Present and future of aptamers applications: A patent review.

Ospina-Villa, JD[1] and Miryan Sánchez[1]

[1]Affiliation not available

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Introduction

Aptamers, single-stranded DNA or RNA sequences, fold into distinctive three-dimensional (3D) structures, enabling them to selectively recognize targets akin to monoclonal antibodies. These molecules are exclusively obtained *in vitro* through a process termed SELEX (**S** ystematic **E** volution of **L** igands by**Ex** ponential enrichment), initially proposed independently by two research groups (1, 2). The SELEX methodology was patented in 1993 by one of its originators and remained under protection for two decades. However, in 2010, the patent expired, rendering it openly accessible to the scientific community (3).

Aptamers exhibit remarkable recognition capabilities across a broad spectrum of targets, ranging from small molecules like ions, antibiotics, and dyes, to larger entities such as proteins and entire cells. This diversity in target recognition translates into a wide array of applications, typically falling into five main categories: 1) Antineoplastic agents, 2) Drugs for specific purposes, 3) Mixtures of active ingredients without chemical characterization, 4) Combinations with antibodies, and 5) Regulation of gene expression.

In recent years, aptamer research has witnessed exponential growth, driven by advancements in SELEX techniques, bioinformatics, and nanotechnology. These advancements have led to the development of aptamers with enhanced specificity, stability, and binding affinity, opening new avenues for their application in various fields.

For instance, aptamers have shown promising results as therapeutic agents in cancer treatment, demonstrating the potential to specifically target tumor cells while minimizing off-target effects. Additionally, aptamers have been utilized in the development of biosensors for the rapid and sensitive detection of pathogens, toxins, and biomarkers in clinical samples, food safety, and environmental monitoring.

Moreover, the versatility of aptamers extends to their integration with other technologies, such as nanoparticles, to enhance drug delivery systems and imaging agents. This interdisciplinary approach has paved the way for innovative solutions in personalized medicine and targeted therapy.

Distinct from conventional scientific literature and news articles, patents offer both technical specifications and insights into potential future applications. Therefore, the objective of this review is to delineate the current applications of aptamers, pinpoint the most promising avenues for commercial utilization, and deliberate on the prospective trajectories of these molecular entities. Through a comprehensive analysis of patents, scientific literature, and technological trends, this review aims to provide valuable insights into the evolving landscape of aptamer-based technologies and their impact on various fields of research and industry.

Materials and Methods

Database Review

A thorough examination of the electronic database LENS (4) was performed with the aim of identifying aptamer patents published between 2010 and February 2024. The search criteria involved the use of "Aptamer" as a keyword in the title, abstract, or full-text sections of the patent documents.

We carried out the identification of the legal status of the analyzed patents, number of patents per year, main countries of the applicants, CPC codes and the most outstanding inventors in this area.

Results

The outcome of the search conducted on February 7, 2024, in the LENS database yielded 135,181 patent records matching the previously specified terms. Subsequently, a legal status analysis was conducted to ascertain the number of patents categorized as active, pending, discontinued, inactive, and expired (Figure 1).

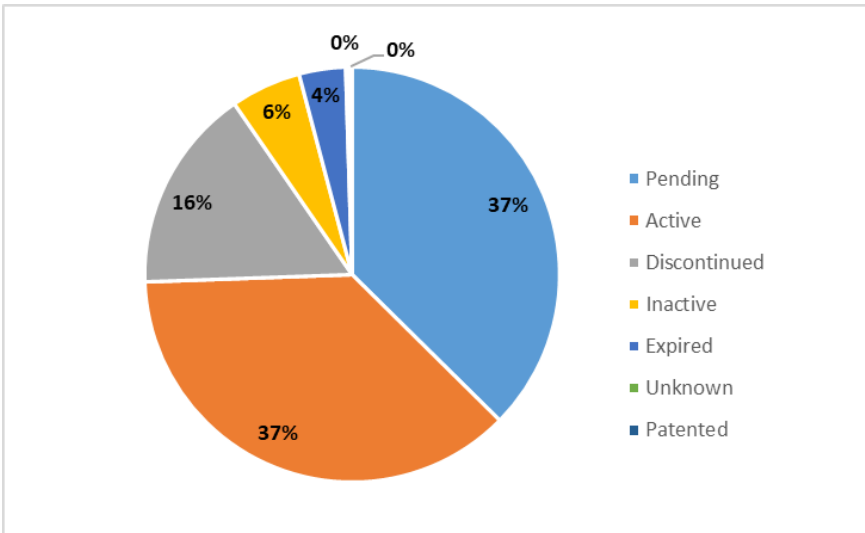

Figure 1. Legal status of patent records deposited in the LENS database.

Our focus lies on patent records categorized as either active or pending in terms of legal status. This approach aims to discern the current applications of aptamers and the potential future exploitations thereof (Figure 2).

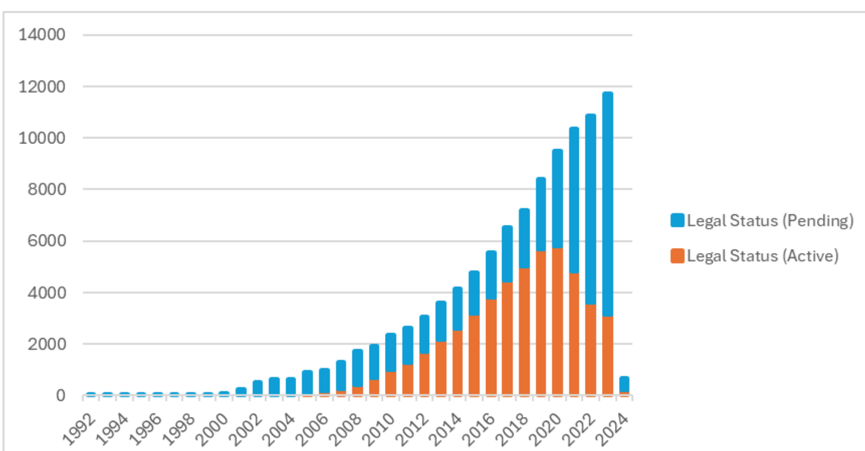

Figure 2. Number of patent applications per year according to their legal status.

Subsequently, countries with the highest number of applications were analyzed, both in active and pending states (Figure 3).

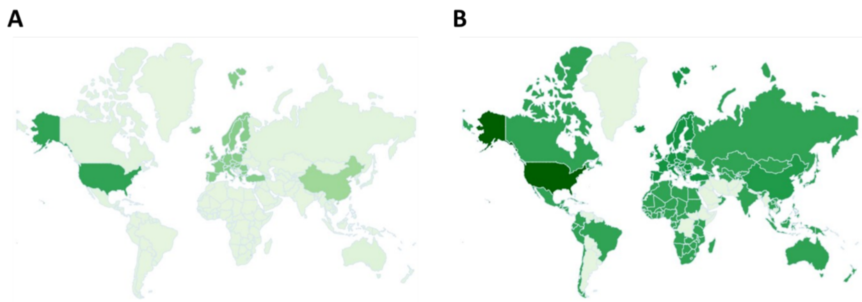

Figure 3. Patent applications at a global level. **A.**Patents with active legal status, **B.** Patents with pending legal status.

The Cooperative Patent Classification (CPC) code aims to categorize patent applications worldwide according to technological areas for more effective searching. The CPC provides crucial information in this case to understand the research areas in which aptamers are being utilized presently (active patents) as well as in the future (pending patents) (Figure 4).

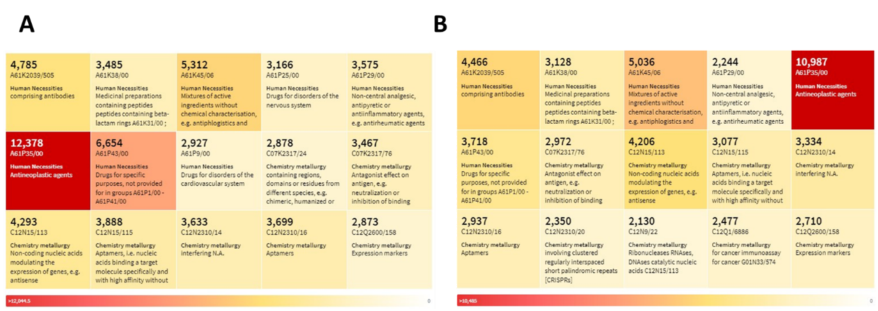

Figure 4. TOP 15 classification of patent applications according to CPC code. **A.** Patents with active legal status.**B.** Patents with pending legal status.

Finally, we have examined the primary applicants and inventors (Figure 5).

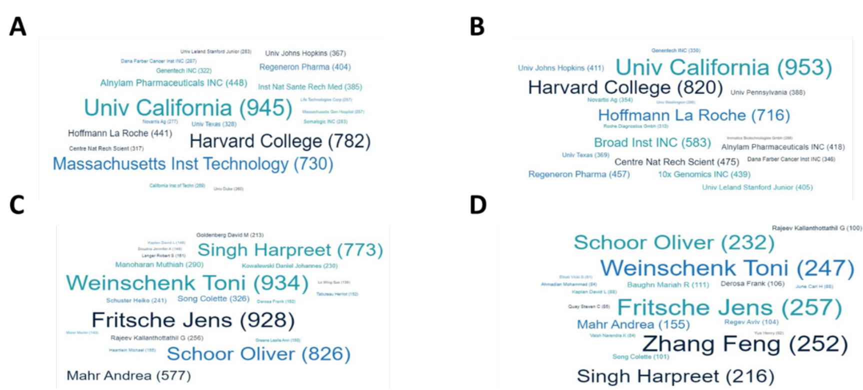

Figure 5. Classification of patents according to primary applicants and inventors. **A.** Primary applicants of patents with active legal status. **B.** Primary applicants of patents with pending legal status. **C.** Primary inventors of patents with active legal status. **D.** Primary inventors of patents with pending legal status.

Discussion

The increasing number of patent applications regarding the use and potential applications of aptamers demonstrates global interest in these molecules. As satisfactory results are obtained, the demand for aptamers increases exponentially over the years (Figure 2).

As is often the case with emerging technologies, developed countries with extensive research infrastructure such as the United States, Europe, and China are the first to invest in research and development. A typical pattern of technological product growth is global expansion as its utility becomes demonstrated. Figure 3B illustrates the global adoption of aptamers following the acquisition of patented technology by developed countries, with other powerful nations such as Canada, India, Russia, Japan, South Korea, Australia, and emerging countries in Latin America and Africa beginning to show interest in patents related to these molecules.

The CPC Code allows us to extract very valuable information about the general utility that patents applied for are being given or intend to be given. In the case of aptamers, the top 15 applications can be seen in Figure 4, and analyzing this information, the top 5 of these applications are framed in the following categories: (1) A61P35/00 (Antineoplastic agents), (2) A61P43/00 (Drug for specific purpose), (3) A61K45/06 (Mixture of active ingredients without chemical characterization), (4) A61K2039/505 (Comprising antibodies), (5) C12N15/113 (Chemistry metallurgy) noncoding nucleic acids modulating the expression of genes.

This does not present significant changes with respect to the active and pending patents (Table 1).

Table 1. Number of active and pending patents by CPC code.

CPC code	Number of active patents	Number of pending patents
A61P35/00	12378	10987
A61P43/00	6654	3718
A61K45/06	4785	5036
A61K2039/505	5312	4466
C12N15/113	4293	4206

Antineoplastic Agents

Dr. Larry Gold, the pioneering discoverer of SELEX technology and aptamers, and inventor of the first related patent (1, 3), serves as the founder and CEO of Somalogic, his latest enterprise. Additionally, he is the inventor of the first aptamer-based drug approved by the FDA, Macugen, for treating age-related macular degeneration in its wet form. This aptamer targets vascular endothelial growth factor (VEGF), which has been extensively studied over the years to understand its role in the pathophysiology of various diseases. Somalogic currently holds a significant number of patents to protect aptamers that bind to both VEGF and Platelet-derived growth factor (PDGF) for the treatment of various conditions, including cancer (5). These patents include specific structural modifications that enhance their stability (6).

Moreover, aptamers have found diverse applications in cancer treatment, including their use as drug carriers. Examples include Vitamin C-Methyl Methacrylate (7) and alpha-Gal liposomes functionalized with modified aptamers, which exhibit high specificity towards cancer cells and low toxicity towards normal cells. Aptamers with modified bases directly bind to cancer cells (8), offering a targeted therapeutic approach.

In diagnostics, aptamers have proven valuable for detecting human choroidal melanoma cells for diagnosis and early detection (9). Additionally, aptamers capable of recognizing the biomarker APE1 in serum from patients with colorectal cancer have been obtained (10). Aptamers specifically targeting CD133 have been developed for both cancer diagnosis and treatment (11), showcasing their versatility in oncology. Moreover, aptamers have been coupled with OFA/iLRP antigens for vaccine development (12), indicating their potential in immunotherapy.

Drug for Specific Purpose

Detection and blocking of IL-6 for associated oncological disorders (13) have been facilitated using aptamers, demonstrating their utility in targeted therapy. Furthermore, aptamers inhibiting TLR9 activation in cells have shown promise for specific drug purposes, highlighting their potential in modulating immune responses. Aptamers recognizing ADAMTS-5, crucial in the pathogenesis of human osteoarthritis, have been developed (14), suggesting their therapeutic potential beyond oncology. Aptamers have also been developed for the diagnosis and treatment of diseases caused by autoantibody formation against protein G (15, 16), further expanding their application in autoimmune disorders. RNA aptamers coupled with proteins, such as tetracycline repressor protein, have been utilized as biosensors, offering a versatile approach in biomedical research (17, 18). Biocompatible hydrogels functionalized with aptamers have been developed for tissue regeneration (19), indicating their potential in regenerative medicine.

Additionally, aptamers recognizing and inhibiting TLR-4 for treating conditions with overexpression of this receptor protein (20) and aptamers targeting interleukin-21 (IL-21) for related pathologies (21) have been developed, broadening their therapeutic scope. Moreover, aptamers recognizing and binding to connective tissue growth factor (CTGF) have enabled the development of anti-CTGF drugs (22), suggesting their potential in fibrotic disorders. Lastly, aptamers binding to Tissue factor pathway inhibitor (TFPI) for treating hemorrhagic disorders or other TFPI-related diseases (23) have been utilized, underscoring their role in hemostasis regulation and therapeutic interventions.

Mixture of Active Ingredients without Chemical Characterization

Aptamers designed to inhibit the function of IL-8 to prevent its association with chemokine receptors such as CXCR1 and CXCR2 (24) offer promising therapeutic avenues. Additionally, a sandwich assay utilizing aptamers exclusively as detection molecules coupled with fluorescent molecules for detection and an anti-aptamer for confirmation of analyte detection in each sample (25) showcases their versatility in diagnostic applications. Moreover, a hydrogel for controlled release of aptamers (S58) addresses the challenge of rapid aptamer degradation, thereby extending their therapeutic duration. Complementing this, the competitive inhibition of the combination of TGF-beta and its receptor TbetaRII is achieved (26).

Aptamers capable of neutralizing mycotoxins in feed and feed ingredients, thereby reducing and/or eliminating their toxic and carcinogenic effects, represent a significant advancement in food safety (27). Furthermore, aptamers serving as drug carriers (anthracycline antibiotics and porphyrin) offer a dual inhibition of tumors through chemotherapy and photodynamic therapy (28). An aptamer specifically targeting LRPPRC (leucine-rich pentatricopeptide repeat-containing), blocking its activity, inhibiting cell proliferation, and interfering with cell cycle progression, presents a promising approach for cancer therapy (29). Aptamers capable of inhibiting Von Willebrand Factor (VWF), either alone or in combination with other chemical agents, show potential in preventing and treating blood clot formation (30). Moreover, the invention provides a PDC-DNA (Polycrystalline Diamond Complex-Deoxyribose Nucleic Acid) aptamer-induced self-assembly body, facilitating drug delivery into cancer cell nuclei with good biocompatibility (31). An aptamer that binds to and inhibits the biological activity of Autotaxin (32) holds promise for therapeutic intervention. Aptamers binding to the extracellular region of CD9, specifically targeting the epitope recognized by Fab, offer therapeutic potential (33). Furthermore, an aptamer recognizing human galectin-1 with high affinity and specificity (34) holds potential in various diseases such as inflammation, fibrosis, septic shock, cancer, autoimmune diseases, metabolic disorders, heart diseases, heart failure, pathological angiogenesis, and ocular diseases. Lastly, a method for pharmaceutical administration of aptamers in animals (35) provides a means of delivering aptamer-based therapies effectively.

Comprising Antibodies

Aptamers coupled with gold nanoparticles offer a multifaceted approach, recognizing the Fc domain of immunoglobulin G (IgG) and facilitating the delivery of antibodies to specific sites within human cells, including the nucleus, cytoplasm, or mitochondria (36). Moreover, the integration of fluorescein isothiocyanate (FITC) with aptamers allows for precise monitoring of localization, enhancing both diagnostic and therapeutic applications. In cellular therapy advancements, a method for genetically modifying lymphocytes is developed, enabling the transduction of T cells and Natural Killer (NK) cells for therapeutic purposes without the need for prior ex vivo stimulation (37). This innovative approach incorporates RNA aptamers targeting acyclovir within the genome of these cells, complemented by miRNA and shRNA sequences that modulate its function. For combating obesity and metabolic disorders, CD36 antagonist aptamers offer a promising therapeutic strategy, effectively inhibiting fat accumulation, enhancing insulin sensitivity, and regulating blood glucose levels (38). This targeted approach holds potential for both the treatment and prevention of metabolic syndrome. Additionally, the synergistic use of species-specific monoclonal antibodies and aptamers presents a novel tactic for disrupting bacterial biofilm formation (39). This combined strategy offers enhanced efficacy in combating bacterial infections and preventing biofilm-related complications.

Chemistry Metallurgy

In the realm of enzymology, aptamers play a pivotal role, as demonstrated by their ability to reversibly bind to DNA polymerase, thereby modulating its activity, and featuring a cleavage site for endonuclease V to facilitate dissociation (40). Moreover, RNA-based Riboswitches incorporating aptamers offer a sophisticated mechanism for suppressing polyadenylation by specifically targeting U1 small nuclear ribonucleoprotein (snRNP) (41). In clinical applications, aptamers prove their versatility, with polynucleotides designed to bind to p53 and exert their therapeutic effects through ribozymes, showcasing simplicity, rapid response, and low immunogenicity (42). Similarly, aptamers coupled with fluorescent proteins (GFP) enhance fluorescence-based assays, augmenting their utility in various research and diagnostic settings (43). Aptamers continue to revolutionize disease detection and therapy, with specific designs targeting Vibrio parahaemolyticus TDH for environmental monitoring, clinical diagnosis, and disease research (44). Meanwhile, RNA-based imaging methodologies employing aptamers fused to single guide RNA (sgRNA) demonstrate multicolor, orthogonal, and highly sensitive imaging capabilities, promising advancements in visualization techniques (45). In cancer therapeutics, aptamers hold immense potential, as evidenced by their integration into devices for detecting and regulating mRNA expression in tumors, thereby enabling early diagnosis and targeted gene therapy (46). Furthermore, aptamers fused with specific silencing RNA (siRNA) offer a promising avenue for the prevention and treatment of cancers and other diseases involving transferrin receptors and CCAAT/enhancer-binding protein β (C/EBPβ) (47). In diagnostics, biosensor kits utilizing aptamers for detecting thiamine pyrophosphate, offering a convenient diagnostic tool for various applications (48). Additionally, aptamers designed to identify and enhance the biological activity of proteins such as high mobility group protein B1 (HMGB1) demonstrate superior sensitivity and specificity compared to traditional antibodies, opening new avenues for protein detection in vitro and in vivo (49). Furthermore, aptamers play a crucial role in cell sorting methodologies, where they selectively bind to surface markers on target cells, facilitating their retrieval through reversible aptamer-cell binding disruption, thereby advancing cell sorting techniques (50).

Conclusions

In conclusion, the diverse applications of aptamers underscore their significance in modern biotechnology and medicine. Patents of Aptamers have answered question posed in the scientific article "Where Are All the Aptamers?" (51) by showcasing their versatility and effectiveness across a spectrum of therapeutic, diagnostic, and research applications. Beyond the applications in basic research, the aptámeros are going through a transition towards applied science with the times and everything necessary that must be fulfilled in the process of technology transfer.

From the pioneering FDA approval of Macugen for age-related macular degeneration to the innovative approaches in cancer therapy, autoimmune disorders, and beyond, aptamers have emerged as indispensable tools in addressing complex medical challenges. Their ability to target specific proteins, modulate biological pathways, and facilitate precise drug delivery highlights their potential to revolutionize healthcare.

The proliferation of aptamer-related patents reflects the growing recognition of their value and the ongoing efforts to explore their full potential. This trend underscores the transformative impact aptamers are poised to have on biomedical research and clinical practice.

Looking forward it is evident that aptamers will continue to play a central role in driving innovation and advancing personalized medicine. By harnessing the unique properties of aptamers and leveraging emerging technologies, researchers and clinicians can address unmet medical needs more effectively and improve patient outcomes. As aptamer research progresses, it holds the promise of unlocking new therapeutic modalities and reshaping the landscape of healthcare in the years to come.

Conflict of interest: The authors declare no conflicts of interest.

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