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Aptamer-drug conjugates: A new frontier in targeted cancer therapy

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Abstract

Targeted cancer therapies strive to eliminate cancer cells while minimizing harm to healthy tissues. Aptamer-drug conjugate is one of the attractive alternatives in this field. ApDCs are a class of agents which utilize the high specificity of aptamers (a single-stranded DNA or RNA oligonucleotide with a high affinity for a target molecule) combined with the therapeutic potential of cytotoxic drugs. It results in the selective drug delivery into neoplastic cells. This review provides an overview of the recent development of new strategies utilizing ApDCs as next generation targeted cancer therapeutics (aiming to obtain improved therapeutic responses and to minimize off-target toxicities), which represent the main power over classical chemotherapeutics. Subsequent studies will seek to optimize the design of ApDCs and broaden their therapeutic use beyond cancer therapy. With the progress of research, ApDCs are predicted to have a greater role for the treatment of cancer in the future.

Keywords: Aptamers; Aptamer-Drug Conjugates (ApDCs); Targeted Therapy; Cancer; Drug Delivery

1. Introduction

Targeted cancer therapies aim to eliminate cancer cells while reducing detrimental effects on adjacent healthy tissues, establishing themselves as a crucial approach in oncology [1,2]. Molecular targeted therapy has revolutionized cancer treatment due to better therapeutic responses and less systemic toxicity [3]. Conventional therapies such as chemotherapy are frequently not specific enough, and cause general toxicity with reduced therapeutic effectiveness [4]. Chemotherapy is directed to retard cell growth and multiplication, but also causes toxic effects due to its effect on normal cells. Chemotoxicity is linked to systemic damage of DNA and inflammation in normal cells [5]. In this sense, to cope with these drawbacks, innovative approaches with high precision of delivery toward tumor cells are being studied and aptamer-drug conjugates are strongly considered as one of the most promising strategy [6,7].

Aptamers, which are often called “chemical antibodies,” are single-stranded DNA or RNA oligonucleotides that have high affinity and specificity for binding with a selected target molecule [8–12]. Apart from typical antibodies, aptamers have several advantages over antibodies, such as their small size, higher chemical stability, easy synthesis, low immunogenicity, penetration into tissues more quickly, and capacity to target a broader range of biomolecules, including those which are not accessible to antibody targeting. ApDCs exploit the distinctive attributes of aptamers to facilitate the direct delivery of cytotoxic agents to neoplastic cells [13,14].Through the association with aptamers, such conjugates may selectively concentrate in the targeted region of cancer cells, augmenting pharmacological efficacy while minimizing unintended adverse reactions [15]. By this targeted delivery system, there's a great potential for enhancing the efficacy of oncologic interventions and reducing the side effects usually associated with traditional therapeutic modalities [15].

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The effectiveness of ApDCs therapy is based on the selective recognition and binding of aptamer to its cognate target residing on the cancer cell surface and it is a consequence of a complex mechanism of action [16]. This selective activity is based on the "lock-and-key" mechanism where the special three-dimensional structure of the aptamer matches the three-dimensional structure of the target molecule such as protein or cell surface receptor overexpressed exclusively in cancer cells [17,18]. Conjointly, as the driving forces determining a strong and specific interaction, the binding forces are mainly manifested through electrostatic interactions, hydrogen bonds, hydrophobic interactions, π−π stacking effect and van der Waals interactions [19,20]. Once bound the ApDCs are internalized by receptor-mediated endocytosis, a process in which it is surrounded by the cell membrane to form a vesicle which assists the molecule in crossing the membrane and entering the cell along a transcellular pathway [21–23]. The internalizing mechanism mediated by ApDCs greatly minimizes systemic toxicity and off-target effects [24,25].

Recent preclinical and clinical research concerning ApDC has demonstrated significant promise for these conjugates. Numerous ApDCs have demonstrated effectiveness against several cancer types-including breast cancer, lung cancer, and leukemia [26–28]. Such findings indicated that ApDCs specifically target cancer cells, inhibit tumor growth, and prolong survival in animal model [29]. Moreover, aptamers can be easily altered and functionalized for designing custom ApDCs with specific features [30].

However, there are a number of issues that still need to be overcome before ApDCs can truly materialize [31] The primary challenge is the in-vivo stability of aptamers, particularly that of RNA-aptamers, which are easily cleaved by nucleases [32]. To address this challenge, researchers are investigating multiple approaches to enhance aptamer stability, including chemical modifications and usage of nuclease-resistant aptamer analogs [33,34]. Apart from its potential use in cancer treatment, ApDCs are also promising candidates for diagnostic, imaging, and drug delivery in other diseases [35]. Through their capacity to identify and quantify particular biomarkers within biological specimens, aptamers enhance the prospects for early disease identification and the advancement of personalized medical approaches.

This review seeks to summarize the new and developing approaches using ApDCs as the next generation of targeted cancer therapeutics designed to enhance treatment response and decrease off-target toxicities relative to traditional approaches. Future studies are going to focus on solving problems in ApDCs development, improving its design and implementation, and expanding their uses beyond cancer treatment. ApDCs are anticipated to become increasingly important in combating cancer as research advances.

2. Mechanism

Aptamer-Drug Conjugates (ApDCs) are a novel and extremely promising platform for targeted cancer therapy in which the high targeting specificity of aptamers is coupled with the strong therapeutic activities of a cytotoxic drug [15]. This is achieved through a sophisticated mechanism involving target recognition and binding, drug release triggered by specific stimuli, and several advantages over traditional antibody-drug conjugates (ADCs) [7,15].

2.1. Target Recognition and Binding

Aptamers, also known as "chemical antibodies," are short single-stranded DNA or RNA oligonucleotides that exhibit extraordinary characteristics that enable them to bind to their target with high affinity and specificity [9].This specificity is based on a "lock-and-key" principle that the unique three-dimensional structure of the aptamer precisely complements the three-dimensional structure of the target molecule (cell surface receptors or proteins overexpressed in cancer cells, etc.) [17,18]. This covalent binding is further supported by electrostatic interactions, hydrogen bonding, hydrophobic interactions, and van der Waals forces to strengthen a stable and specific binding [15]. This sophisticated recognition capability enables ApDCs to preferentially accumulate within the tumor microenvironment, thereby specifically targeting neoplastic cells and delivering their therapeutic agents, all while sparing adjacent healthy tissues [15]. Several Potent aptamers have also been developed against a broad number of cancer-relevant targets such as AXL, CD133, EGFRvIII, PDGFR-α, PDGFR-β, indicating the versatility of aptamers in the treatment of cancer [37].The high specificity of aptamers surpasses that of antibodies, facilitating a reduction of side effects by avoiding off-target binding [15].

Firstly, the aptamer component, a short single-stranded oligonucleotide, selectively binds to the cell surface receptors or proteins expressed on cancer cells [13,37]. These aptamers, ranging from 20 to 100 nucleotides in length are usually selected through Systematic Evolution of Ligands by Exponential Enrichment (SELEX) [14,38]. This screening process guarantees that the aptamers are high affinity and specificity for the target molecules, such as protein, peptide or cellular structure relevant for cancer cells [38]. The aptamer recognizes its target and starts receptor-mediated

endocytosis, leading to the internalization of ApDC into the target cell, which is a determining factor to transfer the drug payload in the intracellular compartment where it is able to produce its therapeutic action. The specificity of this internalization process is a major asset of ApDCs, limiting off-target effects and lowering systemic toxicities [23].

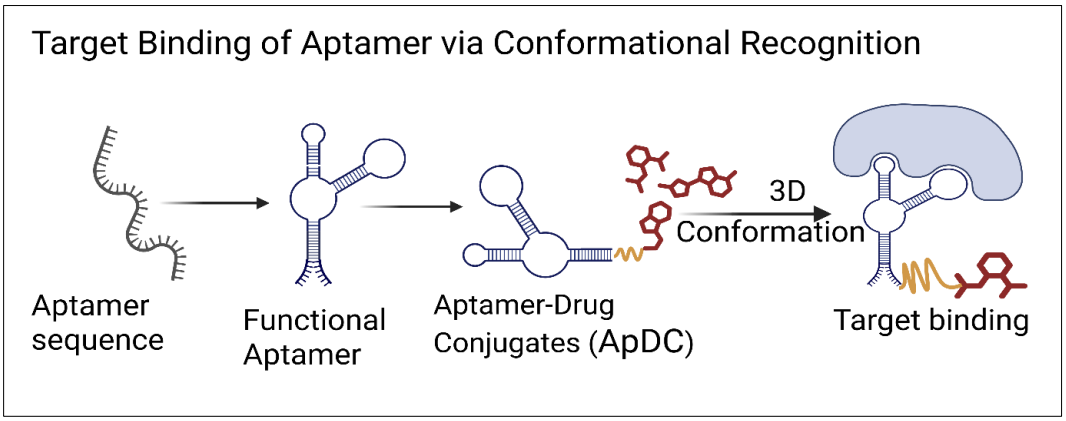

Figure 1 Target Binding of Aptamer via Conformational change

2.2. Drug Release Mechanisms

After binding, the ApDC is internalized inside the cell through receptor-mediated endocytosis where the cell membrane envelops the bound ApDC and forms a vesicle that carries the ApDC into the cell cytoplasm [23,39]. ApDCs have the advantage of precise internalization with few off-target effects and less systemic toxicity [23]. Following internalization of the ApDC, the release of its cytotoxic counterpart (payload) in the cell is the next step for the ApDCs to exert cytotoxic effects. After being released, the drug interferes with critical cellular pathways in the targeted cancer cells, which in turn leads to the death of the cell [40]. These effects are driven by the drugs used for the composition of the ApDCs, of which the most employed payloads are either conventional chemotherapeutics, like doxorubicin or paclitaxel, or novel targeted treatments, for example kinase inhibitors, or drugs inducing DNA lesions [40,41]. This unique biodistribution allows for a high local drug concentration and potentially diminishes the overall dosage required, which may enhance therapeutic effectiveness[42].

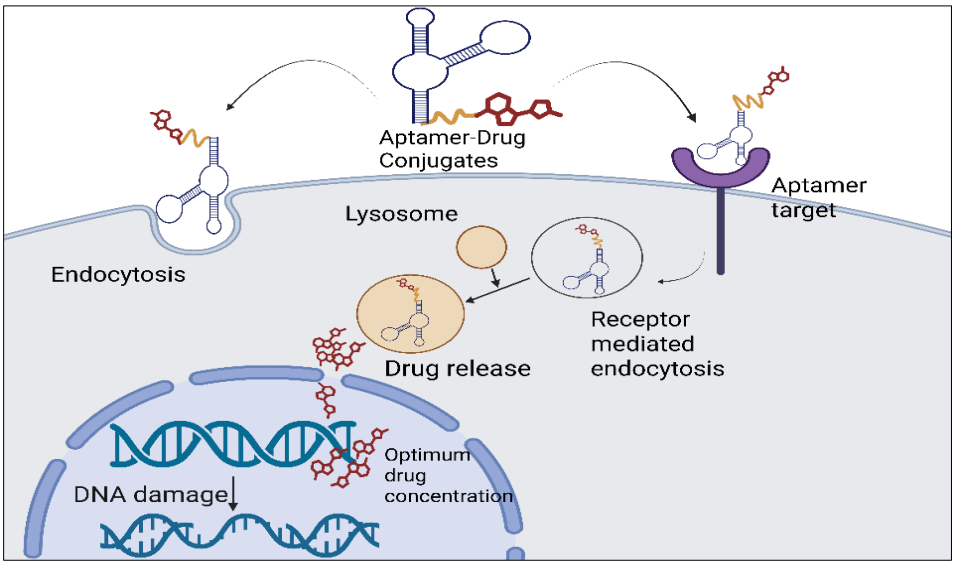

Figure 2 Receptor-mediated endocytosis of cytotoxic drugs. Aptamer-drug conjugates attach to their specific receptor and enter the cell through receptor-mediated endocytosis. Inside the lysosome, the drug is detached from the aptamer, released, and subsequently transported to the nucleus

Several ingenious mechanisms have been developed to achieve this, including enzymatic cleavage, pH sensitivity, and photo-triggered systems, ensuring that the drug is released at the right time and place to maximize its therapeutic effect [43].

Enzymatic cleavage is one such mechanism, exploiting the unique biochemical environment of tumors [44]. Tumors frequently display overexpression of certain enzymes, including lysosomal cathepsin B protease and matrix metalloproteinases (MMPs) [45,46]. ApDCs can be designed with linkers that are specifically cleaved by these enzymes, triggering drug release within the tumor microenvironment [17]. For example, gemcitabine, a common chemotherapeutic, has been conjugated to aptamers via a dendrimer structure and enzymatically cleavable linkers, allowing for controlled intracellular drug release upon cleavage by lysosomal cathepsin B protease [47].

This localization strategy improves the therapeutic index of the drug by enriching it in the tumor itself and minimizing exposure to healthy tissue, which can mitigate many of the side effects that typically arise from conventional chemotherapy [13]. The improved pharmacokinetics and biodistribution of ApDCs, compared to free drugs, can lead to better tumor penetration and retention, known as the enhanced permeability and retention (EPR) effect, resulting in prolonged exposure of cancer cells to the therapeutic agent and potentially improving treatment outcomes [13].

pH-sensitive linkers are yet another option for controlled drug release [48]. Tumor tissues are frequently more acidic because of altered metabolism [49]. Different linkers can be utilized for designing the ApDCs that are stable at physiological pH, but become unstable and cleavable in an acidic tumor microenvironment, thus leading to drug release [48]. To enhance the drug release profiles associated with ApDCs, acid-labile linkers including the hydrazone, amide, imine, cis-acotinyl, oxime, ketal and acetal linkers have been employed [48].

Photo-triggered systems offer a high degree of spatial and temporal control over drug release [50]. These systems utilize light to activate the release of the drug from the ApDC [51]. Upon reaching the tumor site, the ApDC is exposed to light of a specific wavelength, which cleaves a light-sensitive linker and releases the drug. This method enables direct targeting of drug delivery to the tumor site, which is expected to reduce off-target effects [52]. The light-triggering mechanisms can involve changing the hydrophobicity of a nanocarrier constituent, introducing local defects within a nanocarrier, or bond cleavage.

3. Comparison with Antibody-Drug Conjugates

ApDCs have a large number of advantages relative to antibody-drug conjugates or other targeted therapies. Aptamers are smaller in size than antibodies, which contributes to enhanced tissue penetration and accumulation in tumors [17,53]. They also exhibit lower immunogenicity, which minimizes immune-related side effects. Moreover, there is more control over production and modification of aptamers than there is over antibodies since aptamers are chemically synthesized [7,54]. Such benefits offer ApDCs, a potential alternative to ADCs for an effective therapy for cancer.

3.1. Comparison between Aptamers and Antibodies

Table 1 In-Depth Comparison of Aptamers and Antibodies: Analyzing Nature, Size, Stability, and Functional Characteristics.

Characteristic	Aptamers	Antibodies
Nature	Nucleic acid ligands (DNA/RNA-based)	Protein-based molecules
Size	Small (~10–30 kDa, ~2 nm)	Large (~150–170 kDa, ~15 nm)
Molecular Weight	~6–30 kDa	~150–180 kDa
Target	Wide range, including small molecules, non-immunogenic compounds	Mostly immune-related proteins
Affinity	High	High
Specificity	High	High
Synthesis	Simple (chemical synthesis, SELEX process)	Complex (in vivo production using animal models)

Stability	Stable at room temperature, denaturation is reversible	Sensitive to temperature, requires refrigeration; denaturation is irreversible
Modification	Easily modified at both 5’ and 3’ ends	Limited modifications, may affect function
Storage Term	Long	Relatively short
Development Time	Short (~1–3 months)	Long (~4–6 months)
Production Time	Several weeks (~1–3 months)	Several months (~4–6 months)
Generation Time	Few hours to months	Several months
In Vivo Half-life	Short (~20 min)	Long (~one month)
Cost	Low	High
Nuclease Degradation	Sensitive	Resistant
Minimum Target Size	≥60 Daltons	≥600 Daltons
Manufacturing Process	Chemical synthesis (animal-free)	In vivo (cell culture, requires immune response)
Batch Consistency	High	Variable (depends on biological system)
Immunogenicity	Low (non-toxic, non-immunogenic)	High
Optimal Working Concentration	~5 to 10 times lower than antibodies in some applications	Varies by application
Secondary Structure	Hairpin, stem-loop, G-quadruplex	α-helix and β-fold
Penetration Ability	Can infiltrate tissues and cells	Limited penetration
Scalability	Easy to scale up (chemical synthesis)	Difficult to scale (biological production)
Targeting Toxic Compounds	Possible	Difficult due to immune response
Long-term Availability	Sequence is digitally stored and chemically synthesized when needed	Requires frozen cell stocks for production
Target Potential	Can bind very small, non-immunogenic, and toxic targets	Requires an immune response, limiting target options
Production Cost	Lower cost, as aptamers are chemically synthesized	Expensive due to complex in vivo processes
Development Process	Selected in vitro via SELEX, including positive and negative selection	Requires immune response and animal models
Optimal Working Concentration	~5 to 10 times lower than antibodies in some applications	Varies widely by application

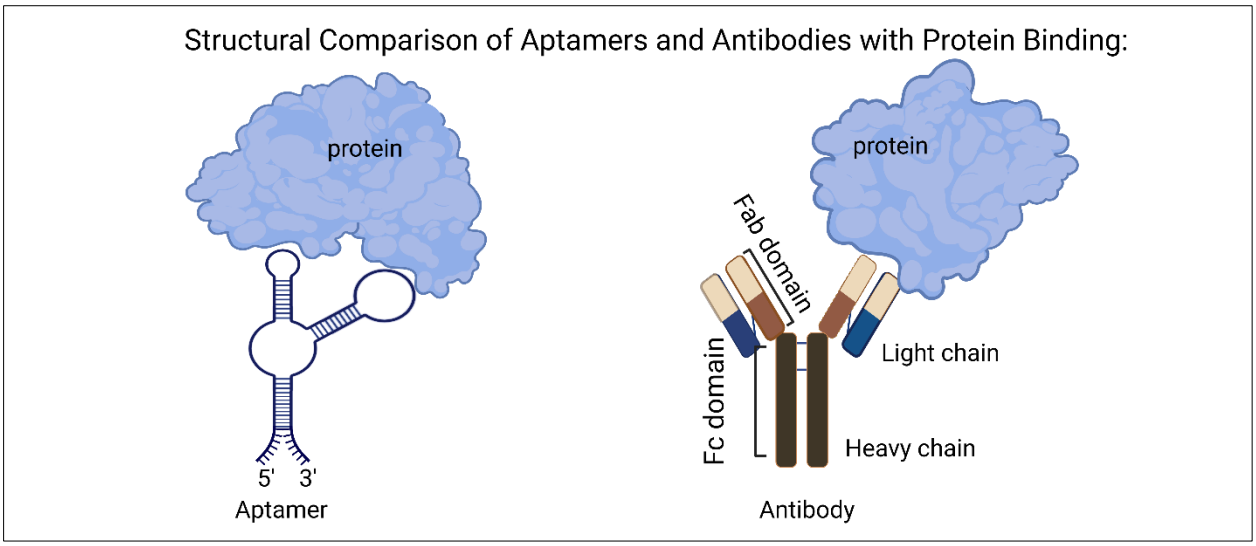

Figure 3 Structural comparison of aptamers and antibodies with protein binding

4. Recent Advances in ApDCs for Cancer Therapy

Aptamer-drug conjugates represent a promising approach for targeted cancer therapy, providing benefits over traditional chemotherapy by directly delivering cytotoxic drugs to tumor locations, thereby reducing off-target effects [6,55]. Recent advances in aptamer development, conjugation strategies, and drug delivery systems have propelled ApDCs to the forefront of cancer research.

4.1. Specific ApDCs and Their Applications

A certain number of ApDCs have been successful in preclinical and clinical trials [3]. For instance, studies have investigated the fabrication of ApDCs such as P19-dFdCMP, P19-5FdUMP, sgc8c-Dox and NucA-PTX [43,56,57]. Aptamer with chemotherapy drugs is a new approach for the targeted drug delivery to tumor cells, resulting in a higher targeting specificity, efficacy and therapeutic ratio [13]. The sgc8c aptamer with high binding affinity towards protein tyrosine kinase 7 (PTK-7) is applicable to drug delivery systems [58]. The sgc8c-Dox conjugate can prevent the non-specific uptake of Dox, reducing cytotoxicity in non-targeted cells [59]. NucA-PTX has targeting effect to the tumor, PTX is localized in tumor and as soon as being taken up by cells, the dipeptide bond linker of NucA-PTX would be cleaved by cathepsin to release PTX [17,60].

4.2. Novel Aptamer Targets

Novel aptamer targets for cancer therapy have also been discovered [61,62]. Such as, nucleolin is a cell surface protein, it makes an ideal carrier for drug internalization, facilitating drug trafficking carrying relevant aptamers that bind to nucleolin [17,63]. Other potential targets are PSMA, HER2 and VEGF which are in progress for development of new ApDCs [64,65]. The aptamer–antibody conjugates induce the T cell response and leads to the destruction of cancer cells effectively [13].

4.3. Improved Drug Delivery Systems

Improved drug delivery systems that incorporate aptamers have further enhanced the therapeutic potential of ApDCs [66]. Plenty of aptamer-based targeted drug delivery systems, including aptamer-drug conjugation and aptamer-nano materials, have been established [14,67,68]. Advanced systems ensure the greatest degree of drug delivery efficiency, lowered toxicity and therapeutic effectiveness [69]. Expands on the application of bioconjugates of nanomaterials and aptamers to advance the development of promising cancer therapy methods [55,67].

In the following table, the discoveries of Aptamer-Drug Conjugates (ApDCs) as a promising targeted cancer treatment have been summarized recently, listing their specificity, therapeutic effectiveness and clinical translation.

Table 2 Recent Developments in Aptamer-Drug Conjugates (ApDCs) for Targeted Cancer Therapy

Aptamer	Target	Drug Payload	Cancer Type	Study Findings	Reference
Sgc8c-Dox	Protein Tyrosine Kinase 7 (PTK7)	Doxorubicin	Leukemia	Enhanced drug uptake in cancer cells, reduced off-target toxicity.	[65]
AS1411-Gem	Nucleolin	Gemcitabine	Pancreatic Cancer	Increased tumor accumulation, improved cytotoxic effects.	[56]
PSMA-Apt-PTX	Prostate-Specific Membrane Antigen (PSMA)	Paclitaxel	Prostate Cancer	Selective drug delivery, inhibition of tumor growth.	[64]
A10-3-Dox	PSMA	Doxorubicin	Prostate Cancer	Enhanced tumor penetration, improved survival rates.	[17]
EpCAM-Apt-Dox	Epithelial Cell Adhesion Molecule (EpCAM)	Doxorubicin	Breast Cancer	Targeted drug release, higher cytotoxicity in tumor cells.	[39]
NucA- PTX	Nucleolin	Paclitaxel	Lung and Breast Cancer	Enzyme-triggered drug release, improved therapeutic index.	[17]

5. Benefits of Aptamer-Drug Conjugates in Cancer Therapy

Aptamer-drug conjugates exhibit a number of advantages over traditional chemotherapy and antibody-drug conjugates for cancer therapy. These advantages are owed to the intrinsic features of aptamers as targeting agents.

5.1. Enhanced Specificity and Reduced Off-Target Effects

The high affinity and specificity of aptamers allow ApDCs to specifically bind to cancer cells, minimizing the toxicities of the cytotoxic drug to healthy tissues [26,70]. This approach results in significantly less off-target effects and toxicities with the greatest advantage of increased safety profile in the treatment of cancer [71]. Comparing to classical chemotherapeutic drug-based therapies, ApDCs provide better specificity and therapeutic advantages. This small size is around 15–20 fold smaller than that of antibodies, allowing for a better tissue penetration and higher accumulation within the tumor, increasing the targeted delivery of drugs [6,29].

5.2. Lower Immunogenicity Compared to Antibodies

The risk of inducing an immune response with ApDCs is less than with antibodies thus minimizing adverse effects and enhancing tolerability of the treatment [13,72]. The non-immunogenic nature of aptamers is crucial for ApDCs, particularly when repeated administrations are necessary, as it minimizes the development of neutralizing antibodies that could compromise treatment efficacy [26]. Preclinical and clinical trials suggest that oligonucleotides do not typically induce the development of neutralizing antibodies [73], and aptamers can shield viruses from these antibodies, allowing efficient delivery to tumor cells [74].

5.3. Potential for Multifunctional Systems

Aptamers can be conveniently modified and conjugated with many types of agents, including imaging and therapeutic moieties [17]. This adaptability allows for the creation of multifunctional ApDCs that integrate diagnostic imaging with targeted therapy in a single agent [75,76]. For instance, an innovative approach involves combining chemotherapy and immunotherapy through ApDCs labeled on bacteria, enhancing drug delivery and overcoming the tumor microenvironment's barriers [26]. These systems allow the real-time tracking of the delivery of drugs and the response to the treatment [61], which facilitates personalized medicine and the optimization of therapeutic outcomes [26].

6. Challenges in ApDC Development

6.1. Limitations of Conventional Anticancer Drug Delivery

Most anticancer agents lack specificity for cancerous cells, resulting in toxicity of surrounding healthy tissues and thus requiring lower doses for effective therapy [77]. Moreover, the upsurge of drug-resistant cells necessitates more selective treatments. Early approaches aimed at targeted drug delivery, relied on ligands based on polyunsaturated fatty acids, folic acid, hyaluronic acid and oligopeptides [77,78]. so as to overcome the limitations of each, including unclear tumor- targeting mechanism, poor performance in conjugates of small size [78] and susceptibility to enzymatic degradation in circulation, they have thus limited application in vivo. However, unmodified aptamers are quickly degraded or lose their ability to specifically bind to the target, so we have modified aptamers as promising targeting agents to improve their stability in biological environments. SELEX to develop aptamers is a complicated workflow that usually relies on optimization [77,79] and has yet to meet the dual challenge of developing highly specific and high-affinity binding molecules. Therefore, aptamer-small molecule conjugates require efficient conjugation strategies to act as both carriers and ligands, whereas proper functionalization of aptamer-nanomaterial conjugates with nanoparticles is needed for effective targeting of these drugs.

6.2. Challenges in Developing Stable Aptamers for Therapeutic Use

The development of clinically relevant aptamer-drug conjugates (ApDCs) is challenged by several issues. Aptamers, especially RNA-based aptamers, are prone to quick digestion by nucleases in physiological environment, a key problem is their stability in vivo [80]. These properties lead to short in vivo half-lives, which are typically less than 10 minutes [81], significantly limiting their therapeutic efficacy considerably. Various strategies have been developed for the stabilization of aptamers. Chemical modifications help to increase the resistance to nuclease degradation without a significant loss of target affinity [80]. TH2 leading to certain cytokines upregulating antibody production whilst others downregulate it such as TH1, B-cells undergo isotype switching which can lead to them producing IgG or IgM, however, if IgG is produced, conjugation occurs where the drug gets bound to a polymer, it can be a polymer like polyethylene glycol (PEG), this increases the molecular weight of the drug making it too large to be filtered through the kidneys, therefore increasing its half-life/circulation longevity. The inherent stability of aptamers can also be improved by optimizing their secondary structure [80].

6.3. Optimization of Conjugation Chemistry for Effective Drug Delivery

Another key issue is the optimization of the conjugation chemistry for drug loading efficiency. Manufacturing aptamers, they use the same sequences, so the conjugation process should retain aptamer affinity to effectively bind the target which is achieved through careful selection of conjugation sites and linkers [82]. Additionally, maintaining a balanced drug-to-aptamer ratio is crucial for uniform therapeutic outcome, thus homogeneous drug-to-aptamer ratio (DAR) preparations are highly favored [80]. These site-specific conjugation approaches provide more control over the properties of the ApDCs (e.g. stability and binding to the target), thereby enhancing their therapeutic potential [83].

6.4. Scalability and Manufacturing Challenges in Clinical Applications

Ultimately, challenges remain in ApDCs scalability and manufacture for clinical applications. Demonstrated high reproducibility is a prerequisite in large-scale aptamer synthesis that translates directly to the clinical setting by ensuring the quality and purity necessary for clinical use [80,82]. Addressing these issues is essential to move ApDCs from bench-based discovery to effective clinical agents.

7. Future Perspectives

Although aptamer-drug conjugates have some shortcoming, they also offer great potential for targeted cancer treatment and continued research is progressing closer to an exciting future in this space. Furthermore, Increased interest in enhancing aptamer selection, mainly in enhancing SELEX approaches, is expected to generate more aptamers targeting cancer biomarkers with high specificity and affinity [84]. There are several significant domains that will influence ApDCs' trajectories.

7.1. Combination Therapies

ApDCs are a very promising approach with the potential to synergize with other treatment modalities. ApDCs have an exquisite specificity for their targets and the dual combination of ApDCs with immunotherapy could additionally enhance anti-tumor immune responses, whereas the dual combination of ApDCs with radiotherapy could improve

tumor targeting while reducing off-target effects [6,84]. Other treatments involve the combination synthesize of above aptamers that are discussed in a chemotherapy study in cancer therapy. The high off-target effects of many chemotherapeutic agents limit how much can be administered due to adverse side effects in healthy tissues and what is considered the maximum tolerated dosage for conventional chemotherapy. The selective delivery of chemotherapeutics to cancer tissues holds potential to solve these complications [15].

Aptamers with Immunotherapies: The aptamers binding to the immune checkpoints including PD-L1, CTLA-4 etc., can be designed as either agonists (enhancing immunity) or antagonists (blocking the inhibitory signal) [85]. Combining with immune checkpoint inhibitors based on antibodies could achieve an even stronger and persistent immune response. Aptamers may be used for directly transporting checkpoint inhibitors of immune the system or other immune inflammatory agents to the tumor microenvironment to activate the local immune system and reduce systemic adverse reactions. Aptamer-mediated delivery of STING (stimulator of interferon genes) agonists to stimulate innate immunity in tumors, together with PD-1/PD-L1 blockade for enhanced adaptive immunity [86,87]. More studies are needed to investigate ideal combinations and administration options for further improving therapeutic efficacy [84].

7.2. Aptamer Selection and modification

Aptamer selection and modification technologies are advancing to improve the ApDCs performance and their clinical translatability [84]. Developing novel aptamers that have high-affinity and specificity for cancer-specific targets is essential [84]. SELEX, a Darwinian evolution-based screening method, is used for aptamer selection, where high-affinity and specific aptamers are enriched through iterative cycles of binding, separation, and amplification. SELEX starts with a pool of random oligonucleotide sequences that are incubated with a target, and the best binding sequences are retained for amplification in subsequent rounds. Advanced techniques, including Cell- SELEX and In Vivo SELEX, increase the specificity through direct selection of aptamers against target cells or within living organisms and are especially useful in identifying biomarkers and targeting diseases [88]. Although, Aptamer modifications improve binding affinity with Chemical modifications at sugar unit, nucleobase, or backbone for nuclease biostability, renal clearance as well as degradation. This problem was addressed by modifications of the 3′ terminus of the oligonucleotide such as 3′-Biotin and 3′-inverted thymidine, which showed a statistically significant improvement of the nuclease resistance, whereas 3′-inverted thymidine provides a major stability since the half-life of an affinity-enhanced aptamers can reach up to 72 hours in serum. 5′-Cholesterol and lipid-modified extend time circulation via reduced renal filtration, with cholesterol-conjugated aptamers showing nine- fold longer half-life in plasma than their unmodified counterparts [88]. Additionally, novel modification strategies to improve their stability, cell uptake, and drug delivery efficiency will be essential in optimizing ApDCs design [89].

7.3. Emerging Trends

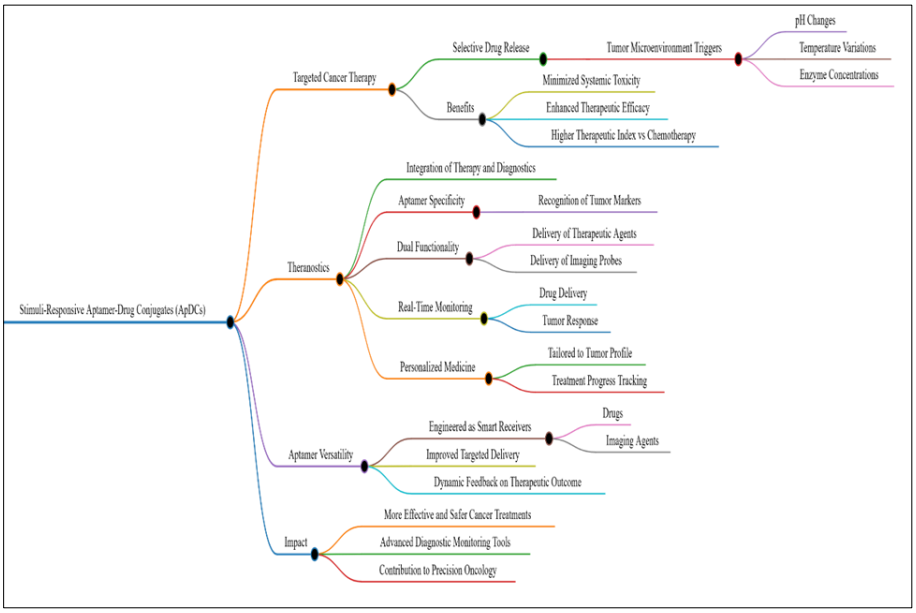

Figure 4 Multifaceted Applications of Stimuli-Responsive Aptamer-Drug Conjugates (ApDCs) in Cancer Therapy, Diagnostics, and Imaging

As an upcoming trend, stimuli-responsive ApDCs are very attractive. These conjugates are capable of releasing their payload by detecting particular stimuli in the tumor microenvironment, including pH, temperature, or enzyme concentration [17,89]. This targeted release of systems can reduce systemic toxicity and improve therapeutic efficacy [89]. Moreover, the theranostic applications of ApDCs (the combination of therapy and diagnostics) demonstrate the promise of personalized medicine approaches [89]. Aptamers can be tailored for use as receivers delivering drugs or imaging agents that can be designed to image and monitor the delivery and response of drugs in real time [89].

8. Discussion

8.1. Oncological and Rationale for ApDCs

8.1.1. Emerging Targeted Therapy

As a new generation of targeted cancer therapy, aptamer drug conjugate (ApDC) shows excellent potential featuring the remarkable specificity both of aptamers and therapeutic cytotoxicity of chemotherapeutic drugs. Through this method, the limitations of conventional chemotherapy, in particular lack of specificity and non-specific toxicities, are circumvented, and it has built on the successes of targeted strategies such as ADCs.

8.1.2. Cancer Treatment Needs

Metastatic forms of cancer that are difficult to treat include metastatic breast cancer, castration resistant prostate cancer (CRPC), and pancreatic cancer. These ApDCs aim at selectively delivering cytotoxic drugs to cancer cells, offering an alternative when other targeted therapies are not available.

8.1.3. Integration into Oncology Paradigm

ApDCs are in concordance with the precision oncology paradigms. Known as “chemical antibodies,” these constructs can be generated quickly against tumor-specific markers and then ferry drugs preferentially to cancer cells with the least amount of killing effect to normal cells.

8.2. Clinical Translatability Across Cancer Types

8.2.1. Breast Cancer

Preclinical studies of EpCAM-specific aptamer–doxorubicin conjugates demonstrated potent tumor cell killing and marked tumor growth inhibition. Translational studies will need to work towards confirming aptamer binding to a variety of subtypes (e.g., triple-negative breast cancer) and achieve deep tumor penetration.

8.2.2. Prostate Cancer

Tumor-specific delivery and anti-tumor activity for PSMA-targeted ApDCs including paclitaxel conjugates has been observed. With clinical validation of PSMA in mind, these findings support the translational potential of PSMA 3B2xCD8-TCB, with the caveat of off-target toxicity observed in normal prostate tissue.

8.2.3. Pancreatic Cancer

The gemcitabine-conjugated AS1411 aptamer has demonstrated enhanced tumor inhibition in pancreatic models. However, the clinical application can be realized only if issues such as the low vascular perfusion and the presence of dense stroma can be addressed achieving drug delivery.

8.2.4. Other Cancers (e.g., Leukemia, Lung)

PTK7-specific ApDCs have displayed leukemia selectivity and survival advantages in preclinical models. Targeting nucleolin within lung cancer as illustrated, nucleolin targeted ApDCs are applicable pan-cancer. Special biodistribution and penetration issues need to be solved according to the type of cancer.

8.3. Comparison with Other Targeted Therapies

8.3.1. Delivery Precision

Just as monoclonal antibodies do in ADCs and CAR-T cells, aptamers target tumor-associated antigens. Nevertheless, aptamers could be able to be selected against non-protein and cell-specific markers with a potentially higher specificity. Contrast to active proliferation of CAR-T cells, ApDCs function in a passive manner in the formation of binding sites.

8.3.2. Tissue Penetration

Because of their reduced size (10–30 kDa), ApDCs can infiltrate the tumor better than larger molecules, such as antibodies (150 kDa) or CAR-T cells, and are a good choice for poorly vascularized or dense solid tumors.

8.3.3. Immune Response

ApDCs are oligonucleotide agents with no or little immunogenicity and no Fc effects as are observed in antibodies. This facilitates multiple administrations without eliciting high levels of immune responses -- a key differentiator from ADCs and CAR-Ts.

8.3.4. Cost and Manufacturing

ApDCs offer the additional advantages of a streamlined, scalable chemical synthesis process that is typically less resource-intensive than antibody generation or CAR T cells engineering. Nevertheless, the development of fitness-inactivating TNAs in such large numbers remains difficult and scale-up in the production, as well as on aptamer folding, drug-to-aptamer ratio is not easily achievable.

8.4. Key Challenges and Limitations

8.4.1. Tumor Heterogeneity

ApDC's efficacy may be restricted by intra- and inter-tumoral heterogeneity when a single marker is targeted. Approaches involve multivalent aptamer cocktails or wider pool selection using cell-based approaches, but general applicability is challenging.

8.4.2. In Vivo Stability

Aptamers do not resist rapid degradation in circulation if unmodified. Chemical modifications (such as 2'-fluoro-, PEGylation) increase half-life and drug stability, but balance is needed to ensure on-target release and avoid pre-release.

8.4.3. Conjugation Chemistry

It is essential that conjugation be rapid and reproducible. The choice of a linker (e.g., enzyme- or pH-responsive) must balance the release of the payload at the tumor with the maintenance of both aptamer activity and drug potency.

8.4.4. Scalability and Mass Production

Despite the benefits of synthetic chemistry, GMP production in abundance of ApDC faces challenges in achieving high purity, reproducible drug loading, as well as cost-effective production.

8.5. Emerging Solutions and Future Strategies

8.5.1. Stimuli-Responsive ApDCs

Tumor specific release mechanisms can be incorporated to ApDCs (such as pH, enzymatic cleavage or redox-sensitivity) to improve safety and therapeutic window by reducing off-target toxicity while promoting site-specific drug activation.

8.5.2. AI-Driven Aptamer Selection

The application of artificial intelligence and SELEXAI can speed up the selection process of aptamers by mining existing in vitro selection data to give promising sequences. This method also facilitates the accelerated generation of aptamers against new targets or patient-specific targets, thus increasing the clinical applicability.

8.5.3. Combination with Immunotherapy

ApDCs could act complimentary to ICB or CAR-T cells by reducing tumors masses (debulking) or producing immunomodulators. Aptamers also exhibited the potential to direct to the immunosuppressive tumor microenvironment, which increasing anti-tumor immunity.

8.5.4. Other Innovative Strategies

Novel formats such as bispecific aptamers, dual drug conjugates, aptamer-nanoparticle conjugates and theranostics are currently being developed. Their multifunctionality is expected to circumvent the current shortcomings and potentiate the development of ApDC as a powerful therapeutic cancer tool.

9. Conclusion

Aptamer–drug conjugates have potential as a targeted cancer therapy, with selective enhancement of efficacy, minimized systemic toxicity, and good prospect for next-generation therapeutics. Aptamer targeting-based and drug-induced ApDCs can specifically kill cancer cells, decrease off-target toxicities. Aptamers showed better tissue penetration and tumor accumulation, likely due to their smaller size than that of antibodies.

For ApDCs to meet their full potential, a continued effort is required to discover new aptamer targets and further improve selection technologies. There are limitations to be tackled, including in vivo off-target effects and the safety. To get a realistic expectation of clinical activity, better preclinical models need to be developed. Optimization of ApDC's pharmacokinetics through nuclease degradation and renal clearance is still important. Formulation drug delivery also depends on conjugation chemistry.

Further effort is needed for ApDC's clinical translation. Tuning the design of ApDC and improving the mechanisms of drug release and circumvention of drug-resistance mechanisms are critical. In addition to oncology, the applications of ApDC platforms are wide ranging.

Progress in the field of ApDCs depends on the cooperation between different disciplines. By working together in this way, the possibilities of new drugs can be realized more quickly, challenges overcome, and these therapies get to patients, transforming cancer treatment, and possibly affecting other diseases.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Credit Authorship Contribution Statement

Afif Abyad Hossain*, Md Roknuzzaman Faisal, Md Shorif Uddin, and Adib Azwad Hossain played pivotal roles in shaping this review paper. Their contributions encompassed the comprehensive literature review, conceptual framework development, data collection, original draft preparation, figure illustration, and the overall generation of ideas that guided the direction of the manuscript.

Nosib Khan and Md Inzamam Ul Haque contributed significantly through formal data analysis, meticulous data curation, table construction, grammatical refinement, software-related adjustments, and thorough proofreading to enhance the clarity and quality of the final manuscript.

References

[1] Min H-Y, Lee H-Y. 1.Molecular targeted therapy for anticancer treatment. Exp Mol Med 2022;54:1670–94. https://doi.org/10.1038/s12276-022-00864-3

[2] Chari RVJ. 2.Targeted Cancer Therapy: Conferring Specificity to Cytotoxic Drugs. Acc Chem Res 2008;41:98–107. https://doi.org/10.1021/ar700108g

[3] Hou J, He Z, Liu T, Chen D, Wang B, Wen Q, et al. 3.Evolution of Molecular Targeted Cancer Therapy: Mechanisms of Drug Resistance and Novel Opportunities Identified by CRISPR-Cas9 Screening. Front Oncol 2022;12. https://doi.org/10.3389/fonc.2022.755053

[4] Schirrmacher V. 4.From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review). Int J Oncol 2018;54:407–19. https://doi.org/10.3892/ijo.2018.4661

[5] Juthani R, Punatar S, Mittra I. 5.New light on chemotherapy toxicity and its prevention. BJC Reports 2024;2:41. https://doi.org/10.1038/s44276-024-00064-8

[6] Mahmoudian F, Ahmari A, Shabani S, Sadeghi B, Fahimirad S, Fattahi F. 6.Aptamers as an approach to targeted cancer therapy. Cancer Cell Int 2024;24:108. https://doi.org/10.1186/s12935-024-03295-4

[7] Li Y, Zhao J, Xue Z, Tsang C, Qiao X, Dong L, et al. 7.Aptamer nucleotide analog drug conjugates in the targeting therapy of cancers. Front Cell Dev Biol 2022;10. https://doi.org/10.3389/fcell.2022.1053984

[8] Mathavan S, Tam YJ, Mustaffa KMF, Tye GJ. 8.Aptamer based immunotherapy: a potential solid tumor therapeutic. Front Immunol 2025;16. https://doi.org/10.3389/fimmu.2025.1536569

[9] Zhou G, Wilson G, Hebbard L, Duan W, Liddle C, George J, et al. 9.Aptamers: A promising chemical antibody for cancer therapy. Oncotarget 2016;7:13446–63. https://doi.org/10.18632/oncotarget.7178

[10] Byun J. 10.Recent Progress and Opportunities for Nucleic Acid Aptamers. Life 2021;11:193. https://doi.org/10.3390/life11030193

[11] Lakhin A V, Tarantul VZ, Gening L V. 11.Aptamers: problems, solutions and prospects. Acta Naturae 2013;5:34–43 . PMID: 24455181

[12] Valadés-Alcaraz A, Reinosa R, González-Hevilla M, Medina-Sánchez C, Holguín Á. 12.Development and characterization of high-affinity aptamers for HIV protease detection. Heliyon 2024;10:e38234. https://doi.org/10.1016/j.heliyon.2024.e38234

[13] He J, Duan Q, Ran C, Fu T, Liu Y, Tan W. 13.Recent progress of aptamer–drug conjugates in cancer therapy. Acta Pharm Sin B 2023;13:1358–70. https://doi.org/10.1016/j.apsb.2023.01.017

[14] Tran BT, Kim J, Ahn D-R. 14.Systemic delivery of aptamer–drug conjugates for cancer therapy using enzymatically generated self-assembled DNA nanoparticles. Nanoscale 2020;12:22945–51. https://doi.org/10.1039/D0NR05652A

[15] Zhu G, Niu G, Chen X. 15.Aptamer–Drug Conjugates. Bioconjug Chem 2015;26:2186–97. https://doi.org/10.1021/acs.bioconjchem.5b00291

[16] Deng R, Qu H, Liang L, Zhang J, Zhang B, Huang D, et al. 16.Tracing the Therapeutic Process of Targeted Aptamer/Drug Conjugate on Cancer Cells by Surface-Enhanced Raman Scattering Spectroscopy. Anal Chem 2017;89:2844–51. https://doi.org/10.1021/acs.analchem.6b03971

[17] Kim D-H, Seo J-M, Shin K-J, Yang S-G. 17.Design and clinical developments of aptamer-drug conjugates for targeted cancer therapy. Biomater Res 2021;25. https://doi.org/10.1186/s40824-021-00244-4

[18] Fu Z, Xiang J. 18.Aptamers, the Nucleic Acid Antibodies, in Cancer Therapy. Int J Mol Sci 2020;21:2793. https://doi.org/10.3390/ijms21082793

[19] Cai S, Yan J, Xiong H, Liu Y, Peng D, Liu Z. 19.Investigations on the interface of nucleic acid aptamers and binding targets. Analyst 2018;143:5317–38. https://doi.org/10.1039/C8AN01467A

[20] Thevendran R, Citartan M. 20.Assays to Estimate the Binding Affinity of Aptamers. Talanta 2022;238:122971. https://doi.org/10.1016/j.talanta.2021.122971

[21] Sakamoto T, Ennifar E, Nakamura Y. 21.Thermodynamic study of aptamers binding to their target proteins. Biochimie 2018;145:91–7. https://doi.org/10.1016/j.biochi.2017.10.010

[22] Zhang N, Wang J, Bing T, Liu X, Shangguan D. 22.Transferrin receptor-mediated internalization and intracellular fate of conjugates of a DNA aptamer. Mol Ther Nucleic Acids 2022;27:1249–59. https://doi.org/10.1016/j.omtn.2022.02.006

[23] Powell Gray B, Kelly L, Ahrens DP, Barry AP, Kratschmer C, Levy M, et al. 23.Tunable cytotoxic aptamer–drug conjugates for the treatment of prostate cancer. Proceedings of the National Academy of Sciences 2018;115:4761–6. https://doi.org/10.1073/pnas.1717705115

[24] Engelberg S, Modrejewski J, Walter JG, Livney YD, Assaraf YG. 24.Cancer cell-selective, clathrin-mediated endocytosis of aptamer decorated nanoparticles. Oncotarget 2018;9:20993–1006. https://doi.org/10.18632/oncotarget.24772

[25] Lv C, Yang C, Ding D, Sun Y, Wang R, Han D, et al. 25.Endocytic Pathways and Intracellular Transport of Aptamer-Drug Conjugates in Live Cells Monitored by Single-Particle Tracking. Anal Chem 2019;91:13818–23. https://doi.org/10.1021/acs.analchem.9b03281

[26] Xiao Y, Pan T, Da W, Liu Y, Chen S, Chen D, et al. 26.Aptamer-drug conjugates-loaded bacteria for pancreatic cancer synergistic therapy. Signal Transduct Target Ther 2024;9:272. https://doi.org/10.1038/s41392-024-01973-3

[27] Bisht A, Bhowmik S, Patel P, Gupta G Das, Kurmi B Das. 27.Aptamer as a targeted approach towards treatment of breast cancer. J Drug Target 2024;32:510–28. https://doi.org/10.1080/1061186X.2024.2333866

[28] Park JY, Cho YL, Chae JR, Kang WJ. 28.Abstract 2009: Gemcitabine-loaded EGFR aptamer for targeted therapy of lung cancer. Cancer Res 2023;83:2009–2009. https://doi.org/10.1158/1538-7445.AM2023-2009

[29] Xiang D, Zheng C, Zhou S-F, Qiao S, Tran PH-L, Pu C, et al. 29.Superior Performance of Aptamer in Tumor Penetration over Antibody: Implication of Aptamer-Based Theranostics in Solid Tumors. Theranostics 2015;5:1083–97. https://doi.org/10.7150/thno.11711

[30] BARRIERE G, RIGAUD M, ARRAT C, COLOMBI H, POLI E. 30.Specific Aptamer Functionalization of Dense Ceramic by Click Chemistry Towards Circulating Tumor Cells Apheresis. Anticancer Res 2023;43:1053–64. https://doi.org/10.21873/anticanres.1625

[31] Lee D, Kang J, Song I. 31.Abstract 6415: CD25-targeted aptamer-drug conjugate (CD25-ApDC) depletes and blocks regulatory T cells selectivel. Cancer Res 2023;83:6415–6415. https://doi.org/10.1158/1538-7445.AM2023-6415

[32] Moore MD, Cookson J, Coventry VK, Sproat B, Rabe L, Cranston RD, et al. 32.Protection of HIV Neutralizing Aptamers against Rectal and Vaginal Nucleases. Journal of Biological Chemistry 2011;286:2526–35. https://doi.org/10.1074/jbc.M110.178426

[33] Murray MT, Wetmore SD. 33.Unlocking precision in aptamer engineering: a case study of the thrombin binding aptamer illustrates why modification size, quantity, and position matter. Nucleic Acids Res 2024;52:10823–35. https://doi.org/10.1093/nar/gkae729

[34] Amero P, Lokesh GLR, Chaudhari RR, Cardenas-Zuniga R, Schubert T, Attia YM, et al. 34.Conversion of RNA Aptamer into Modified DNA Aptamers Provides for Prolonged Stability and Enhanced Antitumor Activity. J Am Chem Soc 2021;143:7655–70. https://doi.org/10.1021/jacs.9b10460

[35] Liao J, Liu B, Liu J, Zhang J, Chen K, Liu H. 35.Cell-specific aptamers and their conjugation with nanomaterials for targeted drug delivery. Expert Opin Drug Deliv 2015;12:493–506. https://doi.org/10.1517/17425247.2015.966681

[36] Alamoudi AO. 36.Radiomics, aptamers and nanobodies: New insights in cancer diagnostics and imaging. Hum Antibodies 2021;29:1–15. https://doi.org/10.3233/HAB-200436

[37] Shigdar S, Schrand B, Giangrande PH, de Franciscis V. 37.Aptamers: Cutting edge of cancer therapies. Molecular Therapy 2021;29:2396–411. https://doi.org/10.1016/j.ymthe.2021.06.010

[38] Zheng L, Zhang Q, Zhang Y, Qiu L, Tan W. 38.Aptamer-based Cell Recognition and Detection. Curr Anal Chem 2022;18:612–21. https://doi.org/10.2174/1573411017666211201163504

[39] Macdonald J, Henri J, Roy K, Hays E, Bauer M, Veedu R, et al. 39.EpCAM Immunotherapy versus Specific Targeted Delivery of Drugs. Cancers (Basel) 2018;10:19. https://doi.org/10.3390/cancers10010019

[40] Hänggi K, Ruffell B. 40.Cell death, therapeutics, and the immune response in cancer. Trends Cancer 2023;9:381–96. https://doi.org/10.1016/j.trecan.2023.02.001

[41] Eralp Y, Wang X, Wang J-P, Maughan MF, Polo JM, Lachman LB. 41.Doxorubicin and paclitaxel enhance the antitumor efficacy of vaccines directed against HER 2/neuin a murine mammary carcinoma model. Breast Cancer Research 2004;6:R275. https://doi.org/10.1186/bcr787

[42] Li J, Wang Q, Xia G, Adilijiang N, Li Y, Hou Z, et al. 42.Recent Advances in Targeted Drug Delivery Strategy for Enhancing Oncotherapy. Pharmaceutics 2023;15:2233. https://doi.org/10.3390/pharmaceutics15092233

[43] Chen K, Liu B, Yu B, Zhong W, Lu Y, Zhang J, et al. 43.Advances in the development of aptamer drug conjugates for targeted drug delivery. WIREs Nanomedicine and Nanobiotechnology 2017;9. https://doi.org/10.1002/wnan.1438

[44] Cao Z, Li W, Liu R, Li X, Li H, Liu L, et al. 44.pH- and enzyme-triggered drug release as an important process in the design of anti-tumor drug delivery systems. Biomedicine & Pharmacotherapy 2019;118:109340. https://doi.org/10.1016/j.biopha.2019.109340

[45] Gondi CS, Rao JS. 45.Cathepsin B as a cancer target. Expert Opin Ther Targets 2013;17:281–91. https://doi.org/10.1517/14728222.2013.740461

[46] Anderson CF, Cui H. 46.Protease-Sensitive Nanomaterials for Cancer Therapeutics and Imaging. Ind Eng Chem Res 2017;56:5761–77. https://doi.org/10.1021/acs.iecr.7b00990

[47] Qi J, Zeng Z, Chen Z, Nipper C, Liu X, Wan Q, et al. 47.Aptamer–Gemcitabine Conjugates with Enzymatically Cleavable Linker for Targeted Delivery and Intracellular Drug Release in Cancer Cells. Pharmaceuticals 2022;15:558. https://doi.org/10.3390/ph15050558

[48] Zhuo S, Zhang F, Yu J, Zhang X, Yang G, Liu X. 48.pH-Sensitive Biomaterials for Drug Delivery. Molecules 2020;25:5649. https://doi.org/10.3390/molecules25235649

[49] Liu Q, Zhan C, Kohane DS. 49.Phototriggered Drug Delivery Using Inorganic Nanomaterials. Bioconjug Chem 2017;28:98–104. https://doi.org/10.1021/acs.bioconjchem.6b00448

[50] Li X, Yu X, Dai D, Song X, Xu W. 50.The altered glucose metabolism in tumor and a tumor acidic microenvironment associated with extracellular matrix metalloproteinase inducer and monocarboxylate transporters. Oncotarget 2016;7:23141–55. https://doi.org/10.18632/oncotarget.8153

[51] Rapp TL, DeForest CA. 51.Targeting drug delivery with light: A highly focused approach. Adv Drug Deliv Rev 2021;171:94–107. https://doi.org/10.1016/j.addr.2021.01.009

[52] Rwei AY, Wang W, Kohane DS. 52.Photoresponsive nanoparticles for drug delivery. Nano Today 2015;10:451–67. https://doi.org/10.1016/j.nantod.2015.06.004

[53] Chen A, Yang S. 53.Replacing antibodies with aptamers in lateral flow immunoassay. Biosens Bioelectron 2015;71:230–42. https://doi.org/10.1016/j.bios.2015.04.041

[54] Dhar P, Samarasinghe RM, Shigdar S. 54.Antibodies, Nanobodies, or Aptamers—Which Is Best for Deciphering the Proteomes of Non-Model Species? Int J Mol Sci 2020;21:2485. https://doi.org/10.3390/ijms21072485

[55] Narwade M, Shaikh A, Gajbhiye KR, Kesharwani P, Gajbhiye V. 55.Advanced cancer targeting using aptamer functionalized nanocarriers for site-specific cargo delivery. Biomater Res 2023;27. https://doi.org/10.1186/s40824-023-00365-y

[56] Dai H, Abdullah R, Wu X, Li F, Ma Y, Lu A, et al. 56.Pancreatic Cancer: Nucleic Acid Drug Discovery and Targeted Therapy. Front Cell Dev Biol 2022;10. https://doi.org/10.3389/fcell.2022.855474

[57] Li F, Lu J, Liu J, Liang C, Wang M, Wang L, et al. 57.A water-soluble nucleolin aptamer-paclitaxel conjugate for tumor-specific targeting in ovarian cancer. Nat Commun 2017;8:1390. https://doi.org/10.1038/s41467-017-01565-6

[58] He S, Du Y, Tao H, Duan H. 58.Advances in aptamer-mediated targeted delivery system for cancer treatment. Int J Biol Macromol 2023;238:124173. https://doi.org/10.1016/j.ijbiomac.2023.124173

[59] Liu P, Ga L, Aodeng G, Wang Y, Ai J. 59.Aptamer-drug conjugates: New probes for imaging and targeted therapy. Biosens Bioelectron X 2022;10:100126. https://doi.org/10.1016/j.biosx.2022.100126

[60] Mohammadinejad A, Gaman LE, Aleyaghoob G, Gaceu L, Mohajeri SA, Moga MA, et al. 60.Aptamer-Based Targeting of Cancer: A Powerful Tool for Diagnostic and Therapeutic Aims. Biosensors (Basel) 2024;14:78. https://doi.org/10.3390/bios14020078

[61] Venkatesan S, Chanda K, Balamurali MM. 61.Recent Advancements of Aptamers in Cancer Therapy. ACS Omega 2023;8:32231–43. https://doi.org/10.1021/acsomega.3c04345

[62] Liu B, Liu J, Hu X, Xiang W, Hou W, Li C, et al. 62.Recent advances in aptamer-based therapeutic strategies for targeting cancer stem cells. Mater Today Bio 2023;19:100605. https://doi.org/10.1016/j.mtbio.2023.100605

[63] Kim M, Kim D-M, Kim K-S, Jung W, Kim D-E. 63.Applications of Cancer Cell-Specific Aptamers in Targeted Delivery of Anticancer Therapeutic Agents. Molecules 2018;23:830. https://doi.org/10.3390/molecules23040830

[64] Jeong HY, Kim H, Lee M, Hong J, Lee JH, Kim J, et al. 64.Development of HER2-Specific Aptamer-Drug Conjugate for Breast Cancer Therapy. Int J Mol Sci 2020;21:9764. https://doi.org/10.3390/ijms21249764

[65] Gao F, Yin J, Chen Y, Guo C, Hu H, Su J. 65.Recent advances in aptamer-based targeted drug delivery systems for cancer therapy. Front Bioeng Biotechnol 2022;10. https://doi.org/10.3389/fbioe.2022.972933

[66] Ghasemii K, Darroudi M, Rahimmanesh I, Ghomi M, Hassanpour M, Sharifi E, et al. 66.Advances in aptamer-based drug delivery vehicles for cancer therapy. Biomaterials Advances 2022;140:213077. https://doi.org/10.1016/j.bioadv.2022.213077

[67] Liu Q, Jin C, Wang Y, Fang X, Zhang X, Chen Z, et al. 67.Aptamer-conjugated nanomaterials for specific cancer cell recognition and targeted cancer therapy. NPG Asia Mater 2014;6:e95–e95. https://doi.org/10.1038/am.2014.12

[68] Zhu L, Zhao J, Guo Z, Liu Y, Chen H, Chen Z, et al. 68.Applications of Aptamer-Bound Nanomaterials in Cancer Therapy. Biosensors (Basel) 2021;11:344. https://doi.org/10.3390/bios11090344

[69] Han J, Gao L, Wang J, Wang J. 69.Application and development of aptamer in cancer: from clinical diagnosis to cancer therapy. J Cancer 2020;11:6902–15. https://doi.org/10.7150/jca.49532

[70] Benigno D, Navarro N, Aviñó A, Esposito V, Galeone A, Virgilio A, et al. 70.Aptamer-Drug conjugates for a targeted and synergistic anticancer Response: Exploiting T30923-5-fluoro-2′-deoxyuridine (INT-FdU) derivatives. European Journal of Pharmaceutics and Biopharmaceutics 2024;201:114354. https://doi.org/10.1016/j.ejpb.2024.114354

[71] Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, et al. 71.Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Mol Cancer 2023;22:169. https://doi.org/10.1186/s12943-023-01865-0

[72] Agnello L, Camorani S, Fedele M, Cerchia L. 72.Aptamers and antibodies: rivals or allies in cancer targeted therapy? Explor Target Antitumor Ther 2021. https://doi.org/10.37349/etat.2021.00035

[73] Doherty C, Wilbanks B, Khatua S, Maher LJ. 73.Aptamers in neuro-oncology: An emerging therapeutic modality. Neuro Oncol 2024;26:38–54. https://doi.org/10.1093/neuonc/noad156

[74] Dymova MA, Kichkailo AS, Kuligina E V., Richter VA. 74.Aptamers Enhance Oncolytic Viruses' Antitumor Efficacy. Pharmaceutics 2022;15:151. https://doi.org/10.3390/pharmaceutics15010151

[75] Liu M, Wang L, Lo Y, Shiu SC-C, Kinghorn AB, Tanner JA. 75.Aptamer-Enabled Nanomaterials for Therapeutics, Drug Targeting and Imaging. Cells 2022;11:159. https://doi.org/10.3390/cells11010159

[76] Fan R, Tao X, Zhai X, Zhu Y, Li Y, Chen Y, et al. 76.Application of aptamer-drug delivery system in the therapy of breast cancer. Biomedicine & Pharmacotherapy 2023;161:114444. https://doi.org/10.1016/j.biopha.2023.114444

[77] Jiang F, Liu B, Lu J, Li F, Li D, Liang C, et al. 77.Progress and Challenges in Developing Aptamer-Functionalized Targeted Drug Delivery Systems. Int J Mol Sci 2015;16:23784–822. https://doi.org/10.3390/ijms161023784

[78] Dosio F, Brusa P, Cattel L. 78.Immunotoxins and Anticancer Drug Conjugate Assemblies: The Role of the Linkage between Components. Toxins (Basel) 2011;3:848–83. https://doi.org/10.3390/toxins3070848

[79] Kohlberger M, Gadermaier G. 79.SELEX: Critical factors and optimization strategies for successful aptamer selection. Biotechnol Appl Biochem 2022;69:1771–92. https://doi.org/10.1002/bab.2244

[80] Cai R, Chen X, Zhang Y, Wang X, Zhou N. 80.Systematic bio-fabrication of aptamers and their applications in engineering biology. Systems Microbiology and Biomanufacturing 2023;3:223–45. https://doi.org/10.1007/s43393-022-00140-5

[81] Didarian R, Ozbek HK, Ozalp VC, Erel O, Yildirim-Tirgil N. 81.Enhanced SELEX Platforms for Aptamer Selection with Improved Characteristics: A Review. Mol Biotechnol 2024. https://doi.org/10.1007/s12033-024-01256-w

[82] Yang LF, Ling M, Kacherovsky N, Pun SH. 82.Aptamers 101: aptamer discovery and in vitro applications in biosensors and separations. Chem Sci 2023;14:4961–78. https://doi.org/10.1039/D3SC00439B

[83] Nerantzaki M, Loth C, Lutz J-F. 83.Chemical conjugation of nucleic acid aptamers and synthetic polymers. Polym Chem 2021;12:3498–509. https://doi.org/10.1039/D1PY00516B

[84] Park D, Lee SJ, Park J-W. 84.Aptamer-Based Smart Targeting and Spatial Trigger–Response Drug-Delivery Systems for Anticancer Therapy. Biomedicines 2024;12:187. https://doi.org/10.3390/biomedicines12010187

[85] Lai W-Y, Huang B-T, Wang J-W, Lin P-Y, Yang P-C. 85.A Novel PD-L1-targeting Antagonistic DNA Aptamer With Antitumor Effects. Mol Ther Nucleic Acids 2016;5:e397. https://doi.org/10.1038/mtna.2016.102

[86] Soldevilla MM, Villanueva H, Pastor F. 86.Aptamers: A Feasible Technology in Cancer Immunotherapy. J Immunol Res 2016;2016:1–12. https://doi.org/10.1155/2016/1083738

[87] Yin S, Chen Z, Chen D, Yan D. 87.Strategies targeting PD-L1 expression and associated opportunities for cancer combination therapy. Theranostics 2023;13:1520–44. https://doi.org/10.7150/thno.80091

[88] Odeh F, Nsairat H, Alshaer W, Ismail MA, Esawi E, Qaqish B, et al. 88.Aptamers Chemistry: Chemical Modifications and Conjugation Strategies. Molecules 2019;25:3. https://doi.org/10.3390/molecules25010003

[89] Zhu S, Gao H, Li W, He X, Jiang P, Xu F, et al. 89.Stimuli-Responsive Aptamer-Drug Conjugates for Targeted Drug Delivery and Controlled Drug Release. Adv Healthc Mater 2024. https://doi.org/10.1002/adhm.202401020

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