediction models, extensive data analysis, and multiomics data incorporation. It also addresses ethical concerns and restrictions related to AI and IoT use in aptamer research. The paper examines progress in computer simulations for nanomedicine. By elucidating the importance of aptamers, understanding their superiority over antibodies, and exploring the historical context and challenges, this review serves as a valuable resource for researchers and practitioners aiming to harness the full potential of aptamers in the rapidly evolving field of nanomedicine.



INTRODUCTION

Short synthetic single-stranded oligonucleotides called aptamers have a high degree of precision when detecting the target molecule. Aptamers have the ability to bind to proteins, nucleic acids, and relatively small chemical molecules. The ancient Latin phrase *aptus* which mean to fit alongside high affinity and specificity is the source of the term "aptamer," invented by Nobel laureates Szostak and Ellington.[1] Aptamers, being frequently compared to antibodies, have several advantages over protein therapeutics, including small molecular size, repeatable synthesis, and low immunity. Aptamers can be conveniently modified chemically, which increases their versatility for an array of biomedical uses.[2] Aptamers have all the benefits of antibodies in addition to some extras like stability, heat resistance, nontoxic, lack of immunogenicity, rapid tissue penetration, ease of modification with different functions for labeling, affordability, and nearly limitless applications. Hence, aptamers represent a relatively new option for use. Aptamers and antibodies share similar functions, but their structures are primarily oligonucleotides, unlike antibodies and proteins. This makes aptamers potentially superior for various applications and may serve as an adjuvant therapy to enhance efficacy, either in place or alongside antibodies.[3] Unlike antibodies, aptamers are readily manipulated and synthesized chemically. Aptamers are perfect for therapeutic usage because of their long storage life and low immunogenicity. Aptamers are connected to an extensive variety of chemical entities for medicinal and diagnostic applications, such as solid phase surfaces, siRNA, chemotherapeutic drugs, and nanoparticles, because of their adaptability despite the effects of modification by chemicals. Aptamer small size, however, poses significant obstacles to their effective clinical translation. Aptamers have short circulatory half-lives due to nuclease breakdown and quick renal clearance, more structural modification is required prior

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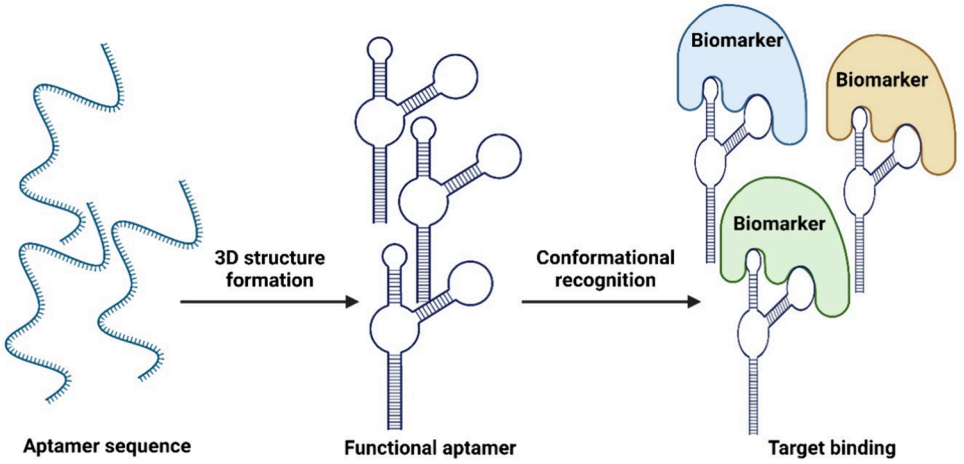

Figure 1. Binding of aptamer to its target through conformational recognition.

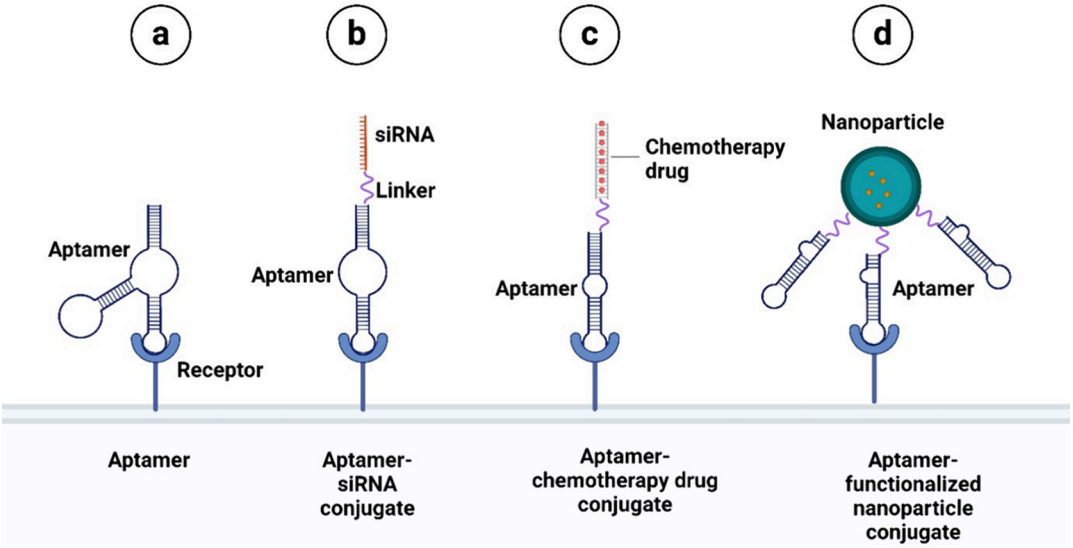

Figure 2. Schematic representation illustrating various types of aptamer conjugates, including (a) aptamer-receptor, (b) aptamer-siRNA, (c) apatmer-chemotherapy drug, and (d) aptamer-functionalized nanoparticles, showcasing their targeted delivery mechanisms for precision medicine applications.

to utilized in therapeutics. Aptamer often faces competition from small compounds and antibodies in medicinal applications. Aptamers that are specifically engineered to bind to Vascular Endothelial Growth Factor first showed promise in treating wet macular degeneration, a condition that may be partially explained by their more prolonged half-live throughout the ocular compartment.[4] Currently systemic aptamers, which are primarily target cell surface receptors such as the epidermal growth factor receptor (EGFR) and circulating influencing variables like as thrombin, factor IXa as well as von Willebrand factor, among others. Aptamers could eventually be able to pass membranes to reach targets inside of cells and distribute additional medications or themselves. Furthermore, the range of aptamers that might be found is starting to broaden and now includes both agonists and antagonists. Eight aptamers, including those made of DNA, modified RNA, and L-ribonucleic acid aptamer, are presently being tested in clinical settings. To date, one aptamer has been commercialized for medicinal use. RNA-based aptamers in particular are susceptible to destruction as nucleic acids by the numerous nucleases found in living settings. Despite this, RNA-based aptamers have been more extensively produced following the first presentation of aptamer technology.[5] This resulted from the ability to couple bases outside of Watson−Crick involving the 2'−OH group, which allowed RNA oligos to become folded into a wide variety of three-dimensional shapes. Moreover, the heightened adaptability of RNA sequences made it easier to generate aptamers with great affinity and specificity.[6]

Drugs can be delivered to cells using various methods, such as liposomes, microspheres, nanofibers, antibodies, or peptides. Figure 1 shows the fundamental principles of conformational recognition underlying the development of functional aptamers. The process of *in silico* aptamer formation begins with the aptamer sequence folding into a unique three-dimensional conformation. This specific 3D structure is crucial, as it creates binding pockets that facilitate the aptamer's interaction with its target molecule.[7] Through conformational recognition, the aptamer 'locks' onto its target based on shape complementarity and a combination of noncovalent inter-

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actions like hydrogen bonding, electrostatic forces, and van der Waals interactions.[8,9] This highly specific binding event signifies the formation of a functional aptamer. The functional aptamer-target complex finds applications in various fields like biosensors in diagnostics, while in therapeutics, they can deliver drugs or modulate biological pathways. Compared to existing tools, aptamers are easily synthesized and can be obtained in a short amount of time (3 months on average) through the SELEX procedure with reduced batch-to-batch variability[10]

Aptamers, demonstrate remarkable potential for therapeutic development through the formation of various conjugate types, as shown in Figure 2. Their ability to selectively bind target molecules with high affinity and specificity can be harnessed by conjugating them with different elements. These conjugates include aptamer-protein/peptide constructs, where aptamers link to proteins or peptides to enhance stability or functionality. Additionally, aptamer-chemotherapeutic conjugates directly attach aptamers to cytotoxic drugs, enabling targeted delivery for cancer treatment.[11] Furthermore, aptamer-functionalized nanoparticles offer advantages like improved drug loading and controlled release. Such innovative aptamer conjugates pave the way for the design of novel therapeutic agents that promise enhanced specificity, reduced side effects, and superior drug delivery capabilities.

The discipline of nanomedicine has expanded during the past few decades, particularly in the treatment of infectious and cancerous disorders. From a conceptual standpoint, "nanomedicine" describes the application of molecular "devices" (10−200 nm) at the nanoscale for the diagnosis, treatment, and avoidance of disease.[12] Nanomedicines have diverse uses, including nanopharmaceuticals, nanoimaging agents, and therapeutics. They provide advantages over standard small-molecule medicines, such as enhanced solubility, rapid metabolic clearance, and a restricted therapeutic window. This extends the circulatory half-life and enhances bioavailability. Additionally, nanomedicine boosts therapeutic efficacy and lowers possible negative effects by enhancing permeability and retention. Data suggests that the EPR effect is actually the main factor influencing the enhanced therapeutic index of nanomedicines. Due to the inadequate lymphatic drainage of sick tissues, particularly in cases of inflammation or cancer, and a highly permeable of neo-vasculature, it has been shown that the adoption of nanobased methods of administration promotes medication accumulation at the intended spot. Currently, the Food and Drug Administration has approved numerous nanomedicines that have demonstrated good patient tolerance. Numerous additional nanomedicines are undergoing clinical development.[13]

Aptamers hold great promise for nanomedicine, offering advantages in targeting, diagnostics, and therapeutics. They can be conjugated to nanoparticles to facilitate targeted drug delivery, minimizing side effects and maximizing drug efficacy at the disease site.[14] Additionally, high binding specificity makes aptamer ideal for biosensing and diagnostic applications,[15] enabling the detection of disease biomarkers, pathogens, or toxins even at low concentrations.[9] Integration of AI, ML, IoT, and IoMT shows immense potential to address these challenges by enhancing aptamer design, automating laboratory processes, and enabling real-time monitoring and analysis. AI algorithms can predict target binding affinities, enabling the design of aptamers with superior specificity and effectiveness.[16] ML techniques can analyze vast data sets of aptamer sequences, revealing patterns and identifying novel candidates with enhanced properties for targeted drug delivery and biosensing.[17] IoT/IoMT can streamline experiments and accelerate clinical translation.[18] This integrated approach could revolutionize aptamer development, leading to personalized medicine with improved drug delivery, diagnostics, and patient outcomes. Further research should focus on addressing data bias, navigating regulatory frameworks, and ensuring the ethical use of these technologies to maximize their benefits in healthcare.[19]

Aptamers, due to their exceptional targeting capabilities, are revolutionizing nanomedicine by enabling the precise delivery of nanoparticles to disease sites. When conjugated with nanomaterials like nanoparticles, nanocapsules, nanosheets, nanofibers, and quantum dots, functionalized with materials like liposomes, polymers etc., aptamers facilitate targeted drug delivery, controlled release, and the development of theranostic platforms.[20] This approach significantly enhances therapeutic efficacy and diagnostic accuracy while minimizing harmful side effects. Ongoing research aims to develop novel nanomaterials, optimize aptamer design, and create integrated systems for personalized medicine. To fully realize the potential of aptamer-nanoparticle conjugates, overcoming challenges such as toxicity assessment, scalable manufacturing, and evolving regulatory requirements is crucial.

DESCRIPTION OF APTAMER

In 1990, Adachi and Nakamura first suggested the use of a single-strand nucleotide specifically ribonucleic acid, or RNA, or single-strand DNA, also known as the ssDNA, refer to Table 1. It is possible to construct RNA and ssDNA aptamers that adhere to the exact same target even when their amino acid sequences along with folding patterns vary.[21] The unique tertiary structures of these single-stranded oligonucleotides enable particular interactions with target molecules. The methodology of the Systematic Evolution of Ligands by Exponential Enrichment approach[22] is used to synthesize aptamers in vitro. These aptamers may be used against a variety of targets, including cells, proteins, tiny molecules, and nanoparticles.[23] SELEX selects and amplifies target-specific sequences of nucleic acids from an enormous selection of random sequences via a number of processes. Target molecules are cultivated in a randomized nucleic acid library as part of the regular SELEX procedure can be seen in Figure 3. After that, sequences that are not particular to the target are removed, and sequences that are exclusive to the target are magnified. The identified aptamers are then separated,[24,25] Until aptamers show sufficient precision to the targeted and attain the anticipated levels of enrichment, this whole process must be repeated. In the last 30 years, a great deal of progress has been achieved to improve the efficiency and economic viability of the initial SELEX method,[26] while also raising the level of selectivity along with affinity of the aptamers that are produced.[27] Enhancing the amplification and characterization of target-specific aptamers, shortening the production time, and quickening the selection process are some of these advancements. For instance, immunoprecipitation-coupled SELEX was created to increase affinity in physiological settings,[28] whereas capture-SELEX was planned to increase aptamer selection efficiency for unidentified short targets of molecular biology.[29] Furthermore, complete cells,[30] tissue, or organs in animals[31] have been employed as SELEX tools for discriminating between healthy and pathological situations,[32]

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Table 1. History of Aptamer Development and Their Application in Nanomedicine

Year	Milestone	Description	Application in nanomedicine	Ref
1990	SELEX technique	Ellington and Szostak developed SELEX, enabling the selection of RNA aptamers.	Aptamers emerged as molecular recognition tools for various targets in nanomedicine.	38
1992	DNA aptamers	Tuerk and Gold pioneered the creation of DNA aptamers using SELEX.	DNA aptamers expanded the scope of aptamer technology, offering new possibilities for nanomedicine applications.	39
1993	Therapeutic aptamer	Approval of Macugen (Pegaptanib) marked the first aptamer-based therapeutic for age-related macular degeneration.	Aptamers entered clinical use, demonstrating their potential as therapeutic agents in nanomedicine.	40
2004	Nanomedicine application	Aptamers found initial applications in nanomedicine, particularly in drug delivery and imaging.	Aptamers became integral components in nanomedicine, facilitating targeted drug delivery and imaging techniques.	41
2006	Targeted drug delivery	Gold nanoparticles functionalized with aptamers were utilized for targeted drug delivery.	The use of nanoparticles functionalized with aptamers enhanced the therapeutic efficiency of nanomedicine by enabling targeted medication delivery to certain cells or tissues.	42
2008	Cancer therapy	Aptamer-functionalizednanoparticles emerged as promising tools for cancer diagnosis and therapy.	In nanomedicine, aptamers have improved treatment results by enabling targeted delivery of medicinal chemicals to cancer cells while reducing off-target effects.	43
2011	Dual-targeting conjugates	Development of dual-targeting aptamer-nanoparticle conjugates for enhanced drug delivery and imaging.	Aptamer-nanoparticle conjugates enabled synergistic targeting of multiple disease markers, improving diagnostic accuracy and therapeutic efficacy in nanomedicine.	44
2015	Biosensors	Aptamer-based biosensors emerged for early disease detection, including cancer and infectious diseases.	Aptamer-based biosensors offered rapid and sensitive detection of disease biomarkers, facilitating early diagnosis and treatment monitoring in nanomedicine.	45
2018	Neurological disorders	Aptamer-functionalized nanomaterials showed promise in targeted therapy and imaging for neurological disorders.	Aptamers facilitated targeted delivery of therapeutics and imaging agents to the central nervous system, enabling precise diagnosis and treatment of neurological diseases in nanomedicine.	46
2020	Personalized medicine	Aptamer-based nanomedicine advanced personalized medicine and targeted therapy approaches.	Aptamer-based therapies offered tailored solutions for individual patients, optimizing treatment outcomes and minimizing adverse effects in nanomedicine.	47

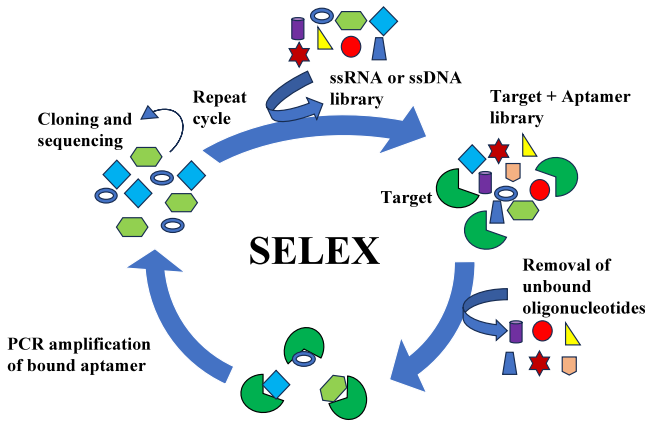

Figure 3. Illustration of the SELEX (Systematic Evolution of Ligands by Exponential enrichment) process, demonstrating the iterative cycles of selection, amplification, and enrichment used to isolate high-affinity aptamers against a target of interest.

monitoring prognosis,[33] and identifying novel biomarkers.[34] Emerging of advanced technologies, like microfluidics,[35] capillary electrophoresis,[36] atomic force microscopy,[37] and numerous *in-silico* methods, were additionally employed to improve the SELEX strategy's effectiveness at this stage.

IMPORTANCE OF APTAMER OVER THE ANTIBODIES

Antibodies are a crucial class of molecules that are widely utilized in studies to enable molecular fingerprinting across a wide variety of applications, which incorporates the diagnosis and treatment of illnesses (Table 2). As a result, antibodies have and wide range of clinical diagnostic processes in modern medical practice.[53] With high affinity and exceptional specificity, SELEX has made the aptamers easier to identify oligonucleotide sequences that can recognize almost any class of target compounds in a systematic manner.[53] Aptamers are expected to develop as a molecular alternative with similar diagnostic along with therapeutic potential, although being fundamentally different from antibodies.[54] In fact, a growing amount of research indicates that aptamers replicate the characteristics of antibodies in a variety of settings. According to Mairal, T et al. there is an increasing need for diagnostic assays that can effectively address common and developing illnesses.[55] Aptamers are able to satisfy a range of molecular recognition needs in these types of tests. Even if aptamer research is still in its early stages, strong data point to quick progress in this area.[56] Aptamers have previously proven to be an effective way to get over some of the main restrictions that come with using antibodies.[57] A critical assessment of the current corpus of research on aptamers and antibodies reveals that both classes have benefits and drawbacks over one another, with numerous empirical findings demonstrating that aptamers offer a wide range of unquestionable advantages over traditional antibodies.[58,59,60,61] Aptamers differ from other molecules in a few important ways, such as their inability to pass through cells that surround them.[62−64] A wide variety of pharmaceutical along with medical uses are made possible by these aptamers' accurate adherence to particular molecules, which eliminates the possibility of binding that is not specific.[65] Additionally, they often have greater binding affinities than antibodies.[64,66] Aptamers have notably shown significantly higher binding capabilities when more than one ligand is

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Table 2. Antibodies Used in Nanomedicine

Antibody type	Target antigen	Nanomedicine application	Ref
Monoclonal antibodies	HER2 (human epidermal growth factor receptor 2)	Targeted drug delivery antibody drug conjugates for cancer therapy.	48
Polyclonal antibodies	ECAM (epithelial cell adhesion molecules)	Cancer diagnostics and therapy used in cancer cells expressing CD19 antigen.	49
Bispecific antibodies	CD3 and CD19	Immunotherapy redirect T cells to target cancer cells expressing CD19 antigen.	50
Engineered antibodies	Various tumor antigens (e.g., EGFR, PD-1, PD-L1)	Immunoconjugates used in cancer immunotherapy and targeted drug delivery.	51
Therapeutic antibodies	VEGF (vascular endothelial growth factor)	Anti-angiogenic therapy used in inhibiting angiogenesis in cancer and retinal diseases.	52

Table 3. Comparison between Antibodies and Aptamers

Features	Antibodies	Aptamers	Ref
Target specificity	Highly specific, usually targeting proteins and cell surface antigens.	Highly specific, can target proteins, small molecules and various biomolecules.	70
Production	Produced in animal (mice, rabbits, etc.) or recombinant technologies.	Chemically synthesized or generated through SELEX process.	71
Stability	Relatively stable, but can be affected by pH, temperature, and other factors.	Stable under various conditions, including extreme pH and temperature.	72
Size	Larger in size (150 kDa for IgG)	Smaller in size (10−25 KDa for most aptamers) allowing better tissue penetration.	73
Synthesis cost	Expensive due to complex production processes and the need for animal facilities.	Relatively cost-effective due to chemical synthesis and SELEX technologies.	74
Modification	Limited modification capabilities.	Easily modified, allowing incorporation of various functional groups for versatility.	64
Immunogenicity	Potential for immunogenic responses, leading to allergic reactions.	low immunogenicity, which lowers the possibility of unfavorable immune responses.	75
Storage and shelf life	Generally, requires refrigeration and specific storage conditions.	Stable at room temperature for long periods, making storage and transport more convenient.	76

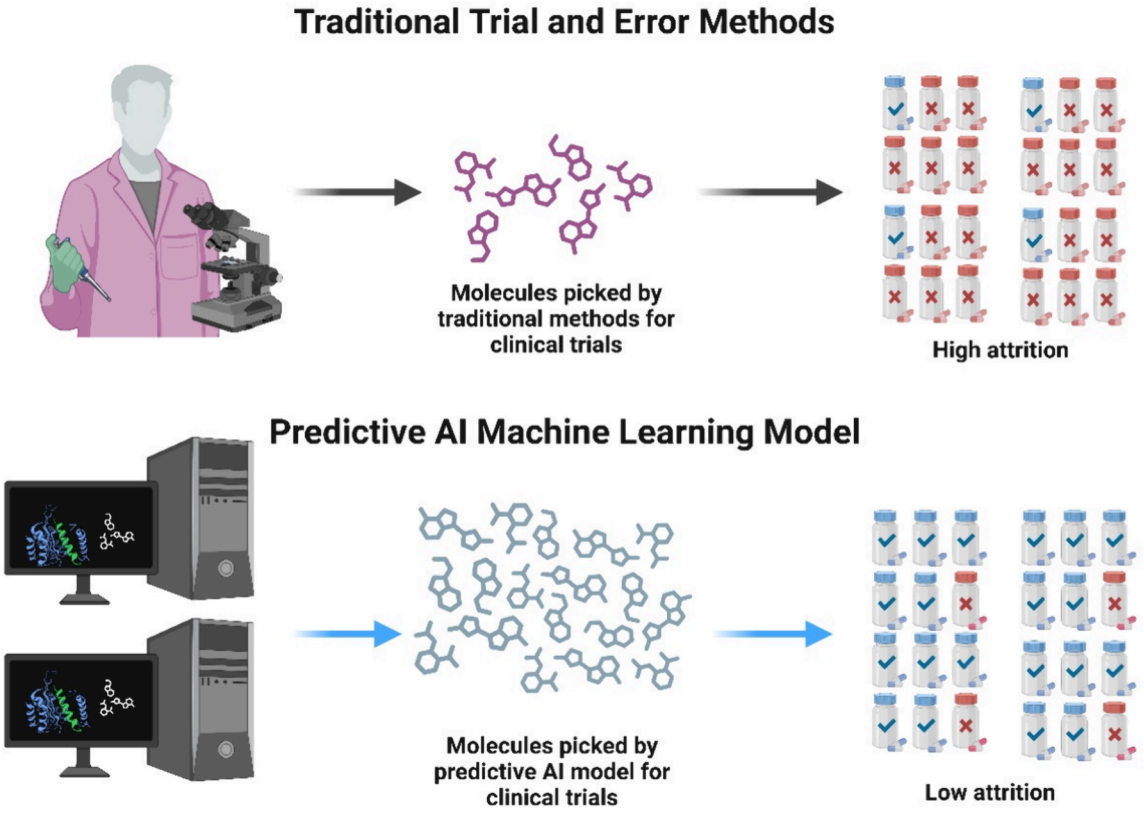

Figure 4. Comparison between the traditional trial-and-error method and Predictive AL (Active Learning) machine learning model for drug development, illustrating the iterative process, efficiency, and accuracy of each approach in identifying potential drug candidates.

attached to the precise same receptor region. Because biological molecules used in molecular recognition have higher affinity, fewer molecules are needed for molecular identification, which might result in lower research costs.[67−69] Additionally, compared to antibodies, aptamers often show greater binding affinity toward target molecules. For example,

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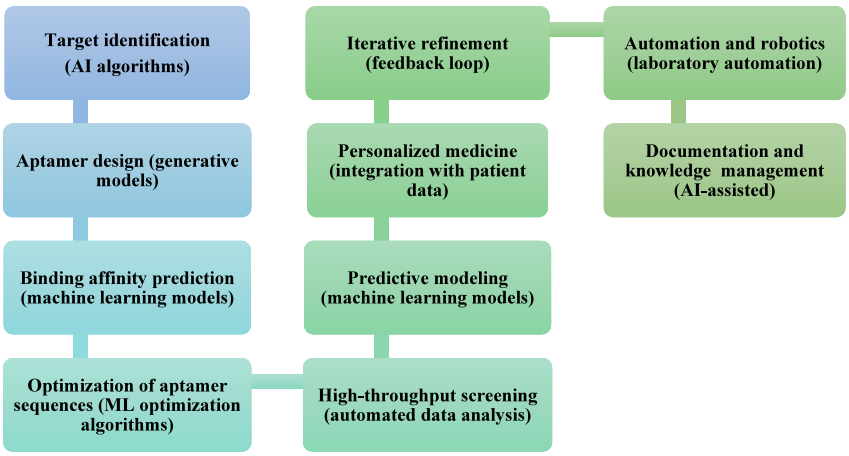

Figure 5. Visualization of the process of developing aptamers for drug development using AI and machine learning, highlighting stages such as data acquisition, feature selection, model training, and validation, culminating in the choosing aptamers with high affinity for medicinal uses.

certain aptamers have a binding affinity for theophylline that is over ten thousand times greater than that of caffeine,[64] which makes them good biomarkers and improves molecular identification accuracy. Aptamers also make it easier to find previously unidentified biomarkers, which has sped up the recent discovery of illnesses and treatments.[64] According to Kedzierski, S et al., aptamers possess many benefits over traditional antibodies, including as faster discovery timeframes, lower from batch to batch uncertainty, improvements in vivo versus in vitro assessment, developed reliability, as well as fewer side effects,[64] refer to Table 3.

AI, ML AND IOT IN APTAMER DEVELOPMENT FOR NANOMEDICINE

The systematic Evolution of Ligands by Exponential Enrichment is a DNA aptamer synthesis technique that starts with a binding step in which a specific target combines with a library of drastically diverse randomized DNA sequences that all share a common fixed-sequence primer area.[77] Following this, a stage of separation is used to remove multiple target-DNA combinations throughout loosely bound DNA. The complexes are then isolated using filtering or chromatography methods, and a polymerase chain reaction, or PCR, amplification is performed.[78] After then, new pools enhanced with DNA aptamers are created from the collected DNA sequences, starting a new round of selection. After several cycles, the pools' DNA aptamers are noticeably enriched. and they are then sequenced and assessed using binding tests.[79] SELEX usually involves 10 to 20 rounds, which makes the procedure laborious and difficult overall.[80] Notwithstanding its usefulness, the SELEX method has a number of drawbacks. Several rounds are necessary, and after seven or more rounds, there may be a rise in by products. After five to six rounds, there is a significant decrease in affinities for the protein as well as smaller molecule target areas.[81−83] Moreover, advancement associated with unspecific binding associated with oligonucleotides while in aptamer getting selected is often reported,[84] and the repeated nature of SELEX strongly biases the sorts of sequences produced.[85] Furthermore, the majority of published aptamers need manual selection, The production of high-affinity and specific aptamers is becoming increasingly time-consuming.[86] As a result, a simplified technique requiring fewer screening rounds is required. Figure 4 illustrates the potential of AI-driven approaches to streamline the aptamer development pipeline in nanomedicine. Traditional SELEX (Systematic Evolution of Ligands by Exponential Enrichment) methods for aptamer selection often suffer from high attrition rates due to factors like poor target binding or challenges in scaling up production. AI and machine learning algorithms could revolutionize this process. By analyzing massive data sets of aptamer sequences, structural characteristics, and target interactions, AI models could potentially predict aptamers with superior affinity and specificity. This would not only expedite the discovery of effective aptamer-based therapeutics but could also enable the design of aptamer-functionalized nanoparticles optimized for targeted drug delivery or diagnostic applications within nanomedicine. Figure 5 depicts a process for developing aptamers for drug development using artificial intelligence (AI) and machine learning. This process incorporates several key stages. First, data is acquired from various sources including target identification and high-throughput data analysis.[87] Next, feature selection is performed to identify the most relevant characteristics from this data that will inform aptamer design.[88] Machine learning models are then trained using this data, allowing them to predict which aptamer sequences will exhibit high binding affinity to the target molecule.[89] Finally, the model is validated to ensure its accuracy in predicting successful aptamers. This approach using AI and machine learning has the potential to significantly accelerate aptamer development for medicinal uses by prioritizing candidates with a high likelihood of success.

The analytical and statistical techniques used in nanomedicine have always evolved. Drug development was profoundly affected by the digital revolution that occurred during the 1980s and 1990s, Notwithstanding the extensive tenure of pharmacometrics in the preliminary research as well as clinical domains.[90] The US-FDA and EMA's determination of necessary requirements for pharmaceutical approval and the harmonization of computational frameworks are two of the most recent advances in this sector.[90] The idea that computers may be "trained to learn" and develop new novel approaches to troubleshooting rather than adhering to a pre-established model structure led to the beginning of AI research in the 1950s. AI has seen several hypes, most of which were brought on by promising methods that eventually fell short of expectations.[91] The primary similarity among the current AI methods is their restricted capacity to resolve intricate issues without a pre-established process or software. These issues

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Table 4. Integration of AI, ML, and IoT in Aptamer Development for Nanomedicine

Aspect	Application	Ref
Target identification and prediction (AI/ML)	Al algorithms for target identification	101
	Machine learning model for binding affinity prediction	102
Aptamer design (AI/ML)	Generative models for aptamer sequence	103
	ML optimization of aptamer designs	104
Laboratory automation (IoT)	IoT sensors and robotics in aptamer development	105
	Remote monitoring of experiments with IoT	106
High-throughput screening (AI/ML)	Automated Data analysis of screening data	107
	Predictive modeling for aptamer success	108
Personalized medicine (AI/ML/IoT)	Integration of patient data for personalization	109
	ML predictive model for patient-specific therapies	108

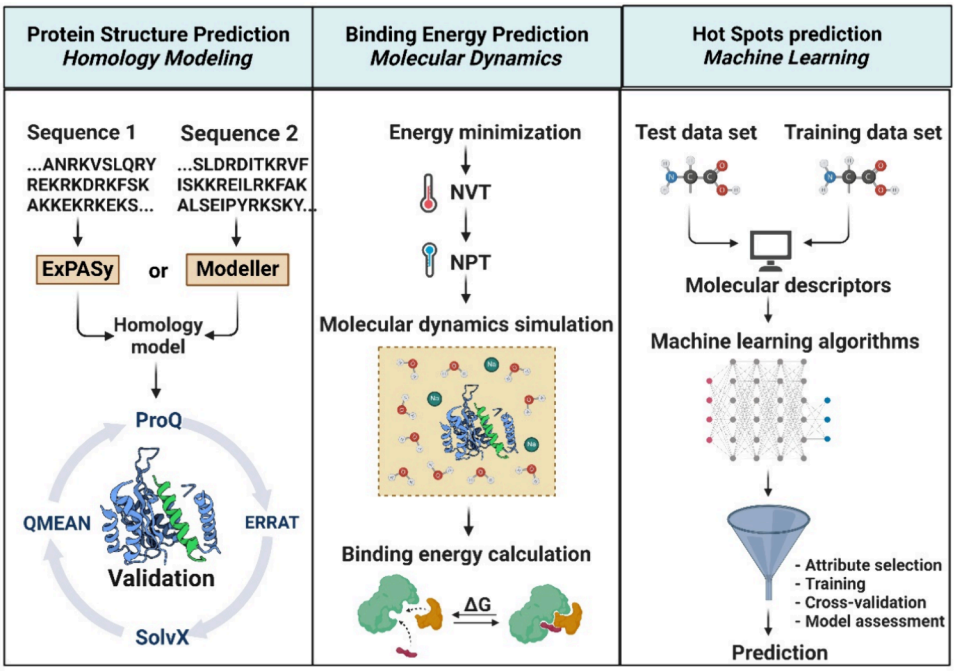

Figure 6. Integrated workflow illustrating the prediction of protein structure using homology modeling, binding energy estimation using molecular dynamics simulations, and hot spot prediction leveraging machine learning algorithms, demonstrating a comprehensive approach for understanding protein−ligand interactions in drug discovery.

include making decisions, thinking, and seeing abstract parallels, rules, and patterns. One phrase utilized in artificial intelligence research is machine learning. that refers to methods for producing knowledge from experience.[92] As expertise is gathered in manufacturing or in the latter phases of in vitro and in vivo testing, the current formulation or test strategy in nanomedicine development frequently offers a preset theoretical framework for data interpretation. Artificial neural networks, or ANNs, and deep learning are two recent examples of AI applications. Originally, information processing in nature served as the inspiration for ANNs.[93] Based on separate neurons, they activate when an input signal surpasses a predetermined threshold.[94] Each individual neuron possesses a distinct activity and maintains a weighted connection with other neurons. As a result of limitations in data accessibility, availability of storage, and parallel processing capability, the fundamental methodology, which originated in the nascent stages of machine learning, persisted largely as a conceptual construct.[95] The resurgence of this idea is closely associated with large-scale cloud infrastructure processing on multicore processors and data collection on a mass scale. The design of hardware enabling machine learning applications is in line with recent advancements.[96] The integration of AI/ML algorithms into aptamer development is rapidly transforming this field refer to Table 4, with a plethora of recent research driving innovation. Computational methods are proving invaluable in streamlining the discovery of high-affinity aptamers from the vast data sets generated through in vitro selection techniques like SELEX. Traditional machine learning algorithms, including Random Forests and Support Vector Machines, demonstrate proficiency in discriminating between binding and nonbinding oligonucleotide sequences and offer insights into structural determinants of binding.[87] Moreover, the advent of deep learning has fostered cutting-edge tools like AptaNet, which leverages convolutional neural networks to accurately predict aptamer-protein interactions.[97] Additionally, generative AI models are emerging, capable of designing novel aptamer sequences with tailor-made affinity and specificity profiles. Figure 6 depicts a streamlined workflow for developing aptamers, which are molecules that bind with high specificity to targets like proteins. The process begins with homology modeling to predict the target protein structure.[98,99] Then, molecular dynamics simulations are used to gauge the strength of the potential aptamer-protein bond.[100] Finally, machine

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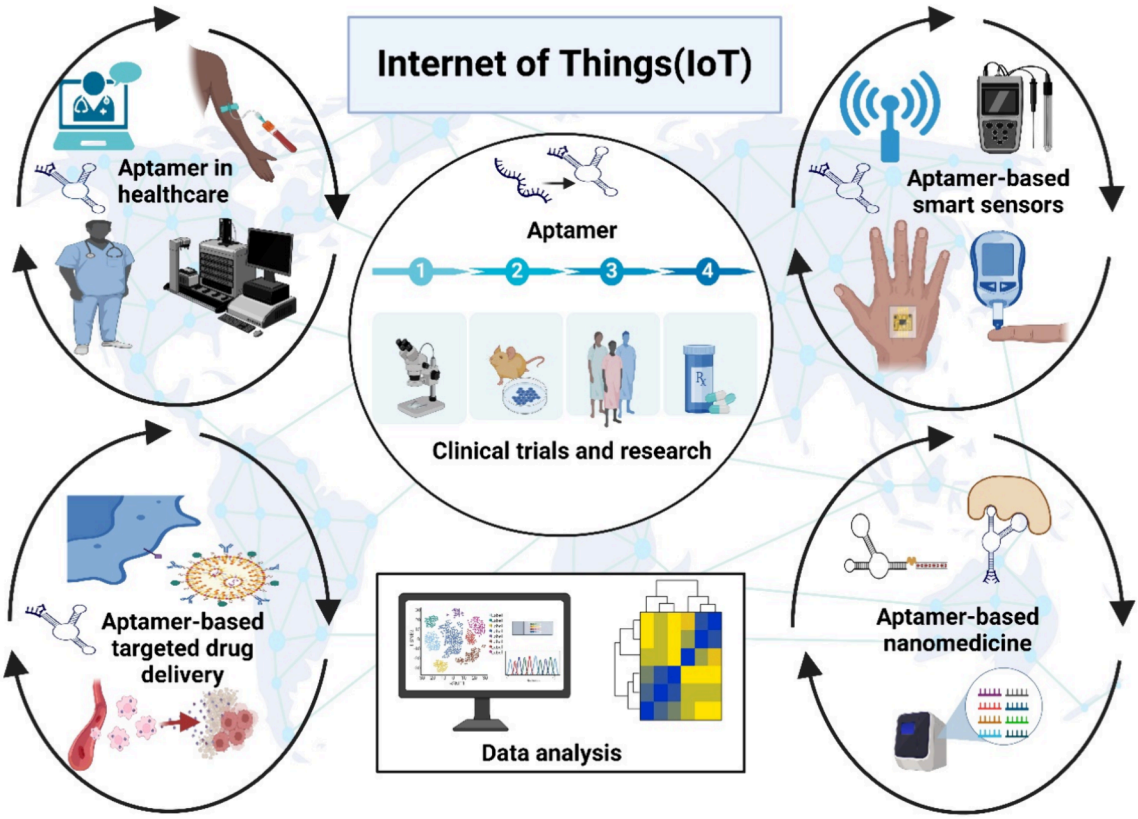

Figure 7. Integration of IoT technology in aptamer-based nanomedicine development for healthcare, showcasing the utilization of sensors, microcontrollers, and transceivers to enable real-time data monitoring and personalized care options.

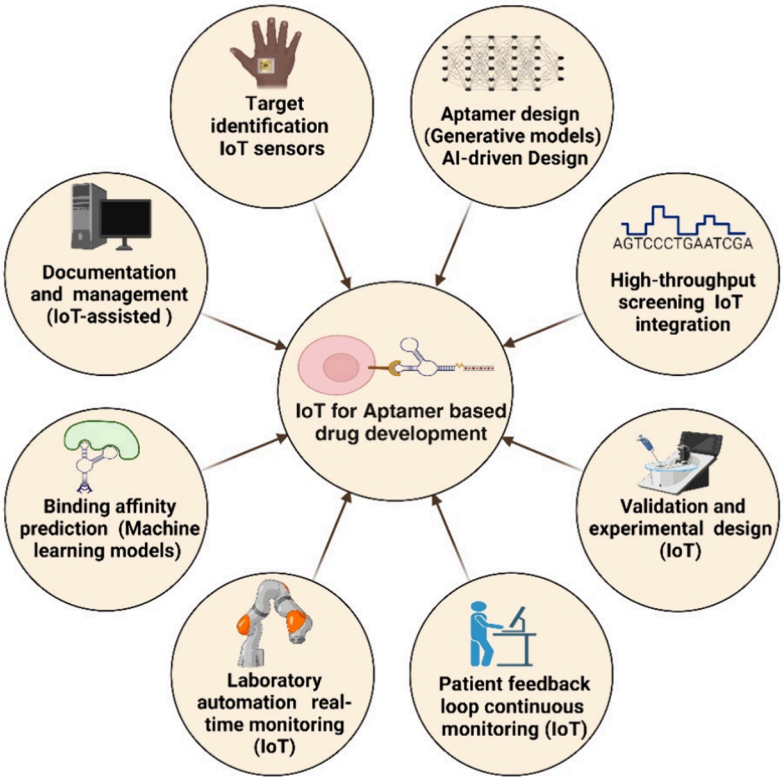

Figure 8. Schematic representation depicting the process of developing aptamers for drug development utilizing Internet of Things (IoT) technology, showcasing IoT-enabled data acquisition, real-time monitoring of experimental parameters, automated analysis, and remote collaboration, facilitating efficient and scalable aptamer discovery and optimization.

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ACS Omega 2024, 9, 26838−26862

learning algorithms pinpoint "hot spots," the most crucial binding areas on the protein.[15] This integrated methodology offers a thorough understanding of protein−ligand interactions, a cornerstone of drug discovery. *In silico* methods offer an advantage over traditional methods by predicting how well an aptamer will bind to a target, potentially saving time and money.[98] These methods utilize various techniques including molecular docking and machine learning.[98] Molecular docking simulates how two molecules interact and fit together, while machine learning algorithms identify patterns within data to make predictions.[98] *In silico* methods can also predict the secondary and tertiary structures of an aptamer, which refer to the folding and 3D shape of the molecule, respectively. These structures are crucial for binding to the target molecule. Another application of *in silico* methods is in identifying point mutations, which are changes in a single nucleotide of the aptamer sequence, that can enhance binding affinity.[98] Overall, *in silico* methods serve as a powerful tool for designing aptamers. By meticulously analyzing aptamer binding behavior, researchers can engineer novel aptamers with therapeutic potential for a wide range of diseases. These computationally driven approaches accelerate aptamer discovery, reduce experimental costs, and enhance the predictability and controllability of the design process, heralding a new era of precision in aptamer-based therapeutics and diagnostics.

As technology advances, so does the demand for comfort and accessibility, which is propelling the development of financing programmes. Patients are frequently compelled to seek medical attention in foreign countries or alternative locations due to the observable inadequacy of local hospitals to fulfill their particular requirements.[110] These days, one of the hottest topics in healthcare is the IoT, which has been shown to be a potential feature to enhance existing technologies and reduce costs in every facet of healthcare. Furthermore, Within the realm of biomedicine, the Internet of Things is seen as the medical equivalent of a man-hour, needed to assist individuals in need by monitoring, controlling, identifying, and acting upon data from the system, thereby cutting down on medical costs.[111] In order to provide the user precise information, sensors, microcontrollers, and transceivers are linked as part of the Internet of Things subcategory of computers as shown in Figure 7. It is used in a variety of healthcare contexts, including as early illness identification, disease monitoring as a way of self-healing, and disease treatment as a means of recovery.[112] IoT includes wearable technology, which was created to assist individuals in receiving the appropriate care. Smart devices known as IoT-based wearables may be implanted into the body, worn as part of an external accessory, tattooed or even affixed to the skin, or incorporated into clothes and accessories. These Internet-connected smart gadgets gather, transmit, and receive data so that users may make informed choices. These wearables are becoming an essential component of IoT technology, and instead of growing as simple accessories, their growth is moving toward more specialized and useful uses.[113] Additionally, for computation and communication reasons, these intelligent wearables may interface with other sets of devices, such as smartphones.

Smart IoT-based technologies are advancing quickly, and their implementations have created a plethora of new opportunities for technological advancements across all spheres of life.[114] Figure 8 shows the process of developing aptamers for drug development utilizing Internet of Things (IoT) technology. This approach leverages several key features of IoT. First, IoT sensors and robotics can be used for data acquisition, such as target identification and real-time monitoring of experimental parameters throughout the aptamer development process.[115] This allows for the generation of vast data sets that can be used to optimize aptamer design. Next, automated analysis of this data can be performed to identify aptamers with high binding affinity to the target molecule. Remote collaboration is also facilitated through IoT integration, allowing researchers to access and analyze data remotely.[115] This approach using IoT technology has the potential to streamline aptamer discovery and optimization for drug development by enabling efficient, data-driven, and collaborative research. Smart have been validated by digitalization as the core idea behind current technology advancements. IoT technologies have a great deal of promise for technological advancement and have become one of the primary components of the current industrial revolution, according to experts. The "Internet of Things" is a new technological innovation based on the Internet that seeks to connect actual items, such as household items as well as industrial machinery.[116] These gadgets might provide users with a range of services and useful data by making use of appropriate communication networks and sensors. Forecasts indicate that over 125 × 109 IoT devices will probably have connections within the 10 years that follow due to the growth of IoT technologies. continues to pick up steam.[117] In addition, the expected finances for IoT technologies are significant, with a compound annual growth rate of around 7.3% and over 120 × 109 USD by 2021.[118] When developing an IoT application, or developing an IoT system from the ground up, the choices made regarding computation, data storage, communication protocols, and sensor devices have to make sense for the intended purpose. A building's HVAC system, for instance, requires the deployment of suitable environmental sensors and pertinent communication technologies on an Internet of Things platform.[119] IoT has effectively changed the globe and had an impact on people lives, both at home and at work.[120] Due to its vast potential for many different applications, especially those that are patient-centric rather than hospital centric, it is anticipated that the medical treatment and care sectors would see significant change in 10 years from now. This makes it the most important field of Internet of Things application.[121] Because of the Internet of Things, patients are becoming more active in their care. Through a portal, they can communicate with their physicians, schedule appointments, and view their medical information. Home monitoring systems allow patients and real-time health monitoring by healthcare providers from the comfort of one's own home, which is beneficial for elderly and chronic illness patients.[122] A number of smart gadgets, including glucose meters, blood pressure monitors, glucose meters, mobile X-ray machines, smart beds, and thermometer units, might enhance patient care thanks to the Internet of Things in the healthcare area.[123] IoT-based portable devices now fall into the following categories somatosensory modulators, which include body and foot sensory control devices, headgear (helmets and spectacles), wrist gear (gloves, wristbands and watches). Furthermore, the Industrial Internet of Things is replacing the Internet of Computers as the primary purpose of the Internet as most linked systems include people and their surroundings, which includes embedded gadgets, innovative items, and infrastructure improvements.

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ACS Omega 2024, 9, 26838−26862

Table 5. Contributions of Internet of Things (IoT) and Internet of Medical Things (IoMT) to the Advancement in the Field of Aptamers

Advancement	Description	Ref
Remote sensing	IoT and IoMT platforms enable remote sensing of analytes by integrating aptamer-based sensors, facilitating real-time monitoring.	128
Wearable devices	Wearable IoT and IoMT devices equipped with aptamer sensors enable continuous monitoring of biomarkers, enhancing personalized healthcare.	129
Point-of-care testing	Aptamer-based IoT and IoMT devices enable rapid and sensitive detection of biomolecules at the point of care, facilitating early diagnosis.	130
Data analytics	Integration of IoT and IoMT with aptamer sensors allows for large-scale data collection and analysis, leading to insights for precision medicine.	131
Telemedicine	IoT and IoMT technologies coupled with aptamer-based sensors enable remote patient monitoring, facilitating telemedicine and healthcare access.	132
Continuous monitoring	IoT and IoMT systems provide continuous monitoring of biomarkers using aptamer sensors, allowing for early detection and intervention.	133
Smart implants	IoT-enabled smart implants incorporating aptamer-based sensors offer real-time monitoring and therapeutic interventions in biomedical applications.	134
Smart drug delivery	IoT and IoMT platforms integrated with aptamer-based drug delivery systems offer targeted and personalized therapies with real-time monitoring capabilities.	135
Agricultural applications	IoT-based aptamer sensors enable real-time monitoring of agricultural parameters such as soil quality, pesticide residues, and plant health.	136

Nevertheless, since every item and piece of data on the Internet is connected to a network structure, cybercriminals may be able gain access to it and exploit it for a range of fraudulent purposes, making the Internet of Things susceptible to ethical and security concerns. Wearable technology and artificial intelligence are often used by the healthcare sector to improve patient outcomes in a number of ways. The goal of artificial intelligence in the present world is to have computers think like reasonable humans.[124] Through its assistance in medical picture processing and diagnosis, artificial intelligence possesses the capacity to enhance the patient's care as well as employee efficiency in the health care industry. Additionally, by using data sets from the Kaggle database repository, doctors may use an AI-enabled IoT, in patient care to diagnose a variety of ailments, such as Type 2 diabetes, coronary artery disease, and anomalies in gait. The Google Brain effort is a prime example of artificial intelligence being integrated into the IoT. Specifically, it uses Deep Learning—a technology that uses artificial neural networks to facilitate iterative learning and self-correction—to identify ocular problems connected to diabetes.[125] the development of wearables for the blind that are of the next generation and use ultrasonic technology to detect obstructions and notify users is another breakthrough that makes it easier for users to navigate their environment safely. Additionally, by tracking their progress, AI wearables may help fitness experts with their regular training routines. If the wearable device is used for 10,000 steps, it will count and display the steps. In addition to gathering data, wearable AI technology may also provide suggestions about the user's diet, sleep schedule, and exercise regimen in order to increase physical well-being.[126] Bluetooth connectivity intelligent biosensors with AI that monitor cardiovascular activity, elevation, motion, physical proximity, as well as touched are found in headphones that also function as tracking devices for fitness. To sum up, accessible artificial intelligence stretches the boundaries by assisting healthcare providers and patients through remotely diagnostics, preventive care, monitoring, and patient decision support. Fitness sector products may now serve as their own personal assistants, helping clients to look after themselves, thanks to artificial intelligence. This section of the review paper also addresses the many electronic devices that are now in operation or are currently under development.[127] In addition to making data collection easier, accessible AI technologies provides personalized recommendations for exercise regimens, sleep schedules, and food choices in order to maximize physical well-being. Bluetooth-enabled smart biosensors with AI algorithms embedded in multipurpose headphones that also work as fitness trackers effectively record and interpret a variety of physiological variables, including cardiovascular activity, altitude, motion dynamics, proximity to one another, and tactile input. In summary, the integration of AI into wearable devices greatly progresses remote health monitoring, preventative interventions, diagnosis capabilities along with decision-making assistance for people and medical professionals. Wearable exercise equipment may now act as individualized wellness assistants for individuals, supporting them in their self-care activities, thanks to AI-driven features. This review part also outlines the emerging field of wearable technologies that are either in development or implementation phases to the advancement in the field of aptamers, refer Table 5.

INTERNET OF MEDICAL THINGS (IOMT)-BASED HEALTHCARE SYSTEM

The Internet of Things is a technical advancement in the field of information technology, or IT, that enables process automation and wireless data transmission without the need for human involvement.[137−139] An age of simplified operations and increased efficiency has been ushered in by this breakthrough, which has penetrated several industries such as energy-efficient smart meters, automotive sensors, smart home systems, and agricultural automation, refer Table 5. IoMT, which is defined by the integration of medical equipment with wireless connections, has emerged in the healthcare sector as a result of the assimilation of IoT technologies.[140] The quality and effectiveness of medical treatment might be enhanced by IoMT devices by optimizing immediate-detail medical diagnosis capabilities within a complex health-tech ecological system.[139] Many healthcare organisations are making large investments in IoMT infrastructure because they see the potential advantages of empowering physicians and improving patient outcomes. Through the implementation of intelligent services made possible by IoT devices and smartphones—which allow imaging, sensing, and diagnostics—this digital revolution has given rise to smart surroundings. Notably,

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optical microscopy as well as flow cytometry have benefited from the efficient use of mobile phone camera high-resolution lenses, which has enhanced accurate diagnostic capabilities.[141] Additionally, point-of-care devices that use Bluetooth Low Energy, technology allow for smooth data communication over short distances, making it easier to always keep an eye on vital indicators and physical activity using noninvasive biological sensors and fitness trackers, among other devices.[142] The creation of smart textiles with sensing properties to track physiological indicators including blood pressure, ECG assessments, respiration rate, and temperature of the body is the focus of ongoing research efforts. The market's abundance of Internet-connected gadgets, such as fitness trackers, medical kiosks, clinical-grade wearable technology, and remote monitoring of patient devices, highlights how the possibilities for IoMT applications are always growing.[143] Furthermore, the noninvasive identification of biomarkers suggestive of common illnesses like HIV, cancer, and viral infections is promising due to developments in eHealth diagnostic technologies. Diagnostic wearables are well-positioned to fulfill a range of healthcare requests within the framework of eHealth systems, providing an affordable and easily accessible option, especially in rural and underprivileged areas. Widespread smartphone use across many demographic groups makes it easier to use point-of-care testing (POCT) without additionally adding to cost pressures, which increases medical access and improves healthcare delivery in environments with limited resources. The need for better social networking, information resource access, and communication at the point of care is a It is one of the key elements accelerating the rapid use of computer devices based on smart technology in the healthcare.[144] Ancillary capabilities like email, GPS functionality, short message services, and conversational voice recordings are also provided by IoMT devices. These features help automate POC diagnoses, gather data, and transmit it all to centralized repositories via satellite networks in an efficient manner. The amalgamation of patient health data inside extensive databases enables thorough investigation of intricate illnesses like cancer, asthma, cardiovascular ailments, diabetes, and Parkinson disease, therefore propelling progress in medical comprehension and therapeutic approaches.[144]

NANOTECHNOLOGY ASPECT OF APTAMER IN NANOMEDICINE

Nanotechnology, which refers to systems with sizes ranging from one to a thousand nanometers, has become a unique delivery platform.[145,146] It was mostly implemented in the pharmaceutical domain in the 1990s, which is when the discipline of nanomedicine emerged. Hydrophobic substances may be made more soluble and biocompatible by using nanotechnologies to help encapsulate and disperse them, which otherwise presents administration-related problems.[147−149] For materials to be used in nanotechnologies, they must be sufficiently resilient, environmentally friendly, biodegradable, and compatible with living things.[150,151] Furthermore, nanoparticles function as efficient microspectroscopic contrast substances or imaging labels, enabling quick, accurate, and sensitive diagnosis—which is especially helpful in identifying minimally recurrent disorders after therapy.[152] Their large surface areas provide multifunctional attributes that allow for the loading of different therapeutic medications in addition to additional components including magnetic properties, triggering mechanisms, invisibility agents, targeting ligands, or imaging features.[153] In order to create theranostic strategies—which investigate as well as monitor the transmission of medication throughout the body by combining therapeutic medications with imaging sensors —the multidimensional characteristics of nanodelivery associations is being thoroughly researched.[154] Theranostics enables real-time tracking of malignant cell growth or regression.[155] Nonetheless, nonviral nanotechnology methods of administration are still in the developmental phase and encounter many challenges, consisting of synergistic therapeutic potential, targeted treatment, controlled release, and negative effects.[156] In order to minimize systemic adverse effects, delivery mechanisms for medicines are designed to precisely transport medications to designated target locations. One way to avoid systemic negative effects is to administer drugs just to sick cells via targeted delivery. A targeting ligand, its particular adherence to target cells, and effective intracellular absorption are necessary to accomplish this specificity. One of these drug delivery systems main benefits is that it may change the pharmacokinetics of the medication, which minimizes its effects on tissues that are not the intended.[157] Targeted carriers known as aptamer-conjugated nanoparticles may be made of an assortment of materials, such as liposomes, polymeric nanoparticles, dendrimers, gold nanoparticles, iron oxide nanoparticles, or quantum dots.[157] Medications may be affixed to the surface of the nanoparticle or encapsulated inside it.[158] Combination of aptamer and nanoparticle that can deliver medicines that are surface-attached and encapsulated simultaneously. During the same period, almost 80% of pharmaceuticals that were surface-attached were released, while 45% of drugs that were entrapped were released. Time-controlled medication delivery may benefit from these qualities.[159] Numerous research teams have shown how drug-loaded and aptamer-functionalized nanoparticles affect cancer cells.[160] One example is the use of polymeric nanoparticles made of poly(lactic-*co*-glycolic acid) (PLGA), which were encapsulated with paclitaxel and immobilized using AS1411. Using drug-loaded and aptamer-modified particles after incubation resulted in a significant reduction in cell survival, indicating effective in vitro targeting of cancer cells. Consequently, by specifically targeting cancer cells, the drug release was enhanced.[160] A plethora of tailored drug delivery strategies have surfaced lately with the goal of improving cytotoxic effects and cellular absorption in vitro. A number of organisations have looked at the possible use of aptamer-modified nanotechnology for targeted drug delivery in vivo. For example, in contrast to systemic delivery tactics, aptamer-modified nanoparticles may concentrate at tumor sites in mice, resulting in less systemic toxicity in various organs although.[161] Multidrug resistance (MDR) is a major problem in cancer treatment because it reduces the effectiveness of chemotherapy.[162] One way to increase intracellular medication concentration among cancer cells while reducing cytotoxicity to healthy cells is to use nanoparticles modified with aptamers. Nanoparticles may pass through hyperpermeable and leaky tumor vasculature because of their tiny size.[163] In order to defeat MDR, anticancer medications and extra chemosensitizers might be added to delivery systems, instance example, created a nanoparticle system for administration that included doxorubicin and combretastatin. Tumour vasculature was destroyed first by the release of the medication affixed on the nanoparticle surface. The release of doxorubicin that had been contained

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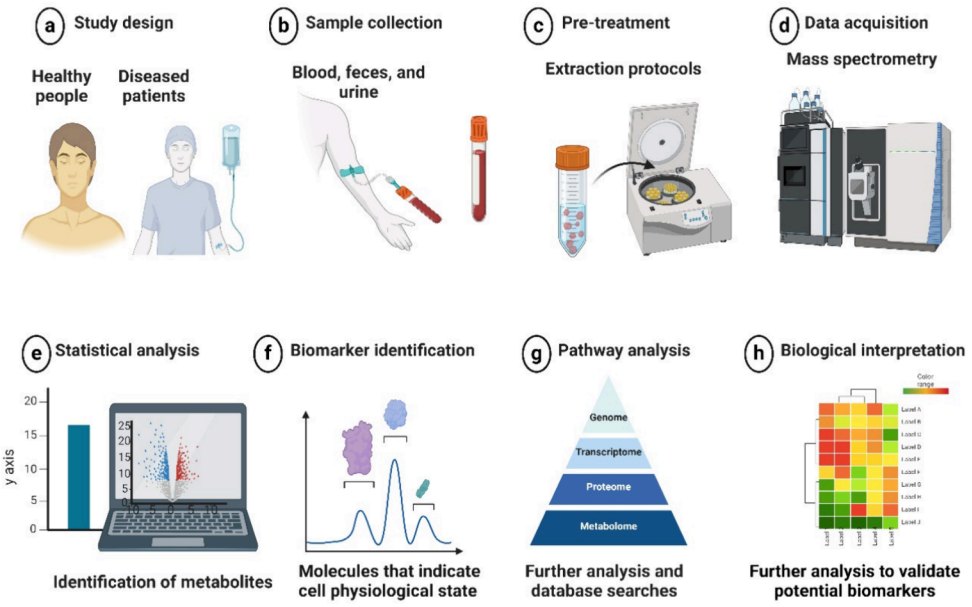

Figure 9. Illustration demonstrating aptamers versatility for identifying biomarkers using a variety of steps. (a) Study design for healthy and diseased individuals. (b) Samples collected from different biospecimens, such as blood, feces, and urine. (c) Pretreatment procedures are used to prepare them for data acquisition. (d) Data acquisition using mass spectrometry it is used to acquire data on the metabolites present in the samples. (e) Statistical analysis is performed to identify metabolites that are significantly different between healthy and diseased groups. (f) Biomarkers identify the putative biomarkers are identified based on their statistical significance and biological relevance. (g) Pathway analysis is performed to identify the biological pathways that are affected by the disease. (h) Biological interpretation for further analysis to validate potential biomarkers.

within the nanoparticles caused cytotoxicity.[164] This strategy could provide a viable way to go over MDR.

Pterostilbene is a naturally occurring compound found in blueberries and other plants, closely related to resveratrol. This idea looks into the possibility of adding pterostilbene to aptamer-based nanomedicine systems.[165] Pterostilbene is a natural compound that has anti-inflammatory, anticancer, and antioxidant properties. They would work as very specific targeting agents to get pterostilbene directly to cells or tissues that are sick. Pterostilbene could be put inside nanoparticles or attached directly to aptamers. This nanomedicine method aims to fix the compound's problems with being stable and bioavailable. The combination seeks to exploit the synergistic potential between aptamers' targeting precision and pterostilbene's therapeutic effects, potentially leading to more potent, personalized treatments with reduced side effects across a range of diseases. Nucleic acid aptamers, aptly also known as chemical antibodies, are revolutionizing biomedical research and therapeutics.[166] Aptamers boast a remarkable array of advantages: they recognize a broader range of targets, exhibit consistency across batches, can be easily modified chemically, are scalable for mass production, and do not trigger immune responses. This makes them invaluable tools for both scientific discovery and potential clinical use.[166] The cutting edge of aptamer innovation lies in their fusion with nanomaterials, creating targeted drug delivery systems that slash side effects and boost treatment effectiveness. This can delve into advanced techniques for craftig high-affinity, stable aptamers and explores their vast potential—from sophisticated biosensors and drug-carrying aptamers to nanomaterial complexes designed to combat diverse diseases.[166]

RECENT ADVANCEMENTS IN APTAMER APPLICATIONS

Aptamers are a novel family of biorecognition elements with potential uses in therapeutic, diagnostic, and sensing fields shown in Figure 10. Their interaction with targets may enhance protein stability in addition to the resistance against denaturation.[167,168] Both the World Health Organisation and the National Institute of Health define biomarkers like any compound, structure, or procedure the fact that can be determined as the body while participating have an impact on or predict the likelihood of a condition or result.[169−171] Similarly, biomarkers are characteristics that are objectively determined and assessed as a representation of biological processes that are normal, pathogenic, or pharmacologic reactions to a therapeutic intervention. Biomarker discovery and validation is one of the most fascinating areas of biological research.[172,173] For this, a variety of proteomics techniques are used. Among these, mass spectroscopy and gel electrophoresis are more well-established instrumental analytical procedures. Nevertheless, they have drawbacks, including high costs and insufficient selectivity and specificity. In light of these difficulties, more sensitive analysis is achieved by the use of antibody-based techniques such as enzyme-linked immune sorbent assay.[174−176] The simultaneous identification of several biomarkers is very promising for illness diagnosis, especially for inflammation or malignant conditions.[177,178] Aptamer technology was developed by scientists to address these issues after this kind of examination additionally demonstrated some limitations in achieving simultaneous identification of multiple targets.[175,179,180] Aptamers are useful for identifying certain antigens in biological samples or for identifying biomarkers shown in Figure 9. Since aptamers would even be chosen against unidentified targets, sample-specific aptamers that may be created even in cases where the molecular components are

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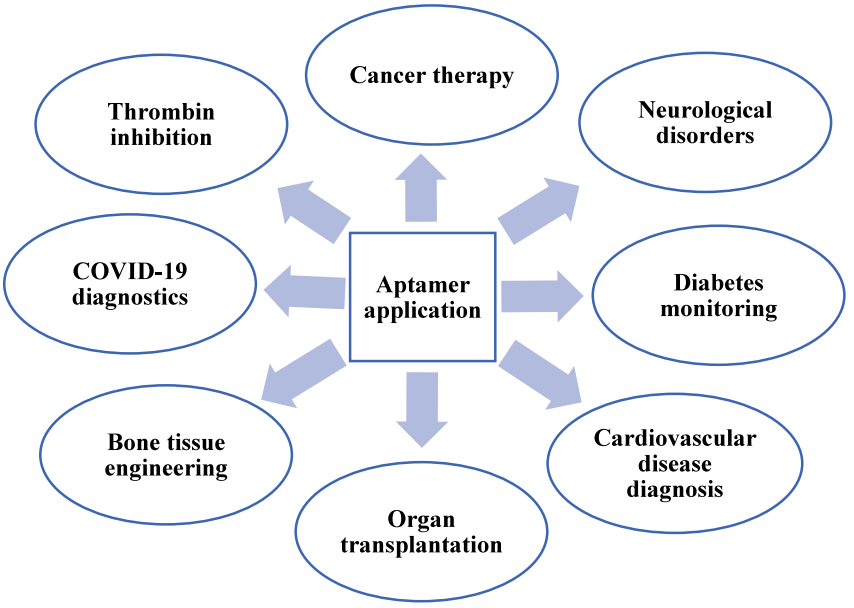

Figure 10. Overview of aptamer application in biomedical research and diagnostics.

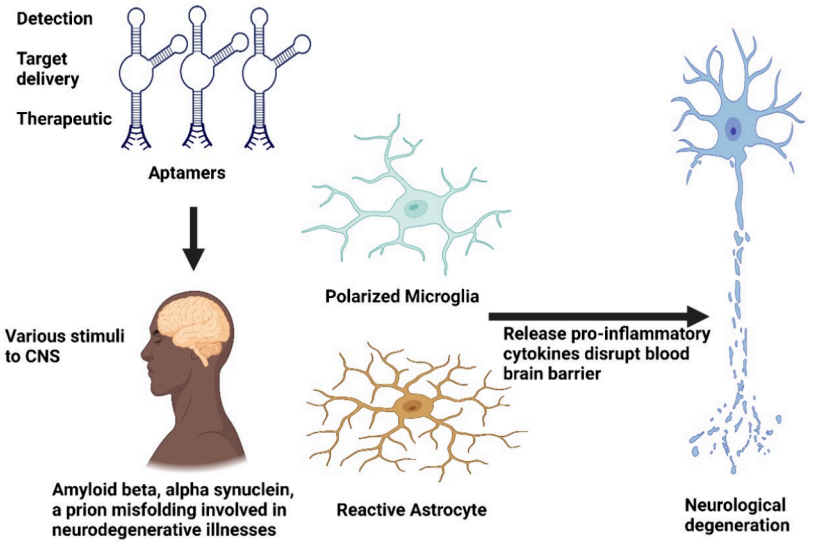

Figure 11. Utilizing aptamers for a novel approach for detection and therapy in neurodegenerative diseases including Parkinson, Alzheimer, and prion diseases.

unknown.[181,182] When aptamer technology is used in proteomic research, biomarkers may be identified from a restricted quantity of early clinical samples, enabling the examination of more people.[180] Furthermore, given the diversity in pathology as well as disease patterns across various populations, it should be feasible to identify and develop diagnostic or therapeutic compounds that are specifically tailored to a given community (Figure 10).[181]

Aptamer technology makes it feasible to screen protein or peptide ligands for unidentified targets.[183−185] The development of aptamers specific to cell surface indicators, such as malignant biomarkers, has become feasible, accordance to the cell SELEX technology. As a result, numerous apta-sensors have been developed created to recognize various cancer kinds.[115,186,187] For therapeutic use or research findings, these aptamers may be engineered to target both known and undiscovered biomarkers.[188−192] Two distinct lanes have been taken into consideration in aptamer biomarker research. From one perspective, aptamer selection or application design was centered around a single biomarker; however, from another, a collection of biomarkers was identified or utilized to accomplish a clinical or analytical objective; an example of this is the work done to create nanosensors that can simultaneously detect multiple cancerous cell line types.[193] Cell SELEX also created selective aptamers against gastric carcinoma cells in this manner, and these agents demonstrated high effectiveness in cancer cell identification and imaging.[194,195]

Amyloid beta, alpha synuclein, along with prion protein misfolding additionally aggregation is involved in neurological illnesses such Parkinson disease, Alzheimer disease, and prion disorders.[196] A potential tool in the detection or therapy of neurodegenerative diseases are aptamers, which are oligonucleotide affinity ligands.[197,198] One example of an aptamer that

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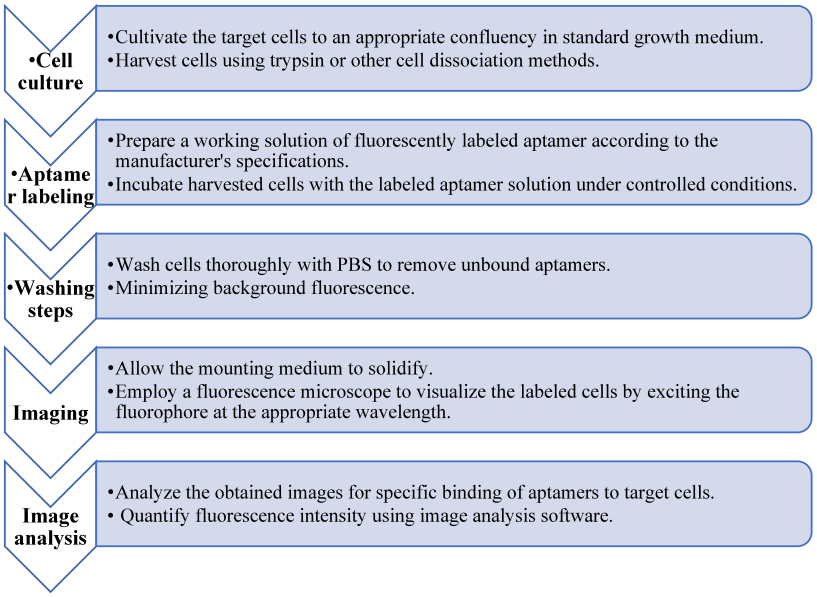

Figure 12. Illustration depicting the process of imaging methodologies utilizing aptamers for enhanced visualization.

is specific to amyloid beta in Alzheimer's disease is aptamer.[199] Aptamers have the potential to be used in tailored drug delivery systems[200] shown in Figure 11, similar to the one utilized to provide curcumin to Alzheimer plaques.[201] Researchers may also be able to create useful diagnostic techniques employing more easily accessible bodily fluid samples, such as plasma, with aptamer technological advancements in proteomics studies and Alzheimer disease biomarker development.[202] Prions is another component that contributes to certain lethal neurodegenerative disorders in animals. As an infectious agent, prions are proteins that are misfolded and may cause illnesses like mammalian transmissible spongiform encephalopathies. Prion infections may potentially be lethal in people.[203] The best course of treatment for dealing with these invasive agents is early detection and prophylactic measures.[204,205] Promising and useful attempts to combat prion infection have included the selection of its unique aptamer[205−208] and the fabrication of several biosensors that utilize aptamer technology.[209−217] Due to its vast potential for ultrafast, ultrasensitive point-of-care detection,[115] numerous investigators have begun dedicated to developing the unique electrochemical apta-sensor for finding evidence of SARS-CoV.[218,219] An electrochemical apta-sensor that is fast, quantitative, and reagent-less for protein detection was described.[218] The sensor used immobilized redox indicator-modified aptamers on gold electrodes to capture viral proteins. The interaction-induced conformational transformation of aptamers generated the electrochemical signal upon the addition of proteins.[219] This sensor demonstrated the ability to quickly and effectively identify SARS-CoV in biological specimens in one stage, including serum and artificial saliva. However, its practical applicability was restricted owing to the matrix's impact on the conformational transformation of aptamers, resulting in a decreased signal gain.[220]

IMAGING METHODOLOGIES UTILIZING APTAMERS FOR VISUALIZATION

The advancement of previously described imaging techniques has led to greater imaging precision, which in turn has demonstrated that classic staining methods that rely on big affinity tags, such antibodies, are inadequate in terms of accuracy.[221] Aptamers are thought to provide a useful benefit in super-resolution imaging since they are much smaller than antibodies.[221−223] The fluorescent labeling of affinities probes, such as aptamers shown in Figure 12, on transferrin receptors in vivo, certain single-label antibody conjugates, or the endogenous receptors ligands transferrin, was specifically studied.[221] When using conventional laser-based confocal microscopy for imaging, the three staining techniques were shown to have negligible differences, according to an analysis of the data gathered. Nevertheless, in the super-resolved pictures obtained using stimulated emission depletion microscopy, the aptamer tag clearly outperformed antibodies. Thus, it was determined that aptamer labeling is superior to both specific monoclonal antibodies and the naturally occurring receptor ligand transferrin in ultrahigh-resolution microscopy.[221]

These single-stranded DNA or RNA oligonucleotides are selected in vitro through the SELEX process, allowing for precise and economical generation of aptamers with exceptional affinity and specificity toward diverse targets.[224,225] Unlike traditional antibodies, aptamers can be readily synthesized chemically, ensuring cost-effectiveness, ease of modification, and batch-to-batch consistency.[226] Moreover, their small size (approximately 10−20 kDa) translates into superior tissue penetration and rapid target binding kinetics compared to larger antibodies.[225] This enables aptamers to efficiently access and visualize biomarkers within complex cellular environments, offering superior insights into biological processes and disease states. Aptamers can target a vast array of molecules crucial to diagnostic imaging, including cell surface receptors, intracellular proteins, and disease-specific biomarkers like prostate-specific membrane antigen (PSMA) and nucleolin.[227] To facilitate their use in imaging, aptamers are often conjugated to reporter molecules. These reporters can be fluorescent dyes, radioisotopes, nanoparticles, or other moieties tailored for specific imaging modalities, allowing for signal transduction and visualization.[227] In fluorescence imaging, aptamers deliver fluorescent probes to the target site, providing high-resolution visualization of cellular dynam-

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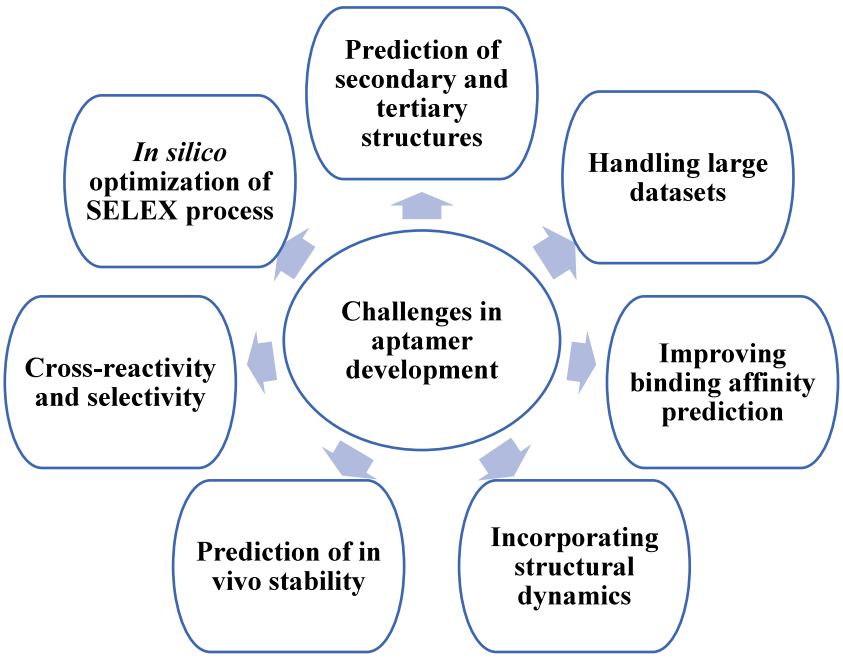

Figure 13. Schematic represents the difference challenges that are occurring in the aptamer development.

ics and molecular interactions in real-time.[9] For nuclear imaging modalities like PET and SPECT, aptamer-linked radioisotopes enable sensitive detection and quantification of biological targets deep within the body, aiding in earlier disease diagnosis and treatment monitoring.[229] In MRI, aptamers can be integrated with contrast agents such as gadolinium-based compounds or superparamagnetic nanoparticles, enhancing image contrast and anatomical detail.[230] The chemical versatility of aptamers allows them to be customized for emerging modalities like X-ray computed tomography (CT), echography, and surface-enhanced Raman spectroscopy (SERS), offering unique diagnostic possibilities.[227] The unparalleled targeting precision of aptamers makes them immensely valuable for diagnosing and imaging various pathologies. In cancer research, aptamers have shown remarkable potential for identifying and visualizing tumor cells with high specificity, enabling researchers to characterize tumor heterogeneity, monitor disease progression, and personalize therapeutic strategies.[228] Aptamers have also emerged as promising tools for combating infectious diseases. They can be designed to target bacteria, viruses, and even prions, facilitating the rapid and accurate diagnosis of infections.[231] Notable recent successes include the development of aptamer-based probes for influenza A and B, Respiratory syncytial virus (RSV), and the coronaviruses responsible for severe acute respiratory syndrome (SARS-CoV and SARS-CoV-2).[232] Such aptamer probes hold the potential to revolutionize outbreak preparedness, improve patient outcomes, and guide the development of novel therapeutics. Recall that comparable findings were documented in studies comparing aptamers to antibodies aimed at distinct epitopes, for example, prostate-specific membrane antigen and EGFR.[233−236] In contrast to most antibodies, aptamers were able to reveal more epitopes and, as a result, provided denser describing of highlighted structures, which enhanced the level of accuracy of the information acquired from imaging.[234] This study focused on 3 membrane receptors that are important to the well-being of humans and the cycle between the interior of the cell and the plasma membrane. Aptamer labeling was beneficial in this work for both light microscopy and imaging at high resolution. In stochastic optically reconstructed microscopy imaging, EGFR aptamer tagging also produced improved quality. Aptamer labeling was used in a recent work to get a precise and thorough structural investigation of the active EGFR, which forms larger clusters than the dormant EGFR. Conventional antibodies have not been able to identify this variation in EGFR structure between active and resting states.[237] Because aptamers can detect minute structural variations, they are useful tools for analyzing morphological transformations that take place in membrane-associated proteins throughout different aspects of biology.[238] Furthermore, increased absorption of 18F-labeled aptamers—which bind particularly to breast cancer cells expressing HER2—was seen during in vivo PET (positron emission tomography) of BT474 mice.[239] The selectivity of 18F-labeled aptamers that to HER2-positive cells was further verified by the confocal images.[239] Particularly suitable structure-changing molecules, aptamers may combine signal transduction with a highly selective biorecognition.[240] Aptamers may be easily selected using SELEX to bind to almost any ligand molecule. This allows aptamers to be easily integrated into functional devices that support novel applications, such as bioseparation and Sensors using DNA machines. Reportedly, binding of ligands frequently affects the degree of sustainability of the specific nucleotides with which they interact directly. Aptamer distal rearrangements are also brought about by ligand binding. These structural alterations are readily observable by cryo-EM evaluation of the cleavage patterns.[100] Prior to the freezing phase, aptamer-based tagging must be completed.[241] According to a research, ssDNA aptamers may be helpful in obtaining precise protein localization when analyzing cellular fine structures using cryo-EM subject to freeze-substitution fixation conditions.[242] They did show that aptamers that are sufficiently soluble in water can be utilized as probes in conjunction with chemical solvents under freeze-substitution conditions, despite their inability to achieve high-affinity

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binding. Together with special physical properties that set them apart from regular antibodies in super-resolution imaging, aptamers are able to achieve the highest resolution possible. Researchers did demonstrate how aptamers that can be sufficiently easily soluble in water may be utilized as probes in combination with organic solvents under freeze-substitution conditions, notwithstanding their inability to achieve high-affinity binding.[242] Together with special physical properties that set them apart from regular antibodies in high-resolution images imaging, aptamers have the capacity to achieve the highest resolution possible. Selecting a suitable photostable probe is a crucial factor that determines the quality of high-resolution imaging.[243−245] In super-resolution microscopy, stable tagged-aptamer-based probes enable the localization of the probes to particular targets while maintaining their integrity against cellular degradation, resulting in a favorable signal-to-noise ratio. Spiegelmer technology is one specific method to attain aptamer stability that is considered acceptable. For instance, endonuclease-resistant aptamers made from RNA that arise from binding to the desired target molecule are chosen by researchers in place of endonuclease-sensitive RNA aptamers.[246−248] It is thus anticipated that the mirror-image aptamer would be binding on to the biological target molecule.[246,248] In addition, the mirror-image aptamer is entirely stable when the native D-ribose is replaced with L-ribose. Optimising the target molecule's density and the library's concentration in a similar manner is another tactic that aptamers may use to get higher resolution.[247,249] The identification of aptamers offers biologists a chance to create new molecular targeted probes and efficient diagnostic and therapeutic instruments for various illnesses.[250] Furthermore, these compounds have shown superiority over traditional antibodies in some situations, making them unquestionably viable instruments for super-resolution imaging.

RECENT CHALLENGES IN APTAMER DEVELOPMENT

The ongoing challenges in aptamer development encompass a multifaceted array of complexities shown in Figure 13. Predicting secondary and tertiary structures remains a formidable task, requiring innovative computational approaches and experimental validation.[251] Handling the vast data sets generated in aptamer research demands robust bioinformatics tools and algorithms for efficient analysis.[77] Enhancing binding affinity prediction necessitates a deep understanding of molecular interactions and the integration of advanced modeling techniques.[252] Moreover, incorporating structural dynamics into aptamer design is crucial for capturing the dynamic nature of biomolecular recognition.[100] Predicting in vivo stability poses a significant hurdle, prompting the exploration of novel strategies to enhance aptamer durability under physiological conditions.[27] Addressing cross-reactivity and selectivity issues demands meticulous screening methodologies and molecular engineering techniques. Additionally, the *in silico* optimization of SELEX (Systematic Evolution of Ligands by Exponential enrichment) process offers promising avenues for streamlining aptamer selection and improving overall efficiency. This discourse underscores the intricate interplay between computational and experimental methodologies in tackling the diverse challenges encountered in aptamer development. Applied microbiology, molecular biology, and medical diagnostic tests have all grown to rely heavily on PCR, where the template is often a combination of complementary sequences of nucleotide.[253] It is expected in these situations that the PCR products are homogeneous. On the other hand, one of the several phases in the SELEX process calls for amplification using PCR of a large variety of DNA templates, which results in a mixture of reactions with intricate and challenging to regulate chemical kinetics. An aptamer library amplified by PCR often yields a large number of artifactual products and bias toward certain nucleotide sequences,[254−256] making the aptamer selection process laborious, time-consuming, and ineffective.

There might be many reasons producing these skewed and phoney PCR results. Single-stranded templates hybridize with one another functioning as initiation primers, yet not each of the aptamer sequences were uniformly prone to primer hybridization upon denaturation, and the polymerase does not expand templates as effectively. Research indicates that PCR amplification is influenced by DNA sequences rich in guanosine and cytosine.[257] While it is not been well studied yet, template folding may potentially alter PCR bias by impeding primer priming areas or influencing polymerase advancement. Therefore, it is reasonable to believe that PCR selection determines the outcome of the PCR, and it is probable that aptamer best binders will be lost in the.[258] There are two methods to lessen the PCR effects one is to execute single-molecule PCR and minimize the amount of SELEX cycles. Using just one template of DNA may greatly enhance PCR, and this is accomplished by compartmentalizing the process in small reactors. Furthermore, PCR-compartmentalization techniques are used for massive genome sequencing in next-generation sequencing systems like the Ion Torrent and Illumina's sequencers. The latter uses bridge-PCR to multiply single-DNA templates in pre-established clusters.,[259] while the former employs emulsion-PCR.[260] Emulsion-PCR has been used for aptamer development to decrease byproduct creation since it is considerably simpler to run in an academic institution.[261,262] Emulsion-PCR essentially entails combining all of the PCR ingredients into an emulsion composed of oil and water and adding a single DNA template, diluted to a certain extent, to each droplet. As a result, droplet amplification reduces PCR product artifacts resulting from inter template hybridization. Reducing the quantity of SELEX cycles is an additional method to mitigate PCR bias and artifacts. Aptamer discovery efficiency is being improved by a number of approaches that have been described before.[263,264] SELEX capillary electrophoresis is one of these techniques.[265] autonomous robotic SELEX platforms microfluidics,[266] capillary electrophoresis for equilibrium mixtures[267,268] and micro free flow electrophoresis, capillary transient isotachophoresis and high-throughput SELEX.[269] While research is being conducted to overcome the obstacles in the production of aptamers, just a few business incubators focused on aptamers, like Somalogic, Noxxon, and Apta Biosciences, have been established. Apta Biosciences and Somalogic have developed aptamer development platforms that utilize nucleotide-base modifications that enhance the likelihood of acquiring highly selective aptamers against a broad variety of objectives.[270] On the other hand, Noxxon's strength lies in their unique spiegelmer technology, which uses aptamer enantiomers to overcome aptamer unpredictability in serum.[271,272]

FUTURE PROSPECTIVES

Aptamers, with their exceptional target specificity, ease of synthesis and modification, and low immunogenicity, are

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poised to revolutionize nanomedicine. Their advantages over traditional antibodies make them ideal for targeted drug delivery, diagnostics, and the development of theranostic platforms. Future research should focus on developing novel aptamers against unexplored disease targets and integrating them with cutting-edge nanomaterials to enhance therapeutic efficacy, imaging, and biosensing capabilities. Computational methods, including AI and ML, will be crucial for predicting aptamer structures, affinities, and potential modifications, accelerating the discovery process and optimizing performance. Integrated platforms combining aptamer-nanoparticle conjugates, imaging modalities, and personalized patient data, driven by AI-powered analysis, will pave the way for precision medicine, particularly in complex diseases like cancer. Multifunctional aptamers, capable of simultaneous targeting, drug delivery, and real-time therapeutic monitoring will enable comprehensive nanomedicine solutions. The Internet of Things (IoT), with its network of connected devices, further expands the potential of aptamer-based nanomedicine. IoT-enabled devices with aptamer-functionalized biosensors will facilitate remote monitoring of biomarkers and vital signs, enabling early disease detection, personalized treatment adjustments, and decentralized care. Wearable IoT devices can continuously track physiological parameters, providing valuable data to inform treatment decisions. IoT integration also promises to streamline clinical trials and drug development by enabling real-time data collection and analysis. Overcoming challenges such as thorough toxicity assessment of complex constructs, scalable manufacturing, and evolving regulatory landscapes is essential for clinical translation. The Internet of Medical Things (IoMT) presents a unique opportunity to transform aptamer-based nanomedicine. IoMT-enabled devices with aptamer-functionalized biosensors will facilitate remote monitoring of biomarkers and vital signs, enabling early disease detection, personalized treatment adjustments, and decentralized care. Overcoming challenges such as thorough toxicity assessment of complex constructs, scalable manufacturing, and evolving regulatory landscapes is essential for clinical translation. Ethical considerations, including data privacy, potential biases, and equitable access to AI/ML-powered nanomedicine must also be proactively addressed. With continued advancements, the integration of aptamers, nanotechnology, AI, and IoMT holds the potential to revolutionize disease diagnosis, treatment, and patient care, ushering in a new era of personalized therapeutic strategies that significantly improve patient outcomes.

CONCLUSIONS

Since the discovery of aptamers as a novel class of biorecognition components, the discipline of biomedicine has seen substantial progress in both therapeutic treatments and diagnostic techniques. Because of their innate accuracy, flexibility, and customizability, aptamers provide an appealing substitute for conventional protein therapies and diagnostic instruments. We have explored the potential and wide range of uses for aptamers in this analysis, as well as their benefits over antibodies and their ability to work with new technologies. The exceptional accuracy with which aptamers are able to identify target molecules is one of their main advantages. Synthetic dsDNA oligonucleotides, known as aptamers, exhibit exceptional affinity and selectivity for various targets, including proteins, nucleic acids, and small molecules, making them powerful molecular recognition agents in various medicinal settings. Aptamers also provide a number of benefits over conventional protein therapies like antibodies. They are ideal candidates for personalized medicine and individualized drug delivery because to their small molecular footprint, repeatable manufacturing processes, and ease of chemical manipulation. Aptamers, in contrast to antibodies, provide additional characteristics including heat resistance, affordability, and almost infinite application possibilities, making them desirable choices for medical therapies and diagnostic tests. Aptamers combined use with emerging technology increases their usefulness in the medical field. The combination of aptamers alongside the Internet of Things enables personalized medical treatments and remote monitoring, and artificial intelligence speeds up the process of aptamer sequence optimization and identification for particular targets. The development and uptake of aptamer-based medicines and diagnostics might be accelerated by these mutually beneficial connections between aptamers and cutting-edge technology. Aptamers have great promise, however, they face several challenges that need to be addressed to facilitate widespread clinical adoption. These obstacles include their shortened half-lives in circulation, rapid elimination by the renal system, and competition with small molecules and antibodies in therapeutic applications. To overcome these challenges, aptamer design, delivery methods, and pharmacokinetic characteristics must be continuously improved, optimized, and refined. The use of aptamers in medical research seems to have a very bright future. With ongoing technological advancements and a better understanding of aptamer biology, we expect previously unheard of advances in precision medicine and customized healthcare delivery. We can open up new avenues for illness detection, treatment options, and patient care by using aptamers capabilities in conjunction with emerging technology, which will eventually transform healthcare delivery globally. In conclusion, aptamers represent a revolutionary development in biomedicine by showcasing unmatched potential for customization, flexibility, and accuracy. Aptamers have the potential to revolutionize the therapeutic and diagnostic landscape by means of coordinated efforts in research, development, and innovation. This might pave the way for a future in which healthcare is customized to an individual's requirements. Aptamers are positioned to play a pivotal role in determining the course of healthcare for future generations as we set out on our path toward a new age of precision medicine.

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Notes

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