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Aptamers functionalized biomolecular nano-vehicles for applications in cancer diagnostics & therapeutics

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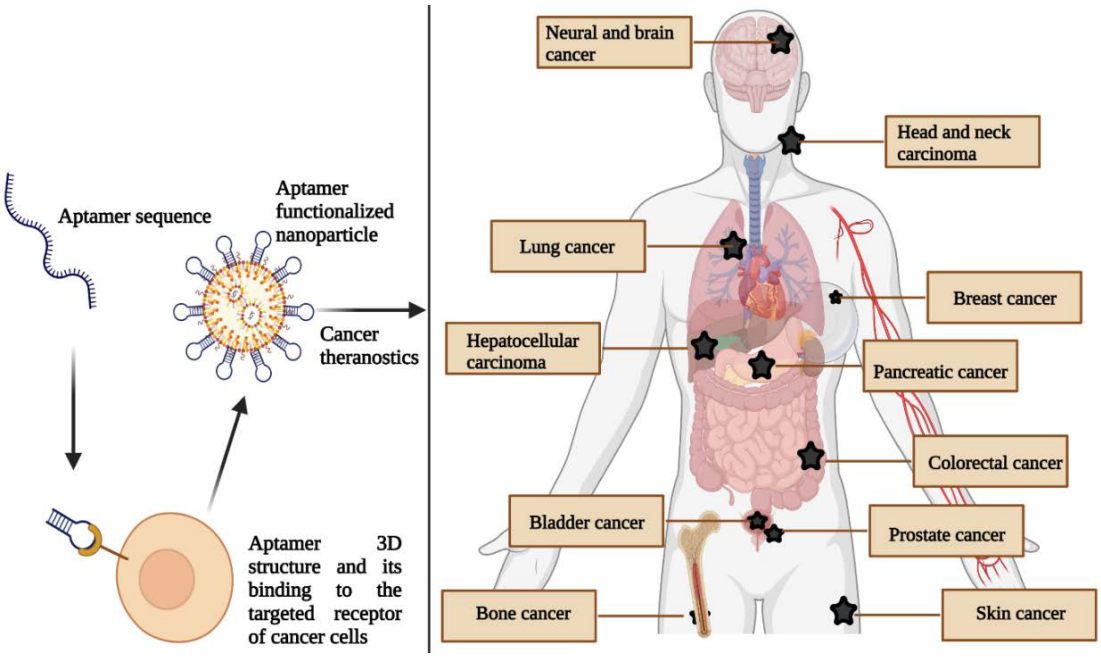
Review Article

ABSTRACT



Given its structural versatility and functional programmability, DNA has emerged as an ideal scaffold for developing nanoscale materials with emerging applications, including the ones in diagnosis and therapeutics. The two main components contributing to the successful sojourn of DNA devices in biological systems are their ability to either encapsulate or functionalize nanoparticles' diversity and their capabilities for specific physical recognitions via modules like targeting entities like aptamers. DNA-based nanoparticles and aptamers functionalized DNA nanodevices enable high biocompatibility, biological targeting, stability, and drug loading. As a result, they have seen their enhanced usage in biomedical applications. This review presents an overall picture and current trends of lipid & non-lipid-based nano-vehicles that can be functionalized with aptamers and loaded for applications like bio-sensing and delivery, especially focusing on cancer diagnosis therapeutics. We conclude with future prospective and directions for improving current systems to interface with biological systems and upgrade materials for clinical transition.

Keywords: Cancer, aptamers, nanoparticles, aptasensors, drug delivery, therapy

INTRODUCTION

Cancer is associated with the uncontrollable growth and spreading of cells caused by genetic and environmental factors.[1] A tumor that can be both benign and malignant is a cluster of cells with unsuppressed growth that have proliferated aggressively. The un-controllably growing cells, blood vessels, and connective tissues are the components of tumors. These tumors become metastatic with the help of matrix metalloproteinase, which are the enzymes that break the provincial host tissues; this helps cancer to enter the blood vessel and migrate to the distant organs. The broken clusters of tumor cells can enter the blood vessels through leaking or damaged capillaries and migrate to remote regions throughout the body.[1] The malignant tumors can promote angiogenesis for their growth

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in secondary organs. Cancer develops due to a series of complex events over a while. Genetic abnormalities, primarily mutations in the tumor suppressor gene or proto-oncogene, result from this chain of events, which is responsible for unstoppable cell growth and differentiation.[2] The initial exposure to cancer diagnosis takes a more extended period, making treatment difficult. The worldwide cancer epidemic is continually rising due to the growing population rate and aging.[2] During 2022, the United States is expected to have 1,918,030 total incidences of cancer and 609,360 cancer-related fatalities, with around 350 mortality each day due to lung cancer, the primary issue of cancer mortality. Notwithstanding a 4 percent to 6 percent annual increment in terminal illnesses since 2011, the frequency of breast cancer persisted to rise slowly (by 0.5 percent annually) from 2014 to 2018, and the occurrence of prostate cancer remained steady.[3] In recent years, numerous advances have been made in treating cancer due to rapid progress. Still, the worldwide high fatality rate from malignant tumors is endangering people's lives due to the challenges arising from cancer diagnosis and clinical management.[3] The conventional treatment strategy includes surgery, radiotherapy, and chemotherapy, but they all have particular disadvantages in clinical application. Surgery is an efficient treatment strategy to remove solid tumors (early stages) but not a potential treatment strategy for non-solid tumors (leukemia) and a less potent treatment strategy for tumors with advanced stages. Although chemotherapy slows down or stops the growth of fast-growing cells, this treatment strategy cannot distinguish between fast-growing cancerous and non-cancerous cells (hair cells, cells that line the intestine and mouth), results in non-specific damage by killing normal cells and side effects such as nausea, hair loss, and mouth sores. Additionally, cancers grow resistant to chemotherapeutic medications in people who use them for an extended time. Radiation therapy applies high-energy ionizing radiation to kill cancer cells by shrinking and damaging their DNA. But radiation therapy often causes severe adverse side effects such as radiation pneumonia, radiation osteonecrosis, and systemic reaction.[4] Despite decades of research on cancer detection and therapy[5], this avenue requires more and more specific targeting to avoid the side effects of conventional treatments.[6] Along with killing the cancer cells, radiotherapy, chemotherapy, and conventional surgery also immensely impact the non-cancerous cells.[7] Hence the lookout for molecular medicine and biologically compatible drugs delivered to the location has been prioritized.[7] With nanotechnology, nanoparticles have been studied immensely to deliver cancer drugs in target locations using various external forces such as magnetic field[2], electric field[7], etc. One more step came forward when aptamer-based therapy targets the tumor cells using a molecular recognition strategy.[8]

In the 1990s, the technology of producing biomolecules capable of specific binding was the systematic evolution of ligands by exponential enrichment (SELEX), and “aptamers” were created by this technique.[9] Aptamers, which are single-stranded (usually 30 -100 nucleotides) oligonucleotides (DNA or RNA), have exclusive spatial structure (3D) for binding with the target molecule with higher affinity and specificity. [10] There are various aptamers targets, including cells, proteins, and ions. The aptamers regulate the function of the proteins by explicitly targeting the protein.[11,12] The aptamers have advantages over conventional antibodies, which can bind with target molecules, such as higher specificity, stronger affinity, easy modification, accessible storage, and good stability. [5,6] The unique properties of aptamers have made them useful in detecting cancer and targeted therapy for cancer treatment.[13]

As a modification of aptamers is easy, many modifications have been made to the aptamers to make them versatile, such as modifications with radionuclides, biotins, and fluorescent dyes. The aptamer's pharmacokinetics or biodistribution is mostly determined by its biochemical and physical characteristics. [14] The grafting modification improves aptamers' stability, biocompatibility, and bioavailability, enhancing their biochemical properties and helping them meet the criteria for clinical usage.[15,16] In addition, aptamers are potent vehicles to deliver drugs and proteins to the specific components of cells by conjugating with drug molecules, nanoparticles, and small interfering RNAs (siRNAs), thereby lessening the side effects.[6,17] drug-loaded nanoparticle–aptamer conjugates embody an advancing technology that can promote the targeted delivery of drugs to the site of tumors.[6]

Nanoparticles, which are small particles (1–100 nm), are mostly biodegradable and biocompatible materials. These are used as a carrier to deliver peptides, proteins, or nucleic acids into the cells. Regardless of efficacy, many anti-cancer drugs with bulky polycyclic structures are hydrophobic; they lack selectivity towards cancer cells and have poor bio-distribution, which results in serious side effects. Nano-sized drug delivery vehicles (inorganic and polymeric nanoparticles) have been studied to overcome the disadvantages. The drug-loaded nano-sized vehicles protect the drug from the external environment and aid the drug molecule from being trapped by the reticuloendothelial system (RES) due to enhanced permeability and retention effect (EPR), which results in prolonged circulation time of drug molecule in the blood.[7] These nano-sized vehicles more likely accumulated at the site of the tumors, thereby escaping the drainage through leaky blood vessels and the lymphatic system.[7] A prime requirement in cancer therapeutics is a biocompatible nano-sized anti-cancer drug delivery vehicle targeting cancer cells with higher efficacy and sustainably releasing anti-cancer drug molecules. Surface modification of nanoparticles with ligands such as antibodies, peptides, and aptamers is necessary to develop cancer cell-targeted nanoparticles. The property of the nanoparticle conjugated aptamers to recognize the tumor cell-specific biomarkers and accumulate specifically to the tumor sites reduces the side effects. In recent times, the nanoparticle-aptamer complex has been applied in cancer detection and therapy. This aptamers-nanoparticle complex helps detect circulating tumor cells (CTCs) due to their higher affinity towards tumor biomarkers, opening a new horizon for personalized cancer medicine.[18] Schematic 1 represents the role of the aptamer-nanomaterial conjugate in cancer therapy, imaging, and diagnosis. The aptamer-nanomaterial conjugate targets cancer cells by recognizing tumor-specific biomarkers,

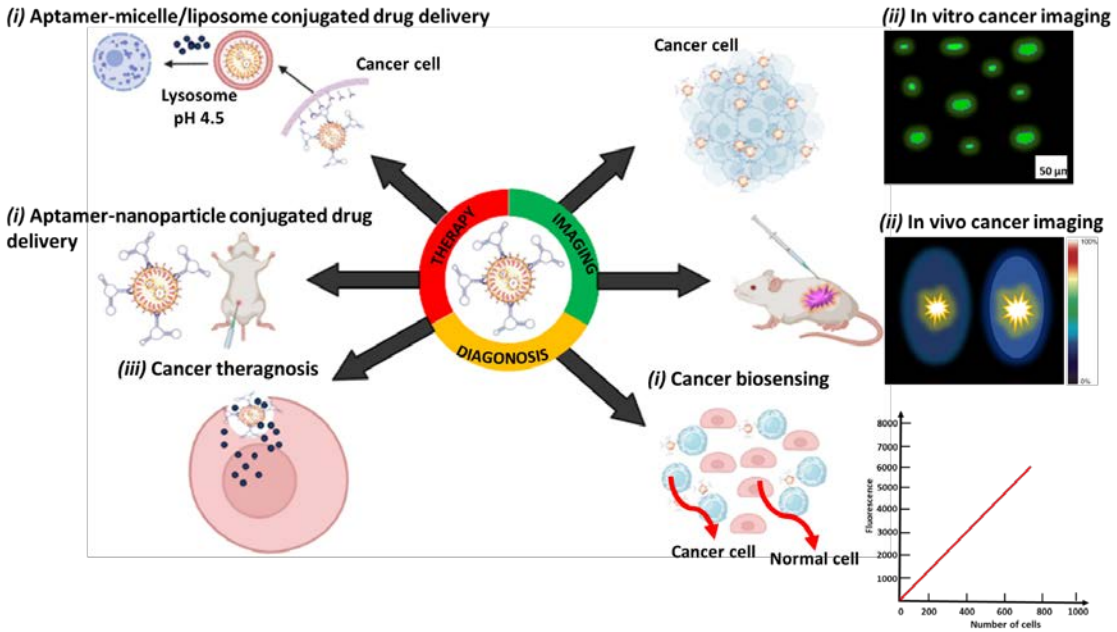

Figure 1. Schematic representation of aptamer-nanomaterial conjugate and its role in **(i)** designing aptamer – micelle/ liposome/ nanoparticle-based drug delivery as cancer therapeutics **(ii)** aptamer-nanomaterial based in vitro and in vivo cancer cell imaging and **(iii)** aptamer- nanoparticle-based cancer diagnosis by particularly detecting and targeting cancer cells from the pool of both normal cells and cancer cells. (Figure is created with BioRender.com.)

which help in tumor-specific drug delivery, detection, and cancer cell imaging. Specific biomarkers distinguish the cancer cells from the normal cells, which aid in cancer cell imaging and diagnosis. This review has discussed the role of different aptamer conjugated nanovehicles in the current problem associated with cancer therapy and detection and future perspectives.

Role of Aptamer in Cancer Detection and Therapy

Conventional anti-cancer medications are often non-selective and have resulted in significant toxic adverse effects in clinical trials.[19] Aptamers are short oligonucleotides with specificity and affinity for their specific targets.[20] Aptamers can be used as prescription medications. They can also serve as a drug carrier by attaching with siRNA, drugs, nanoparticles, and other compounds to form a targeted drug carrier that can specifically target cancer cells, limiting toxic effects to normal cells, lowering therapeutic dosages, and improving therapeutic effectivity. SELEX technique is screening several aptamers that attack tumor cells, including AS1411 (anti-nucleolin aptamer) A10 (anti-prostate-specific membrane antigen aptamer), Sgc8 (anti-protein tyrosine kinase 7 aptamer) EpCAM (anti-epithelial cell adhesion molecule aptamer).[21–23] Different drug delivery carriers have also been devised for all these aptamers for targeted therapy of certain cancer cells. Precise tumor diagnostic techniques can assist clinicians in determining initial treatment recommendations, assessing the clinical outcome, monitoring tumor relapse and metastasis, and determining prognosis. Aptamer has been extensively utilized in detecting circulating tumor cells (CTCs), immunohistochemical examination, and in vivo studies in the field of cancer imaging. With the development of aptamer screened through Cell-SELEX, a list of aptamers are potentially leveraged in cancer detection and therapy shown in table 1.

Aptasensors, which employ aptamers as bio-receptors, have garnered a great deal of interest as a way to detect cancer biomarkers.[24] After attaching to the target analyte (biomarker in case of cancer), the conformation of the aptamer alters, enabling the fabrication of a unique and diverse biosensor. A potential sensing material has been employed in developing cancer-specific markers, including aptamer-based optical sensors, electrochemical sensors, etc.[25–28] Optical sensors based on aptamers have produced massive progress in several disciplines, including bioscience, health, and environmental sensing.[28] For instance, An aptamer-based optical fiber sensor has been developed to diagnose breast cancer utilizing the HER2 biomarker, according to Loyez et al. For detection, a 50 nm Au film was linked to HER2 ssDNA aptamers.[29]

Some cancer biomarkers, such as CTCs, are suitable targets for liquid biopsy because they are secreted into the circulation by cancer cells. CTC detection is challenging due to the limited number of cancer cells in blood compared to a vast majority of blood cells.[30,31] In recent times, a plethora of aptamer-based analytical techniques have been developed to detect CTCs by coupling signal reporting technologies like magnetic, colorimetry, fluorescence, and electrochemistry. For instance, to attain high capture of CTCs and precise localization of the primary tumor, Jia et al. developed a combined strategy based on in-vivo capture employing an antibody cocktail and multicolor fluorescence imaging via aptamer.[30] Danesh et al. used 5,6,7-trimethyl-1,8-naphthyridin-2-amine (ATMND) as a fluorescence dye to construct a label-free aptasensor with a limit of detection of 1.5 pg/mL for detecting carcinoembryonic antigen (CEA) which is a cancer biomarker that may be exploited to detect a

wide range of clinical conditions, including gastric cancer, ovarian cancer, pancreatic cancer, and colorectal cancer.[32]

The application of molecular imaging in cancer diagnosis, monitoring, and the prognosis is crucially significant.[33] Aptamers are an emerging tool for cancer detection by integrating with radionuclides, fluorescent molecules, and other imaging molecules.[34–36] Luminescence imaging, magnetic resonance imaging (MRI), computed tomography (CT), and radionuclide-based positron emission tomography (PET) are all in-vivo imaging modalities for cancer diagnosis. For example, Sgc8-c aptamer coupled with Alexa Fluor 647 fluorophore was developed by Liu et al. as an imaging probe for molecular imaging of colon cancer.[37] Li et al. designed aptamer PDGC21-T coupled fluorescent nanoparticle quantum dots (QDs) as a molecular imaging tool for detecting poorly differentiated gastric cancer, which is critical for treatment and diagnosis.[38]

Aptamers have now been extensively employed in the Immunohistochemical examination of tumor tissues, and they have exhibited various practical properties that are preferable to antibodies. Leveraging aptamers as probes and immunohistochemical analysis of various kinds of cancer tissue specimens, Li X et al. screened a set of aptamers that can precisely detect metastatic lymph node tissues of colon cancer. No signal was spotted in non-metastatic colon cancer clinical specimens or other control specimens. This implies that the aptamer's target is associated with metastatic colon cancer.[39]

The cornerstone of contemporary tumor therapy is targeted drug delivery. Aptamers have emerged as a novel approach to tumor-targeted medication treatment. Because of their particular physiochemical features, aptamers are an excellent tool for clinical use. Aptamer-functionalized nanomaterials and aptamer-drug conjugates (AptDC), are examples of therapeutic aptamers.

CHEMISTRY OF FUNCTIONALIZING NANOPARTICLES WITH APTAMERS

Aptamers can be directly or indirectly tethered to nanoparticles via covalent or non-covalent interactions. Indirect tethering requires the presence of a linker molecule. High-affinity couplings and electrostatic interactions are types of non-covalent functionalization. Interactions involving avidin-biotin, and streptavidin-biotin, are instances of high-affinity couplings. The electrostatic interactions are most widely encountered when a linker molecule is utilized. In this scenario, the opposing charges on the extended oligonucleotide sequence of the aptamer and linker molecule bind.

A functional group including a primary thiol or an amino group is linked to one end of the aptamer during covalent coupling. This can interact with the functioning group on the end of the linker molecule or surface of the nanoparticle. The carboxylic acid group and amino group reaction generally result in an amide linkage, the thiol group, and thiol group interaction that eventually lead to disulfide bond, and the carboxylic acid group and thiol group reaction which results in a thioester bond are all instances of prevalent interactions.

The covalent method was used in the majority of the aptamer–nanoparticle conjugates produced so far. Fewer works have

Table 1. Different roles of aptamers in cancer theranostics

Aptamer	Role	Target	Cancer type	Limit of detection (LOD)	Clinical trial phase	Ref
SYL3C	Targeted therapy and imaging probe	EpCAM	breast cancer	-	N/A	40
Apt928	Aptasensor	CD70	ovarian cancer	-	N/A	41
Apt1	Drug delivery system	CD44	lung cancer	-	N/A	42
CD24	Diagnostic and therapy	CD24	colon cancer	-	N/A	43
A10	Detection tool and targeted drug delivery	PSMA	prostate cancer	-	N/A	44
AS1411	Therapy	Nucleolin	80 cancer types including lung, renal, breast	-	Approved	45
NOX-A12	Therapy	SDF-1	Leukemia	-	Phase II	46
CD30	Molecular imaging probe and immunostaining	CD30	lymphoma	-	N/A	47, 48
LXL-1-A	Detection and imaging	Extracellular proteins	Metastatic breast cancer	-	N/A	49
XL-33-1	Molecular imaging probe	Cell surface membrane protein	Colon cancer	-	N/A	39
Wy-5a	Diagnosis and therapy	Membrane protein	Prostate cancer	-	N/A	50
A15	Molecular imaging and therapy	CD133	liver cancer	-	N/A	51

KH1C12 aptamer	Detection and imaging	KH1C12	leukemia	-	N/A	[52]
GBI-10	Diagnosis and therapy	Tenascin-C	glioblastoma	-	N/A	[49]
36t	Therapy	PDGF (platelet derived growth factor)	Breast, Ovarian, cervical thyroid, lung cancer	-	N/A	[53]
NX-191	Therapy	VEGF (vascular endothelial growth factor	Breast, melanoma, myeloid, leukemia, brain, pancreatic, lung, gastric, colon,	-	N/A	[54]
EpCAM	Aptasensor	MCF7	Breast cancer	10 cells/ml	N/A	[55]
KH1C12	Aptasensor	HL-60	Leukemia cancer	250 cells/ml	N/A	[56]
TLS11a	Aptasensor	HepG2	Liver cancer	15 cells/ml	N/A	[57]
MUC1	Aptasensor	DLD-1	Colon cancer	40 cells/ml	N/A	[58]
AS1411	Aptasensor	HeLa	Cervical cancer	10 cells/ml	N/A	[59]
EpCAM-apt	Drug delivery system	Hepatocellular carcinoma cells	Hepatocellular carcinoma	-	N/A	[60]
CD33	Drug delivery system	Hepatocellular carcinoma cells	Hepatocellular carcinoma	-	N/A	[61]

employed a linker molecule to join the aptamer with the nanoparticle. These are taken into concern in order to prevent any spatial constraints on the aptamer's attachment to the target molecule. For aptamer coupling with polymeric NPs, EDC-NHS combination is preferable over maleimide-thiol reaction. The benefit of this approach is that the residual carboxylic acid group on the nanoparticle surface will give the nanoparticle a little negative electrical charge. The nonspecific contact between aptamers and the nanoparticle is diminished as a result of this decreased interaction. Furthermore, in maleimide-thiol chemical reactions, a problem arises when the thiol present on the aptamers is being oxidized during retention, resulting in dimerization of aptamers that are unable to conjugate with the maleimide on the nanoparticle surface.[62]

Confocal microscopy, flowcytometry, zeta potential measurement, Xray photoelectron spectroscopy, and agarose gel electrophoresis may all be used to establish aptamer attachment to the surface of nanoparticles. The aptamers must be fluorescently tagged for subjective evaluations utilizing confocal microscopy and flow cytometry.[63–66]

THERANOSTIC IMPLICATIONS OF APTAMER-CONJUGATED NANOPARTICLES (NPS) IN ONCOLOGY

Nanoparticles (NPs) of size 10-250 nm are extensively used for imaging, diagnosis, targeted therapy, and drug delivery. However, their toxicity and non-targeted delivery to normal cells limited their applications in biomedicine. The half-life of aptamers in the circulatory system is minimal due to their low molecular weight, which significantly impacts medicinal effectiveness. Nanoparticles with a predefined range of diameters can attack cancer cells through the influence of enhanced permeability and retention (EPR). However, this is a "passive" targeting form that is vulnerable to factors including blood pressure, distinct features in the vasculature, and location and type of tumor tissues, leading to massive individual impacts differences. Integrating aptamers with nanoparticles can prolong the half-life of drugs and aptamers in the bloodstream, but the substantial surface area of nanoparticles can also augment the drug loading, and the uniform shape allows for optimal physiological distribution. In recent times, aptamer-functionalized NPs have been pretty thoroughly utilized in the creation of theranostic platforms due to their particular capabilities in targeted medication delivery platforms, detection, and assessing therapy response.[67] Warner developed the word "theranostics" to describe a method that combines diagnosis and therapy. This is a key concept when developing nanotechnology-based imaging techniques and imaging-guided therapies; this is a crucial concept. [68,69]

Recent studies have demonstrated enhanced cancer-specific cytotoxicity by the aptamer-nanoparticle bioconjugate. [5,6] Several advantages of aptamer-based nanoparticles [70] include **(1)** drug delivery, **(2)** specific detection of cancer cells due to the target specificity of aptamer, **(3)** ease to synthesize, and modification **(4)** the high loading capacity of nanoparticles can lead to successful drug delivery to cancer cells and **(5)** aptamer attached to the nanoparticle surface can aid in cellular uptake via internalization and active targeting of the drug delivery vehicle to the site of action. Nanoparticles are categorized based on their composition, such as quantum dots (QDs), carbon-based NPs, polymer- and lipid-based NPs, dendrimers, and hybrid NPs. The unique optical properties of QDS increase their role in

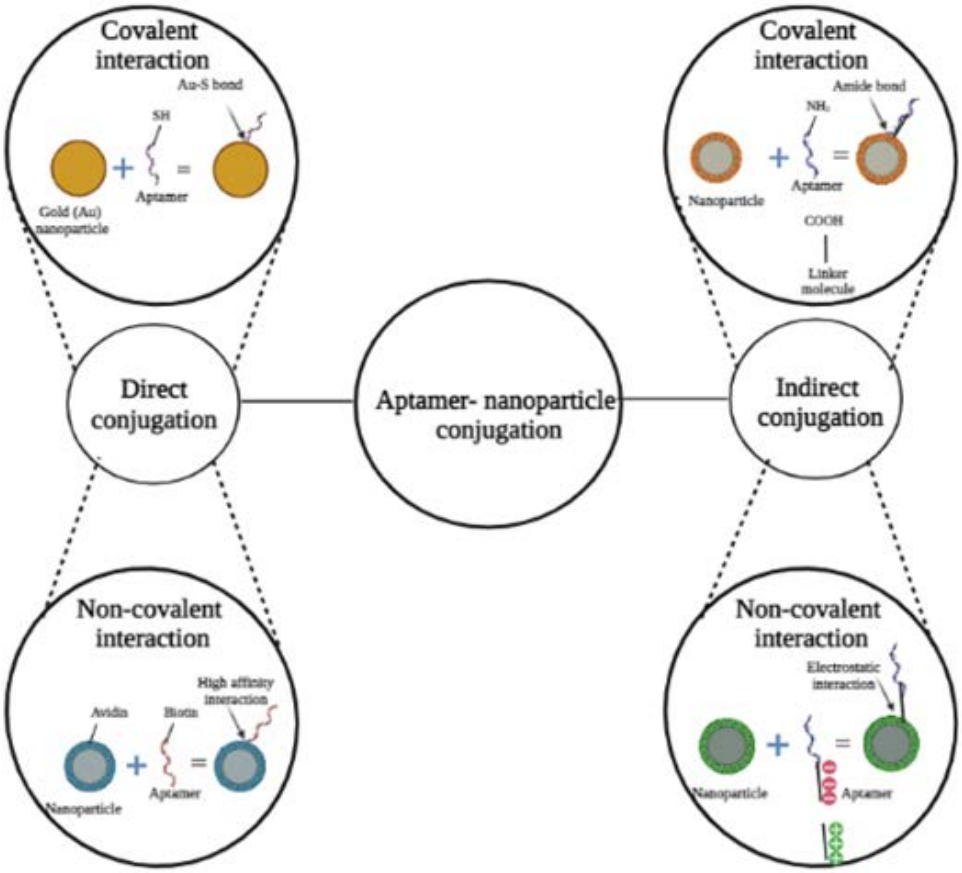

Figure 2: Schematic representation of nanoparticle-aptamer coupling methods that are commonly used. (Figure is created with BioRender.com.)

bioimaging and sensing applications. Further, their surface modification with targeted biomolecules such as proteins, antibodies, aptamers, peptides that bind to targeted receptors on cells or tissues resulted in sensitive and selective theragnostic applications.[69]

Lipid-based nanoparticles comprise agents with drug-carrying capabilities such as liposomes, nanostructured lipid carriers (NLCs), and solid lipid nanoparticles (SLNs). SLNs are a type of lipid-based nanoparticle that comprises a solid hydrophobic lipid structure that can entrap drugs and release them in a controlled manner depending on the nature of drug molecules and properties of lipids.[71–73] Several aptamer-based nanoparticle systems have been developed to increase drug efficacy and have been discussed in subsequent sections. Another class of biocompatible polymer, i.e., dendrimers, has potential applications in cancer therapeutics. Their small size, exceptional symmetry, usefulness, and internal chambers for encapsulating desired components make them ideal for encapsulating materials. In vitro and in vivo, dendrimers contain NPs or biomolecules and are functionalized with aptamers to improve biocompatibility and cellular absorption.[74] The potential advantages and disadvantages of aptamer conjugated nanoparticles have been discussed in table 2.

Table 2. Advantages and disadvantages of different types of aptamer conjugated nanoparticles

Type	Nano-composite	Advantages	Disadvantages	Ref.
Non-lipidic	Aptamer-quantum dots nanomaterial	· low photobleaching · Chemically stable · Good biocompatiility	· low water solubility · poor biodistribution	75–77
	Aptamer-dendrimer nanomaterial	Enhanced surface area, higher potency, better interaction with target entity.	· Potential toxicity	78,79
	Aptamer-mesoporous silica anomaterial	high thermal stability, uniformly porous, biocompatible	· The surface abundance of silanol clusters interacts with the phospholipid layer o	80–83

			red blood cells, causing hemolysis and melanoma formation.	
	Aptamer-magnetic nanomaterial	lower immunogenicity, better stability, high specificity	· The aggregation of magnetic nanoparticles may cause blockage of blood vessels inside the target area. · Toxic side effects	84
	Aptamer-polymeric nanomaterial	High drug-loading yield, good cellular targeting	· Potential toxicity	85,86
	Aptamer-metallic nanomaterial	High porosity for therapeutic encapsulation, large surface areas.	· Non-biodegradable · Their preparation takes a considerable amount of time.	87,88
	Aptamer- 2D nanomaterial	· Easy to fabricate · Presence of optical, electronic, and thermal properties	· Potential toxicity	89
Lipidic	Aptamer-liposome nanomaterial	· Both hydrophilic and hydrophobic drugs can be encapsulated · Sustainable drug release	· A limited capacity for loading · Poor bioavailability	90
	Aptamer-micelle nanomaterial	· Enhanced binding affinity · Resistant to degradation	· Poor drug loading · Poor stability	91,92
	Aptamer-solid lipid nanoparticle	· Higher drug loading efficacy . Biocompatible	· Initial burst release of the therapeutic molecule	92
	Aptamer-hybrid lipid polymer nanomaterial	· Good tolerability · Sustainable drug release · Both hydrophilic and hydrophobic drugs can be encapsulated	· poor colloidal stability	93

Aptamer conjugated non-lipid-based nanoparticles for cancer detection and therapy

Over the past several years, there has been extensive research on the various cancer detection and therapies approaches. The current cancer therapy involves chemotherapy and radiotherapy but has several disadvantages like target specificity and collateral effects on the neighboring cells. The ultimate goal is to develop a probe that can easily distinguish cancer cells from normal cells and act as a detection tool and drug delivery system with targeted therapy, stimuli-responsive drug release, and effective killing of tumor cells without causing any adverse effect to normal cells. These goals can be achieved by developing an aptamer conjugated nanostructure that could efficiently target the tumor cells due to the target recognition property of aptamers which are helpful for cancer diagnosis and imaging (in vitro & in vivo), and drug loading capacity of nanostructures, which can release drugs in the presence of external stimuli.

Doxorubicin (Dox), well known anticancer drug, is successfully used to treat different types of cancers.[94] Dox inhibits cancer cell growth by distinct mechanisms resulting in the generation of oxidative stress, DNA damage, and apoptotic pathways of cell death.[95] Although Dox is an effective anticancer therapeutic drug, its poor solubility, resistance, toxicity, and side effects caused to the non-targeted organs limited its applications.[96–99] Therefore to enhance therapeutic effects and reduce side effects of Dox, its targeted delivery is of utmost importance.[95,100] Aptamers are small single-stranded oligonucleotides that can specifically bind to the target molecules via van der Waals forces, hydrogen bonding, salt bridges, electrostatic interaction, and shape complementarity.[101,102] The aptamer is synthesized by an in vitro procedure known as "Systematic Evolution of Ligands by Exponential Enrichment" (SELEX).[103,104] Due to the property of aptamer to bind to the target with remarkable affinity, aptamers are being extensively exploited in cancer diagnosis and therapy.[105–107]

Over the past decade, there has been rapid development in the field of nanotechnology. The theranostics properties of nanomaterials have been widely used in several biomedical applications.[108] These nanomaterials accumulate in the target cells non-specifically, i.e., passive targeting via enhanced permeability and retention (EPR) effect. Cell-specific and active targeting can be achieved by conjugating specific aptamers acting as targeting ligands to nanomaterials to treat cancer efficiently. In the past few years, there has been remarkable progress in the field of aptamer-based nanomaterials drug delivery; however, to reach the target cells successfully, the therapeutic complex needs to overcome a variety of biological barriers such as nuclease activity in plasma and tissues; renal clearance; reticuloendothelial system clearance; endothelial barrier; membrane barrier, etc. [109,110] There is essential to create effective drug delivery systems to improve drug target efficiency and therapeutic effects.

Farrokhzad et al. developed an aptamer-nanoparticles-based drug delivery system for targeted delivery to the prostate cancer cell. Poly(lactic acid)-block-polyethylene glycol (PEG) copolymer with a terminal carboxylic acid functional group (PLA-PEG-COOH) was used as a nanoparticle, and rhodamine-labeled dextran (as a model drug) was encapsulated within PLA-PEG-COOH nanoparticles. They used A10 RNA aptamers specific to prostate-specific membrane antigen (PSMA), a transmembrane protein well-expressed in prostate cancer epithelial cells. Encapsulating rhodamine-labeled dextran in pegylated PLA nanoparticles with a negative surface charge as a model drug. The PSMA aptamer was conjugated to the nanoparticle-drug complex, and the complex's uptake efficiency was assessed. To conclude, the nanoparticle-aptamer bioconjugates are a suitable candidate for efficient and specific targeted drug delivery to prostate cancer cells.[110]

Dhar et al. demonstrated remarkable cisplatin encapsulated pegylated PLGA NPs for specific delivery of cisplatin to prostate cancer cells. Due to the insolubility of cisplatin in organic solvents and partial solubility in water, it is difficult to construct and stabilize cisplatin-encapsulated-PLGA drug-release systems for a long duration.[111,112] Recent studies have revealed the release of cisplatin from a Pt(IV) precursor. The study shows that this biomolecular system can be encapsulated in pegylated PLGA aptamer-nanoparticle bioconjugates. Targeted therapy of prostate cancer cells can result in drug molecule release upon intracellular decrease. The extracellular domains of PSMA were targeted using a 10-fluoropyrimidine RNA aptamer functionalized on the surface of Pt(IV)-encapsulated pegylated NPs. [112] The study reveals the aptamer-facilitated cellular uptake of Pt(IV)-encapsulated nanoparticles by the prostate cancer cells. The process was demonstrated by antibodies specific for endosome formation. This study unravels future cancer therapeutic prospects of delivering platinum drugs to various cancer. [6]

Kim group has developed a prostate-specific membrane antigen (PSMA)-specific, aptamer-conjugated multifunctional Gold Nano Particles (GNPs) capable of acting as a drug delivery vehicle. The PSMA specific aptamer can form a GC-rich duplex that can serve as a drug loading site for Dox. Furthermore, the authors demonstrated that Dox-loaded aptamer-conjugated GNP could effectively work on the target cells suggesting target-specific drug delivery. [113] PSMA aptamer-conjugated GNP showed more than 4-fold greater CT (Computed Tomography) intensity for targeted LNCaP prostate epithelial cells than control cells. Nair et al. developed a nano surgeon to surgically remove the tumor cells in the presence of the three-dimensional rotational magnetic field. Aptamer (GB-10) conjugated to magnetic nanoparticles resulted in rapid screening and detection of leukemia cells from a pool of whole blood cells. In vitro studies and cell-based assays revealed that the nano surgeon could successfully induce cell death. This study's major advantage is that nano surgeons can act on targeted sites and remove the diseased cells, which is not possible by normal surgery. [114] Chang et al. and coworkers created a six-point-star motif to intramolecularly construct a DNA icosahedron as a nanocarrier for Dox. The construct can release drugs in a pH-dependent manner and store/intercalate drugs to deliver them to targeted cells. [115]

Yu et al. demonstrated a MUC-1 aptamer-nanoparticle system for targeted delivery of paclitaxel (PTX) to the target cells; MCF-7 breast cancer cell was used as a MUC1-overexpressing model. The MUC-1 aptamers were conjugated to the PTX loaded PLGA nanoparticles through a DNA spacer. The studies reveal that the complex was about 225.3 nm in size and has a stable drug release profile. 65% of the drug was gradually released over the first 48 hours, the amount of PTX released in PBS was observed at 227nm UV absorption. The in vitro drug delivery studies reveal that the aptamer-conjugated nanoparticles enhanced the release of drugs and cytotoxicity to the target cells. Flow cytometry results confirm the enhanced uptake of aptamer-conjugated nanoparticles into the MUC1-overexpressing tumors.[116]

Another study by Kolovskaya et al. developed a DNA aptamer-conjugated magnetic nanoparticle (MNP) designed for selective elimination of tumor cells using magneto dynamic therapy. The study uses aptamer specific to fibronectin (AS-14) and arabinogalactan (AG), which promotes the internalization of nanoparticles via asialoglycoprotein receptors. In vitro studies confirm that in the presence of a low frequency alternating magnetic field, the aptamer-functionalized MNPs induced cell death and tumor reduction. Histological studies confirmed tumor tissues' total necrosis, cell lysis, and mechanical disruption. This study can open a potential non-invasive therapy for cancer treatment.[117]

Mesoporous silica nanoparticles (MSNs) possess a wide variety of physicochemical properties. These include a well-organized porous structure, a higher pore and surface area volume, and low in vivo toxicity, making it an excellent drug carrier. [118] MSNs, when conjugated with aptamers, can deliver drugs with high efficiency to the target cells. MCM 41 [119], hollow mesoporous sphere [120], and SBA-15 [121] are some successfully approved mesoporous silica materials for drug delivery systems that exhibit stimuli-responsive drug release. Zhu et al. demonstrated a promising drug delivery system based on MSN-Polyelectrolyte multilayers (PEM) aptamer conjugate. PEM controls the drug release in external stimuli under reducing conditions and prevents premature drug release. MSM-41 mesoporous silica particles were used as a drug container for loading Dox due to their high surface area and loading efficiency. The SH-tailed aptamer was conjugated through disulfide linkages for target recognition to the MSN-PEM particles. This delivery vehicle can be an ideal drug delivery system owing to the high payload, cell-recognition properties, and stimuli-responsive drug release. [122]

Ma et al. demonstrated peptide-AS1411 co-assembly nanoparticles for efficient drug delivery to targeted cells. The Wpc peptide spontaneous co-assembles with AS1411 to form a uniform nanoparticle diameter ~100 nm. Flow cytometry and confocal microscopy imaging confirm that this peptide-based aptamer nanocarrier can efficiently penetrate through cell membranes in several cell lines. MTT assay conducted on T47D and HeLa cells confirms tumor cell growth inhibition when treated with these nanocarriers and shows negligible cytotoxicity

in normal cell lines. These nanocarriers can successfully induce cell apoptosis and cell cycle arrest in targeted cells. [123]

Zhang et al. developed an aptamer-nano train assembly charged with doxorubicin to selectively kill HepG2 liver cancer cells. Doxorubicin can be intercalated in the constructed nano train tethered with variants of LZH5 aptamer reported previously as a product LIVE targeting liver cancer HepG2 cells. This aptamer-nano train-dox complex can be internalized into a lysosome where due to the digestion of these complexes will release dox and achieve cytotoxicity in the liver cancer cells. To conclude, this bioconjugate could successfully kill the liver cancer cells due to the selective binding of the aptamer to the targeted cells. [124]

4.1.1 Aptamer conjugated quantum dots for cancer detection and therapy

According to the unique properties of quantum dots (QDs) which include minimal photobleaching, excellent quantum yield, strong resilience to severe chemical damage, and wide absorbance with narrow photoluminescence spectrum, are increasingly being employed in clinical diagnosis. [69] To develop biosensor systems for proteins and small molecules, distinct photophysical fluorescence and chemiluminescence processes of QDs are coupled with precise recognition properties of aptamers. [125] Several techniques for conjugating aptamers onto QDs have been documented recently, including electrostatic interaction and covalent conjugation. The implementation of aptamer-conjugated QD biosensors for sensitive and precise detection of biomolecules in clinical contexts has been easier due to the good biocompatibility and strong photoluminescence properties of QDs. Hashemian et al. developed an aptasensor based on FRET that uses CdS QDs (donor molecule) and polypyrrole (Ppy) (acceptor molecule) to analyze adenosine in the urine samples from patients with lung cancer. [126] The QDs were covalently linked to the anti-adenosine aptamer. Tenascin-C is a commonly found extracellular matrix protein located on the surface of glioma cells. Chen et al. designed an innovative bio-probe by combining GBI-10 aptamer to a QD substrate (QD–Apt) to detect Tenascin-C proteins in-vitro diagnostic experiments. [127] Tang et al. created a new type of QD conjugated aptamer (QD-Apt) nanoprobe by combining aptamer 32 (A32) to the QDs, which can specifically bind to tumors via epidermal growth factor receptor variant III (EGFRvIII) which is specifically found on the surface of glioma cells and helps to fluorescently label glioma.[75]

Apart from being used as a sensor tool for bio-analysis for cancer imaging, aptamer conjugated QDs are also used in anti-cancer drug delivery. Chemotherapeutics can be loaded via covalently or noncovalently onto aptamers. Conventional amide bond, thioester, and carboxyl ester link medicinal drugs to aptamer coupled QDs covalently. Hydrophobic coupling or electrostatic adsorption techniques are frequently used for non-covalent attachment. Due to their biocompatibility after the conjugation procedure, conjugated aptamer-QDs are ideal for in-vivo usage irrespective of the drug loading mechanism. For instance, Nanohydrogels- QDs (NHG-QDs) combined nano-system (NS) coupled with amino-functionalized Mucin-1 (MUC-1) aptamer (Ap) and loaded with hydrophobic paclitaxel (PTX) were produced by Ranjbar-Navazi et al. to attack and kill cells with breast cancer. The nanoconjugate was also coupled with the inhibitor of lactate dehydrogenase (LDH) and sodium oxamate (SO) (Ap-NHG-QDs-PTX-SO) to impede the transition of lactate

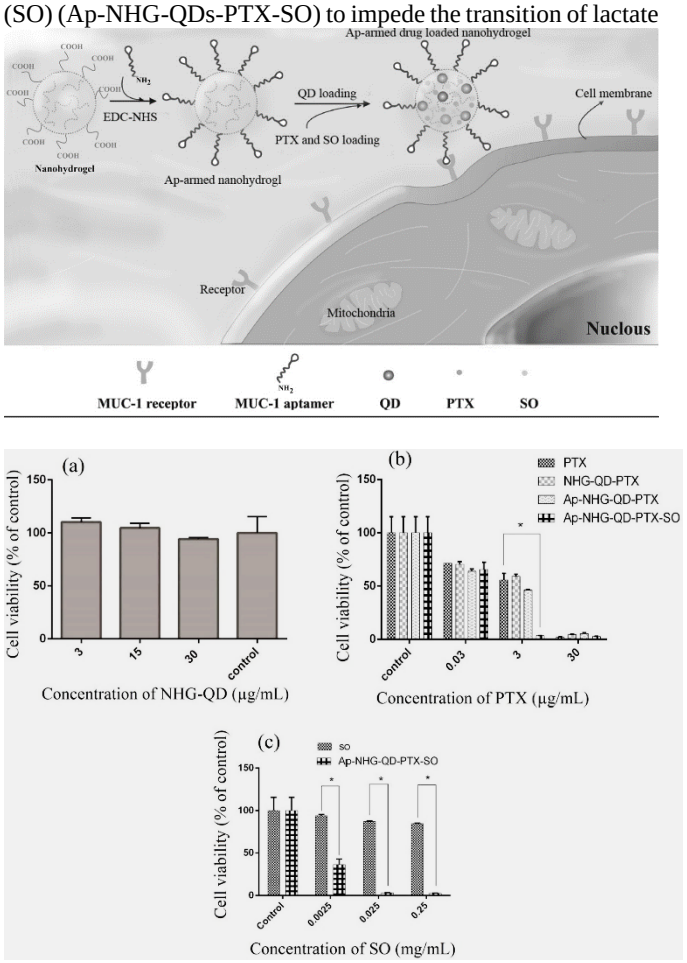

Figure 3: (A) MUC-1 Ap coupled NHG-QDs compound represents mitochondria-assisted apoptosis of cancerous cells in a notional diagram. (B) MCF-7 cells were incubated for 48 hours with (a) NHG-QDs (b) NHG-QDs-PTX, Ap-NHG-QDs-PTX, Ap-NHG-QDs-PTX-SO, PTX, and SO (b, c). [128] (Adapted with modification from Ranjbar-Navazi, Z., Fathi, M., Abdolahinia, E. D., Omidi, Y., & Davaran, S. (2021). MUC-1 aptamer conjugated InP/ZnS quantum dots/nanohydrogel fluorescent composite for mitochondria-mediated apoptosis in MCF-7 cells. *Mater. Sci. Engin. C*, *118*, 111469.)

from pyruvate and impair glycolysis, allowing it to successfully attack and destroy breast cancer MCF-7 cells. [128] Ap-NHG-QDs-PTX-SO NS could considerably target and kill MCF-7 cells and cause mitochondria-mediated apoptosis, according to in-vitro findings shown in Figure 3. Lin et al. created new daunorubicin (DNR)–loaded MUC1 aptamer–near-infrared (NIR) CuInS2 quantum dot (DNR–MUC1–QDs) compound that can be utilized as a probe for cancer cell imaging, therapy, and sensing system in-vitro. This unique bio-nano-system can administer DNR to prostate cancerous cells. Still, it can also detect DNR by detecting changes in the intensity of photoluminescence for QDs while simultaneously imaging the cancer cells. [129]

Aptamer conjugated dendrimers for cancer detection and therapy

Dendrimers are nanosized 3D structured macromolecules with large surface groups and high branching points that can be utilized for successful drug delivery medical imaging modalities. Dendrimers, unlike polymers, possess a well-defined molecular weight, multivalent, monodisperse, excellent solubility, drug-loading potential, pharmacokinetic features, convenience of synthesis, and functionalization. [130,131] Due to their dearth of immunogenicity, minimal toxicity, and good biocompatibility, dendrimers are used to treat cancer. [132] Dendrimers can be conjugated with aptamers via multiple types of interaction, allowing for more effective therapeutic transfer and detection. [133,134] Aptamer-dendrimer bioconjugates (Apt-D bioconjugates) incorporate the benefits of both elements and have offered an exciting new field of research. According to pharmacokinetic investigations, the dox-loaded dendrimer inhibits tumor growth and has a longer retention time in the tumor microenvironment. The aptamer-dendrimer bioconjugate is more efficient with stronger anticancer potency, cancer-specific targeting capacity, and greatly reduced toxicity. Lee et al. developed an Apt-D conjugate for prostate cancer treatment utilizing A9-RNA aptamer targeting prostate-specific membrane antigen (PSMA) (A9-RNA apt), G4 Polyamidoamine (PAMAM) as dendrimer, Dox as a drug, and duplex oligonucleotides (dONT) as an immunostimulatory agent. [135] Epirubicin is an anthracycline medication used to cure breast cancer, colon cancer, gastric cancer, and ovarian cancer. [136,137] Epirubicin, on the other hand, can harm non-cancerous cells. As a corollary, this becomes vital to specifically target cancer cells to attain maximized therapeutic benefit while minimizing adverse effects on healthy cells. Tagdishi et.al; developed an aptamer conjugated dendrimer delivery carrier for epirubicin and tested it in vitro and in vivo. Although they only used one aptamer, they used three, including MUC1 aptamer that binds to MUC1, a glycoprotein that is abundantly expressed in prostate, ovarian, and breast cancers. ii) The AS1411 aptamer attaches to nucleolin, a nucleus membrane protein that is significantly elevated in cancers of the breast, colon, and lung. iii) ATP aptamer, which served as the dendrimer's foundation.[138] Fig. 4 has shown the aptamer-dendrimer-epirubicin compounds to target Epirubicin delivery to C26 (colon cancer cells) and MCF-7 (malignant breast cells). [139] Zhang et al. created the Apt-D bioconjugate by grafting an Aptamer AS1411 on the surface of PAMAM dendrimer mounted persistent luminescence nanoparticles (PLNPs), which may preferentially attach to abundantly expressed nucleolin on cancer cell membranes and improve nanoparticle intracellular accumulation. PH-sensitive hydrazine loads DOX onto PLNPs-PAMAM nanoparticles, which may be delivered precisely in an intracellular acidic milieu, causing cancer cells to succumb and suppress tumor growth. [140] GBI-10, a DNA aptamer conjugated dendrimer-modified QD nanocomposites were developed by Li et al, to precisely target the extracellular matrix protein tenascin-C found on glioblastoma cells and used as a nanoprobe for molecular imaging. [74]

Aptamer conjugated mesoporous silica nanoparticle for cancer detection and therapy

MSNs (mesoporous silica nanoparticles) have a wide range of criteria for delivery of therapeutics. MSNs can be effectively transported to target places after they are equipped with targeting equipment such as aptamers. Numerous studies on the development of aptamer decorated MSNs for improved cancer

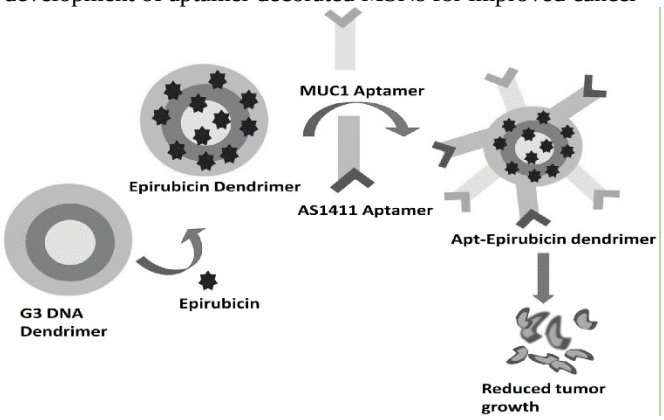

Figure 4: A pictorial illustration of an anti-cancer treatment premised on aptamer-dendrimer bioconjugates that inhibit cancer cell proliferation.[139] (Adapted with modification from Sheikh, A., & Kesharwani, P. (2021). An insight into aptamer engineered dendrimer for cancer therapy. *Eur. Polymer J.*, *159*, 110746.)

treatment and imaging have shown significant results, despite several critical concerns remaining unresolved. Since the revelation of mesoporous silica materials in 1990, researchers have been increasingly interested in their possible implications in the development of drug delivery systems. Because of their excellent physicochemical features, including a well-organized porous morphology, a greater porosity and surface area, and limited toxicity, mesoporous silica nanoparticles (MSNs) satisfy a wide list of needs for efficient drug delivery. Aptamer conjugated MSNs can proactively deliver drugs to target areas with minimal off-target consequences and enhanced therapeutic efficacy with a minimal dose of medicine. Using photochemical response, pH shift, and chemical change, the particles generated with these materials exhibit stimuli-responsive discharge of medication capabilities. [141–143] Zhang et al. designed a new MSN-based redox-responsive drug delivery system for triplex treatment for cancer. The 50 -thiol AS1411 aptamer was attached to the cytochrome C (Cyt C)-conjugated MSNs for specific recognition of tumor cells. The MSNs carrying DOX were bonded by Cyt C via a redox-cleavable disulfide linkage. The discharge of DOX into the cytoplasm might result from breaking SeS bond inside cells by glutathione. They showed that this technique has a lot of promise for synergistic effects on triple cancer treatment. [144] The fabrication of maytansine derivative filled MSNs adorned with PDA (hydrochloride polydopamine), PEG (Poly(ethylene glycol)), and EpCAM aptamer (MSNsDM1@PDA-PEG-Ap) for the targeted treatment of colorectal cancer was described. [145] Because of its pH-responsive properties, the PDA coated system performs a vital gatekeeper function in release of drug. The findings revealed a thin film

coating containing PEG, PDA, and aptamer on the surface of produced spherical MSNsDM1@PDA-PEG-Ap.

Cancer imaging has emerged as the most significant need for effective image-guided therapeutic administration in biomedical studies. According to the survey results, just a small fraction of

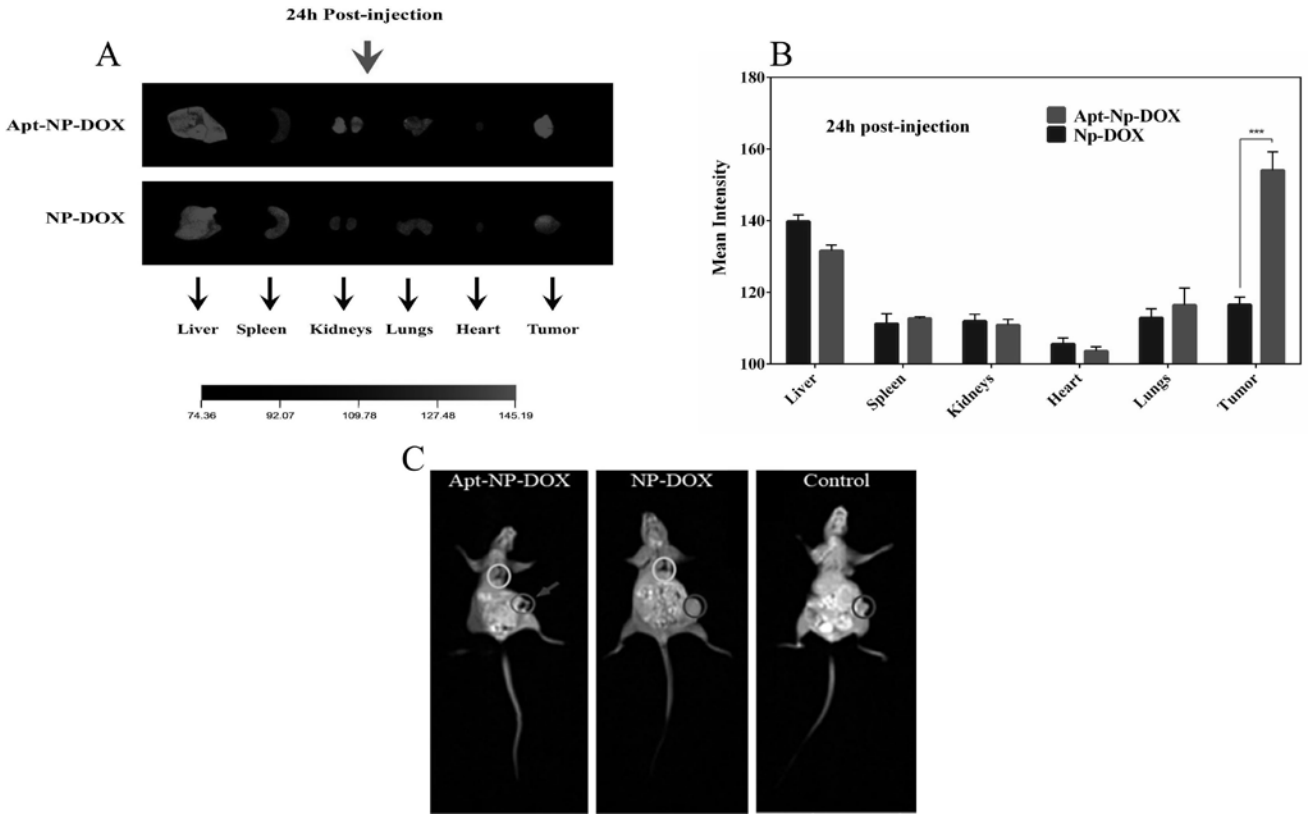

Figure 5. (A) Ex vivo NIR fluorescence pictures. (B) ROI analysis of the tumor, liver, spleen, kidneys, heart, and lungs, 24 hours after Apt-NP-DOX and NP-DOX administration. (C) MR images of tumor-bearing mice, pre-injection and 24 h after administration of Apt-NP-DOX, NP-DOX. The tumor region is indicated by red circles, while yellow circles indicate the liver area.[144] (Adapted with modification from *Int. j. pharmaceutics*, *570*, 118645.)

administered drug-loaded nanoparticles were discovered in tumor cells. Image-directed administration of drugs approaches have emerged as a viable framework for improving targeting efficacy by managing the quantity and quality of nanoparticle medication delivery applications. [146] MSNs have special properties that render them reliable components in developing fluorescent-tagged and radioactively labeled cancer imaging and detection methods. Akbarzadeh et al. created a dual imaging probe based on a fluorescent and magnetic resonance (MR). QDs were coated with MSNs, and EpCAM DNA aptamer was coupled to the surfaces of amine-functionalized silica. The findings of in vivo MR and fluorescence imaging indicated that the nanoprobe accumulated and stayed in tumor milieu of tumor-bearing animals following a 24-hour administration shown in Figure 5. [147] Xu et al. developed an MSN-based fluorescence nanoprobe (bMSN@T2-RGD-Acrk) with an emission of 550 nm that could be used to detect breast cancer cells selectively. RGD-N-e-acryllysine (RGD-Acrk) peptides were conjugated onto MSNs in the nanosensor via photo-triggered mode. In vitro results demonstrated that the breast cancer cells may be detected and imaged successfully in the mice.[148]

Aptamer conjugated magnetic nanoparticle for cancer detection and therapy

Multifunctional magnetic nanoparticles (MNPs) having magnetic properties have already been described as biosensors, medicinal cargo delivery, imaging, and the isolation of particular cells throughout the last few years. [149,150] Aptamer-modified MNPs are becoming useful for detecting, trapping, sorting, and collecting biological specimens with minimum effect due to the exact identification and binding capacity to particular targets.[151] Molecular imaging is a widely employed noninvasive approach for detecting early-stage malignancies and tracking clinical responses to disease. Magnetic resonance imaging (MRI) is the most potent technology for acquiring tomographic pictures with excellent spatial resolution and virtually unlimited penetration depth and also giving excellent physiological details.[152,153] MRI contrast agents, including MNPs, can considerably improve MRI. [154] Furthermore, in terms of tumor diagnosis, these MNPs require incorporating certain targeted components required for precise detection and delivery to target areas via strong interactions with receptors molecule on the specific malignancy, while limiting detrimental consequences including toxicity, accumulation in healthy tissue, and immune clearance.[153,155–157] Aptamers, in

particular, can fold into unique structures to attach to their target receptors with strong affinity and fine selectivity, which makes them better at targeting moieties. [158–160] By functionalizing iron oxide MNPs with l-cysteine and conjugating to streptavidin, Kiplagat et al generated aptamer conjugated MNPs. To detect breast cancer, the functionalized MNPs-streptavidin was coupled to biotin bearing an aptamer with sensitivity to the breast cancer biomarker protein MUC1.[161]

Aptamer conjugated MNPs also serve as a platform for delivering drugs to the tumor site. For instance, Khodadadi et al. developed aptamer-conjugated paclitaxel-loaded MNPs for breast cancer therapy. [162] The SYL3C aptamer was conjugated to superparamagnetic iron oxide nanoparticles (SPIONs) and loaded with Paclitaxel (PTX) (aptameric SPIONs@PTX). The drug encapsulation and loading efficacy were determined to be 77.6% and 7.76%, correspondingly. In cellular experiments, aptameric SPIONs@PTX was more deadly than the non-targeted system and had a greater cell uptake efficiency than the non-targeted system, indicating that aptamer-functionalized SPIONs@PTX has a good capability for identifying and suppressing its target cells' growth and proliferation.[163] Another work described the fabrication of a theranostic system of SPION-deferasirox compounds targeted with the AS1411 aptamer. [163] SPION serves as a diagnostic agent, whereas deferasirox serves as a treatment drug in this system. In this case, 3-aminopropyl)trimethoxysilane (ATPMS) was used to functionalize SPION, and subsequently, deferasirox was covalently attached to its surface. The cellular toxicity experiment revealed that the targeted compound was more harmful than the non-targeted complex. (Fig 6A) The diagnostic potential was also tested using tumor-bearing mice, which showed that the inclusion of an aptamer aids in the targeted delivery of the medicine into tumor tissue. (Fig 6B) This indicates that construction offers an efficient and safe foundation for battling cancer.[163]

Aptamer conjugated polymeric nanoparticle for cancer detection and therapy

Aptamer–functionalized polymer nanoconjugates are a potential new type of targeted cancer treatment agent. Compared to free medication treatment, the aptamer can function as a

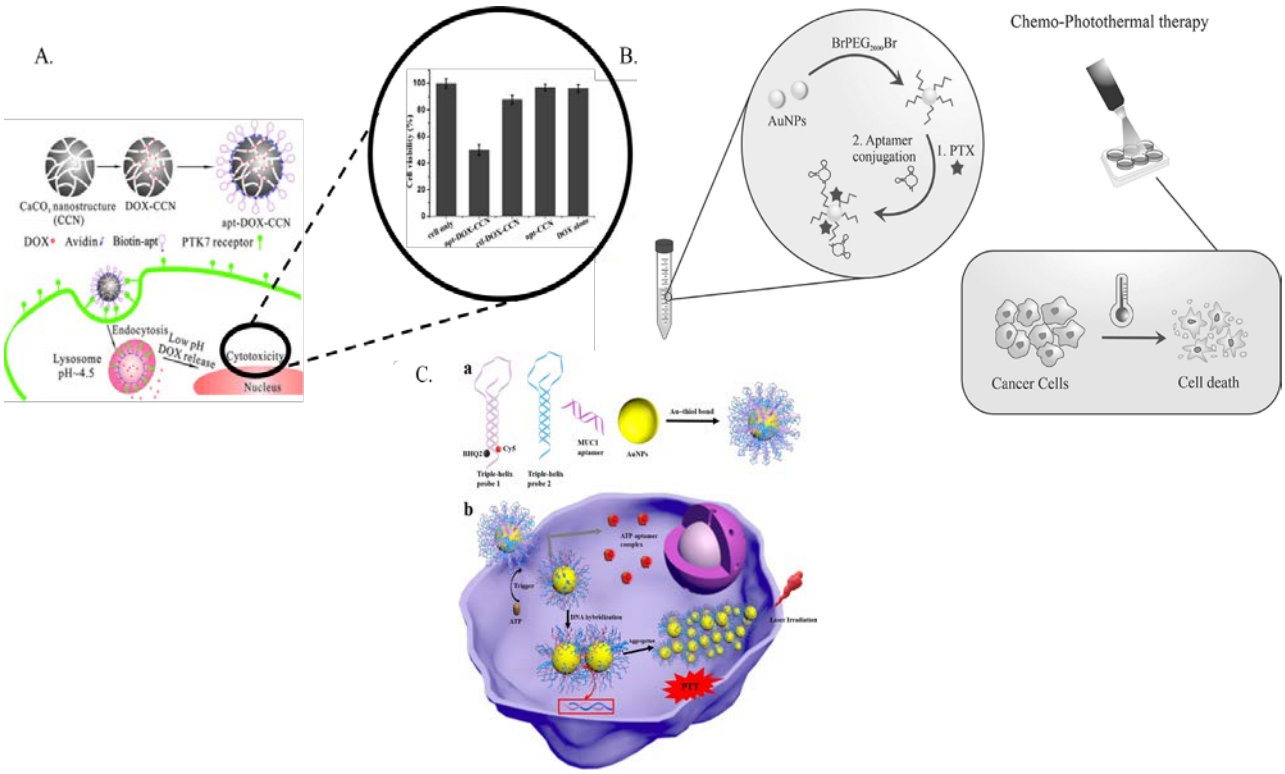

Figure 7. (A) Schematic depiction of aptamer-CaCO3 for targeted delivery of anticancer drug and cytotoxicity compared among target cells treated with apt-DOX-CCN, ctl(control)-DOX-CCNs, apt-CCNs, and DOX only.[172] (Reprinted with permission from Zhou, C., Chen, T., Wu, C., Zhu, G., Qiu, L., Cui, C., ... & Tan, W. (2015). Aptamer CaCO3 nanostructures: a facile, pH-responsive, specific platform for targeted anticancer theranostics. *Chemistry–An Asian Journal*, *10*(1), 166-171.) (B) Pictorial depiction of synthesis and therapeutic application of PTX/PEG-AuNPs@antiMuc1.[173] (Adapted with modification from Kadkhoda, J., Aghanejad, A., Safari, B., Barar, J., Rasta, S. H., & Davaran, S. (2022). Aptamer-conjugated gold nanoparticles for targeted paclitaxel delivery and photothermal therapy in breast cancer. *Journal of Drug Delivery Science and Technology*, *67*, 102954.) (C) Design and fabrication of THP-AuNP, and ATP-stimulated aggregation of THP-AuNP for imaging and PTT of a tumor.[175] (Reprinted with permission from Jiang, Y., Zhao, W., Zhou, H., Zhang, Q., & Zhang, S. (2022). ATP-Triggered Intracellular In Situ Aggregation of a Gold-Nanoparticle-Equipped Triple-Helix Molecular Switch for Fluorescence Imaging and Photothermal Tumor Therapy. *Langmuir*, *38*(12), 3755-3764.)

cancer-targeting molecule and also as a controllable drug delivery carrier with improved therapeutic effectiveness at minimal concentrations. A number of experiments have shown that medications may be delivered successfully via an aptamer-mediated method. For instance, Paclitaxel (Ptxl or PTX)–PLA nanocomposites coupled with an aptamer were discovered to be effective delivery nanostructures for prostate targeting cancer cells. An aptamer-functionalized polymeric NPs containing cyanine dyes were also developed to allow monitoring of these nanoparticles.[164] The researchers used a particular ring opening polymerization of lactide method to covalently attach Cy5 dye to PLA and then used a nanoprecipitation technique to create NPs. In vitro tests demonstrated that the nanoparticles were capable of delivering good outputs with little background fluorescence in different organs.[164] Tang and colleagues created PLGA nanobubbles that were filled with PTX and aimed toward PSMA. This group looked into the approach for prostate cancer imaging and therapy using ultrasound (US).[165] Targeting prostate cancer cells, Wu et al. employed a polyamidoamine (PAMAM)-based microRNA (miR-15a and miR-16-1) vector. [166] Taghavi and colleagues devised a 5TR1 aptamer-based targeted treatment. They used a physical adsorption approach to create epirubicin (Epi) encased PLGA altered with chitosan. EpiPLGA-CS-Apt was shown to have tremendous promise as a potential nano-carrier for in vitro treatment of cancer in this research.[167]

Aptamer conjugated metallic nanoparticle for cancer detection and therapy

The emergence of aptamers has resulted in a novel class of targeting molecules that are tiny, simpler to produce, and possibly more stable than antibodies.[168] Aptamers have been employed in cancer theranostics with efficient receptor recognition and cell uptake including fluorescent/electrochemical sensors and drug carriers.[169,170]A plethora of polymers have already been coated on the faces of metallic nanoparticles used in photothermal treatment (PTT) and photodynamic therapy (PDT) to increase stability and solubility. [170,171]Tan and colleagues created gold-coated thiolate-functionalized Fe3O4 magnetic nanoparticles functionalized with sgc8 aptamers for location-specific release of DOX to the lysosome of human leukemic lymphoblasts (CCRF-CEM) cell lines for the treatment of acute lymphoblastic leukemia; the DOX-release was surveilled using fluorescence.[172] NIR radiation was utilized in conjunction with medication delivery to cause a regional temperature upsurge. In cervical cancer HeLa cells, zirconium-based metal-organic structures encapsulating the photosensitizers TMPyP4 and porphyrin have indeed been described for targeted biological imaging and PDT.[173,174] A Manganese(II) (Mn(II))-silver aptamer complex utilized for targeted MRI of pancreatic cancer, which uses an aptamer targeted to hypoxia-inducible factors. Metal carbonates can be employed as potential targeted therapeutics as well. Tan et.al created pH-responsive DOX-loaded CaCO3 nanomaterials (CCNs) bearing sgc8 aptamers (apt-DOX-CCN) for targeted therapy for leukemia. When subjected to the acidic pH of lysosomes, Dox is secreted into the nucleus of leukemia cells and tracked by fluorescence.[175] The targeted system is more cytotoxic than the non-targeted system. (Fig 7A)[175] For the treatment of breast cancer, Kadkhoda et al. developed a NIR/pH-responsive therapeutic carrier consisting of poly (ethylene glycol) modified gold nanoparticles (AUNPs) linked with mucin1 (MUC1) aptamer loaded with paclitaxel (PTX). In vitro cytotoxicity tests revealed that the developed system has the requisite selectivity for MUC1-positive cells. It was also observed that PTX/PEG-AuNPs@antiMuc1 in conjunction with NIR irradiation can ablate MUC1-positive cancerous cells with good systemic absorption. (Fig 7B) [176]

The MUC-1 aptamer, which binds the Muc-1 receptor, has been functionalized on AuNPs. To target breast cancer MDA-MB-468 cells, researchers employed an additional imaging molecule with an extra silica coating.[177] Photoluminescent gold–silver nanomaterials was formed using AuNPs and silver nanoclusters with DNA template to target the nucleus of cervical cancer cells with nucleolin expression for theranostics. The exterior of the AuNPs was coated with 5'- thiolated oligonucleotides bearing the AS1411 aptamer.[177] Jiang et al. created a molecular switch using a triple-helix probe (THP) and MUC1 aptamer-functionalized gold nanoparticles (AuNPs) that shows variable aggregation characteristics through intracellular ATP and the PTT impact. [178] ATP causes THP-AuNPs to aggregate and generates a robust coupling activity, which may be employed for both imaging and tumor PTT. (Fig 7C)[178]

Aptamer conjugated 2D nanomaterial for cancer detection and therapy

Platform materials are especially appealing because they have a high capacity for loading medicines and acting as PDT/PTT medications. Decitabine which is an anti-leukemia medication was loaded into pH-responsive graphene oxide (GO) nanomaterial, which was then modified with the A1 aptamer to attack A549 lung cancer cells.[179] MCF-7 breast cancer cells were able to selectively internalize GO coated with MSNs and AS1411 aptamer. Following that, laser radiation disassembled the nanoparticles, allowing the contained DOX to escape. [180] Using the aptamer AS1411, a 2D MoS2 was altered with PEG doped with CuS nanoparticles and loaded with DOX for lung cancer theranostics. Lung cancer cells and tumor-bearing animals were proven to have PTT-directed release of the drug and photothermal imaging.[181] The ability of a 2D MoS2-based substrate to recognize ATP and operate as a PDT agent to create ROS in response to laser illumination has been demonstrated. [181] The fluorescence of the aptamer ATP was quenched owing to FRET (fluorescence resonance energy transfer), but regained after specific interaction between the oligonucleotides and ATP in HeLa cancerous cells. [181]

A three-way connection compartment DNA nanomaterial with the AS1411 assembled with a PEG linker was reported, having DOX-loading capability for selective drug administration to prostate cancer cells and murine mammary carcinoma cells with strong nucleolin expression.[182]

Lipid nanocarriers in cancer detection and therapy

Early diagnosis possesses a significant role in the treatment of carcinomas. When a patient has been appropriately and thoroughly examined, nanomedicine-based treatment can be initiated. The co-encapsulation of diagnostic molecules and therapeutics in the same nanocarrier device might help doctors track the health progression of the patients.[183,184] Lipid nanocarriers have been reported to be preferable in the cancer theranostic application over polymeric nanoparticles with respect to safety, biocompatibility, and biodegradability. Based on the kind of lipidic nanoparticles used, various forms can be created such as liposomes, nanoemulsions, solid lipid nanostructure etc. The theranostic agents and medications are encapsulated in oil globules for particular tumor locations in nanoemulsions.[71] Imaging molecules can be enclosed with therapeutics either in an aqueous core or a bilayer shell for liposomes.[185] The imaging molecule is entrapped in the lipid matrix in solid lipid nanostructure (SLN). [71] The medicine and diagnostic agent are disseminated in the dispersion medium of the oil and lipid composite matrix in nanostructured lipid carrier (NLC).[71]

Aptamers can easily distinguish between cancer cells and normal cells, an essential parameter for efficient drug delivery and cancer therapeutics. Several strategies based on aptamer-based cancer therapeutics have been developed for targeted drug delivery. Aptamers can act as therapeutic agents but have a few drawbacks, such as the requirement of high amounts of aptamers for therapy, which led to drug delivery vehicles with greater potency and less selectivity in conjugation with aptamers.[185] Hence, aptamer-functionalizing lipid nanoparticles have applications in both cancer detection and therapy. Therefore, in the second part of this review, we have focused on aptamer-functionalized lipid nanoparticles as a theranostic tool for cancer.

Aptamer-functionalized liposome-based cancer detection and therapy

Liposomes are nanostructures made up of unilamellar lipid bilayers which surround an aqueous center. According to current articles, liposomes are one of the most prominent fields of cancer theranostics investigation. Presently, contrast compounds such as 64Cu, gadolinium, 14C isotopes, and fluorescent probes are being studied for integrating and targeting malignancy. One of the benefits of liposomes is their large cavity, which may readily be filled with multiple treatment cargos for theranostic purposes, such as diagnostic agents, medicines, genes, and proteins. [186–189]Aptamers can be attached to the liposomes via conjugation or hydrophobic interaction.[190] The conjugation of the aptamers to the liposomes provides advantages of increased aptamer lifetime in vivo, ease of penetration inside the cell membranes due to its amphiphilic nature, overcome renal filtration, prolonged circulation time, and effective biodistribution of drugs within the human body. [191–193] For instance, Wang et al. created a fluorescent "turn-on" Cy3-tagged MUC1 coupling aptamer functionalized polydiacetylene (PDA) liposome nanosensor for the detection of MUC1 in cancer cells with a detection limit of 0.8 nM.[194] Because of the energy transfer between the PDA conjugated backbone and fluorogen in the sensor device, the fluorescence of Cy3-tagged aptamer could be quenched. Identification of MUC1 with aptamer causes both liposomes and the aptamer to switch configurations, restoring red fluorescence in the presence of MUC1.[194]

Liposomes being biocompatible and their property of enhanced drug delivery via passive targeting are known to be promising in drug delivery and therapeutics. The liposome is a soft spherical vesicular structure comprising amphiphilic monomers, mimicking the human lipid bilayer present in the cell membranes.[195] The main advantages of liposomes are biocompatibility, ease of modulating surface properties, and deliverability of drug molecules irrespective of their charges in the cells and cellular compartments.[50] The hydrophilic drugs can be loaded into the aqueous core of the liposomes, whereas; the hydrophobic drugs can be incorporated in their lipid bilayer. [196]For instance, Xing et al. developed a liposomal drug delivery system against MCF-7 breast cancer cells. The liposomes were loaded with Dox and conjugated with the functionalized DNA aptamer AS1411. The DNA aptamer acting as a targeting agent has a strong affinity for nucleolin. The proposed Apt-Dox-Liposome exhibited promising results for tumor inhibition.[197] Zhen and co-workers developed an aptamer-liposome-CRISPR/Cas9 chimera for efficient delivery of therapeutic CRISPR/Cas9.[198] The aptamers are conjugated to cationic liposomes via the post-insertion method for targeted therapy CRISPR/Cas9 to tumor cells.[198] Kang et al. reported an aptamer-liposome structure constructed using 250 aptamers bound to the surface for target binding. PEG-coated liposomes were modified with sgc-8 aptamers to check the selectivity binding of the aptamer-liposome complex to CEM (full form of CEM) cells. The liposomes were coated with PEG polymers to increase the liposome stability and sustain aptamer stability in serum. The flow cytometry results showed that the sgc8 aptamer-liposome complex could successfully bind to the target (mention target).[199] Zehui et al. and group have formulated an aptamer (AS1411)-conjugated with cisplatin-encapsulated liposomes with a high affinity towards nucleolin (NCL). The study shows that the aptamer-based liposome complex facilitates the endocytosis of drug-delivery vehicles.[200] Another study has utilized magnetic liposomes, which contain magnetic particles in their aqueous core or magnetized polymers within their lipid bilayer structure. [201] The study involves using thermo-sensitive magneto liposomes (TMs), which combine the temperature-sensitive drug release and delivery based on the magnetic properties of liposomes. The paper aims to design a drug delivery model containing methotrexate in TMs that can target specifically and release drug molecules to the skeletal muscles. The study shows enhancement in the release and specificity of the drugs in the presence of magnetic and temperature-dependent conditions. One of the studies by Dou et al. and the group developed a HER3ECD-targeted aptamer functionalized liposomal Dox against tumor cells in the MCF-7 cell line. The study showed reduced cardiac toxicity and prolonged survival time in the mice. Flow cytometry and confocal microscopy confirmed the binding of aptamer-conjugated liposomes to the tumor cells. Studies suggested that Apt#13 was co-localized in cytoplasm and nucleus and could bind to the EGFR family.[202] The Moosavian group developed a

TSA14 aptamer conjugated PEGylated liposomal doxorubicin (PL-doX). The liposomes were tested in vitro for tumor cell binding, cellular uptake, and cytotoxicity and in vivo for biodistribution, blood clearance, and therapeutic efficacies in TUBO breast tumor-bearing mice. The study concludes by suggesting that the aptamer conjugated PL-doX can significantly improve the selectivity and therapeutic efficiency of liposomal doX.[203] The Alavizadeh developed cisplatin formulated PEGylated liposomes with phospholipids having different transition temperatures, thus releasing drugs at different time intervals against the C26 colon carcinoma. The liposomes are comprised of different phosphatidylcholines with various phase transition temperatures (Tm). By performing in vitro cytotoxicity, the results suggested that by lowering the Tm of the lipids, there is an increase in cisplatin release. The study suggests that the choice of Tm for lipid mixture contributed to a certain extent to the rate of cisplatin elimination from plasma and its therapeutic effects.[204] Jiang and the group developed a core-shell-based "nanodepot" comprising a liposomal core and a crosslinked-gel shell for sequential and site-specific delivery of an anticancer protein and small-molecule drug. They developed a core-shell complex to incorporate two separate depots for a programmed release profile. The inner core of the liposome loaded with dox targeted the nucleus, whereas the outer shell made up of crosslinked gel could encapsulate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The Dox is loaded in the aqueous region of the liposome, whereas TRAIL acts on the death receptor on the plasma membrane. The results suggest that the Dox co-loaded Gelipo (TRAIL/Dox-Gelipo) could significantly inhibit tumor growth in the xenograft animal model.[205] Yu et al. created an AS1411 aptamer-functionalized liposome-based nanomedicine for breast cancer treatment that can administer paclitaxel (PTX) and siRNA to MCF-7 cells concurrently in vitro and in vivo.[206] The introduction of PTX and siRNA at the same time enhanced the percentage of apoptotic cells while decreasing angiogenesis.[206] Lafi and group developed anti-nucleolin aptamer (AptNCL) functionalized PEGylated pH-sensitive liposomes (PEGLippH) for selective targeting and pH-responsive delivery of echinomycin into cancer cells. The findings show an anti-proliferative effect for three different cancer cell lines MDA-MB-231, MCF7, A549.[207]

Aptamer conjugated micelle-based cancer detection and therapy

Micelles comprised of lipid molecules have a spherical shape that allows them to orient in aqueous systems. This type of lipid nanocarrier system has yet to be investigated, but it could be a viable diagnostic and therapeutic nanomedicine for cancer detection and therapy.[71] In addition to liposomes, aptamer-conjugated micelles have been widely used as a drug carrier and molecular probe.[208–210] The micelles are a hybrid constructed from hydrophilic oligonucleotide and hydrophobic polymer.[209,211] This amphiphilic polymer structure can self-assemble to form a three-dimensional spherical micellar structure when exposed to an aqueous solution. This 3D structure functionalized with aptamers efficiently carries cargoes such as drug molecules to the target cells. [209] The aptamer micelle complex displays a multivalent effect which increases the binding affinity to the target cells. Due to the steric hindrance from the closed structure in the micelle-aptamer structure, the complex exhibits high resistance to enzymatic degradation. Furthermore, hydrophobic drugs can be loaded in the hydrophobic core of the micelles via chemical conjugation or physical entrapment. Due to the amphiphilic nature of the micelles, which contain both hydrophobic and hydrophilic parts, there are several advantages to using micelles as a drug carrier, including stability, nanosized, prolonged blood circulation rate, slow and sustained drug release, improved bioavailability, and solubility of hydrophobic.[212] The addition of lipid to the aptamers provides an internalization avenue for these particular nanostructures. Additional advantages include an extremely minimal off rate once attached to target sites, and quick detection potential with increased sensitivity. For instance, Wu and colleagues developed a self-assembled aptamer–micelle nanostructure for cancer cell identification and therapeutic delivery. In a human whole-blood sample, this nanostructure demonstrates specific recognition capacity under flow circulation.[213]

Various ways have been investigated to obtain thermodynamic stability in self-assembled nanoparticles.[211] Unimolecular micelle, which is formed by individual hyperbranched amphiphilic block copolymers, exhibits in vivo stability due to its covalent nature.[214–217] The advantages of a unimolecular micelle are high drug loading capacity, chemical versatility due to ligand conjugation, and narrow nanoparticle size distribution. In a study by Xu et al., an aptamer conjugated unimolecular micelle comprising of a dendritic H40 core, a hydrophobic poly (L-lactide) (PLA) inner shell, and a hydrophilic poly (ethylene glycol) (PEG) outer shell. The A10 aptamer conjugated to the unimolecular micelle is used for targeted prostate cancer (PCa) therapy. Doxorubicin was encapsulated in the hydrophobic core of the unimolecular micelle. In vitro and in vivo studies examining cellular uptake, cytotoxicity, and tumor biodistribution revealed that unimolecular micelles could be a suitable drug carrier for targeted PCa therapy.[208] Wu et al. developed a TDO5 aptamer-micelle structure by adding a hydrophobic tail to the end of the aptamer, which can self-assemble to form a highly ordered micelle-like structure.[213] The TDO5 aptamer acts as a building block to the nanostructure and contributes to recognizing the target molecules. The authors mimicked a tumor site in the bloodstream by constructing a flow channel device by immobilizing tumor cells onto the surface. Flowing the aptamer-micelle through the device demonstrated a selective ability of the aptamer-micelle to bind to the target. The study shows excellent dynamic specificity inflow channel systems and can be a potential nanostructure for cancer cell recognition and in vivo drug delivery applications. [213] Liu et al. and co-workers constructed a DNA-diacyl-lipid micelle with excellent thermal stability, and the size can be modified by changing the length of the DNA sequence. The highly charged DNA micelles can enter and disintegrate the cell membranes via endocytosis. Due to the excellent biocompatibility, high stability,

cell permeability, and non-toxicity of DNA-micelle are potential therapeutic nano-vehicle for drug delivery systems.[218] Smith et al. designed an attractive vehicle for the delivery of therapeutic and prophylactic peptides. The aptamer displaying peptide amphiphile micelles (A/PAM) system comprises a peptide amphiphile micelle (PAM) incorporated with DNA oligonucleotide amphiphile (anti tail amphiphile-AA). A cell targeting C10.36 DNA aptamer with a 3' extension complementary sequence (tail) to AA is used to conjugate with PAM to form aptamer-displaying PAMs (Aptamer-A/PAMs). The authors demonstrated a striking similarity in the stability of the complex in serum albumin levels compared to the blood and cell membrane models. The results also showed the high specificity of the complex to the human B leukemia cells in vitro. Due to the intrinsic property of PAMs to possess high drug loading capability, increased stability for several hours in biofluids, and ability to selectively bind the target cell due to aptamer conjugation, these Aptamer-A/PAMs are a promising technology for the delivery of peptide cargoes in terms of stability, effectiveness, and selectivity.[219] Li et al. developed a multifunctional composite micelle (CM) decorated with AS1411 aptamer (CM-Ap) for the targeted delivery of Dox to the human breast tumor cells. In addition to the aptamers, they selected Pluronic F127 and beta-cyclodextrin-linked poly (ethylene glycol)-b-polylactide 37 block copolymers (β-CD-PELA) as co-carriers for Dox, which enhanced the Dox-loading capacity and micelle stability. In contrast to the pristine CM, the CM-Ap showed higher cellular uptake due to the nucleolin-mediated endocytosis effect. The in vivo studies in the MCF-7 tumor-bearing mice demonstrated enhanced antitumor activity and reduced cardiotoxicity. The AS1411- functionalized composite micelles also showed prolonged circulation time in blood and enhanced accumulation of the complexes in the target cells.[220]

Aptamer conjugated solid lipid nanoparticles-based cancer detection and therapy

Solid lipid nanoparticles (SLN) are spherical colloidal nanoparticles with a solid lipid core composed of waxes, triglycerides, and fatty acids and stabilized by surfactants.[71] Their size ranges between 50 -100 nm, and is well recognized for their biocompatibility, long-term drug release, and lymphatic absorption susceptibility.[72] Chemotherapeutics infused SLN is incredibly promising in cancer therapy.[73,221] Moreover, as demonstrated by the findings of current studies, SLNs are capable of effectively carrying contrast molecules as well as anticancer medications and providing simultaneous therapy and diagnostics. Aptamer functionalized SLN has been widely used in the field of cancer detection and therapy. For instance, a sequential treatment approach to conquer hepatocellular carcinoma was created by Jianghong et.al using two aptamer/peptide-modified lipid-based therapeutic delivery carriers, aptamer A54-polyethylene glycol-solid lipid nanoparticle/oxaliplatin (A54-PEG-SLN/OXA) and peptide A15-polyethylene glycol-solid lipid nanoparticle/salinomycin (A15-PEG-SLN/SAL).[221] The nanomedicines were potent to target the BEL-7402 (hepatocellular carcinoma cell line) with high targeting capacity and anticancer efficacy. The spheroid made of CD133+ cancerous cells could be targeted and infiltrated profoundly by the A15-PEG-SLN/SAL which considerably halted the tumor growth after administration and tumor cells were killed by A54-PEG-SLN/OXA. Furthermore, when administered consecutively, the nanomedicine-based therapeutic carriers A54-PEG-SLN/OXA and A15-PEG-SLN/SAL could selectively target cancer cells and showed a clear anticancer impact. [221] Aptamer-functionalized lipid nanoparticles (LPNs) were developed to deliver cabazitaxel and curcumin to prostate cancer patients.[222] The functionalized-LPNs showed superior cell uptake and cytotoxicity for cells expressing PSMA and suppressed cancer progression more effectively than non-functionalized LPNs in a xenograft model of prostate cancer. Co-encapsulation of therapeutics has a synergistic effect, and conjugation with an aptamer enhances PSMA absorption which renders them a potential therapeutic strategy for prostate cancer.[223]

Aptamer conjugated hybrid lipid-polymer nanoparticles-based cancer detection and therapy

PHLNPs (polymer-lipid hybrid nanoparticles) integrate the benefits of both liposomes and polymeric nanoparticles. The constraints of polymers and lipids are solved by this hybrid approach, which has significant promise in the realm of nanomedicine.[222] Three primary elements make up PLHNPs: (1) a hydrophilic/hydrophobic polymeric core that efficiently encapsulates drugs, eventually resulting in controlled release kinetics; (2) a lipid layer encompassing the polymeric core that has good biocompatibility, stability, and decreased drug retainment within the polymeric core; (3) an external component made up of a lipid-polyethylene glycol (PEG) that is encased by a lipid layer to improve steric stabilization, protracted circulation time, and thwart immune recognition.[224] Van der Waals interactions, noncovalent interactions, hydrophobic, and electrostatic are related to the polymeric matrix and lipid layer, but the hydrophilic polymeric core is often coupled with the adjacent lipid layers via covalent connections. [225–227] PLHNPs have a number of advantages over conventional drug delivery carriers, including better physiological properties, preferable release kinetics, excellent capacity to entrap both hydrophobic and hydrophilic therapeutic molecules, immense plasma stability, longer circulation times, molecular and cellular recognition, and better biodegradability and biocompatibility.[93,222,227] Like other lipid-based nanoparticles PLHNPs can be functionalized with aptamers for selective molecular targeting. For instance, one research group explored the capacity of the MUC1 aptamer to treat a malignant tumor when combined with drug-loaded PLHNP. They used an amide link to attach MUC1 aptamers to the PEG layer at varying densities and discovered that increasing the density boosted cell targeting effectiveness.[228] Gui and colleagues created PLHNPs incorporating CD133 aptamers to administer retinoic acid for the treatment of osteosarcoma. [229] The development of an aptamer-functionalized hybrid nanocomposite to target prostate-specific membrane antigen (PSMA), which is abundantly expressed in prostate cancer, led to the sustained release of cisplatin. [230] EpCAM is a cellular adhesion factor that is abundantly expressed in tumors and is

thought to be a biomarker for cancer stem cells. CUR-NPs (curcumin-loaded lipidpolymer-lecithin hybrid nanoparticles) were created by Li et al. and functionalized with EpCAM aptamer. The administration of new chemotherapeutic drugs to colorectal cancer cells was enhanced with this technique. [231]

Table 3: Aptamer-functionalized nanoparticles for cancer detection, therapy, imaging and actively targeted drug delivery

Aptamer	Nanoparticle	Type of nanoparticle	Conjugation type	Clinical use	Drug	Cancer type	Target molecule	LOD	Ref.
S6 aptamer	Au@Ag/Au	Non-lipid	thiol–gold bond	Therapy and imaging	N/A	Lung cancer	Membrane receptor	N/A	232
MUC1	Mesoporous SiO_2	Non-lipid	electrostatic and hydrogen bonding	Therapy and imaging	Doxorubicin	Breast cancer	MUC1	N/A	233
AS1411	Au nanocluster	Non-lipid	amide bond	Therapy and imaging	Doxorubicin	glioblastoma	nucleolin	N/A	234
AS1411	Au nanocage/ SiO2	Non-lipid	covalent	Therapy and imaging	N/A	Breast cancer	nucleolin	N/A	235
sgc8c	Fe3O4@carbon	Non-lipid	amide bonds	Therapy and imaging	Doxorubicin	Lung cancer	N/A	N/A	236
MUC1	Silver (Ag) nanocluster	Non-lipid	thymidine linkage	Therapy and imaging	miR-34a	breast cancer	MUC1	N/A	237
5TR1	Fe3O4	Non-lipid	amide bonds	Therapy and imaging	Epirubicin	Colon carcinoma	MUC-1	N/A	84
AS1411	PEGylated liposome	Lipid	PEG linker	Cancer therapy and targeted drug delivery	Anti-BRAF siRNA	breast cancer	Nucleolin	N/A	238
SRZ1	DOTAP:DOPE liposome	Lipid	N/A	Cancer therapy and targeted drug delivery	Doxorubicin	Breast cancer	4T1 cells	N/A	239
TSA14	PEGylated-liposome	Lipid	covalent	Cancer therapy and targeted drug delivery	Doxorubicin	Breast cancer	TUBO cells	N/A	203
A10-3.2	Lipid-polymer hybrid	Lipid	Covalent	Cancer therapy and targeted drug delivery	Curcumin and Cabazitaxel	Prostate cancer	PSMA	N/A	223
A10–3.2	PEG-PAMAM	Non-lipid	Direct, covalent	Cancer therapy and targeted drug delivery	MicroRNA	Prostate cancer	PSMA	N/A	240
EpCAM-Ap	PEI	Non-lipid	electrostatic interactions	Cancer therapy and targeted drug delivery	EpCAM-siRNA	Breast cancer, retinoblastoma	EpCAM	N/A	241
MUC1-Ap	Au-SPION	Non-lipid	Direct, covalent	Cancer therapy and targeted drug delivery	N/A	Colon cancer	MUC1	N/A	242
AS1411	PLGA NPs	Non-lipid	Noncovalent	Cancer therapy and targeted drug delivery	Gemcitabine	lung cancer	Nucleolin	N/A	243
MUC1-Ap	Ag_2S nanodots	Non-lipid	streptavidin-biotin interaction	Cancer detection	N/A	Breast cancer	MUC1	N/A	244
MUC1-Ap	SPION@SiO2	Non-lipid	N/A	Cancer therapy and targeted drug delivery	Doxorubic	Breast cancer	MUC1	N/A	245
Sgc8c-Ap	Fe3O4-carbon	Non-lipid	Direct, covalent	Cancer therapy and targeted drug delivery	Doxorubicin	Lung cancer	Sgc8c	N/A	236

AS1411	carbon nanodots	Non-lipid	N/A	Cancer detection	N/A	All	hnRNP A2/B1 protein	~100 cells/mL	246
PSA-Ap	MoS2	Non-lipid	N/A	Cancer detection	N/A	Prostate cancer	PSA	0.2 ng/mL	247
Endo28	RNA NPs	Non-lipid	N/A	Cancer therapy and targeted drug delivery	Doxorubicin,	ovarian cancer	Annexin A2	N/A	248
Sgc8c	Gold NPs	Non-lipid	electrostatic interaction	Cancer therapy and targeted drug deliver	Daunorubici n	leukemia	PTK7	N/A	249
MUC1-AP, HER2-AP,	silica nanoparticles	Non-lipid	Avidin-biotin interaction	Cancer detection	N/A	Breast cancer	MUC1 and HER2	1 cell/100 µL	250
Sgc8 & Td05	gold nanoparticle	Non-lipid	Au–S bond	Cancer detection	N/A	Lymphoma, breast, leukemia and lung	CCRF-CEM cells	4 and 3 cells/mL	251
sgc8c	PAMAM dendrimer	Non-lipid	covalent	Cancer therapy and targeted drug delivery	N/A	All	CCRF-CEM cell	N/A	252
A10	SPION	Non-lipid	Covalent	Cancer therapy and targeted drug delivery	Doxorubicin	Prostate cancer	PSMA	N/A	253
AS1411	Liposome	Lipid	Covalent	Cancer therapy and targeted drug delivery	Cisplatin	Breast cancer	Nucleolin	N/A	254
TLS1c	Liposome	Lipid	Avidin-biotin interaction	Cancer therapy and targeted drug delivery	Cabazitaxel	Hepatoma	MEAR cells	N/A	255
A15	Liposome	Lipid	thiol-maleimide	Cancer therapy and targeted drug delivery	Curcumin	Prostate cancer	CD133	N/A	256
S15	Quantum dots	Non-lipid	covalent	Cancer therapy and targeted drug delivery	N/A	Lung cancer	NSCLC	N/A	257
A15, CL4	Lipid-polymer	Lipid	covalent	Cancer therapy and targeted drug delivery	Salinomycin	Osteosarcoma cells and CSCs	CD133, EGFR	N/A	258
AS1411	Gold	Non-lipid	PolyA linker	Cancer therapy and targeted drug delivery	Anti-miR-155	Breast cancer	Nucleolin	N/A	259
AS1411	Carbon nanotubes	Non-lipid	electrostatic interaction	Cancer therapy and targeted drug delivery	Doxorubicin,	gastric cancer	Nucleolin	N/A	260
EGFR	Albumin NPs	Non-lipid	N/A	Cancer therapy and targeted drug delivery	Cisplatin	prostate cancer	PSMA	N/A	261
5TR1	PLGA NPs	Non-lipid	electrostatic interaction	Cancer therapy and targeted drug delivery	Epirubicin	breast cancer	MUC1	N/A	167
AS1411 + S2.2	Gold-coated liposome	Lipid	S-Au bond	Cancer therapy and targeted drug delivery	Docetaxel	Breast Cancer	Mucin-1, Nucleolin	N/A	262
A6	Lipid-polymer liposome	Lipid	Direct, covalent	Cancer therapy and targeted drug delivery	siRNA	Breast Cancer	HER2	N/A	108

A10,	Liposome	Lipid	Covalent	Cancer therapy and targeted drug 39delivery	CRISPR-Cas9 plasmid	Prostate cancer	PSMA	N/A	[198]
AS-14	Gold-coated magnetic NP	Non-lipid	Thiolated ONT primer	Cancer therapy	N/A	All	Fibronectin protein	N/A	[263]
FKN-S2, in	PEG-aptamer micelle	Lipid	ssDNA-amphiphile	Cancer therapy	N/A	Colon adeno-carcinoma	Fractalkine	N/A	[264]
trCLN3,	Lipidated GC-rich DNA hairpin	Lipid	Lipid-mediated self-assembly	Cancer therapy	Doxorubicin,	Lung Cancer	cMet	N/A	[265]
HB5	aptamer cobalt phthalocyanines – Cerium oxide nanoparticle conjugate	Non-lipid	-	Cancer detection	-	Breast cancer	HER2	0.2 ng/mL	[266]
EpCAM-Ap	Aptamer-liposome	Lipid	-	Cancer therapy and targeted gene delivery	siRNA	Breast cance	EpCAM	-	[267]

CONCLUSIONS AND PERSPECTIVE

Single-stranded oligonucleotides aptamer produced by SELEX technology has captivated augmenting attention for cancer detection and therapy. We have discussed the role of different aptamer conjugated nanomaterials (micelle, lipid nanoparticle, non-lipid nanoparticle) in the field of cancer therapy and diagnosis in this review. The specified three-dimensional conformation of the aptamers helps them in binding with target molecules with higher affinity. Numerous researches have already been done in the field of aptamer-based drug delivery. However, a deeper understanding of the interaction between aptamer and target molecule is still required for clinical purposes. Although aptamers have made advancements in cancer therapeutics, improvements need to be made with binding affinity, drug loading rate, circulation time, and targeting efficiency. Despite several drawbacks, such as limited pharmacokinetics studies, unpredictable in vivo off-target effects, and toxicity, aptamers can be applied as a molecular tool for translational cancer research. [104] This is an area where extra effort should be put in. Current preclinical and clinical results support the idea that tailored nanoparticles-aptamer conjugate could be used to deliver medications to specific cancer sites at a slower rate and detect cancer shown in table 3. These targeted nanoparticle-aptamer complex will provide the enhanced cancer treatment alternatives that are so desperately needed. [104] The aptamer- nanocarrier conjugate can solve the issues with circulation time due to its EPR effect. Moreover, aptamer conjugated liposomes load both hydrophobic drugs (lipid bilayer) and hydrophilic drugs (aqueous core). The multivalent effect of the aptamer-micelle complex increases the binding affinity with the target molecule. Recent advancements in DNA aptamer conjugated nanoparticles have been discussed here to highlight the potential avenues for cancer diagnosis and therapy in one shot. Of course, this is highly reliant on the stability of the aptamer and the nanoparticle in vivo [268], which usually requires complete conjugate optimization first in vitro and then in living systems. [103]Along with this, numerous different factors such as toxicity [105], renal filtration [106], in vivo stability [163], etc., are significant. Once these aptamer-conjugates pass all of these tests, they can advance to clinical trials and become available on the market. Several modifications have been reported to make the DNA-aptamer more stable, including backbone modification, while keeping its targeting ability. Because DNA is easier to manipulate chemically than the other nucleic acid family members, various aptamers are modified to withstand in vivo degradation. A number of limitations currently hampers effective oligonucleotide therapies. Stability and efficacy issues have mainly been resolved. Despite many inventive attempts to solve it, however, effective intracellular delivery continues to be a problem. Accumulation in endosomes and ineffective release to the cytosol are still challenges for monomeric oligonucleotides and different nanocarrier-oligonucleotide moieties.[269] The intracellular trafficking of nucleic acids and nanoparticles seems to be an area in which we still have a lot to learn, and even more research should be done in this area. This review clearly shows that plenty of studies have been performed that show successful diagnosis and cure of detected cancer because there is still a lot of research to be completed to make these prototypes more robust for other types of cancer, other types of drugs, and so forth. This field holds enormous promise in reducing the side effects of cancer treatment by selecting and releasing the required number of medications at a time. Depending on the severity and spread of cancer, a combination of external fields and internal target-aptamer binding may expedite recovery in the future.

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AUTHOR CONTRIBUTION

BC and DB conceived the idea and implementation. SD, AG, VTV, SW collected the references and wrote the review. SD took the lead in arranging the figures and communication of drafts. All the authors read the paper and gave their suggestions and inputs.

CONFLICT OF INTEREST

The authors do not disclose any conflict of interest for this article.

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