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REVIEW

Innovative Applications of Nucleic Acid Aptamers in Colorectal Cancer Diagnosis and Therapy: From Selection Optimization to Clinical Translation

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Abstract: Colorectal cancer (CRC), a gastrointestinal malignancy with persistently high global incidence and mortality rates, urgently demands more efficient early screening strategies and precision therapeutic approaches. Nucleic acid aptamers, recognized as "chemical antibodies", have emerged as a research hotspot in CRC diagnosis and treatment due to their high target specificity, flexible chemical modifiability, and cost-effective synthesis. In diagnostic applications, integrating aptamers with fluorescence, surface-enhanced Raman scattering (SERS), and electrochemical biosensors, along with functionalized nanomaterials such as quantum dots, gold nanoparticles, and graphene, has enabled ultrasensitive detection of biomarkers including carcinoembryonic antigen (CEA), miRNAs, exosomes, and circulating tumor cells (CTCs). In the therapeutic arena, we highlight aptamer-decorated lipidic, polymeric, and inorganic nanocarrier systems for targeted drug delivery featuring pH/glutathione (GSH)-responsive release mechanisms, and we review emerging immunotherapeutic regimens that employ PD-1/PD-L1 blocking aptamers alone or in combination with immunomodulatory agents or small activating RNAs. Finally, current challenges in aptamer applications—such as in vivo stability, targeted delivery efficiency, large-scale production, and clinical translation—are critically discussed. Future perspectives propose AI-assisted intelligent aptamer design, multi-omics-integrated diagnostic and therapeutic platforms, and standardized clinical trials to advance the implementation of nucleic acid aptamers in CRC precision medicine.

Keywords: nucleic acid aptamers, colorectal cancer, molecular diagnosis, targeted drug delivery, biosensor, clinical translation

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide and ranks among the leading causes of cancer-related mortality. Its initiation and progression are closely associated with multiple factors, including genetic susceptibility, immune dysregulation, and environmental and lifestyle influences.[1,2] In recent years, particularly in developing countries, the incidence and mortality of CRC have continued to rise, making early screening and precision therapy urgent medical challenges.[3] Current clinical treatments, including surgery, radiotherapy, and chemotherapy, remain limited by severe toxic side effects, drug resistance, and the inability to address recurrence and metastasis effectively.[4] Consequently, improving the accuracy and sensitivity of early diagnosis and developing low-toxicity, high-efficacy personalized therapeutic strategies represent critical goals in current CRC research.

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Early diagnosis can markedly enhance patient survival, and the detection of biomarkers is key to realizing effective CRC screening. Although chemiluminescence immunoassay (CLIA) and enzyme-linked immunosorbent assay (ELISA) have improved detection sensitivity, they still face challenges such as nonspecific adsorption of biomarkers, low abundance of circulating tumor cells (CTCs), and inter-patient expression heterogeneity.[5–7] To overcome these limitations, nucleic acid aptamers—often called "chemical antibodies" for their designable sequences, high affinity, facile chemical modification, and low synthesis cost—have rapidly emerged in tumor diagnostics and targeted therapy.[8] Through systematic evolution of ligands by exponential enrichment (SELEX), numerous high-performance aptamers targeting CRC-related proteins, microRNAs, and exosomes have been identified.[9]

As novel molecular recognition elements, nucleic acid aptamers possess unique three-dimensional conformations and target-binding capabilities, demonstrating significant advantages in the detection of CRC molecular biomarkers.[10] Compared to traditional antibodies, these molecules exhibit superior thermal and chemical stability, along with unparalleled advantages in chemical synthesis convenience and scalable production costs (Table 1). Studies have confirmed that SELEX-derived specific aptamers can precisely recognize overexpressed antigen epitopes on CRC cell surfaces, offering innovative avenues for developing new liquid biopsy technologies and targeted therapeutic strategies. Notably, the synergistic integration of aptamers with functional nanomaterials enables the construction of smart drug delivery systems that markedly enhance the therapeutic index and reduce off-target toxicity via spatiotemporal controlled-release mechanisms.[11]

In CRC therapeutic research, nucleic acid aptamers demonstrate remarkable application potential. Compared with monoclonal antibodies, aptamers have a smaller molecular weight and superior tissue penetration.[12] Unlike CRISPR-based gene editing, aptamers do not directly alter genomic DNA; instead, they bind and regulate key molecular targets with high affinity, act rapidly and reversibly, and generally offer greater safety.[19] Relative to antibody–drug conjugates (ADCs), aptamers offer greater engineering flexibility in molecular design, chemical modification, and conjugation.[20] Although chemotherapy and immunotherapy have achieved some success in prolonging patient survival, drug resistance and systemic toxicity remain unresolved challenges. The integration of aptamers with nanocarriers has facilitated the

Table 1 Comparative Analysis of Nucleic Acid Aptamers and Antibodies in Cancer Diagnosis and Therapy

Characteristic	Aptamer	Antibody
Chemical composition	Nucleic acid (DNA or RNA)	Protein
Molecular weight[12]	Small (10–50 kDa)	Large (~150 kDa)
Tissue/tumor penetration ability	High	Limited
Production method[13,14]	In vitro chemical synthesis; rapid, controllable; minimal batch variation; relatively low cost	In vivo culture in mammalian cells; long, complex; batch variation; high cost
Chemical modification flexibility[15,16]	Easy incorporation of functional groups (eg, fluorophores, drugs, nanoparticles) at precise sites without affecting activity	Limited modification sites; complex coupling; may alter conformation and reduce activity
Target range[17,18]	Ions, small molecules, proteins, cells, extracellular vesicles	Primarily proteins and polypeptides
Immunogenicity[12]	Negligible	Possible immune responses (eg, human anti-mouse or anti-drug antibodies)
In vivo stability[16]	Prone to nuclease degradation (can be improved via nucleotide modification)	Generally stable; potential aggregation or deamidation
Clinical translation status	Early-stage; Phase I/II trials for select candidates	Established; multiple FDA-approved diagnostics and therapeutics

Abbreviation: FDA, Food and Drug Administration.

development of efficient targeted chemotherapy platforms, significantly improving drug selectivity and efficacy while minimizing systemic toxicity. For instance, PD-L1 aptamer-based multimodal nanoplatforms have demonstrated both safety and therapeutic advantages.[21,22] These findings highlight the dual role of aptamers in early diagnosis and their vast potential in targeted therapy.

Although several reviews have discussed the application of aptamers in CRC diagnosis,[8] a comprehensive overview covering their roles in early screening, targeted chemotherapy, and immunotherapy is still lacking. In this review, we integrate the latest research advances to systematically summarize aptamer selection and chemical modification strategies, elaborate on their innovative applications in CRC molecular diagnostics and targeted therapeutics—including biosensor- and nanomaterial-based detection platforms, drug delivery systems, and immunotherapy approaches—and analyze the challenges hindering clinical translation. We also explore future directions such as artificial intelligence–assisted aptamer design, with the aim of providing valuable insights to advance the research and clinical application of nucleic acid aptamers in CRC precision medicine.

Advances in Aptamer Selection and Optimization Technologies

Conventional SELEX Methods and Limitations

Since its development in 1990, the SELEX technique has been the gold-standard for isolating high-affinity nucleic acid aptamers.[23,24] Its core workflow comprises: (i) construction of a random single-stranded DNA/RNA library with 10^-14–10^15 unique sequences; (ii) incubation with the target to enrich specifically bound sequences; and (iii) iterative PCR amplification and selection rounds (typically 2–15 cycles).[25,26] Although traditional SELEX can yield aptamers with nanomolar affinities, it suffers from several drawbacks: lengthy screening periods (weeks to months), PCR bias leading to sequence distortion, and the use of recombinant targets that may not recapitulate native conformations.[26] These limitations often lead to reduced targeting efficiency of SELEX-derived aptamers in CRC in vivo applications, significantly hindering clinical translation.

Emerging SELEX Strategies

To overcome the bottlenecks of conventional SELEX, a variety of improved approaches have been developed in recent years (Figure 1).[27–33] Microfluidic SELEX integrates binding, washing, and elution steps into a single microfluidic chip. By leveraging precise hydrodynamic control to minimize reaction volumes and reagent consumption, this approach enables completion of a screening cycle within hours while supporting parallel processing, thereby enhancing throughput

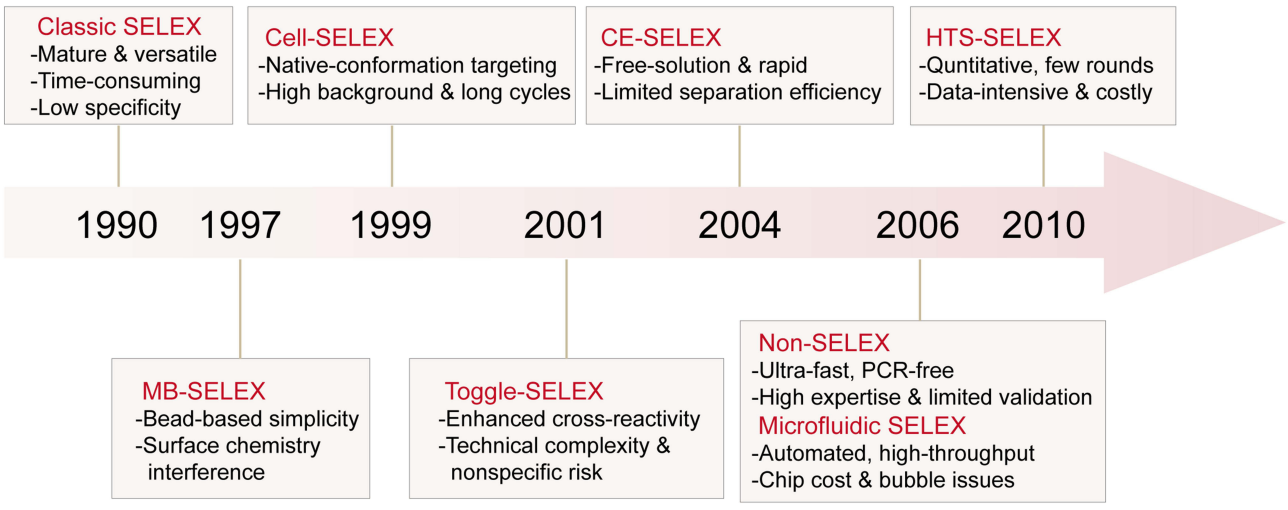

Figure 1 Evolution and comparative analysis of SELEX technologies.
Abbreviations: SELEX, Systematic Evolution of Ligands by Exponential Enrichment; Cell-SELEX, Cell-based SELEX; MB-SELEX, Magnetic Bead-based SELEX; Toggle-SELEX, Alternating Target SELEX; CE-SELEX, Capillary Electrophoresis-based SELEX; HTS-SELEX, High-Throughput Sequencing-assisted SELEX; Non-SELEX, PCR-free selection methods without iterative cycles; Microfluidic SELEX, Microfluidics-based SELEX.

and reproducibility.[32] High-Throughput Sequencing–SELEX (HTS-SELEX) combines next-generation sequencing with bioinformatics algorithms to monitor sequence enrichment dynamics in real time after each selection round. This strategy significantly improves the accuracy and speed of identifying high-performance aptamers, reducing the overall screening period to days.[33] Additional advancements, such as chromatography separation, capillary electrophoresis (CE), and magnetic bead (MB)-based selective capture, have further diversified SELEX methodologies.

Chemical Modifications and Stability Optimization

Despite advancements in screening efficiency, the clinical translation of natural nucleic acid aptamers remains hindered by their rapid degradation via serum nucleases and short in vivo circulation half-lives. To address these shortcomings, a variety of chemical modifications have been introduced at multiple structural levels to enhance both nuclease resistance and pharmacokinetic properties. At the ribose sugar 2′-position, substituents such as 2′-O-methyl, 2′-fluoro, unlocked nucleic acids (UNA), and locked nucleic acids (LNA) have been widely adopted to improve structural stability and target affinity.[34–36] In the phosphate backbone, replacement of nonbridging oxygen atoms with phosphorothioate (PS) or boranophosphate (PB) linkages effectively reduces the risk of bond cleavage,[37,38] while 3′-end capping with inverted nucleotides or alkyl groups serves to block exonuclease activity.[39]

Beyond structural modifications, macromolecular conjugation with polyethylene glycol (PEG), cholesterol, or albumin-binding peptides has proven effective in prolonging circulation time and reducing renal clearance. Additionally, encapsulation within lipid nanoparticles, DNA origami structures, or dendrimers, as well as the incorporation of mirror-image L-nucleic acids or unnatural bases, provides innovative avenues to optimize in vivo stability and pharmacokinetic profiles.[40,41] These multifaceted engineering approaches collectively address the limitations of natural aptamers, paving the way for their robust application in CRC diagnostics and therapeutics.

Applications of Nucleic Acid Aptamers in CRC Diagnosis

Aptamer-Sensor Platforms for Early CRC Screening

Traditional biorecognition elements such as enzymes and antibodies suffer from poor stability, lack of reusability, and high cost, which severely limit the development and deployment of related sensors for early CRC screening.[42,43] Nucleic acid aptamers, owing to their excellent thermal and chemical stability as well as their facile and repeatable synthesis and modification, have emerged as ideal recognition elements for next-generation biosensors.[44,45] By integrating the high specificity of aptamers with diverse signal transduction mechanisms, these sensors significantly enhance detection sensitivity and specificity, offering innovative platforms for CRC early diagnosis and prognosis monitoring. Current aptamer-based sensors are primarily categorized into optical and electrochemical biosensors.[46,47]

Optical Aptasensors

Optical aptasensors translate aptamer-target binding events into measurable optical signals, including fluorescence, chemiluminescence, colorimetry, or surface-enhanced Raman scattering (SERS). These systems are distinguished by high sensitivity, real-time response, and label-free or minimally labeled detection, positioning them as powerful tools for CRC early diagnosis.[46] Zhang et al constructed a SERS-based dual-target detection system using aptamer-functionalized gold nanopolyhedrons (Figure 2).[48] In this design, gold nanocubes (AuNCs) were covalently modified with Raman reporters (4-MBA and DTNB) and immobilized via complementary DNA strands onto a substrate coated with self-assembled gold nanodecahedra (AuNDs). The AuNDs generated intense localized surface plasmon resonance hotspots, amplifying SERS signals. Upon introducing target miRNAs (miR-21 or miR-18a), aptamers preferentially bound to the miRNAs, displacing the SERS probes and reducing signal intensity. This method achieved rapid (5-minute), simultaneous quantification of miR-21 and miR-18a with detection limits as low as 6.8 pM and 7.6 pM, respectively, demonstrating a novel approach for high-throughput, ultrasensitive CRC screening.

Electrochemical Aptasensors

Electrochemical aptasensors detect tumor biomarkers by monitoring changes in current, resistance, or potential induced by aptamer–target binding. They combine simplicity of operation, low cost, and ease of miniaturization, making them

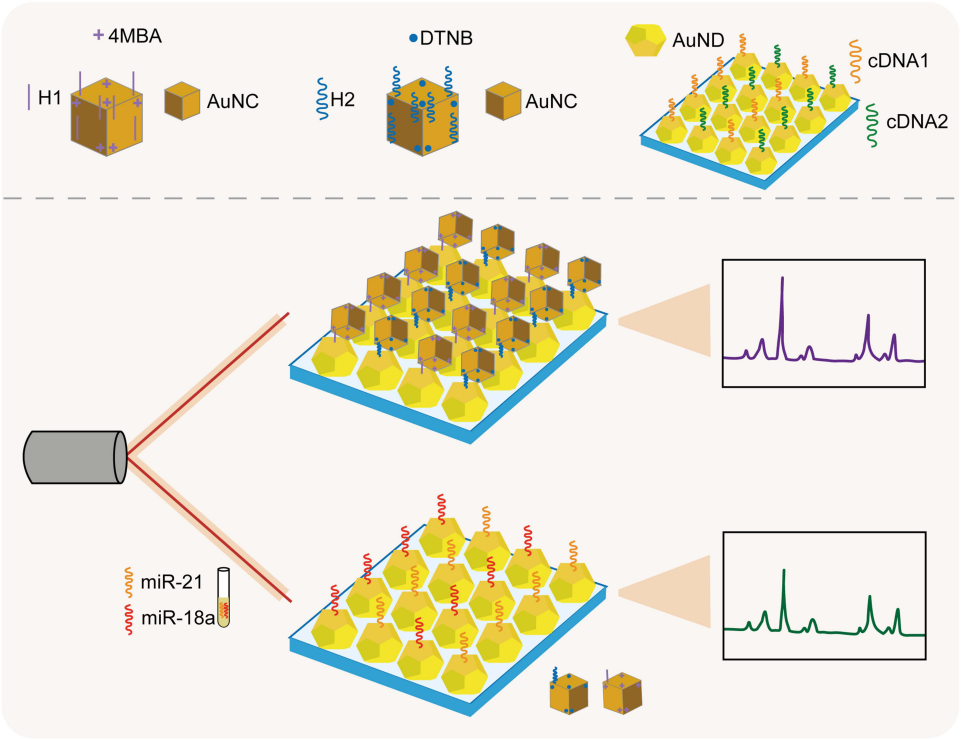

Figure 2 Schematic illustration of a SERS-based aptasensor for synchronous dual-target miRNA detection. AuNCs are used as SERS tag carriers and covalently modified with two Raman reporters—4-mercaptobenzoic acid (4-MBA) and 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB)—as well as with DNA aptamers H1 (for miR-21) and H2 (for miR-18a). The detection substrate consists of AuNDs self-assembled at the oil–water interface into a dense monolayer and functionalized with complementary capture strands cDNA1 and cDNA2. Upon sample addition, SERS tags hybridize to their respective capture probes, producing strong Raman signals. In the presence of target miRNAs, miR-21/miR-18a competitively bind to H1/H2, displacing the corresponding SERS tags and causing a concentration-dependent decrease in Raman intensity, thereby enabling simultaneous quantitative detection of both targets.

effective for CRC early screening.[49] Shi et al developed a smartphone-integrated point-of-care testing (POCT) platform for carcinoembryonic antigen (CEA) based on a dual-signal PdPt@PCN-224/Fc labeling system coupled with a reverse self-validation mechanism. This platform achieved a detection limit of 0.27 pg/mL, consistent with ELISA results in clinical serum samples,[50] demonstrating the feasibility of miniaturized sensors for onsite clinical testing. Wang et al combined microfluidic paper-based technology with nanocomposite materials to fabricate an electrochemical aptasensor for simultaneous detection of CEA and neuron-specific enolase (NSE) (Figure 3).[51] Dual working electrodes were modified with amino-functionalized graphene-thionine-AuNPs (NG-THI-AuNPs) and Prussian blue-PEDOT-AuNPs (PB-PEDOT-AuNPs), leveraging the electrocatalytic activity of nanomaterials to enhance electron transfer efficiency. Upon sample introduction, CEA/NSE binding to aptamers formed insulating complexes, reducing differential pulse voltammetry (DPV) currents. The system achieved ultra-low detection limits of 2 pg/mL for CEA and 10 pg/mL for NSE, demonstrating a robust, multiplexed approach for precise CRC diagnosis.

Functionalized Nanomaterial-Assisted Biomarker Detection

The integration of functionalized nanomaterials with nucleic acid aptamers combines the high surface-to-volume ratio and superior electronic/energy transfer properties of nanomaterials with the molecular recognition capabilities of aptamers. This synergy enables the construction of biosensing platforms with exceptional sensitivity, rapid response, and multiplexed detection capabilities. In recent years, various quantum dots, metal nanoparticles, and graphene-based two-dimensional materials have been successfully coupled with aptamers to afford diversified solutions for early detection of CRC-related biomarkers (eg, CEA, miRNA, exosomes, circulating tumor cells) as summarized in Table 2.

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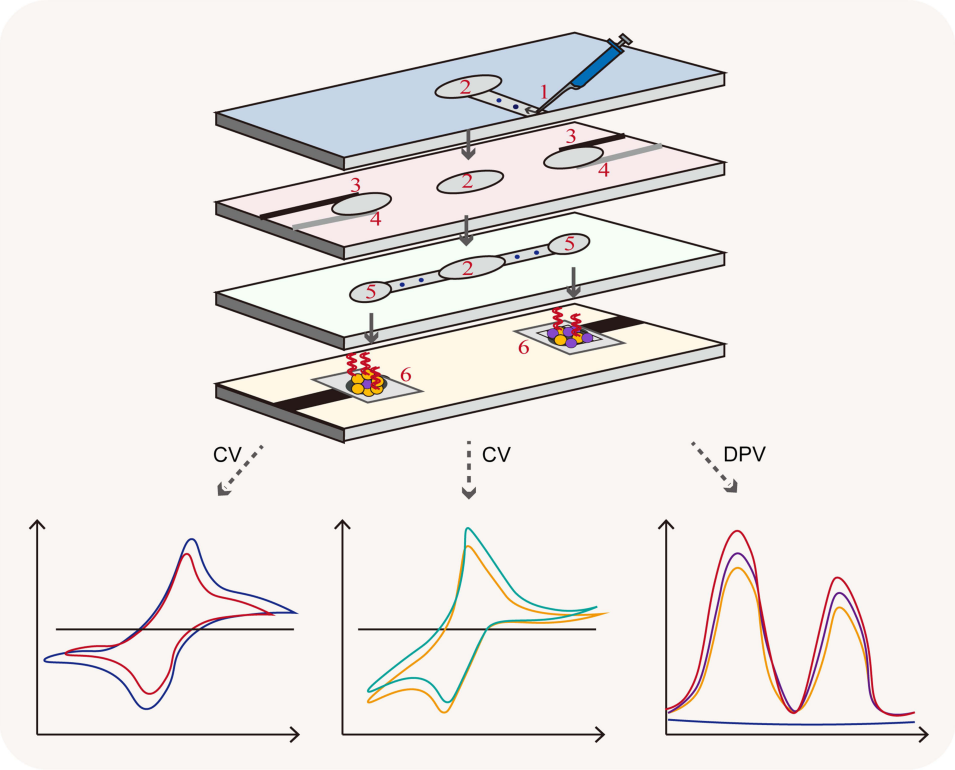

Figure 3 Working principle of a microfluidic paper-based electrochemical aptasensor for multiplex CEA/NSE detection. Microfluidic channels are defined on paper by wax printing, and counter (3), reference (4) and two working electrodes (6) are fabricated by screen printing. Working electrode I is modified with NG-THI-AuNPs and immobilized with a CEA-specific aptamer; working electrode II is modified with PB-PEDOT-AuNPs and immobilized with an NSE-specific aptamer. The sample is introduced at the inlet (1), filtered (2), and flows into the detection zone (5), where target binding to its aptamer impedes electron transfer. Signal changes are monitored by cyclic voltammetry (CV) and differential pulse voltammetry (DPV), enabling simultaneous ultrasensitive quantification of CEA and NSE.

Quantum Dot-Aptamer Conjugates

Quantum dots (QDs), semiconductor nanocrystals with diameters of 2–10 nm, exhibit narrow emission spectra (full width at half maximum <30 nm), broad excitation spectra (300–600 nm), and high quantum yields (>80%).[61] Immobilizing aptamers on QD surfaces via thiol bonds or biotin-streptavidin systems facilitates efficient molecular recognition of CRC-related biomarkers such as CEA and miRNA-21. Target binding to aptamers amplifies QD fluorescence signals through mechanisms like fluorescence resonance energy transfer (FRET), inner filter effect (IFE), or chemiluminescence, significantly enhancing detection sensitivity and signal-to-noise ratios.[62,63]

Several studies have demonstrated the ultrasensitive detection of tumor biomarkers using QD-aptamer systems. For instance, Cheng et al developed a QD-aptamer fluorescent sensor that specifically binds to the epithelial tumor marker MUC1, achieving a detection limit of 250 nM via FRET signal modulation.[52] Sun et al further enhanced this approach by coupling QDs with MoS_2 nanosheets to create a dual-channel fluorescence platform capable of simultaneously monitoring CEA (LOD = 0.7 fg/mL) and PSA (LOD = 0.9 fg/mL), highlighting its potential for multiplexed biomarker analysis.[53]

Metal Nanoparticle-Aptamer Systems

Metal nanoparticles (AuNPs and AgNPs in particular) have been widely employed in high-sensitivity aptasensors due to their tunable localized surface plasmon resonance (LSPR) effects and ease of surface functionalization.[64] Aptamers can be anchored to nanoparticle surfaces via thiol or amine groups. Upon target binding, changes in nanoparticle aggregation or dispersion states induce measurable optical or electrochemical signal shifts, enabling rapid, low-detection-limit assays suitable for real-time monitoring.

AuNP-aptamer hybrids have demonstrated remarkable performance in CRC biomarker detection. Liu et al constructed a label-free fluorescent sensing platform using AuNPs and hybridization chain reactions, achieving ultrahigh

Table 2 Representative Aptamer-Nanomaterial Biosensors for the Detection of CRC Biomarkers

Nanomaterials	Biomarker	LOD/Sensitivity	Linearity Range	Detection Strategy	Ref
AuNDs, AuNCs	miR-21/ miR-18a	6.8 pM/ 7.6 pM	10 pM-10 μM	SERS	[48]
PdPt@PCN-224	CEA	0.27 pg/mL	1 pg/mL- 100 ng/mL	DPV	[50]
AuNPs	CEA/NSE	2 pg/mL/ 10 g/mL	0.01–500 ng/mL 0.05~500 ng/mL	DPV	[51]
QDs	MUC1	250 nM	0-2 μM	FRET	[52]
QD-MSNs	CEA/PSA	0.7 fg/mL 0.9 fg/mL	1 fg/mL-10 pg/mL 1 fg/mL-0.1ng/mL	FRET, IFE	[53]
AuNPs	CEA	0.03 nM	0.1–2.5 nM	Fluor	[54]
PtμEs/Au	CEA	7.7 pg/mL	0.01–100 ng/mL	SWV	[55]
AuNPs	IL-6	1.6 pg/mL	0.005–100 ng/mL	EIS	[56]
AuPt DNs/GO	Exosomes	20 /μL	100-5×10^5 /μL	DPV	[57]
Au/MXene	Exosomes	19 /μL	50-5×10^4 /μL	DPV	[58]
COOH-graphene	CEA	0.5 ng/mL	0.5–500 ng/mL	SWV	[59]
GO	mCRC cells	70 cells/mL	0-107 cells/mL	FRET	[60]

Abbreviations: LOD, limit of detection; AuNDs, Au nano-dodecahedrons; AuNCs, Au nano-cubes; SERS, surface-enhanced Raman scattering; PdPt, Palladium-Platinum; PCN, Porphyrinic Coordination Network; MSNs, mesoporous silica nanoparticles; FRET, fluorescence resonance energy transfer; IFE, internal filter effect; AuNP, gold nanoparticle; PtμE, platinum microelectrode; SWV, square wave voltammetry; EIS, electrochemical impedance spectroscopy; AuPt DNs, AuPt dendritic nanocrystals; GO, graphene oxide; DPV, Differential Pulse Voltammetry; mCRC, Metastatic Colorectal Cancer; Fluor, Fluorescence.

sensitivity for CEA detection (LOD = 0.03 nM).[54] Zhai et al developed an electrochemical sensor by modifying platinum microelectrodes with AuNPs, lowering the CEA detection limit to 7.7 pg/mL.[55] Additionally, Tertis et al employed AuNP-based impedance spectroscopy to quantify IL-6 with a precision of 1.6 pg/mL.[56] Feng's and Gao's groups further advanced exosome detection using AuPt-Ti_3C_2 MXene and AuPtPdCu-MXene composites, achieving detection limits as low as 20 exosomes/μL and 19 exosomes/μL, respectively, thereby enhancing exosome-based CRC diagnostics.[57,58]

Graphene and Other Two-Dimensional Materials

Two-dimensional (2D) materials such as graphene, graphene oxide (GO), and MXene are ideal substrates for aptasensors due to their ultrahigh surface area, excellent conductivity, and fluorescence quenching capabilities.[65] In fluorescence-based assays, single-stranded aptamers adsorb onto GO surfaces via π-π stacking; target binding induces conformational changes and desorption, triggering fluorescence "on/off" switching. For electrochemical detection, graphene-modified electrodes reduce interfacial impedance and enhance electron transfer efficiency, amplifying signal outputs.[66]

In practical applications, 2D material–aptamer systems have shown outstanding performance. Ma et al designed a carboxylated graphene (COOH-graphene)-based sandwich electrochemical sensor capable of detecting CEA at 0.5 ng/mL, offering a novel approach for CRC monitoring.[59] Chen et al developed a wash-free GO fluorescent aptasensor that accurately identified mCRC LoVo cells at concentrations as low as 70 cells/mL while maintaining high specificity even in mixed samples containing only 5% target cells, underscoring its utility for complex biological sample analysis.[60]

Applications of Nucleic Acid Aptamers in CRC Therapy

Aptamer-Mediated Targeted Delivery of Chemotherapeutic Agents

Current clinical management of CRC primarily relies on surgical resection, supplemented with oxaliplatin-based chemotherapy regimens (eg, FOLFOX/CAPOX) for stage II high-risk and stage III patients.[67,68] However, conventional chemotherapeutic agents suffer from systemic toxicity, poor tumor specificity, and drug resistance, which severely compromise therapeutic efficacy and patient quality of life.[69,70] Nucleic acid aptamers, with their high affinity and specificity, enable precise targeting of CRC cell surface receptors. By mediating active tumor-targeted delivery via nanocarriers, aptamers significantly enhance drug accumulation at tumor sites while minimizing off-target toxicity, offering a promising strategy to improve chemotherapy outcomes.[71]

Nanocarrier Design and Aptamer Functionalization

A wide range of nanocarriers have been explored for aptamer-mediated drug delivery, including inorganic materials (eg, AuNPs, GO), lipid formulations (liposomes, lipid nanoparticles, LNPs), polymeric particles (PLGA, PEG-PLGA, chitosan), and metal-organic frameworks (MOFs). AuNPs not only allow covalent aptamer conjugation via thiol-gold bonds but also exhibit photothermal conversion and imaging capabilities. GO efficiently loads hydrophobic drugs through π-π stacking and oxygen-containing functional groups, enhancing carrier stability.[72–74] Liposomes and LNPs encapsulate both hydrophilic and hydrophobic drugs within their phospholipid bilayers, and PEGylation or aptamer modification can prolong circulation time and improve targeting.[75,76] PLGA and its copolymers enable controlled drug release and multifunctional surface engineering.[77–79] MOFs, with their ultrahigh surface area and tunable porosity, are emerging as platforms for high drug-loading and multimodal therapy.[80]

Aptamers are conjugated to carriers via covalent (eg, EDC/NHS-mediated amide bonds, azide-alkyne click chemistry) or non-covalent (eg, electrostatic adsorption, biotin-streptavidin systems) strategies.[81,82] For example, Babaei et al covalently linked the AS1411 aptamer to AuNPs via maleimide-thiol reactions, significantly enhancing CRC cell-specific recognition and uptake.[83] Khatami et al employed electrostatic self-assembly to adsorb AS1411 onto polymeric nanoparticles, achieving mild coupling and promoting intracellular drug release and anti-tumor efficacy.[84]

Cellular Uptake Mechanisms and TME-Responsive Release

Nanocarriers passively accumulate in tumor interstitium via the enhanced permeability and retention (EPR) effect. Surface-modified aptamers then bind specifically to membrane receptors (eg, nucleolin, EpCAM), facilitating receptor-mediated endocytosis.[77,85] Zhang et al demonstrated that AS1411-functionalized carriers markedly increased uptake in CRC cells, correlating with enhanced drug cytotoxicity.[86]

To achieve spatiotemporally controlled drug release, researchers exploit tumor microenvironment (TME) features such as acidity and high redox potential. Khatami et al designed chitosan-coated mesoporous silica nanoparticles (MSNs) that utilize the "proton sponge effect" under acidic pH to protonate amine groups, opening mesopores and triggering drug release.[84] Zhao et al developed glutathione (GSH)-sensitive PEGylated prodrug nanoparticles, where high GSH concentrations cleave disulfide bonds for tumor-specific drug activation.[87] In addition, Liu et al integrated AuNPs' photothermal properties with near-infrared (NIR) laser irradiation to trigger drug release and activate methylene blue for singlet oxygen ($^1O_2$) generation, achieving combined chemo-photodynamic therapy.[88]

These mechanisms collectively enhance drug accumulation and release at the tumor site while minimizing systemic toxicity, thereby improving both safety and efficacy. Figure 4 schematically depicts the process from EPR-mediated accumulation and receptor-mediated endocytosis to tumor microenvironment-triggered drug release.

Therapeutic Efficacy and Pharmacokinetic Profiles

Numerous studies have shown that aptamer-mediated nanocarriers substantially improve the pharmacokinetics and therapeutic index of chemotherapeutic agents, increasing anti-tumor efficacy while reducing adverse effects (Table 3). Surface-grafted aptamers prolong systemic circulation and promote active tumor accumulation, achieving a dual benefit of enhanced efficacy and reduced toxicity.[89,90]

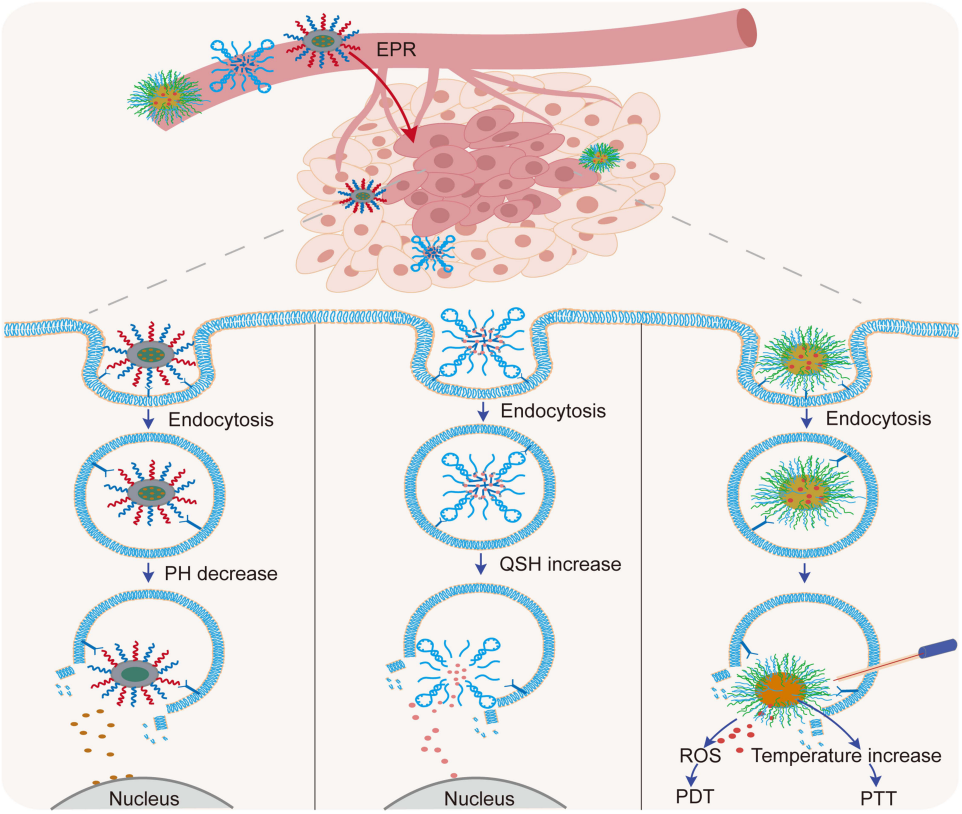

Figure 4 Mechanism of aptamer-mediated targeted drug delivery with multi-stimuli responsive release. Three aptamer-decorated carriers—chitosan-coated mesoporous silica nanoparticles (MSNs), PEGylated prodrug nanoparticles, and photosensitizer-loaded gold nanoparticles (AuNPs)—accumulate in tumors via the EPR effect and bind cell-surface receptors to trigger endocytosis. In the acidic tumor microenvironment, protonation of chitosan opens MSN pores to release payload; elevated glutathione cleaves the prodrug's sensitive linker in PEGylated NPs; and NIR irradiation of AuNPs generates ROS (PDT) and localized heat (PTT). The combined stimuli responsiveness yields enhanced anti-tumor efficacy.

Shakib et al developed AS1411-conjugated PEGylated solid lipid nanoparticles (SLNs) loaded with docetaxel, which increased cellular uptake by 2.3-fold, reduced IC_{50} to 0.11 nM, and extended survival in tumor-bearing mice.[91] Gonzalez-Valdivieso et al designed CD44-targeted nanocarriers co-delivering docetaxel and an Akt inhibitor, achieving >50%

Table 3 Efficacy of Aptamer-Based Nanocarriers for Targeted CRC Therapy

Aptamer	Drug	In vitro Efficacy	In vivo Efficacy	Key Pharmacokinetics	Ref
AS1411-SLNs	DTX	IC_{50} = 0.11 nM (6 h); uptake ↑2.3×	TGD:103.09% MST ↑44%	Not reported	[91]
CD44-ELR polymers	DTX + Akt inhibitor	Caco-2 viability: 2.5% (24 h)	Polyps: 3.83 vs 8.83 (control); >4 mm ↓14%	$t_1/_2$ = 5.5 h; AUC = 137 μM·h	[92]
AS1411-PLA-PEI micelles	CPT + shRNA	Uptake ↑; apoptosis +20.9%; viability 40%	Tumor suppression: 93%; 40% remission	Not reported	[93]
5TR1-PEGylated liposomal	DOX	IC_{50} = 21 μM (72 h); DOX uptake ↑2.5×	MST 16 → 50 days	$t_1/_2$ = 14.5 h; AUC = 1755 μg·h/mL	[94]
SYL3C–PLGA nanoparticles	5-FU	IC_{50} = 16.1 μM (CT-26), 13.2 μM (HCT-116); uptake ↑	Tumor growth delayed	Not reported	[95]

Notes: Symbols: ↑, increase; ↓, decrease; →, prolong; ×, multiple.
Abbreviations: DTX, docetaxel; IC_{50}, half-maximal inhibitory concentration; TGD, Tumor growth delay; MST, median survival time; $t_{1/2}$, terminal half-life; AUC, area under the curve; CPT, camptothecin; DOX, doxorubicin; 5-FU, 5-fluorouracil.

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tumor burden reduction and extending drug half-life to 5.5 hours.[92] Sanati et al demonstrated synergistic chemo-gene therapy using AS1411-decorated PLA-PEI micelles co-loaded with vincristine and Survivin shRNA, achieving 93% tumor suppression.[93]

Moreover, Moosavian et al reported a 5TR1 aptamer-PEGylated liposomal doxorubicin system that doubled tumor drug accumulation, prolonged half-life to 14.5 hours, and extended mouse survival to 50 days.[94] Yavari et al highlighted the superior tumor targeting and efficacy of EpCAM aptamer-PLGA nanoparticles for 5-fluorouracil (5-FU) delivery.[95] These studies validate the potential of aptamer-mediated delivery systems to enhance therapeutic precision, pharmacokinetics, and safety in CRC treatment.

Aptamer-Mediated Immunotherapy Strategies

The tumor microenvironment of CRC is highly heterogeneous and often exploits multiple mechanisms to evade immune surveillance, rendering conventional surgery, radiotherapy and chemotherapy insufficient to eradicate residual disease and prevent distant metastasis.[96] In recent years, immune checkpoint blockade (ICB) therapies targeting the PD-1/PD-L1 axis have achieved remarkable clinical success across various malignancies.[97,98] However, monoclonal-antibody-based ICB still suffers from high immunogenicity, limited tissue penetration and substantial manufacturing costs.[99–101] As "chemical antibodies", nucleic-acid aptamers combine high affinity and specificity with low immunogenicity, facile chemical modification and cost-effective large-scale synthesis, making them an attractive new platform for tumor immunotherapy.[102] In CRC, aptamers can serve not only as standalone checkpoint inhibitors but also be co-delivered with chemotherapeutic agents, photodynamic therapy agents or immunomodulators to achieve multimodal synergistic anti-tumor effects.

Immune Checkpoint Blockade

PD-L1 (programmed death-ligand 1), a critical immunosuppressive molecule on tumor cells, binds to PD-1 on T cells to suppress effector T cell activity and promote immune escape.[103] Using SELEX technology, researchers have developed high-affinity PD-L1-specific aptamers. For instance, Gao et al identified a DNA aptamer (Kd≈95.7 nM) via cell-SELEX that restored T cell proliferation and IFN-γ secretion in vitro and demonstrated tumor suppression comparable to antibodies in murine models, with no adverse effects.[100] Lai et al employed nitrocellulose membrane-SELEX to isolate a DNA aptamer (Kd≈72 nM) that significantly inhibited CRC growth, enhanced T cell proliferation and cytokine secretion, and showed no hepatorenal toxicity or weight loss in mice.[104]

Owing to their small size and ease of chemical modification, PD-L1 aptamers can be efficiently conjugated to chemotherapeutic drugs or nanocarriers, enabling simultaneous immune checkpoint blockade and cytotoxic therapy. Wu et al reported a PD-L1 aptamer-paclitaxel conjugate that accumulated selectively in tumors and significantly improved intracellular paclitaxel uptake and anti-tumor activity.[105] In recent years, photoimmunotherapeutic strategies have shown significant potential in modulating the tumour microenvironment and enhancing anti-tumour immunity. For example, Watanabe's team developed an antibody-photosensitiser conjugate targeting fibroblast activation protein (FAP), which could specifically eliminate cancer-associated fibroblasts (CAFs) under near-infrared light irradiation, effectively inhibiting tumour progression with a good safety profile.[106] Meanwhile, Huang et al proposed a combinatorial strategy integrating CAR-NK cells with photodynamic nanoparticles; CAR-NK cells recognize tumor cells, and upon laser activation, the nanoparticles release reactive oxygen species (ROS) to induce tumor cell death. This synergistic mechanism offers a novel therapeutic concept for CRC.[107] Building on these advances, Zhang et al designed a spherical nucleic acid–metal–organic framework–aptamer (SNA–MOF–aptamer) nanosystem that, under NIR irradiation, produced singlet oxygen ($^1O_2$) for photodynamic therapy. This platform, in combination with oxaliplatin, induced immunogenic cell death (ICD) while blocking the PD-1/PD-L1 axis, thereby activating effector T cells and inhibiting both primary and metastatic CRC lesions.[108]

This PD-L1 aptamer-mediated combinatorial approach leverages a cascade of physical disruption, chemical modulation and immune remodeling to deliver multilayered, multidimensional intervention within the tumor microenvironment, thereby markedly enhancing anti-tumor efficacy (Figure 5). Compared with monoclonal antibodies, aptamers exhibit

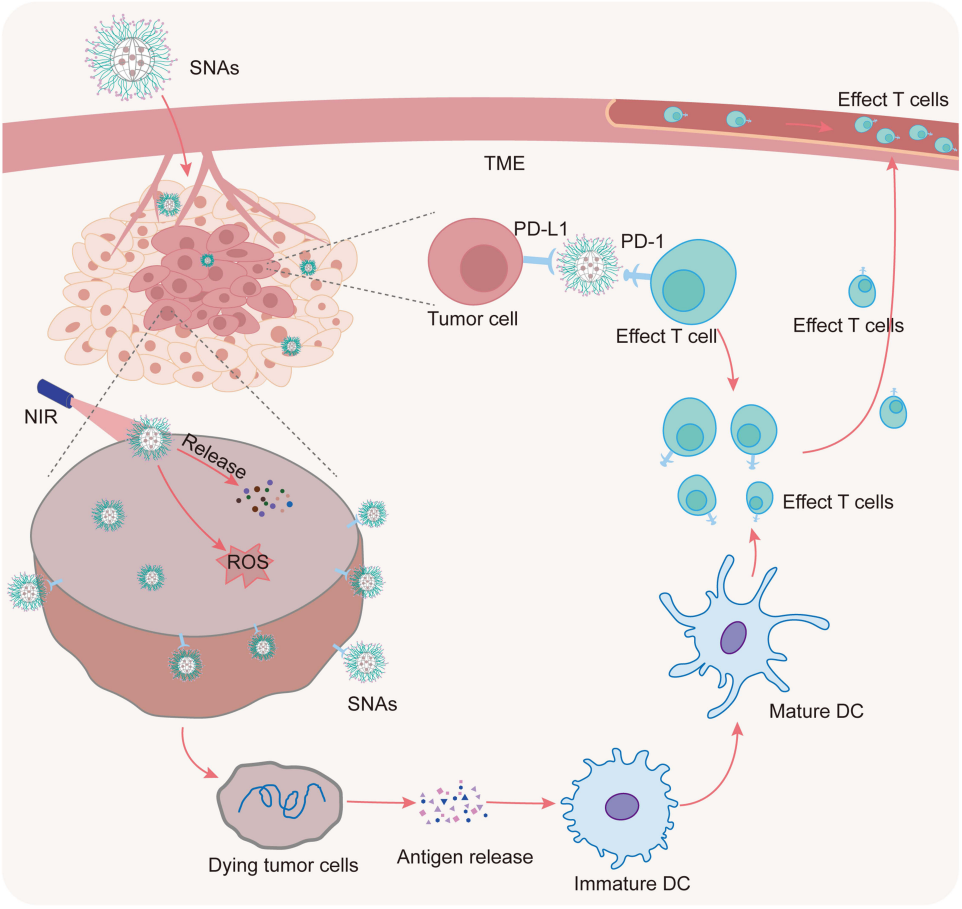

Figure 5 PD-L1 Aptamer-Functionalized MOF Spherical Nucleic Acids for Targeted Multimodal Anti-tumor Therapy. AptPD-L1@MOF-SNAs consist of an oxaliplatin (OXA)-loaded metal–organic framework (MOF) core enveloped by a dense shell of PD-L1 aptamers. They accumulate in tumors via the enhanced permeability and retention (EPR) effect and are internalized through PD-L1-mediated endocytosis. Under near-infrared (NIR) irradiation, the MOF generates reactive oxygen species (ROS) and concurrently releases OXA to induce tumor cell apoptosis and antigen release, promoting dendritic cell (DC) maturation and effector T-cell activation/infiltration. Simultaneously, surface-bound aptPD-L1 blocks the PD-1/PD-L1 checkpoint, relieving T-cell suppression. The combined photodynamic therapy (PDT), chemotherapy, and immunotherapy achieves synergistic inhibition of both primary and metastatic tumors.
Abbreviations: MOF, metal–organic framework; SNAs, spherical nucleic acids; OXA, oxaliplatin; EPR, enhanced permeability and retention; NIR, near-infrared; ROS, reactive oxygen species; DC, dendritic cell; PDT, photodynamic therapy.

lower immunogenicity and superior tissue penetration, achieving significant therapeutic effects at reduced dosages and offering promising prospects for clinical translation.[109–111]

Combination of Aptamers with Immunomodulatory Factors

Beyond direct immune-checkpoint blockade, aptamers can be engineered to precisely target pro-inflammatory cytokines and thereby synergistically remodel the tumor immune microenvironment. In CRC, both TNF-α and IL-1 drive tumor proliferation, invasion and stromal remodeling via activation of NF-κB, MAPK, and related pathways.[112–114] TNF-α antagonists such as etanercept have been shown to inhibit tumor growth in murine CRC models markedly.[115] Mashayekhi et al screened a dimeric DNA aptamer that, although its inhibition rate (~40%) was slightly lower than that of etanercept (~60%), demonstrated superior targeted delivery and tissue penetration owing to its lower immunogenicity and facile chemical modification.[116] Meanwhile, members of the IL-1 family play key roles in CRC immune escape by promoting angiogenesis and recruiting immunosuppressive cells, thus accelerating tumor progression.[112] In preclinical studies, the anti-IL-1α monoclonal antibody Xilonix significantly prolonged survival in advanced CRC patients.[117,118] More recently, Ren et al identified an IL-1α-specific aptamer, SL1067, which can neutralize IL-1α and reprogram the tumor immune microenvironment by modulating T- and B-cell differentiation, offering a novel approach for precise immunomodulatory therapy.[119]

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Moreover, aptamers can serve as efficient delivery vehicles for nucleic-acid therapeutics such as small activating RNAs (saRNAs) and microRNAs (miRNAs), further expanding their therapeutic potential. saRNAs upregulate tumor-suppressor genes, while miRNAs downregulate oncogene expression.[120,121] Wang et al employed a hyaluronic acid-CD44-targeted lipid complex to deliver p21-saRNA-322, achieving sustained tumor suppression in an orthotopic CRC model.[122] Laowichuwakonnukul et al co-loaded AS1411, miR-143, and doxorubicin into nanoparticles, achieving synergistic KRAS-pathway inhibition alongside controlled release of the chemotherapeutic agent.[123] In addition, PSMA-specific aptamer delivery of CRMP4-saRNA significantly reduced metastatic lesions in a prostate-cancer metastasis model,[124] and a PDAC-specific aptamer carrying C/EBPα-saRNA successfully reversed chemoresistance in pancreatic cancer.[125] These studies demonstrate that combining aptamers with nucleic-acid drugs harnesses a "weak signal + strong targeting" synergy, opening new avenues for multimodal, personalized immunotherapy in CRC.

Translational Research of Nucleic Acid Aptamers in CRC Diagnosis and Treatment

Owing to their exceptional molecular recognition capabilities, nucleic acid aptamers have driven the development of a variety of innovative strategies for CRC diagnosis and therapy. In diagnostics, aptamer-based biosensors—such as electrochemical and optical platforms—combined with functionalized nanomaterials (eg, quantum dots, gold nanoparticles, graphene) have achieved ultrasensitive and multiplexed detection of key CRC biomarkers in both complex simulated matrices and clinical specimens (Table 4). Therapeutically, aptamers can act as targeting ligands on diverse nanocarriers (eg, liposomes, polymer micelles, mesoporous silica) to enable tumor-specific delivery of chemotherapeutic drugs and nucleic acids (eg, siRNA, miRNA) in animal models. Beyond serving as delivery agents, certain aptamers can directly engage immune-related targets such as PD-L1, TNF-α, and IL-1α, thereby exerting immunomodulatory effects

Table 4 Representative Aptamer-Based Strategies for CRC Diagnosis and Therapy

Target	Method	Key Advantages	In vitro Outcomes	In vivo Outcomes	Ref
Serological Diagnosis					
miR-21/18a	SERS competitive assay using AuNDs arrays	Rapid, multiplex detection	LOD: 6.8/7.6 pM; accurate in serum vs qRT-PCR	Dynamic monitoring in mouse serum	[48]
CEA	Smartphone-based dual-signal electrochemical aptasensor	Portable POCT; wide linear range	LOD: 0.27–0.98 pg/mL; matches ELISA in patient serum	N/A	[50]
mCRC cells	One-step fluorescent aptasensor (graphene oxide)	Simple, rapid	LOD: 70 cells/mL; 93–102% recovery in blood	N/A	[60]
Targeted Therapy					
Nucleolin	Aptamer-modified PEG-rod mesoporous silica NPs (CPT + survivin shRNA)	Active co-delivery, synergistic	Enhanced uptake and apoptosis in C26 cells	Tumor suppression, prolonged survival, low toxicity in mice	[83]
Nucleolin	Aptamer-modified solid lipid NPs loaded with DTX	High loading, stable	IC_{50} = 0.28–0.11 nM; selective for C26 cells	Superior tumor inhibition and survival vs Taxotere®; safe in mice	[91]
MUC1	Aptamer-targeted liposomes with DOX	High specificity	Enhanced uptake/toxicity in $MUC1^+$ cells	Tumor suppression, prolonged survival, low systemic toxicity	[94]

(*Continued*)

Table 4 (Continued).

Target	Method	Key Advantages	In vitro Outcomes	In vivo Outcomes	Ref
Immunotherapy					
PD-L1	Cell-SELEX-derived DNA aptamer	Antibody alternative	Restores T-cell proliferation and IFN-γ secretion	Tumor inhibition (82%), minimal toxicity in mice	[100]
PD-L1	Aptamer-MOF NPs with OX plus phototherapy	Multimodal synergy	Blocks PD-1/PD-L1, induces ICD	Suppresses primary and distant tumors, boosts $CD4^+/CD8^+$ T cells	[108]
Combination Immunotherapy					
TNF-α	Dimeric aptamer from protein SELEX	Enhanced affinity and activity	Inhibits TNF-α (40%)	N/A	[116]
IL-1α	5'-naphthalene-modified DNA aptamer	High affinity, stable	Inhibits IL-1α signaling; reduces IL-6/IL-8 secretion	N/A	[119]

Abbreviations: SERS, surface-enhanced Raman scattering; AuNDs, Au nano-dodecahedrons; LOD, limit of detection; POCT: Point-of-Care Testing; ELISA: Enzyme-linked immunosorbent assay; NPs: Nanoparticles; IC_{50}, half-maximal inhibitory concentration; DOX: Doxorubicin; MOF, Metal–organic framework; OX: Oxaliplatin; ICD, immunogenic cell death; SELEX, Systematic Evolution of Ligands by Exponential Enrichment.

(Table 4). Preclinical studies employing clinical patient samples and murine models have yielded robust proof of concept and a solid experimental foundation for translating aptamer-based strategies into clinical applications.

Encouraged by these promising preclinical outcomes, multiple research teams and biotechnology companies are advancing aptamer technologies toward clinical application. At present, only a small number of aptamers targeting CRC have entered clinical evaluation. Notably, the single-stranded DNA aptamer Sgc8, which binds protein tyrosine kinase 7 (PTK7), is undergoing an early Phase I trial in China to differentiate benign from malignant CRC via positron emission tomography (PET) imaging.[126] Another example is AM003, currently in a phase I trial in Israel for various solid tumors, including CRC, with the primary goals of safety and tolerability assessment.[127] Although aptamer-based therapeutics specifically for CRC remain in their infancy, this field is expanding steadily within oncology research. As summarized in Table 5, several ongoing global clinical trials—spanning CRC and other malignancies—demonstrate the growing translational potential of aptamers and outline possible avenues for future CRC diagnosis and treatment.[128,129]

Table 5 Representative Global Clinical Trials of Nucleic Acid Aptamers in Oncology

Aptamer	Target	Indications	Country/Phase	Key Objective
Sgc8	PTK7	Colorectal cancer	China/Early Phase I	Safety and tumor imaging via PET
AM003	Tumor cells	Various solid tumors (incl CRC)	Israel/Phase I	Safety and tolerability
AST-201	GPC3	HCC, NSCLC	South Korea/Phase I	Safety, tolerability, preliminary efficacy
EYE001	VEGF	Hippel–Lindau disease	USA/Phase I	Safety and exploratory efficacy
AS1411	Nucleolin	AML	Multi-country/Phase II	Response rate, remission duration, DFS, OS
AS1411	Nucleolin	RCC	USA/Phase II	Overall response rate, PFS, safety

Note: The table content is sourced from ClinicalTrials.gov.
Abbreviations: CRC, Colorectal cancer; PET, Positron emission tomography; HCC, Hepatocellular carcinoma; NSCLC, Non-small-cell lung cancer; AML, Acute myeloid leukemia; DFS, Disease-free survival; OS, Overall survival; RCC, Renal cell carcinoma; PFS, Progression-free survival.

Challenges and Future Perspectives

Challenges and Limitations

Aptamers possess notable advantages in the early diagnosis and targeted treatment of colorectal cancer (CRC) owing to their high programmability and precise molecular recognition capabilities. Nonetheless, their pathway to clinical translation remains hindered by a range of challenges and limitations. These issues extend beyond the inherent properties of aptamers themselves to include deficiencies in research methodology, such as the absence of standardized protocols, limited clinical validation, and insufficient long-term safety data. Addressing these bottlenecks will be critical for realizing the full clinical potential of aptamer-based platforms in CRC diagnosis and therapy.

At the technical level, the application of nucleic acid aptamers in physiological environments is restricted by their intrinsic physicochemical properties. Unmodified single-stranded aptamers are highly susceptible to nuclease degradation, resulting in a plasma half-life often shorter than one hour, which significantly reduces their bioavailability.[12,130,131] Although chemical modifications such as phosphorothioate (PS) backbones or locked nucleic acids (LNAs) can extend circulation time and enhance nuclease resistance, they inevitably increase synthesis costs and may impair biological activity or trigger undesired immune responses.[132,133] In addition, complex biological samples—such as serum, plasma, or tissue homogenates—can induce nonspecific adsorption to proteins or lipids, thereby increasing false-positive rates and reducing detection sensitivity, especially when detecting low-abundance biomarkers like circulating tumor cells or exosomes.[134–136] While nanocarriers (eg, liposomes, mesoporous silica nanoparticles, or polymeric nanoparticles) and polyethylene glycol (PEG) modification can improve delivery efficiency and pharmacokinetic behavior, the balance among target specificity, carrier biocompatibility, and potential toxicity remains challenging.[137,138] Notably, PEGylated aptamers such as Pegnivacogin have been reported to induce anti-PEG antibody production, leading to severe hypersensitivity reactions,[139] and LNA-modified nucleotides have been associated with hepatotoxicity.[10]

Methodological limitations severely constrain the reliability and clinical translational value of aptamer research. Currently, no standardized procedures exist for SELEX screening and validation in this field. Significant variations among research teams—in aspects such as initial library design, screening pressure, negative selection strategies, sequencing depth, and data analysis workflows—result in poor reproducibility and low cross-platform comparability of aptamer sequences, thereby undermining the reliability and generalizability of findings.[140] Many published studies rely on a narrow range of cell lines or immunodeficient animal models, are conducted with small sample sizes, and have insufficient statistical power. Such approaches fail to capture the complexity of the human tumor microenvironment or the regulatory role of the immune system, greatly reducing their clinical predictive value. Furthermore, clinical sample collections are often limited to single-center studies and lack cross-racial, multi-pathological classification, randomized controlled trial (RCT) data, making it challenging to generate high-level evidence with broad applicability. Of particular concern is that most existing in vivo and in vitro experiments lack comprehensive dose–response evaluations, toxicological assessments, and long-term follow-up, while often neglecting detailed investigations into potential off-target effects, mechanisms of drug resistance, and organ-specific toxicities. Together, these methodological shortcomings—including non-standardized experimental systems, inadequate sample sizes, and poorly generalizable models—substantially impede the advancement and clinical translation of aptamers in colorectal cancer diagnosis and treatment.

Future Development Directions

Multimodal theranostic platforms that integrate nucleic acid aptamers with liposomes, gold nanoparticles or polymeric nanoparticles have been shown to enable image-guided targeted drug delivery coupled with real-time efficacy monitoring, thereby reducing systemic toxicity while improving the therapeutic index.[141–143] To date, several CRC-targeted aptamer candidates have advanced into phase I/II clinical trials, and preliminary results demonstrate favorable safety profiles and high tolerability. However, to accelerate their translation into large-scale clinical use, further optimization of dosing regimens and the establishment of standardized clinical endpoints and evaluation criteria are still required.

Looking ahead, artificial intelligence (AI) and big data-driven intelligent design are poised to revolutionize aptamer development. AI-based approaches have shown great promise in the rational design and optimization of aptamers. For example, Li et al developed a machine learning framework based on Random Forest, which integrates aptamer sequence

features with the physicochemical properties of target proteins, and employs maximum relevance minimum redundancy (mRMR) and incremental feature selection (IFS) algorithms for feature screening. This strategy achieved highly accurate prediction of high-affinity aptamer–target interactions, significantly enhancing screening efficiency while reducing experimental costs.[144] In addition, deep learning architectures such as convolutional neural networks (CNNs), recurrent neural networks (RNNs), and general regression neural networks (GRNNs) have been applied to conformational prediction and binding free energy estimation of aptamer–target complexes, providing new strategies to reduce the trial-and-error nature of traditional screening.[145]

Building on these advances, AI-assisted aptamer design is evolving from single binding-affinity prediction toward an integrated, end-to-end pipeline. Machine learning and molecular simulation can predict binding affinities and secondary structures during virtual screening and sequence optimization, significantly shortening SELEX cycles and increasing hit rates. At the same time, integrating multi-omics data, patient clinical records, and biomarker databases will enable the customization of aptamer sequences tailored to CRC subtypes and drug-resistant phenotypes.[146] Furthermore, smart drug release systems responsive to tumor microenvironmental stimuli (eg, pH, enzymatic activity) offer the potential to dynamically control therapeutic payload delivery. The convergence of AI-driven design, multimodal theranostics, and rigorous clinical validation has the potential to position nucleic acid aptamers at the forefront of CRC management, paving the way for precision medicine characterized by high efficacy, low toxicity, and customizable therapeutic outcomes.

Conclusions

In summary, nucleic acid aptamers—with their small molecular weight, versatile chemical modifiability, high affinity, and specificity—have demonstrated tremendous potential for early detection and precision therapy of CRC. By employing cutting-edge selection strategies such as microfluidic SELEX and HTS-SELEX, researchers have developed multiple high-performance aptamers targeting CRC biomarkers and, in combination with electrochemical biosensors and functionalized nanomaterials, have achieved marked improvements in detection sensitivity and multiplex target recognition. Therapeutically, aptamer-based smart nanocarriers not only enable selective accumulation of chemotherapeutic agents or immunomodulators in the tumor microenvironment but also trigger precise drug release in response to pH, redox, or photothermal stimuli, thereby significantly enhancing anti-tumor efficacy while minimizing toxicity to healthy tissues. Although challenges remain in shortening selection cycles, enhancing in vivo stability, suppressing nonspecific binding, and ensuring consistency in large-scale production, these can be addressed through optimized chemical modification strategies, integration of artificial intelligence and big data–assisted screening, and personalized clinical trials across diverse pathological subtypes and patient populations. Looking forward, nucleic acid aptamers are poised to play an even greater role in CRC precision medicine, offering patients safer, more effective, and individualized therapeutic options.

Abbreviations

POCT, Point-of-care testing; CRC, Colorectal cancer; CLIA, Chemiluminescence Immunoassay; ELISA, Enzyme-Linked Immunosorbent Assay; CTCs, Circulating tumor cells; SELEX, Systematic Evolution of Ligands by Exponential Enrichment; CE, Capillary electrophoresis; SPR, Surface Plasmon Resonance; SERS, Surface-Enhanced Raman Scattering; AuNCs, Au Nanocubes; AuNDs, Au Nanododecahedrons; 4-MBA, 4-mercaptobenzoic acid; DTNB, 5,5′-Dithiobis (2-nitrobenzoic acid); LSPR, Localized surface plasmon resonances; CTRMs, Circulating tumor related materials; CEA, Carcinoembryonic antigen; PSA, Prostate-Specific Antigen; MOFs, Metal-Organic Frameworks; ERP, Enhanced Permeability and Retention; AuNP, Gold nanoparticle; AuPt, Dendritic nanocrystals; MSNs, Mesoporous Silica Nanoparticles; GSH, Glutathione; mCRC, Metastatic colorectal cancer; ICB, Immune Checkpoint Blockade; CAFs, Cancer-Associated Fibroblasts; saRNA, Small activating RNA; miRNA, MicroRNA; LNA, Locked Nucleic Acid; PDAC, Pancreatic ductal adenocarcinoma; ctDNA, Circulating tumor DNA; TME, Tumor microenvironment; mRMR, Maximum relevance minimum redundancy; IFS, Incremental feature selection; CNN, Convolutional neural network; RNN, Recurrent neural network; GRNN, General regression neural network.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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