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Review

The application and frontier progress of aptamers from targeted technology to clinical diagnosis and treatment

Jie Wen[1], Tonggong Liu[3], Jie Zhao[4], Shengjie Wu[1] and Dayong Gu*[,2]

[1] Department of Guangxi University of Chinese Medicine, Nanning 530200, China
2 Department of Shenzhen Second People's Hospital, Shenzhen 518035, China
3 Northeastern University, Shenyang 110819, Liaoning Province, China
4 Fujian Medical University, Fuzhou 350122, Fujian Province, China

* **Correspondence:** Email: wanhood@163.com.

Abstract: Aptamers, including nucleic acid and peptide aptamers, are small biological molecules whose development has consistently represented the forefront of science and technology. With advances in synthetic biology, bioinformatics, and cell biology, alongside the integration of multidisciplinary approaches, researchers have been able to construct aptamers of diverse structures and functions based on peptide self-assembly, thereby continuously driving innovation in this field. The maturation of various synthesis techniques has further facilitated the gradual translation of aptamers into the market. Supported by the establishment of aptamer information libraries, as well as their inherent excellent affinity and specificity, aptamers can now be synthesized, chemically modified, and applied across a broad spectrum of biomedical scenarios. They function not only as therapeutic agents and diagnostic probes, but also as biosensing tools and delivery vehicles for other drugs. These characteristics underscore the significance of aptamer development within the field of molecular recognition. In this paper, we conduct a comprehensive review of various research directions centered on their targeting properties, including their use as therapeutic and diagnostic agents, biosensors, platforms for new drug development, and drug delivery vehicles.

Keywords: biotechnology; nucleic acid aptamers; peptide aptamers; therapeutic and diagnostic agents; new drug development; drug delivery vehicles

1. Therapeutic and diagnostic tools

Aptamers are small molecules that are relatively easy to generate and can exert biological functions in vivo—numerous studies have explored their applications in clinical therapy [1]. In addition, engineered peptide molecules have been designed to target and detect a variety of clinical biomarkers and viruses. Moreover, aptamers can be employed to identify rare populations of unstable cells exfoliated from primary neoplasms that circulate in the bloodstream and give rise to metastatic lesions known as circulating tumor cells (CTCs) [2]. By specifically binding to molecular markers that are either uniquely expressed or highly overexpressed on CTCs, aptamers can be utilized for the sensitive detection and detailed characterization of these cells. This has significant implications for patient stratification, monitoring therapeutic responses, and evaluating prognosis [3].

One of the defining features of aptamer-based drugs is the enhancement of the tumor-targeting ability of chemotherapeutics. For example, in the treatment of hematologic tumors, because healthy T cells and malignant T cells are of a similar origin, traditional oncology drugs can mistakenly kill healthy T cells. Ian I. Cardle et al. discovered a DNA aptamer called HR7A1 that exhibits high affinity in the low nanomolar range for integrin α4β1 (VLA-4), which is associated with chemotherapy resistance and recurrence in hematologic malignancy patients. This discovery led to the establishment of targeted therapeutics that can be effective in treating T-cell leukemias and lymphomas [4]. After truncating HR7A1 to a minimal binding sequence, it was found that the aptamer had a significantly higher binding capacity to T-cell lineage cancer cells than to healthy immunocompetent cells. Cryo-electron microscopy and competition experiments demonstrated that HR7A1 overlaps with the binding sites of fibronectin and VCAM-1 on α4β1, which is crucial for the normal survival of immune cells during chemotherapy and for alleviating the side effects of chemotherapeutic drugs in patients. Additionally, the researchers investigated in vivo translational barriers to aptamer drugs, including serum stability, thermally sensitive ligand-receptor interactions, and a short circulating half-life. To address these issues, they synthesized an aptamer–polymer conjugate, thus providing a new therapeutic tool for the targeted treatment of hematopoietic malignancies [5].

In the research conducted by Cardle et al., a copolymer composed of N-(2-hydroxypropyl) methacrylamide (HPMA) and 11-azido-3,6,9-trioxaundecan-1-methacrylamide (AzP3MA) was synthesized through the reversible addition–fragmentation chain transfer (RAFT) polymerization technique. The resulting polymer was functionalized with biotin-PEG4-CCP as a chain-transfer agent and incorporated multiple azide groups, thus enabling conjugation through strain-promoted azide–alkyne cycloaddition (SPAAC) [6].

The polymer enhances serum stability through several mechanisms: steric hindrance—the hydrophilic HPMA-based polymer forms a protective shell around the conjugated aptamer, thus physically blocking nucleases from accessing and degrading the DNA backbone [7]; the shielding effect—the bulky polymer structure reduces aptamer exposure to degrading enzymes, thus slowing enzymatic cleavage; improved structural stability—conjugation to the polymer helps maintain the aptamer's folded conformation under physiological conditions (e.g., 37 °C), thereby minimizing thermal denaturation and preserving binding functionality; and reduced renal clearance—although modest in this study, the increased molecular weight and size of the conjugate delay renal filtration, thus contributing to a longer circulation half-life [8]. In summary, this strategy highlights a biomaterials-based approach to enhance the in vivo performance of nucleic acid aptamers [9].

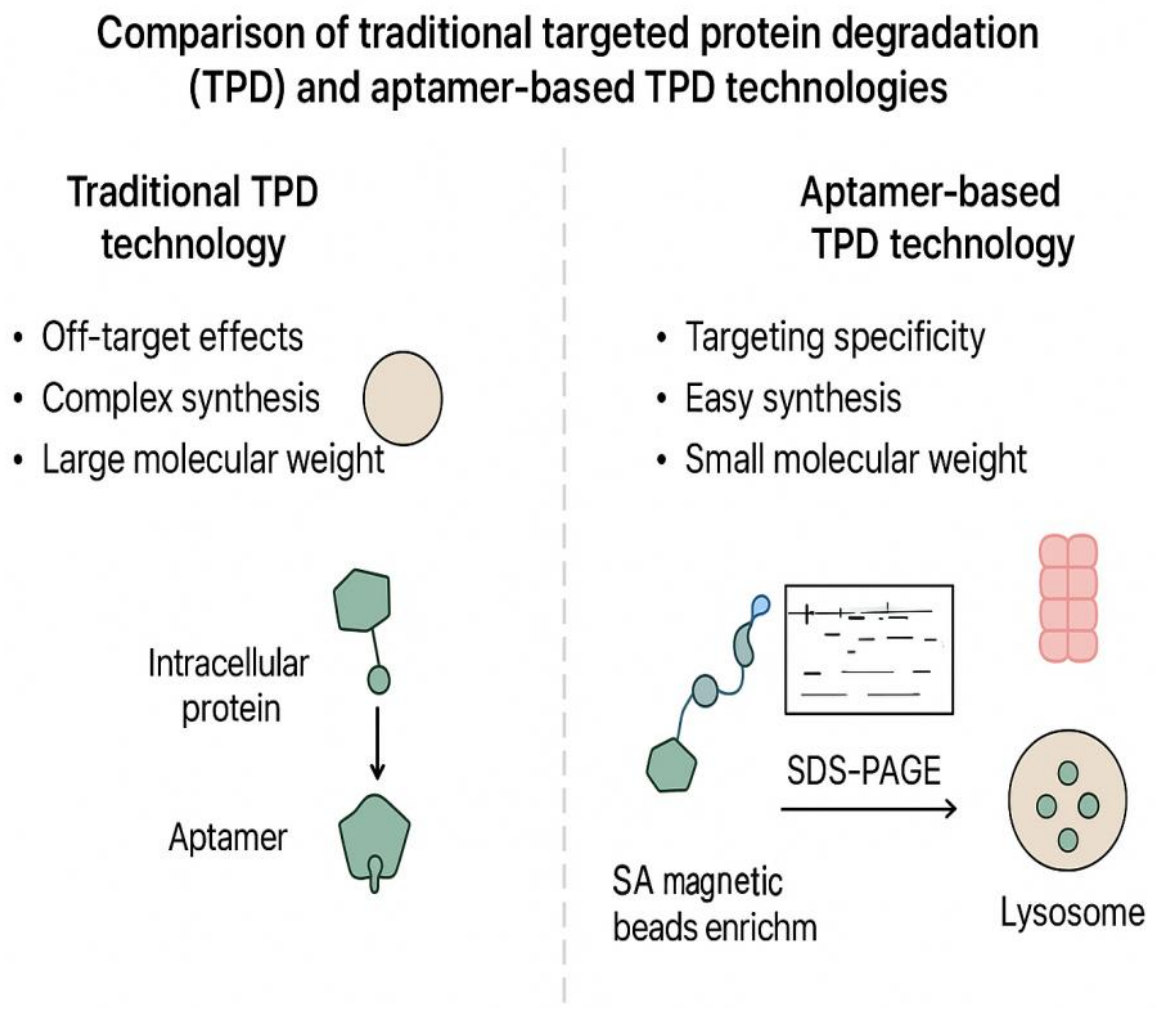

Figure 1. Comparison of traditional targeted protein degradation (TPD) and aptamer-based TPD technologies.

Aptamers are also widely used in anti-tumor research, in which one fundamental strategy is to screen for aptamers that specifically target transcription factors or their structural domains. Abnormally activated transcription factors such as STAT3 and STAT5 are well-established anti-tumor targets [10]. Peptide aptamer therapy against STAT3 has demonstrated that small aptamers can reduce its phosphorylation levels and accelerate its degradation [11]. Similarly, peptide aptamers that target aberrant STAT5 in tumor cells, which were identified through yeast two-hybrid screening, have been shown to markedly decrease the DNA-binding capacity of STAT5 and promote its intracellular degradation following transfection and expression [12].

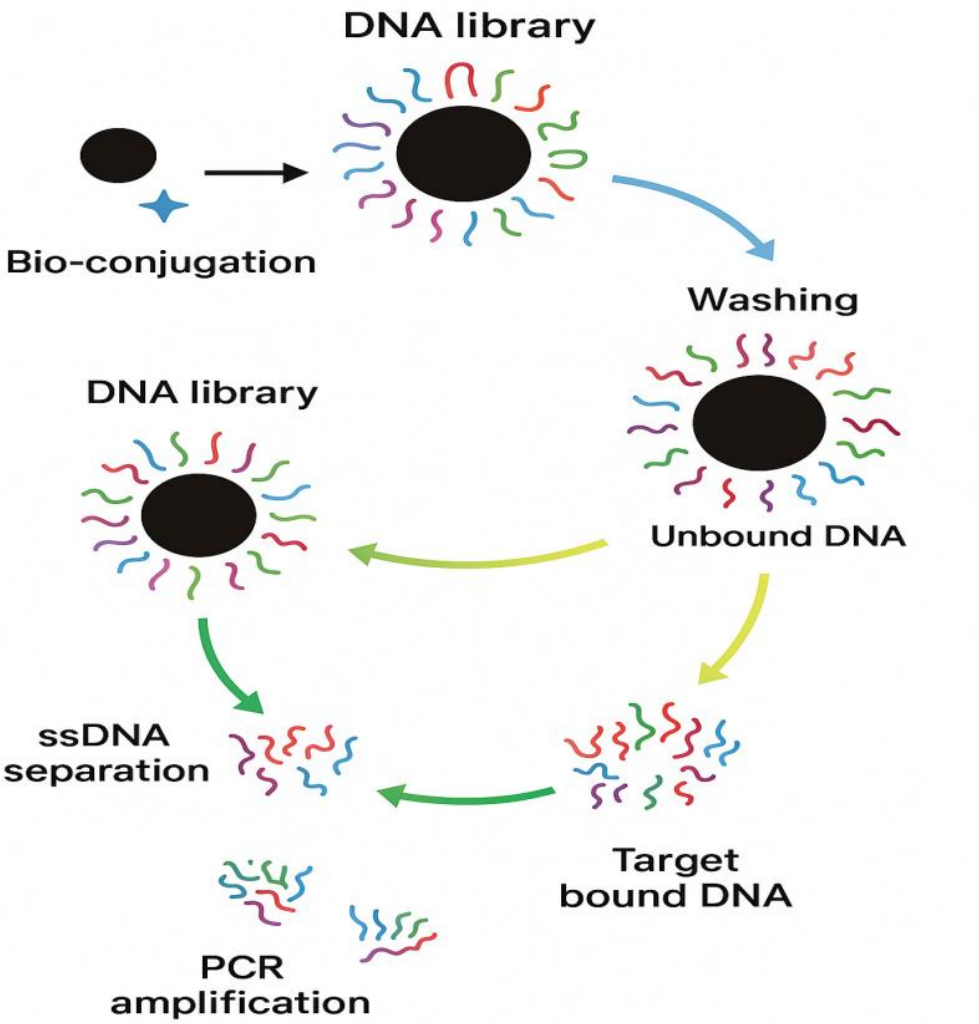

Figure 2. Working principle of aptamer selection by SELEX procedure.

Different tumors may share common oncogenic targets, including gene loci such as NTRK, ALK, ROS1, and BRAF. For example, inhibitors of differentiation or DNA-binding proteins (IDs) are aberrantly expressed in ovarian and breast cancers [13]. In breast, ovarian, prostate, and other reproductive system cancers, an abnormal expression of IDs is frequently observed [14]. Such dysregulation is not only associated with malignant biological behaviors of cancer cells, including proliferation and invasion, but may also influence the patient's treatment responses and prognoses. Therefore, ID genes have emerged as important targets in the study of these cancers, and the efficiency of anticancer drug development can be greatly improved if aptamers were screened against this target [15]. Likewise, in non-small cell lung cancer (NSCLC), aptamers have been designed to target the epidermal growth factor receptor (EGFR), such as the anti-EGFR aptamer MinE07 [16].

Aptamers and aptamer–drug conjugates (ApDCs) have shown considerable promise as precision oncology interventions in oncological therapeutics; however, their stability in complex biological environments and their ability to evade lysosomal degradation remain major challenges. To address these constraints, Fangfang Xia et al. devised a one-step self-assembly methodology that

augments the structural stability of aptamers and aptamer-drug conjugates (ApDCs), while simultaneously enhancing their cellular delivery efficiency and therapeutic potency via lysosome-independent endocytic pathways [17]. In this approach, stable nanoparticles (Sgc8 NPs and Gem–Sgc8 NPs) are formed through the covalent conjugation of gemcitabine to the Sgc8 aptamer and exhibit an enhanced binding capacity compared to free Sgc8 aptamers or Gem–Sgc8 alone. In the study by Xia et al., regarding the lysosome-independent uptake mechanism of self-assembled Gem–Sgc8 NPs, the authors proposed a mechanism centered on thiol-mediated endocytic uptake, rather than direct membrane fusion or caveolae-mediated endocytosis. This mechanism was validated by an intervention with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB), a modest antagonist of thiol-dependent endocytic pathways. DTNB significantly inhibited NP uptake, thus indicating that thiol groups play a crucial role in this process. Furthermore, glutathione (GSH) triggered NP depolymerization and drug release, further supporting this mechanism [18].

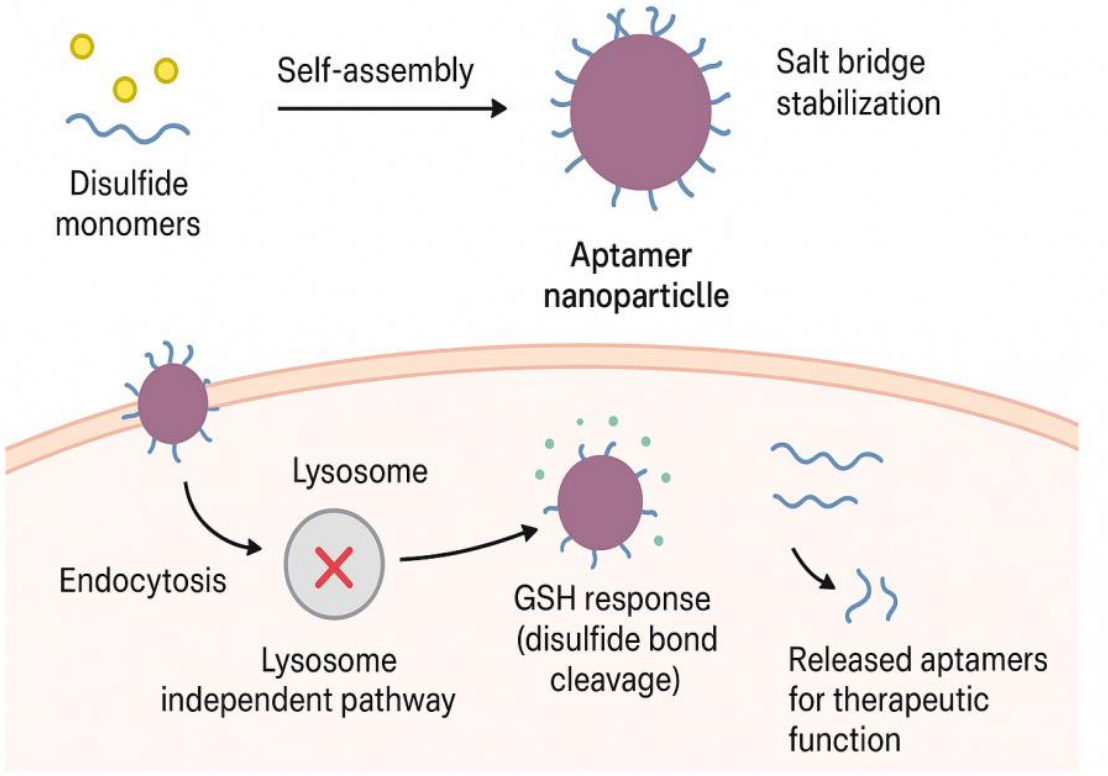

Figure 3. Cartoon illustration of Sgc8 NPs preparation and uptake.

Significantly, the lysosome-independent endocytic pathway was markedly enhanced, which resulted in a 2.5-fold augmentation of the antitumor activity of Gem–Sgc8 nanoparticles compared to Gem–Sgc8 alone. Experimental data corroborated that these nanocarriers effectively suppressed tumor proliferation. This self-assembly approach effectively mitigates issues related to nanoparticle instability and lysosomal degradation, while also exhibiting versatile applicability across various aptamer targets, including MJ5C and c-MET. These findings underscore its potential as a robust platform for the development of targeted oncological therapeutics [19].

While aptamer-based drugs have rapidly advanced, current research still faces significant limitations. First, the evidence for clinical translation remains weak, with most findings restricted to cellular and animal models [20]. Second, their applicability is limited; optimization strategies such as self-assembly and polymer conjugation are often tailored to specific aptamers and have not been broadly validated across diverse targets or tumor types [21]. Third, the exploration of combination therapies is inadequate. Most studies emphasized aptamer monotherapies or aptamer–drug conjugates, without integrating them with mainstream treatments such as immunotherapies or radiotherapies, thereby missing opportunities to exploit the synergistic potential of targeted delivery [22]. Finally, mechanistic insights remain superficial; for example, the detailed interactions between thiol groups and cell surface receptors in thiol-mediated uptake, as well as the molecular regulatory networks underlying GSH-triggered drug release, require deeper investigations [23]. Moving forward, research should prioritize clinically oriented studies, promote early-stage clinical trials, and focus on bridging the gap between basic research and practical applications [24].

2. Biosensing probes

Peptides have been explored as sensor elements across diverse research fields, including medicine, agronomy, and chemistry [25]. As early as 2017, Yang Yu et al. investigated various peptide-based detection components to assess the feasibility of biomedical testing [26]. Leveraging the principle of sense–antisense peptide interactions, they designed and synthesized small linear peptides, homopeptide dimers, and heterologous targeting peptides using the highly expressed tetraspanin protein CD81 in exosomes—and its extracellular small loop—as the recognition target [27]. Among these, heterologous divalent peptides, which were modeled on the structural features of natural antibodies and designed to bind different receptors, exhibited the strongest binding performance in the experimental validation [28]. These peptides were subsequently immobilized on an Solid-Phase Reversible Immobilization (SPRi) chip, and their applicability in biosensing was further confirmed through integration with nanomaterials, sensing technologies, and functional agents [29].

The key recognition components of biosensors predominantly encompass six classifications: enzymatic sensors, nucleic acid sensors, immunosensors, tissue-based sensors, microbial sensors, and cellular sensors. Notably, aptamer-based biosensors employ aptamers as biorecognition elements, thereby capitalizing on their exceptional specificity and binding affinity to facilitate precise target analyte detection. In this approach, a suitable small-molecule sequence is designed for the target, and a quantitative relationship between the electrochemical signal and the analyte is established based on its properties, thus enabling qualitative or quantitative detection [30].

Current electrochemical detection methods mainly include amperometry, potentiometry, and impedance spectroscopy [31]. The immobilization of aptamers on the electrode surface is a critical step in constructing electrochemical biosensors, which is primarily achieved through electrostatic interactions or covalent bonding. Typically, charged aptamers are immobilized on electrode surfaces modified with specific materials via electrostatic interactions. Furthermore, various covalent immobilization methodologies have been engineered to improve the stability and functional efficacy of aptamer-based biosensors [32].

Common strategies for peptide aptamer immobilization include the following: (1) Au–S self-assembly, where cysteine residues at the peptide terminus form Au–S bonds with gold electrodes

or gold nanoparticle-modified surfaces; (2) covalent coupling, which is achieved by linking terminal amino or carboxyl groups to functionalized electrodes using coupling agents such as glutaraldehyde; (3) phage display-based immobilization, which utilizes phage-displayed peptides for surface attachment; and (4) biotin–avidin interaction, where biotinylated peptides bind to streptavidin-modified substrates or magnetic beads.

Standard immobilization methods for nucleic acid aptamers can be classified according to their mechanism of action. Covalent coupling is the most common and stable strategy, in which functional groups on the aptamer are covalently linked to active groups on the carrier surface via chemical reactions. This approach provides a strong attachment and high stability, thus making it suitable for most detection scenarios. Typical examples include amino–carboxyl/aldehyde coupling and thiol–gold/maleimide coupling, where terminal amino (–NH_2) or thiol (–SH) groups react with carrier surface groups to form amide or imine bonds. Biotin–streptavidin/avidin coupling offers a rapid and highly specific strategy (Kd ≈ 10^{-15} M), where biotinylated aptamers bind to streptavidin- or avidin-modified carriers such as microplates, magnetic beads, or quantum dots. However, it is an indirect form of covalent immobilization, as streptavidin/avidin must first be covalently attached to the carrier. Other covalent strategies include silanization, where glass or silica surfaces are treated with silane reagents (e.g., APTES) to introduce amino groups, which subsequently couple with carboxyl or aldehyde groups on the aptamer. Non-covalent immobilization is a simple and rapid approach that relies on interactions such as electrostatic attraction, hydrophobic forces, and hydrogen bonding. Although less stable, it minimally affects the aptamer activity and is suitable for temporary or low-stability applications, such as electrostatic adsorption or complementary base pairing [33].

On this basis, in recent years, researchers have increasingly applied electrochemical impedance spectroscopy (EIS) to aptamer studies. EIS investigates interactions at the electrode/solution interface and offers distinct advantages in molecular recognition; subsequently, it is becoming a popular technique for acquiring analytical signals in aptamer-based biosensors. Neuropeptide Y (NPY), the predominant neuropeptide in human physiology, is critically involved in stress modulation and various biological functions, thus necessitating precise quantification. Although EIS that utilizes NPY-specific aptamer-functionalized electrodes presents a promising biosensing modality, the mechanistic relationship between the impedance signals and the adsorption kinetics at the electrode interface remains inadequately characterized. To elucidate this correlation, Luis López et al. investigated the binding interactions between aptamer-functionalized planar electrodes and their target analyte, NPY [34]. They used ω*Zimag as an analytical signal and employed a Langmuir isotherm equation to analyze the adsorption process. Their aim was to directly and sensitively measure the interfacial capacitance changes induced by the binding of the NPY protein to the aptamer. If Rct is derived from Nyquist plots, then it becomes susceptible to interference from non-specific adsorption. Proteins, such as HSA, that absorb onto the electrode surface directly impede the charge transfer of the redox probe, which leads to an elevated Rct. Such non-specific changes may mask the weak signal generated by NPY binding, thus reducing the detection specificity. This method differs from implantable microelectrodes in that it utilizes Friedrich adsorption isotherms. The assay obviates the need for redox mediators, thus enabling the quantification of NPY at concentrations as low as 20 pg/mL. Moreover, this method exhibits an excellent specificity, with a signal-to-interference ratio exceeding 20 : 1.

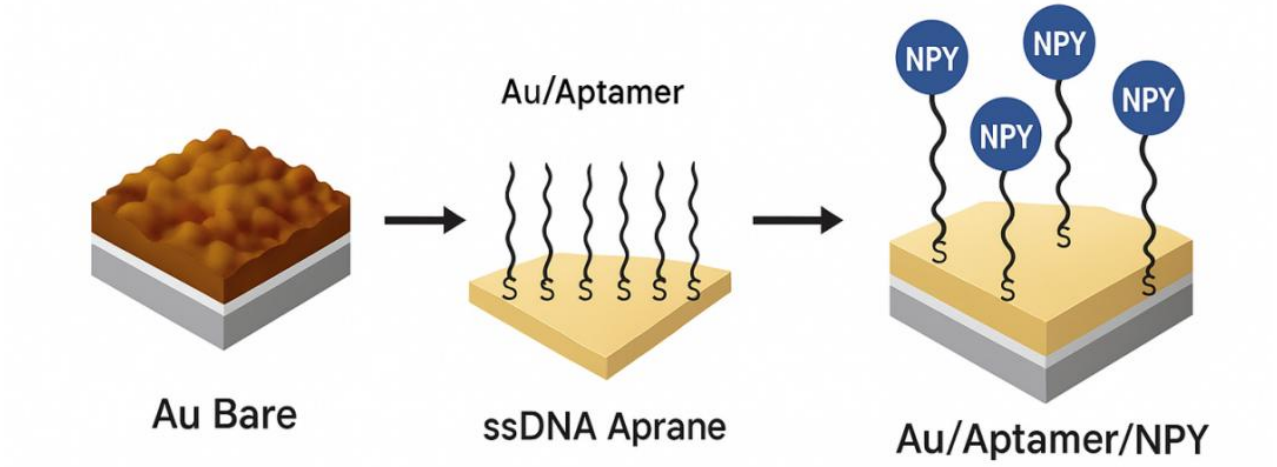

Figure 4. Schematic for modification of the Au surface of the working electrode with ssDNA-aptamer specific for NPY.

Simultaneously, Beijia Ji et al. utilized a surface-enhanced Raman scattering (SERS)-based biosensing platform to identify aptamers, thereby facilitating the rapid quantification of alpha-fetoprotein (AFP) as a biomarker for hepatocellular carcinoma and cardiac troponin I (cTnI) as an indicator of acute myocardial infarction in clinical serum specimens within a three-minute timeframe. This method is not only more streamlined but also provides direct experimental data to understand the adsorption behavior of molecules on electrode surfaces (as demonstrated by Langmuir isotherm fitting), thereby offering a valuable methodological reference for the development of next-generation biosensors [35].

Xiaoyu Zhou et al. integrated a DNA cell classifier (DCC) with a self-powered electrical signal amplifier (SSA) to engineer a dual-aptamer DNA logic-gated tandem luminescent probe (DApt-SLP), thus enabling the rapid and highly sensitive detection of CTCs in blood specimens [36]. The precise detection of malignant cells within intricate biological milieus is essential for non-invasive diagnostic procedures and the advancement of tailored therapeutic strategies. The DCC employs a two-receptor co-recognition strategy, thus enabling aptamer–receptor matching at the cell membrane twice. This design allows for the precise localization of specific, narrow cell subpopulations within larger populations of similar cells, thereby improving the specificity and enabling an accurate discrimination of target cells. With its integrated architectural framework, the DApt-SLP system exhibits exceptional sensitivity and precision, thus underscoring its potential as a viable instrument in personalized therapeutics and biomedical engineering applications.

Junbo Li et al. engineered an EGFR aptamer (Apt 1) and a human epidermal growth factor receptor 2 (HER2) aptamer (Apt 2) conjugated with gold nanoparticles (AuNPs) to develop probe I (Apt 1–AuNPs) and probe II (Apt 2–AuNPs) [37]. Utilizing Eca109, KYSE510, and KYSE150 cell lines as biological models, a sandwich scattering assay system (comprising probe I–cell–probe II) was developed based on aptamer-functionalized probes for tumor biomarker detection, and the resonance Rayleigh scattering (RRS) spectra were subsequently characterized. The results showed

that the system enabled the quantitative detection of Eca109 cells within the range of 5.0×10^1–5.0×10^5 cells/mL, with a detection limit of 15 cells/mL. Similarly, KYSE510 cells were detected over the same linear range with a detection limit of 18 cells/mL, while KYSE150 cells were detected over the range of 3.0×10^1–5.0×10^5 cells/mL with a detection limit of 12 cells/mL. To evaluate potential applications in real sample analysis, cells were spiked into blank serum at concentrations of 1.0×10^2–1.0×10^5 cells/mL. The assay recovery efficiencies varied from 97.0% to 102.3%, with relative standard deviations (RSDs) spanning 1.1% to 4.9%, thereby validating the applicability of the proposed RRS protocol for the detection of esophageal squamous cell carcinoma (ESCC) CTCs.

Multiple seminal investigations have elucidated the capacity of aptamers to enhance the analytical sensitivity and diagnostic specificity of viral detection assays [38]. For example, Muslihati reviewed the recent progress in the detection methods of flaviviruses, where the use of peptide aptamers as novel sensor elements proved to be simple and efficient [39]. Similarly, Kim D.T.H. et al. utilized three immunoinformatics platforms from an epitope database analysis to identify novel antigenic determinants within the Zika virus (ZIKV) envelope glycoprotein, which were subsequently optimized through peptide modification. This high-throughput diagnostic assay effectively differentiated ZIKV infection from other flavivirus infections, including yellow fever virus [40]. Consequently, their research demonstrated that this detection method can effectively overcome the high cross-reactivity of existing biosensors with other flaviviruses. In a separate investigation, Yang Li and colleagues created an optical-fiber probe that quantitatively detected SARS-CoV-2 by exploiting the specific interaction between the viral spike (S) protein and an aptamer; the probe remained functional for up to 19 reuse cycles [41]. Moreover, Yumna M. Aloraij et al. constructed an aptamer-based colorimetric sensor platform using cotton swabs to integrate sample collection, preconcentration, and detection. In this approach, activated and functionalized cotton swabs, coupled with colored nanosphere-linked specific aptamers, formed a sandwich structure with the antigen, thus enabling the rapid and convenient detection of SARS-CoV-2 within 4 minutes [42].

Furthermore, for malaria, one of the most lethal infectious diseases, Qiuyue Yang et al. investigated an electrochemical aptamer-based (EAB) sensor for the quantitative detection of the malaria biomarker Plasmodium falciparum lactate dehydrogenase (PfLDH) [43]. The researchers re-engineered the aptamer sequence to enhance the conformational shift triggered by target binding, which is a modification verified through comprehensive optical and electrochemical analyses. Subsequent experiments showed that the refined biosensor could rapidly (within minutes) quantify clinically relevant levels of PfLDH in the blood with a single-step assay. In a separate investigation, Jian Tang and colleagues created a dual-mode aptamer sensor that merged colorimetric and electrochemical readouts to detect aflatoxin A (OTA), which is a toxin that harms both proteins and DNA. They attained highly sensitive OTA detection by coupling the aptamers with cerium-FMA (Ce-FMA), a material which possesses phosphatase-mimicking activity [44].

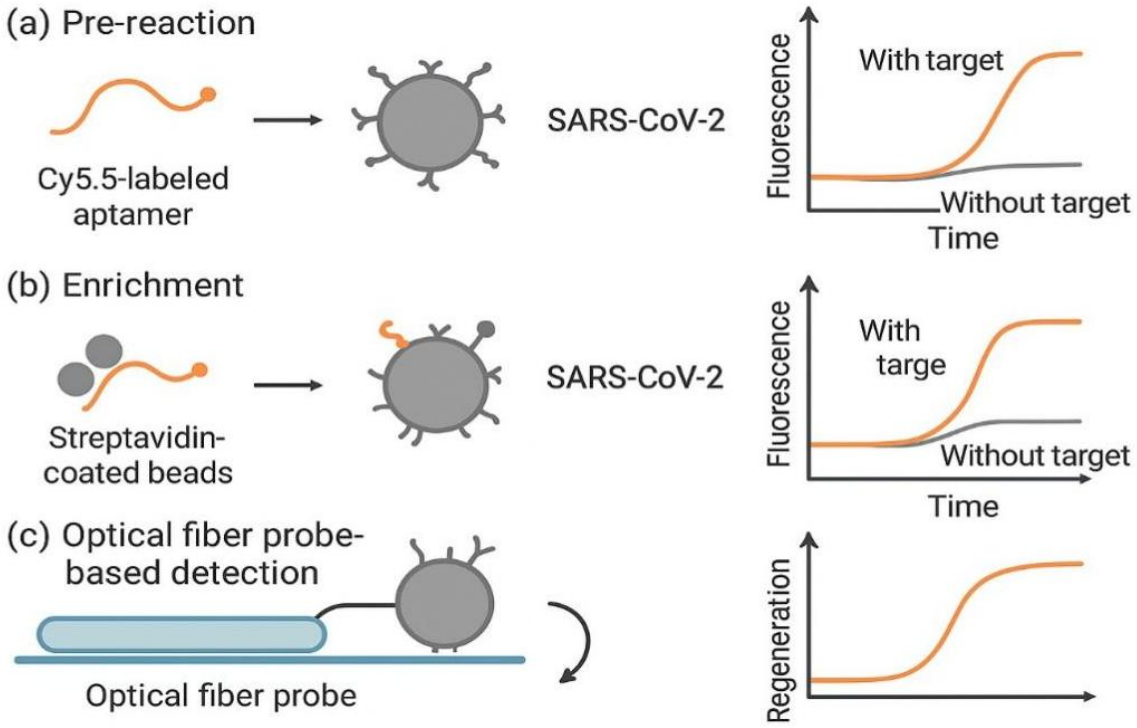

Figure 5. Principle and steps of aptamer-based S protein detection.

Notably, Lianju Chen and colleagues developed a straightforward and quick aptamer-based sensor system, which enables the sensitive and selective identification of human non-small cell lung cancer (NSCLC) cells [45]. Under standard conditions, gold nanoparticles (AuNPs) are stable and display a distinct absorption peak at 520 nm. However, the introduction of sodium chloride neutralizes their surface charge, leading to aggregation. This salt-induced aggregation can be effectively prevented when the AS1411 aptamer adsorbs onto the AuNP surface, thus forming a protective layer. The adsorption is primarily mediated by electrostatic interactions, van der Waals forces, hydrophobic interactions, and weak coordinate bonds between the nitrogen/oxygen atoms of DNA bases and gold atoms. This adsorption is non-covalent, relatively weak, and non-specific. Consequently, aptamer molecules lie flat on the AuNP surface, where their three-dimensional structures not fully stabilized, thus enabling dynamic adsorption and desorption [46].

The A549 cell line, a commonly used human NSCLC model, overexpresses the nucleolin protein on its cell membrane, which serves as the binding target of the AS1411 aptamer. Upon interacting with nucleolin, the aptamer experiences a conformational transition that results in the formation of a stable G-quadruplex. With a high affinity and specificity, this G-quadruplex binds to nucleolin, which is analogous to the traditional "lock-and-key" binding mode. Through competitive binding, the strong aptamer–nucleolin interaction replaces the weaker aptamer–AuNP interaction. The aptamer bases disengage from the gold surface and rearrange to form the G-quadruplex, thus embracing the target protein. Because the aptamer's affinity for nucleolin far exceeds its affinity for AuNPs, a stable, low-energy aptamer–nucleolin complex is formed. Once detached, the AuNPs lose their protective coating; thus, upon NaCl addition, the nanoparticles rapidly aggregate, and the solution color shifts from red to blue [47].

The experimental results demonstrated that in the presence of A549 cells, AS1411 was induced to form a stable G-quadruplex that specifically bound to the cells, thereby triggering AuNP aggregation in NaCl solution. This aptamer-based sensing platform exhibited a high specificity toward A549 cells and highlights its valuable potential for clinical applications, including evaluating the therapeutic efficacy. Moreover, it provides a novel and convenient approach for the early diagnosis of lung cancer, with lower instrumentation requirements and simplified operation.

In summary, a wide variety of biosensors can be constructed based on aptamer recognition. Within the binding system, aptamers undergo adaptive conformational changes according to the structure of their targets, thereby forming secondary structures such as hairpins, pseudoknots, bulges, or G-quadruplexes [48]. Then, stable complexes are formed with the targets through hydrogen bonding, van der Waals forces, base-stacking interactions, electrostatic forces, or hydrophobic interactions. In addition, various aptamer-based sensors that incorporated nanozymes have been reported [49]. By combining the unique catalytic properties of nanozymes with the specificity of aptamers, these sensors can be applied to the detection of diverse biomolecules [50]. Furthermore, the analysis and comparison of cross-linking agents for aptamer sensors conducted by Samuel De Penning et al. provided valuable insights that support the advancement of aptamer-based detection strategies [51].

It is worth mentioning that, due to the extremely low abundance, heterogeneity, and dynamic characteristics of CTCs, their broad-spectrum detection and long-term monitoring have remained major medical challenges. Huifei Zhong et al. developed a dual-affinity nanostructure platform capable of capturing different CTC subsets and monitoring them during treatment [52]. This biomimetic, stimuli-responsive, multivalently bound nanointerface was constructed through the stepwise assembly of fiber scaffolds, exchangeable ligand spacers, and peptides targeting lysosomal protein transmembrane 4β (LAPTM4B), thus enabling the direct capture of CTCs from whole blood with high yield, high purity, and high viability. The stable overexpression of the targeted LAPTM4B protein in CTCs, together with the enhanced peptide–protein binding, allowed the platform to efficiently capture rare CTCs at early stages, detect both epithelial-positive and non-epithelial CTCs, and track treatment responses. The consistency between the study and clinical diagnoses further supports the potential of this platform for early cancer diagnoses, metastasis predictions, and prognosis evaluations [53].

In summary, research on biosensing probes is shifting from “single-target detection” toward a “multi-dimensional intelligent analysis”. The integration of aptamers with nanomaterials and emerging detection technologies is expected to further expand their applications in precision medicine, infectious disease control, and public health, thus ultimately contributing to earlier diagnoses, more accurate detection, and improved disease management [54].

3. New drug development

Given the strong reliance of new drug research and the development on interdisciplinary collaboration, aptamers offer great potential by enabling the generation of functional molecules that target specific biological markers through the rational design and directed modification of amino acid or nucleic acid sequences [55]. Consequently, owing to their precise molecular design, aptamers demonstrate broad application prospects in innovative drug development [56]. In the context of extensive ongoing research on therapeutic genes, leveraging the specificity and versatility of

aptamers to target defined biomarkers represents an efficient strategy for developing novel therapeutics [57].

For example, the overexpression of the C-C motif chemokine receptor 2 (CCR2) negatively affects neuroinflammatory diseases such as traumatic brain injury (TBI), yet few drugs are currently available to address this problem. As of 2016, only two CCR2-specific drugs had reached the market; however, both yielded unsatisfactory outcomes, thus underscoring the urgent need for new therapeutic strategies. In response, Kilian R. Sachdev et al. employed novel pharmacological mechanisms and models to screen potential ligands for CCR2. Out of 871 candidates, two novel ligands—A102 and A435—were identified through multiple screening approaches, thus showing promise for the treatment of diseases driven by CCR2 overexpression [58].

There are many types of aptamers, some of which are single-stranded oligonucleotides with specific spatial structures that exhibit a high affinity and specificity toward diverse biological targets. For instance, AS1411 is a nucleic acid aptamer that targets nucleolin, which is overexpressed on the membrane of cancer cells and is considered one of the most promising and extensively studied aptamers. Shaowen Yang et al. used AS1411 as a model to investigate how albumin conjugation could improve the tumor-targeting ability of aptamers in vivo [59]. HSA–AS1411 was synthesized via a maleimide–sulfhydryl reaction, and both in vitro and in vivo experiments demonstrated that HSA–AS1411 possessed good serum stability and a strong targeting affinity [60].

Moreover, immunofluorescence staining of tumor tissues further confirmed that AS1411 accumulates more extensively within tumors due to its prolonged circulation time. According to the literature, albumin conjugation extends the circulation half-life of AS1411 from 0.92 hours to 14.28 hours, while increasing the area under the plasma concentration–time curve from 1.05 MBq/L·h to 101.49 MBq/L·h. The primary advantage of this modification is its ability to significantly prolong the drug's "effective exposure window" in the bloodstream, thus facilitating greater tumor accumulation. Unmodified AS1411 typically undergoes rapid renal clearance, which results in an extremely short blood residence time and minimal tumor delivery. In contrast, HSA–AS1411 leverages albumin's long-circulation profile to maintain elevated blood concentrations (still >10% ID/g at 12 hours and ~5% ID/g at 36 hours). This sustained presence continuously supplies the tumor with the drug, thus markedly increasing both the frequency and duration of drug–tumor vascular interactions. Therefore, the HSA conjugation strategy holds a broad clinical potential to enhance the tumor-targeting capability of aptamers [61].

Similarly, Yu Zhou et al. selected a specific aptamer for PD-L1 as an example and improved its stability using a real-sample-assisted capture-Systematic Evolution of Ligands by EXponential enrichment (SELEX) strategy [62]. Compared with the traditional capture-SELEX screening strategy, the aptamer Apt-S1 obtained through this method exhibited a higher binding affinity and specificity to PD-L1. In complex environments containing serum, nucleases preferentially degrade aptamer sequences with "loose conformations that expose phosphate backbones". During SELEX assisted by real samples, nucleases continuously "attack" the aptamer library, thus solely allowing sequences with compact conformations that protect the phosphate backbone to resist degradation and ultimately become enriched. Furthermore, sequences prone to binding non-target serum proteins (e.g., albumin, immunoglobulins) are "captured" or "masked" by serum components, which leads to their elimination during magnetic bead-based capture of the target (PD-L1). Thus, only sequences that specifically bind PD-L1 while resisting interference from other serum components are successfully enriched [63].

In addition, compared with traditional aptamers, Apt-S1 exhibited more pronounced conformational changes upon binding PD-L1, and its degradation rate in 10% diluted serum or pure human serum was lower than that of conventional aptamers under physiological temperature and pH conditions. Therefore, Apt-S1 demonstrates a higher stability and a greater suitability for use as a biorecognition element. Collectively, these findings highlight the strong clinical application potential of aptamers.

Muscle atrophy resulting from complications of type 2 diabetes mellitus severely reduces a patient's quality of life, yet effective treatment strategies remain lacking. To address this challenge, Jia Song et al. coupled skeletal muscle–specific aptamers with MSC-derived exosomes (MSC-EXOs) and administered them to diabetic db/db mice. The treatment improved their grip strength, muscle weight, and muscle fiber cross-sectional area to varying degrees, thus highlighting the therapeutic potential of muscle-targeting aptamers and MSC-EXOs to treat muscle atrophy [64].

Aptamer-based drugs have also been designed to regulate cellular signaling pathways. Since cellular communication heavily relies on the transmission of chemical signals, phosphorylation is one of the most common mechanisms that regulates cellular behavior. Receptor tyrosine kinases (RTKs) act as key mediators of cascade reactions and signal amplification, thereby becoming activated through autophosphorylation upon ligand binding. Currently, monoclonal antibodies (mAbs) and small-molecule tyrosine kinase inhibitors (TKIs) are the primary drug classes used to interfere with RTK function, thereby targeting the extracellular domain (ECD) and the cytoplasmic tyrosine kinase domain, respectively. Although these agents provide clinical benefit for many cancer patients, adaptive and acquired resistance often limits their long-term efficacy. Therefore, developing effective combination therapies that simultaneously inhibit both the ECD and the intracellular kinase domain is of significant importance.

To address this, Wei Li et al. proposed a bispecific antibody–aptamer chimera (Ab–Ap) as an effective strategy to achieve the dual inhibition of RTK extracellular and intracellular functions [65]. Their study demonstrated that the Ab–Ap chimera inhibited tumor cell longitudinal migration by 49%, lateral migration by 49%, and cell proliferation by 42%. By combining an antibody with an aptamer, this approach also mitigates inherent limitations of each component, such as the complexity of monoclonal antibody production and the susceptibility of aptamers to nuclease degradation. Given the widespread expression of CD148 and RTKs in various cell types, this strategy has the potential to be adapted for other RTK-associated tumors through the selection of appropriate aptamers, thus offering promising avenues for the development of kinase inhibitor–based cancer therapies.

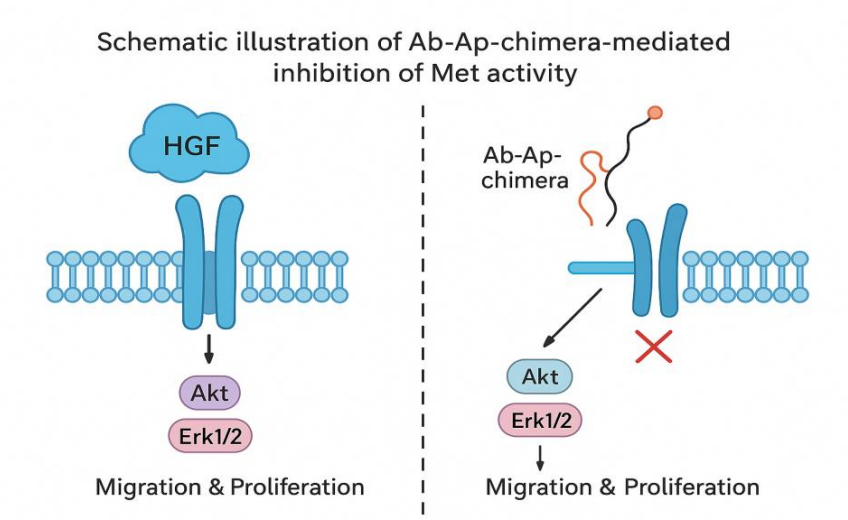

Figure 6. Schematic illustration of Ab-Ap-chimera-mediated inhibition of Met activity.

Currently, peptide drugs have emerged as a promising option for the treatment of human diseases and are continuously being optimized. Numerous studies have focused on the synthesis of increasingly complex peptide molecules [66]. In parallel, chemical modifications or the conjugation of therapeutic oligonucleotides have been explored to enhance their stability and specificity, improve binding affinity or inhibitory activity, and address delivery challenges [67]. For instance, a novel targeted therapy system employing aptamers was developed to facilitate the rapid intracellular accumulation of MCF-7 (a breast cancer–targeted drug) using the MUCI aptamer (Apt-M). Notably, the experimental results demonstrated that HCNs/DOX/PEG/Apt-M exhibited excellent combined therapeutic effects and significantly improved the active targeting efficiency of MCF-7 toward tumors. This work provides a new approach for the aptamer-based targeted therapy of breast tumors using advanced nanomaterials.

In another study, circular aptamers were assembled with gold nanoclusters to create a nucleic acid nanomedicine for psoriasis treatment. Following topical application, this nanomedicine, was able to penetrate the stratum corneum and reach deeper psoriatic tissues, thereby carrying vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α) aptamers, where it specifically inhibited VEGF-mediated keratinocyte proliferation and TNF-α–mediated inflammatory responses. Consequently, this study offers a potential general strategy for the targeted modulation of the complex pathological microenvironment of psoriasis [68].

Overall, aptamer drugs have been extensively studied, and owing to their small-molecule properties, they are particularly suitable for the development of novel therapeutics in cancer treatment [69]. Several studies have reported diverse applications of aptamers, including the regulation of the small-molecule inflammatory factor NLRP3 [70], the preparation of self-healing hydrogels using aptamer-based systems for antibacterial activity, wound healing, biological adhesion, and hemostasis [71], and the design of multivalent aptamer nanodrug conjugates with ribosome-like structures, such as CuPEs@PApt, which deliver copper ions to tumor cells, induce cytotoxicity, and exhibit an exceptionally low drug resistance [72]. Additionally, aptamers have been explored in the field of stomatology [73]. Furthermore, studies have revealed their immunomodulatory effects on immune and adaptive immune cells, and the interaction between aptamers and both the innate and

adaptive immune systems has been preliminarily investigated [74]. Collectively, these findings highlight the broad therapeutic potential of aptamer drugs across diverse disease contexts [75].

However, the mechanistic studies remain insufficiently explored. For example, the interactions between aptamers and adaptive immune cells have only been preliminarily investigated, and the specific regulatory pathways have yet to be clearly defined [76]. In addition, major challenges persist in the production and cost: the synthesis of bispecific Ab–Ap chimeras and multivalent aptamer nanodrugs (such as CuPEs@PApt) involves highly complex processes, which makes large-scale manufacturing both difficult and expensive. These limitations hinder clinical translation and underscore the need for further optimization.

4. Drug delivery system

At present, many drugs have demonstrated clear therapeutic effects in in vitro experiments; however, their in vivo application remains challenging due to the difficulty of accurately targeting the lesion site. This limitation not only reduces their therapeutic potential but also increases the risk of toxic side effects arising from non-specific distribution. Therefore, enhancing the targeted delivery of drugs and developing suitable carrier systems have become core topics and important directions in drug research and development. Targeted delivery enables drugs to directly reach the lesion, thus improving therapeutic efficacy while minimizing systemic toxicity caused by elevated blood drug concentrations. Over the past decade, precision medicine has made continuous progress in this regard, and ongoing research is actively exploring novel carriers capable of precise drug delivery [77].

Monoclonal antibody therapy and antibody–drug conjugates (ADCs) are well-established examples of targeted drug delivery. However, the construction of ADCs is often limited by the need for antibody humanization and the complexity of chemical modifications. In contrast, aptamers and aptamer–drug conjugates (APDCs) represent an emerging class of targeted delivery systems. APDCs are designed by covalently linking aptamers to therapeutic agents (e.g., cytotoxic drugs, small-molecule inhibitors, radionuclides) via chemical linkers. The core design principle is similar to that of ADCs but employs aptamers as targeting carriers instead of antibodies. Aptamers exhibit affinities comparable to antibodies, typically within the picomolar to nanomolar range, and are readily synthesized and chemically modified. Moreover, they possess a low pathogenicity and a low immunogenicity, which are critical for clinical translation. Therefore, utilizing aptamers for targeted drug delivery holds great promise to enhance the therapeutic efficacy [78].

In the field of targeted drug delivery, Peptide Transduction Domains (PTDs), also known as Cell-Penetrating Peptides (CPPs), are a class of short peptides typically comprised of 5–30 amino acids. Their core function is to serve as synergistic delivery components, thereby facilitating the efficient intracellular transport of therapeutic agents across biological barriers. By doing so, they address a key limitation of traditional targeted drugs, which can recognize specific targets but often struggle to penetrate cells and reach intracellular sites of action, thus improving the delivery efficiency.

The transmembrane mechanism of PTDs has not yet been fully elucidated, though several mainstream theories provide valuable insights. It is generally accepted that the process begins with the electrostatic interaction between positively charged arginine and lysine residues in the PTD sequence and negatively charged phospholipids or proteoglycans on the cell membrane surface. This initial binding facilitates the local accumulation of PTD molecules, which induces a temporary and

reversible perturbation of the membrane. Contrary to earlier assumptions of direct translocation through the phospholipid bilayer, current evidence indicates that PTDs primarily enter cells via endocytic pathways, particularly macropinocytosis. Once internalized, PTDs and their associated cargos are usually sequestered within endosomes, and their therapeutic efficacy largely depends on successful endosomal escape; a failure to do so results in subsequent lysosomal degradation. Importantly, the transmembrane efficiency of PTDs is closely associated with the number and spatial distribution of positive charges within the peptide, among which arginine residues play a pivotal role in mediating membrane interaction and cargo release.

Sonal Deshpande et al. reported a targeted drug delivery platform capable of delivering cell-inhibitory nucleobase analogues with high drug loading. In this study, 5-fluorodeoxyuridine monophosphate (5-FdUMP), which is the active metabolite of 5-fluorouracil (5-FU), was utilized as an antitumor agent. Terminal deoxynucleotidyl transferase (TdT) was employed to polymerize 5-fluorodeoxyuridine triphosphate (5-FdUTP) at the 3' end of a peptide aptamer. Remarkably, TdT enabled the spontaneous self-assembly of anti-nuclease micelles by incorporating hydrophobic non-natural nucleotides at the 3′ end of the 5-FdU polynucleotide. The aptamer component on the micelle corona specifically recognized homologous receptors on tumor cells, thus facilitating the targeted transport of 5-FU with enhanced cytotoxicity compared to the free drug. This platform adopts a modular design comprised of targeting moieties, polynucleotide drugs, and self-assembly domains; additionally, it can be adapted to a range of polymerizable therapeutic nucleotides and targeting units [79].

In most therapeutic drugs for skin diseases, even when the drug itself exhibits clear therapeutic activity, it often fails to effectively penetrate the skin barrier to reach the lesion site, thus limiting its therapeutic efficacy [80]. To address this challenge, certain aptamers with biofilm-penetrating properties, such as CPPs, have emerged as novel biological carriers for the transdermal delivery of macromolecules, thus offering new strategies to overcome skin barrier limitations and enhance the drug delivery efficiency. CPPs are effective biological tools for the non-invasive intracellular delivery of therapeutic molecules; however, the lack of specificity in most CPPs limits their application in targeted drug delivery.

To overcome this limitation, Zhao Xue-Li et al. utilized phage display technology to identify a CPP, named MT23, which is capable of specifically targeting melanoma cells [81]. MT23 selectively delivered Apoptin, a cancer apoptosis inducer, to melanoma B16 cells and successfully induced apoptosis. The study revealed that MT23, a 12-amino-acid peptide, exhibited significant targeted permeability: it selectively penetrated the melanoma cell line B16, thus specifically delivering Apoptin to induce apoptosis, while showing no permeability to other cell lines such as PC13, A549, HSC-T6, and L929 [82].

In addition, the low pathogenicity and immunogenicity of aptamers are of great significance for their practical clinical application. For instance, traditional paclitaxel therapy often causes significant side effects due to its lack of specific targeting toward cancer cells. To address this, an aptamer–paclitaxel conjugate was developed, in which paclitaxel was covalently linked to a universal polypeptide aptamer via a chemical linker, thus creating a therapeutic alternative with both an enhanced targeting capability and reduced side effects [83]. Increasing evidence indicates that such aptamer–drug conjugates can penetrate solid tumors more efficiently, further underscoring their potential in targeted cancer therapies [84].

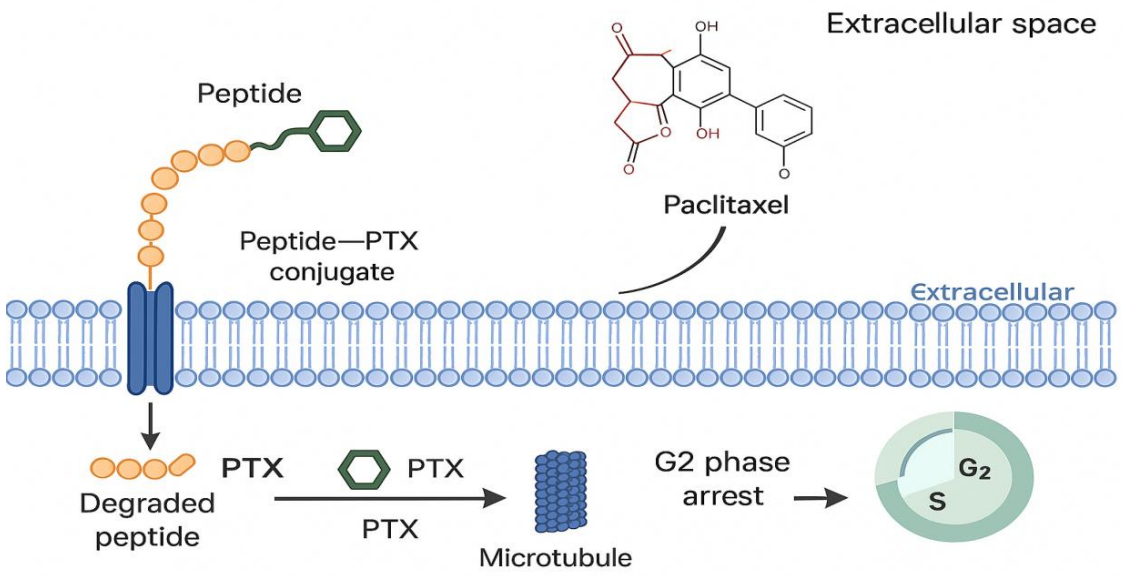

Figure 7. Schematic illustration depicting the mechanisms of PAPC in cancer cells. Created in BioRender.

Epithelial cell adhesion molecule (EpCAM) is a tumor-associated antigen that is abnormally overexpressed in many epithelial cancers, including cholangiocarcinoma (CCA). Therefore, developing EpCAM-targeted therapies for CCA is of a significant interest. Julia Driscoll et al. designed a short heptamer DNA aptamer with a three-dimensional structure that binds protein targets with a high affinity and specificity. Moreover, aptamers possess advantages such as good tissue penetration, low production costs, and efficient cellular internalization [85], which enable the direct delivery of therapeutic agents to target cells. Using a silicon-based screening method, they identified two DNA aptamers—PLD01 and PLD02—which bind to both EpCAM monomers and homodimers and were validated in vitro. Both aptamers exhibited strong affinities for EpCAM-positive CCA cells but showed minimal binding to EpCAM-negative leukemia cells. Furthermore, PLD01-functionalized nanovesicles successfully delivered therapeutic drugs to CCA cells via EpCAM targeting. In summary, these EpCAM-targeted aptamers represent a promising strategy to deliver therapeutic agents to EpCAM-expressing tumors.

In the field of aptamer-targeted drug delivery, Cathal Meehan et al. designed a Neomer library containing 16 random nucleotides flanked by fixed sequences. The inclusion of fixed sequences minimized the potential for undesired hybridization, thus ensuring that the secondary structure was primarily determined by the random nucleotide region [86]. Using 16 random nucleotides, the possible library size was reduced to 4.29×10^9 sequences, and this approach was employed to select aptamers with potential specific binding affinity for interleukin-6 (IL-6) [87].

In many studies, isolated aptamers have demonstrated strong targeted delivery capabilities. These aptamers can act as precise "navigation devices" by coupling with therapeutic agents such as drugs, nanocarriers, or nucleic acid molecules to accurately localize lesions within complex physiological environments in vivo [88]. For instance, in cancer therapies, aptamers which target specific receptors on the surface of cancer cells can guide chemotherapeutic drugs or gene therapy vectors to preferentially accumulate in tumor tissues, thus reducing the toxic side effects on healthy

cells. In antiviral research, aptamers that bind to viral surface proteins can mediate the targeted delivery of antiviral drugs to infected cells, thus enhancing the inhibition of viral replication. Similarly, in inflammatory diseases such as rheumatoid arthritis, aptamers which target highly expressed molecules at inflammatory sites can precisely deliver anti-inflammatory drugs to diseased joints, thus improving the localized therapeutic outcomes [89].

However, aptamers still have considerable room for improvement. For example, their ability to penetrate complex lesions remains insufficient. Although APDCs have been reported to penetrate solid tumors, they do not resolve the issue of "insufficient targeted accumulation" caused by dense tumor stroma and heterogeneous vascular permeability. In dermatological applications, the transdermal efficiency of CPP-conjugated aptamers has solely been validated in melanomas. Moreover, balancing carrier specificity and stability is challenging, as most CPPs still pose risks of non-specific penetration. Although aptamers are characterized by a low immunogenicity, they are easily degraded by nucleases in vivo. Current anti-degradation strategies, such as TdT-mediated micelle self-assembly, are limited to specific drugs (e.g., 5-FdUMP) and lack generalizability. Additionally, screening and optimization approaches have limitations. For instance, although the Neomer aptamer library reduces non-specific hybridization through fixed sequences, its sequence scale of 4.29×10^9 may still miss high-affinity candidates, and the relevance of silicon-based in vitro screening results to complex in vivo environments requires further validation. Therefore, future research should actively address these challenges and promote clinical translation.

5. Perspective and conclusion

Although aptamers have been widely applied across various fields, there remains considerable room for optimization and further development. Taking peptide aptamers as an example, one of the major challenges is how to accurately design aptamers that can bind to specific sites on the surface of a target protein when only limited structural information is available. Longxing Cao et al. proposed that the extensive conformational space of potential binding modes on the selected protein regions should first be broadly explored, followed by a more focused search around the most promising binding sites [90]. With the aid of big data, peptides can be specifically designed to target core sites on diverse proteins for both therapeutic and diagnostic applications [91,92]. Synthetic peptides capable of mimicking natural interactions to compete for binding represent attractive candidates to modulate protein–protein interactions within cells [93]. However, target–aptamer interactions are typically dynamic and weak, which presents a key challenge for the rational design of aptamers with an enhanced binding affinity and specificity toward their protein targets [94]. Cross J.A. et al. developed a fragment ligation strategy to enhance peptide function within cells [95]. Moreover, numerous strategies for peptide optimization have been proposed, thus offering valuable insights for the future advancement of peptide-based therapeutics [96].

As small, easily synthesized, and modifiable proteins, peptides hold great potential for functional enhancements and broader applications through multidisciplinary collaboration in the future. Recent advances—such as the optimization of quantum dot–conjugated aptamer detection [97], multivalent peptide–based signal amplification strategies [98], novel high-throughput aptamer screening techniques [99], the development of new multivalent aptamer constructs [100], the refinement of SELEX methodologies [101], and emerging selection approaches that enable free interaction between targets and potential aptamers in solution [102]—collectively provide strong

technical support for the future integration of aptamers into medical systems [103]. Advances in chemical technologies and the analysis of chemical bonds between amino acids have enabled artificially designed amino acid sequences to possess virtually limitless combination possibilities [104]. Furthermore, the ease of generation and modification of aptamers allows for their rapid application in antibody detection and the timely development of novel therapeutics for emerging or unexpected targets [105]. For example, Narlawar Sagar Shrikrishna et al. developed aptamers for the detection of SARS-CoV-2 [106], while Maik Pietzner et al. reported therapeutic drugs targeting SARS-CoV-2 [107].

Nucleic acid aptamers are short DNA or RNA sequences capable of folding into unique three-dimensional structures, which allows them to specifically bind to target molecules with a high affinity, comparable to that of antibodies. A notable characteristic of many aptamers is their ability to form G-quadruplex (G4) structures—four-stranded conformations composed of guanine-rich sequences. Long-term studies on the G4 folding behavior of specific aptamers have demonstrated that all sequences with G4 Hunter scores ≥ 1.31 exhibit a confirmed G4 formation [108]. Predicting the folding tendency of aptamer sequences can further facilitate the optimization of existing designs [109]. Moreover, recent advances in big data modeling have enriched and enhanced the reliability of aptamer library datasets [110], thereby supporting the continued development of aptamers identified through manual design approaches [111].

As a novel class of targeted molecules, aptamers offer significant advantages in biomedical applications due to their high specificity and strong affinity. They are capable of precisely distinguishing structurally similar homologous molecules (e.g., nucleic acid aptamers can differentiate between various EGFR subtypes, while peptide aptamers can distinguish HER2 from HER3), with a level of specificity comparable to that of antibodies. Moreover, aptamers can be selectively screened using SELEX technology, thus providing substantially greater operational convenience compared to the complex processes required for antibody preparation [112]. This technology eliminates the need for cell culture or animal immunization, thus enabling the rapid acquisition of target-specific aptamers [113] delivery.

Currently, research on aptamers has progressively transitioned from fundamental mechanistic studies to translational applications. In targeted drug delivery, aptamer–drug conjugates (APDCs) can accurately target tumor cells while minimizing the off-target toxicity. In biosensing, aptamer-modified electrodes enable the highly sensitive detection of tumor markers such as PD-L1 and EpCAM. Both approaches exhibit a substantial potential for clinical translation.

However, the development of aptamers still faces several critical challenges. From a stability perspective, nucleic acid aptamers are prone to degradation by nucleases, whereas peptide aptamers are susceptible to protease-mediated hydrolysis. For large-scale production, peptide aptamers often suffer from low synthesis yields for long chains and challenges in achieving consistent conformational folding. Although nucleic acid aptamers benefit from relatively mature synthesis protocols, maintaining batch-to-batch stability in clinical-grade modifications remains difficult. For clinical translation, peptide aptamers require a reduced immunogenicity due to exogenous sequences, whereas nucleic acid aptamers need strategies to mitigate non-specific protein interactions that arise from their negatively charged phosphate backbone. Addressing these challenges will be essential to fully realize the potential of aptamers in precision medicine and advanced bioassays.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Wen Jie, Tonggong Liu; Literature Review and Data Curation: Zhao Jie,Shengjie Wu; Writing – Original Draft Preparation: Wen Jie; Visualization and Figure: Wen Jie, Tonggong Liu; Supervision: Dayong Gu; All authors have read and agreed to the published version of the manuscript.

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