REVIEW

Aptamers as Versatile Ligands for Biomedical and Pharmaceutical Applications

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¹Department of Nephrology, The First Affiliated Hospital of Jinan University, Guangzhou 510630, People's Republic of China; ²Department of Pharmaceutics, College of Pharmacy, Jinan University, Guangzhou 510632, People's Republic of China **Abstract:** Aptamers are a class of targeting ligands that bind exclusively to biomarkers of interest. Aptamers have been identified as candidates for the construction of various smart systems for therapy, diagnosis, bioimaging, and drug delivery due to their high target affinity and specificity. Aptamers are accounted as chemical antibodies that can be readily linked to drugs, sensors, signal enhancers, or nanocarriers for functionalization. Use of aptamer-guided medications, especially nanomedicines, has resulted in encouraging outcomes compared to those use of aptamer-free counterparts. This article reviews recent advances in the use of aptamers as targeting ligands for various biomedical and pharmaceutical purposes. Special interests focus on aptamer-based theranostics, biosensing, bioimaging, drug potentiation, and targeted drug delivery.

Keywords: aptamer, theranostics, biosensor, biomedical imaging, drug delivery

Introduction

Aptamers are short RNA or single-stranded DNA comprise 20–80 nucleotides (Figure 1) that can fold into unique three-dimensional conformations to specifically bind to targets. Aptamers are intentionally designed oligonucleotide sequences that differ from naturally occurring ligands.¹ They can specifically recognize and interact with diverse targets such as receptors, antigens, and biomarkers via van der Waals forces, hydrogen bonding, electrostatic interactions, stacking of flat moieties, and shape complementarity.² Upon binding to targets, aptamers induce a series of biochemical effects, such as antagonism, agonism, suppression, and destruction.^{3,4} Aptamers can be synthesized through a systematic evolution of ligands by exponential enrichment (SELEX) technique, and have several advantages over commonly used small-molecule ligands, including excellent tissue permeability, unlimited availability of targets, good stability, and modifiability.⁵

Discovery and use of artificial antibodies have provided a viable platform for the development of precision medicines. In recent years, the potential for use of aptamers for biomedical purposes has been evaluated in a variety of fields. Aptamers have been evaluated for use in molecular therapy, diagnosis, biosensing, biomedical imaging, drug potentiation, and targeted drug delivery. Aptamers can be customized to target specific molecules using well-established techniques.⁶ The concept of a "magic bullet" has inspired practitioners to use aptamers to construct smart devices.⁷ For instance, a nucleolin-targeted intelligent DNA nanorobot that utilized an aptamer and DNA origami was constructed to obstruct vasculature feeding for cancer therapy.⁸ Hao et al developed aptamer-functionalized microfluidic devices based on dendrimers for

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Figure I Aptamer structure, characteristics, and functional illustration for biomedical applications.

sensitive and rapid detection of foodborne pathogenic bacteria.⁹ A study by Luo et al examined the delivery potential of CD30 aptamer-modified polymeric nanoparticles for targeted delivery of doxorubicin to anaplastic large cell lymphoma cells.¹⁰ These studies showed that aptamers have the versatility as specific functional ligands that can induce positive theranostic responses.

Aptamers are considered to be "chemical antibodies" based on their biomimetic nature and simple synthetic procedures. Aptamers are pleiotropic ligands that have potential for use in the development of smart and intelligent systems. Previous investigators have presented reviews on aptamer discovery and applications.^{11,12} However, these reports revolved around the synthesis of aptamers, aptamer-guided drug delivery, and targeted therapy. The biomedical and pharmaceutical applications of aptamers have not been fully reviewed. This article includes a full review of the application of aptamers in the biomedical and pharmaceutical fields. Aptamer-mediated theranostics, biosensing, bioimaging, drug potentiation, and targeted drug delivery are discussed in this work.

Use of Aptamers in Theranostics

Aptamers can specifically recognize molecular targets and modulate their biological activities, which allows aptamers to be used for therapeutic and diagnostic purposes. Aptamers can regulate biological pathways by interfering with pathological processes. Aptamers can also be used to target biomarkers for diagnostic purpose. Use of aptamers for therapeutic purposes began in 1990 when Tuerk and Gold performed the first SELEX experiment for the selection of an RNA aptamer against bacteriophage T4 DNA polymerase.¹³ Sullenger et al reported the inhibitory effect of trans-activation response (TAR) decoy, an RNA sequence, on HIV-1 viral infection in host cells.¹⁴ Presently, only one aptamer drug (Macugen) has been approved by the FDA, but several others are being evaluated in clinical trials.¹⁵ In addition, aptamers have been used to treat aging-related disorders,¹⁶ obesity and diabetes mellitus,^{17,18} cardiovascular diseases,¹⁹ infectious diseases,^{20,21} blood coagulation,²² bone diseases,²³ immuno-logical diseases,²⁴ and cancers²⁵ (Figure 2).

Aptamers used for diagnostic purposes are typically conjugated to suitable nanoparticles (NPs) to enable detection. Zhao and colleagues developed aptamer-modified fluorescent silica NPs (FSNPs) by conjugating amine-labeled Sgc8 aptamer to carboxyl-modified FSNPs via amide coupling to detect leukemia cells.²⁶ They assessed the sensitivity and specificity of Sgc8-FSNPs using flow cytometry and fluorescence microscopy. The results showed that Sgc8-FSNPs could be used to accurately detect leukemia cells with high sensitivity, which indicated that Sgc8-FSNPs were a highly sensitive tool for specific detection of leukemia cells. Sakvi et al produced RNA aptamers that specifically bound to mycolactone for diagnosis of buruli ulcer (BU) using the SELEX technique.²⁷ The results of this study indicated that diagnosis of BU using RNA aptamers was feasible. Recently, aptamers have received attention as potential agents for disease prevention and treatment. Fibroblast growth factor 2 (FGF2) plays a key role in bone remodeling and disease progression. Jin et al constructed a novel human FGF2-specific RNA aptamer, APT-F2,²³ which



Figure 2 Aptamers as theragnostic agents for various diseases by targeting to etiological loci and interfering with pathological processes.

blocked FGF2 binding to its four cellular receptors, inhibiting FGF2-induced downstream signaling. This resulted in decreased cell proliferation and restored osteoblast differentiation. Polyethylene glycol-modified APT-F2 (APT-F2P) effectively prevented arthritis and osteoporosis. These findings illustrated the dual therapeutic potential of APT-F2P for the treatment of bone disease and pain. In another case, AS1411 and modified AS1411 aptamers that bind to nucleolin were investigated for their potentials in treating hepatocellular carcinoma.²⁸ Modified AS1411-aptamer significantly suppressed HCC cell growth in vitro and in vivo by upregulating galectin-14 expressions. Introducing aptamers into the field of theranostics may provide more sensitive and precise alternatives to conventional approaches. Aptamer-based theranostics have advantages over traditional diagnosis and drug therapy. The underlying reason lies in the specificity and targeted regulation of an aptamer to a given disease.

Aptamer-Based Biosensors

Biosensors are comprised of a transducer and a biological element that recognizes a biological response. The transducer

converts the signal to provide a diagnostic indicator. The biological element may be an enzyme, an antibody, or a nucleic acid (eg, aptamer) with or without a modified detectable molecule. Aptamers can bind to target molecules with high affinity and specificity, which is ideal for use as biosensor component. Aptamer-linked biosensors, also known as aptasensors, can be detected using fluorescence, chemiluminescence, electrochemistry, or immunoluminescence techniques.²⁹ Figure 3 provides an illustration of components, detection techniques, and signal read-outs associated with aptasensors. Aptamer-based biosensors have been used for accurate and rapid detection of disease markers, pathogens, antibiotics, toxins, pollutes, and other chemicals or biomolecules.^{30–34} Biosensors utilize the specificity of aptamers to disease targets and the convertibility of transducers to translate the biological response into a detectable signal.

Current diagnostic procedures for tumors typically involve biopsy. No mature techniques have been available for rapid and sensitive detection of tumors. Li et al developed aptamer-functionalized gold nanorods as a diagnostic



Figure 3 Aptamer-mediated biosensors for analysis using fluorescence, chemiluminescence, electrochemistry, or immunoluminescence.

biosensor for MCF-7 breast cancer cells.³⁵ Gold nanorods with aptamers specific to mucin 1 protein (MUC-1) allowed for rapid diagnosis of human breast carcinoma MCF-7 cells with a detection limit of 100 cells/mL. The interactional signals between the biosensor and cancer cells were readily translated into unique localized surface plasmon resonance (LSPR) spectra. Ahmadzadeh-Raji et al developed an optically transparent aptasensor for diagnosis of colon cancer that consisted of gold NPs with electrodeposited indium tin oxide.³⁶ The aptamer-containing electrodeposited gold NPs functioned as nanoprobes for cancer cell targeting and could be detected using a conventional optical microscope or an electrochemical method. Another study reported the development of aptamer-conjugated gold-coated magnetic NPs for intelligent detection of leukemia cancer cells.³⁷ In addition to cancer detection, aptasensors have been used to trace microRNAs,³⁸ C-reactive protein,³⁹ and lysozyme.⁴⁰

Aptamers for Biomedical Imaging

Non-invasive imaging of various disease markers using aptamer-modified probes has shown numerous advantages over traditional imaging techniques. Ligand-mediated non-invasive imaging allows for visual observation of diseases at the cellular and molecular levels.⁴¹ This technique provides high accuracy and predictability for early diagnosis and treatment, resulting in improved prognosis. Aptamer-aided biomedical imaging can be achieved through direct or activatable optical imaging by linking an aptamer to a fluorescent molecule or a fluorescent

mediator (NPs or quantum dots), or through other tomographic techniques, such as MRI, ultrasound, and PET (Figure 4). Optical imaging can be used to detect fluorescence or bioluminescence of aptamer-linked signal transducers. Optical imaging is a simple, low-cost solution for visualization of diseases using aptamers. For example, Li et al synthesized a DNA aptamer, R13, and labeled it with FAM and Cy5 at the 5' terminal of the DNA sequence for in vivo imaging of ovarian cancer.⁴² Aptamer R13 was highly specific for ovarian cancer, exhibited good stability, and was able to bind to extracellular membrane proteins. In addition, fluorescence-labeled R13 allowed for excellent ex vivo tissue and in vivo tumor imaging. Although aptamers possess good affinity to their targets, they are frequently off-target to specific tissues in vivo due to short half-life. To improve tissue targeting, aptamers are often conjugated with various nanovectors, including gold/silver NPs, silica NPs, and quantum dots (QDs). Chen et al constructed a versatile protein labeling platform with aptamer-mediated NPs for intracellular imaging and tracking of endocytosis dynamics.43 This platform exhibited good cellular tracing ability and provided valuable insights into NPs endocytosis, which may be promising for biomedical labeling of cell activities. Tan et al developed a novel theranostic system based on endoglin aptamer (YQ26)-modified fluorescent silica NPs (YQ26-FsiNPs) for tumor imaging, treatment, and monitoring.⁴⁴ Use of YQ26-FSiNPs resulted in high targeting efficiency and excellent therapeutic effects via aptamer YQ26-mediated binding. In vitro and in vivo studies showed that YQ26-FSiNPs was



Figure 4 Design rationale and imaging methods for aptamer-facilitated biomedical imaging (**A**) with a demonstration of PET molecular imaging for HER2 in cancer (**B**). The illustration was used with permission from Zhu G, Zhang H, Jacobson O, et al. Combinatorial screening of DNA aptamers for molecular imaging of HER2 in cancer. *Bioconjug Chem.* 2017;28(4):1068–1075. doi:10.1021/acs.bioconjchem.6b00746, Copyright (2017) American Chemical Society.⁵⁰

a promising agent for clinical tumor diagnosis and treatment. Quantum dots are inorganic fluorescent semiconductor NPs used for imaging. Aptamers can be conjugated to QDs for bioimaging without the need for the addition of a fluorescent agent. Aptamer-conjugated QDs were used by Kaur to image cellular uptake in cancer cells.⁴⁵ Fluorescence imaging showed that the conjugates containing QD-SL(2)-B aptamer, an aptamer that targets the heparin-binding domain of VEGF165 protein, specifically recognized Hep G2 cells and were internalized in the absence of an additional transfecting agent. This aptamer conjugate provided a smart strategy for liver cancer imaging and cellular labeling.

Activatable aptamer probes take advantage of the "on/ off" rational of fluorescence resulting from biological interactions or during fluorescence resonance energy transfer (FRET) for imaging. Xu et al used the fluorescence quenching properties of graphene oxide (GO) to design an aptamer-based four-color fluorometric system for simultaneous detection and imaging of α -fetoprotein, VEGF-165, carcinoembryonic antigen, and human epidermal growth factor receptor (HER2) in living cells.⁴⁶ Due to strong π interactions, the fluorescence of the labeled aptamers was quenched by GO. Four fluorophore-labeled aptamers targeting to tumor-associated proteins were adsorbed on GO to form four-color nanoprobes with quenched fluorescence. Upon being internalized into cells, the aptamer/GO nanoprobes interacted with the intracellular tumor-associated proteins, which resulted in dissociation of the aptamer from GO, and resulted in the activation of fluorescence. Aptamerbased probes allow for rapid discrimination of tumor cells from normal cells via imaging. Using hybridization chain reaction (HCR), Yuan et al constructed a multifluorescence FRET detection method for specific imaging of cell-surface glycosylation.⁴⁷ Intramolecular multi-FRET occurred due to a short donor-acceptor distance when aptamer-tethered nanoassemblies bound to receptors through metabolic glycan labeling. Amplification effects and spatial flexibility of aptamer-linked HCR nanovectors enhanced the multi-FRET imaging resolution that could allow for real-time observation of cell-surface glycosylation.

Aptamer-mediated tomographic imaging has become an important arena of aptamer application. Aptamers can be conjugated to signal enhancers (not luminophores) used for targeted MRI, ultrasound, and PET imaging. Aptamer-based MRI contrast agents are generally designed by linking an aptamer with superparamagnetic iron oxide (SPIO) NPs. For example, a glypican-3 (GPC3)-specific aptamer (AP613-1) has been tethered to ultrafine SPIO NPs (USPIONPs) for targeted imaging of hepatocellular carcinoma.⁴⁸ This study demonstrated specific uptake of Apt-USPIONPs into Huh-7 cells, and in vivo T2-weighted MRI showed significant negative enhancement of Huh-7 tumors through imaging of Apt-USPIONPs. The combination of aptamers and ultrasound contrast agents (UCA) can enhance ultrasonic signal detection. Commonly used UCAs include gas-containing micro/ nanobubbles, which have intense ultrasonic scattering properties that can significantly enhance the ultrasonic echo signals following administration, resulting in improved imaging for tissues or organs. Conjugation of specific aptamers to UCAs can result in enhancive effects of UCAs due to targeting. Zhu et al developed carbonic anhydrase IX (CAIX) aptamerimmobilized targeted nanobubbles for ultrasound molecular imaging of various tumors.⁴⁹ Targeted nanobubbles loaded with CAIX aptamer penetrated the tumor vasculature to allow for ultrasound molecular imaging (USMI) of tumor parenchymal cells. Nanobubbles containing CAIX aptamer exhibited higher peak intensity and larger area under the curve than non-targeted nanobubbles in 786-O and Hela xenograft tumor tissues. Aptamer-containing targeted nanobubbles exhibited superior imaging effects in tumor parenchymal cells, which resulted in enhanced diagnostic accuracy of malignant tumors in various organs. Radionuclide-based imaging techniques such as SPECT and PET have greater diagnostic capability than other molecular imaging techniques due to superb tissue penetration and quantifiability. Coupling of aptamers to radioisotopes (eg, 125I, 99Tc and 18F) can result in highly specific and sensitive radiopharmaceuticals. In one study, HER2-targeted DNA aptamers (heraptamers) were screened and labeled with ¹⁸F for PET imaging of ovarian cancer.⁵⁰ Aptamers labeled with ¹⁸F exhibited high tumor uptake ratio and specific HER2 imaging in SKOV3 tumorbearing mice. These studies demonstrated the potential of aptamers for targeted bioimaging. In addition, aptamers have been evaluated for use in other imaging applications, such as computed tomography (CT), transmission electron microscopy (TEM), surface plasmon resonance (SPR), and surface-enhanced Raman spectroscopy (SERS).

Drug Potentiation via Aptamer Modification

The potency of therapeutic agents can be compromised by limited selectivity, "off-target" effects, and lack of synergy. Targeted or combined therapy can enhance the selectivity and potency of medications. One approach is to utilize diseasespecific aptamers with high affinity or bioactivity to potentiate the effects of therapeutic agents. Aptamers can achieve drug potentiation in three ways (Figure 5): (1) combinatorial administration using simple mixtures; (2) formation of aptamer-drug conjugates; and (3) development of aptamer-drug chimeras. Combinatorial administration utilizes the therapeutic properties of aptamers to synergistically enhance the therapeutic effects of the counterpart drugs. Aptamer-drug conjugates allow conjugated drugs to be specifically delivered to disease targets by aptamers. In the case of aptamer-drug chimeras, the "drug" is typically a therapeutic RNA (siRNA or miRNA). Aptamers are directly hybridized into therapeutic RNAs and serve as active targeting ligands to guide the therapeutic RNA to the target site. Cell- or receptor-specific chimeric RNAs have been shown to improve the in vivo pharmacokinetic distributions of prototype RNAs, and facilitate transport into cells by receptor-mediated endocytosis.⁵¹

Combined use of therapeutic aptamers and therapeutic drugs has been reported. Schilling et al investigated the radiosensitizing effect of a peptide aptamer, A17, which inhibits Hsp70, in combination with the Hsp90 inhibitor NVP-AUY922.⁵² Co-administration of A17 with NVP-AUY922 significantly enhanced the pro-apoptotic effects of NVP-AUY922, but it did not significantly affect the radiosensitivity of human lung or breast cancer cells. Inhibition of Hsp70 by A17 potentiated the radiosensitizing effect of NVP-AUY922. A combined strategy based on simultaneous inhibition of PD-1 and C5a/C5aR1 signaling using a RMP1-14 antibody and C5a L-aptamer to synergistically inhibit growth and metastasis



Figure 5 Synergy and attenuation of therapeutic agents through three aptamer-related approaches: co-administration of a therapeutic aptamer and a drug, development of an aptamer-drug conjugate, and construction of an aptamer-RNA chimera.

of lung cancer was proposed by Ajona et al.⁵³ This study showed that C5a and PD-1 inhibition by an RMP1-14 antibody and C5a L-aptamer significantly reduced tumor growth and metastasis, which resulted in increased survival.

Design of aptamer-drug conjugates is an innovative drug modification technique. In these conjugates, the aptamer does not exert pharmacological effects or modulate the activity of the parent compound, but targets the therapeutic molecule to the tissue of interest. Antibiotic resistance is a substantial clinical concern. Lijuan et al developed aptamer-ampicillin conjugates to penetrate bacterial biofilms, which helped to overcome antibiotic resistance.⁵⁴ These conjugates exerted distinct synergistic antibacterial activity greater than that of either component alone. Coupling of an aptamer to a cytotoxic drug to treat local and metastatic tumor lesions is another important aptamer application. Powell et al synthesized tunable cytotoxic aptamer-drug conjugates for the treatment of prostate cancer.⁵⁵ A prostate cancer-specific aptamer (E3) was produced using cell SELEX selection. The aptamer was internalized into prostate cancer cells, but not into normal prostate cells. Conjugation of E3 to MMAE and MMAF (monomethyl auristatin E and F) resulted in potent cytotoxic agents that efficiently killed

prostate cancer cells, but not normal prostate epithelial cells, in vitro. In addition, the cytotoxicity of E3 aptamer-drug conjugates can be inhibited by an oligonucleotide against the E3 aptamer. This provides a means to intervene in the unexpected event of normal cell killing in vivo.

The therapeutic superiority of aptamer-RNA chimeras has been demonstrated in recent years.⁵⁶ Wang et al constructed an aptamer-siRNA chimera targeted to epithelial cell adhesion molecule and survivin to deliver a high dose of siRNA and silence resistance to doxorubicin.⁵⁷ Silencing of survivin (a key protein involved in drug resistance) resulted in a significant reversal of chemoresistance. This chimera, in combination with a low dose of doxorubicin, inhibited stemness, eliminated cancer stem cells via apoptosis, suppressed tumor growth, and prolonged survival of tumor-bearing mice. In brief, aptamers can be used to potentiate drugs or actives by synergistic interaction, inspiring specific drug delivery, and conferring affinity to the underperformed entities.

Aptamers for Targeted Drug Delivery

The in vivo distribution of medicines plays a key role in pharmacological action. Most of drugs exhibit diffuse

1065

biodistribution following administration, resulting in unsatisfactory therapeutic outcomes and pronounced side effects. Targeted drug delivery systems (TDDS) represent the most promising drug delivery strategy for drug accumulation in the tissues of interest in vivo. A targeted drug delivery system typically consists of a nanocarrier and a targeting moiety. The targeting component is referred to as "ligand." Many ligand molecules are currently available for the development of TDDS,^{58,59} including vitamins, saccharides, bile salts, transferrin, lectins, oligopeptides, antibodies, and aptamers. Aptamers have been shown to be outstanding TDDS ligands due to facile synthesis, high specificity, and potential for simple modification. Aptamers are known as chemical antibodies with modifiable groups at the terminal end, which can be synthesized using the in vitro SELEX technique. In addition, aptamers can be flexibly anchored to a variety of nanocarriers via various conjugation approaches (Figure 6). Organic nanocarriers (liposomes, polymeric-lipid hybrid NPs, micelles, and dendrimers) and inorganic nanocarriers (Au/Ag NPs, silica NPs, carbon NPs, selenium NPs, and other inorganic NPs) can be modified with specific aptamers to achieve targeted drug delivery. Aptamer-mediated targeted



Figure 6 Various organic and inorganic nanocarriers functionalized using aptamers for targeted drug delivery, and commonly used strategies for aptamer conjugation with nanocarriers.

drug delivery can be used to treat a broad spectrum of diseases, including tumors, immunological diseases, genetic diseases, infectious diseases, and cytopathic disorders.

Aptamer-mediated drug delivery has shown potential as a cancer treatment strategy. The primary considerations in the design of TDDS are to promote the accumulation of chemotherapeutic agents in the tumor tissue and overcome drug resistance. Ligands can guide nanocarriers to tumors and facilitate the transport of these nanocarriers into tumor cells, resulting in cell death. Liposomes are the most commonly used vehicles functionalized with aptamers for targeted drug delivery. To overcome drug resistance from erlotinib, Li et al developed lung cancer-specific liposomes using EGFR aptamer-chitosan conjugates to deliver erlotinib to the tumor.⁶⁰ The nanocarrier showed good biostability and binding specificity for EGFR-mutated cancer cells, which facilitated liposomal erlotinib internalization into EGFR-mutated cancer cells. Aptamer-modified liposomes exhibited better delivery of erlotinib to EGFRmutated cancer cells than standard delivery techniques, which resulted in greater cytotoxicity. In another study, tumoral delivery of cabazitaxel was improved using aptamer-modified liposomal delivery system (apt-liposomes) .⁶¹ In this study, apt-liposomes increased the accumulation of cabazitaxel in the tumor tissue. These findings suggested that specific binding of aptamer (TLS1c) to the targeted cells (MEAR) facilitated the accumulation of liposomes in the target tissue. Coupling of aptamers to NPs, including polymeric and lipid-based NPs, is also a common delivery strategy to augment the anticancer efficacy of chemotherapeutic agents. Chen et al constructed docetaxel-loaded polymeric NPs (DTX-apt-NPs) targeting to prostate cancer using an aptamer-mediated delivery strategy.⁶² DTX-apt-NPs enhanced in vitro antitumor activity and cellular uptake compared with conventional NPs. Clathrin-dependent endocytosis was involved in intracellular trafficking of these NPs. Anti-PSMA aptamer-mediated delivery significantly improved the antitumor effect of docetaxel.

Micelles are likewise excellent drug delivery systems that can be aptamer-modified. Charbgoo et al engineered MUC1 aptamer-targeted DNA micelles for systemic delivery of doxorubicin and KLA peptide for dual tumor therapy.⁶³ Anti-MUC1 aptamer specifically delivered micelles into MCF-7 cells by improving the cellular uptake. Co-delivery of doxorubicin and KLA using aptamer-modified micelles significantly enhanced anti-tumor efficacy through synergy and attenuation of drug combination. In addition, aptamers are often used to modify dendrimers for targeted drug delivery. Therapeutic RNA and small-molecule drugs can all be delivered to tumor targets using aptamer-modified dendrimers.^{64,65} In vitro and in vivo study results have shown that aptamer-modified dendrimers specifically bound to tumor cells and enhanced antitumor efficacy compared with aptamer-free dendrimers.

Aptamers have also been used to modify inorganic nanocarriers to optimize drug delivery. Inorganic nanocarriers that can be coated with functional aptamers include, but not limited to, gold/silver NPs, silicon NPs, carbon NPs, and selenium NPs. Chemical drugs or photosensitizers, or both, can be incorporated into aptamer-modified inorganic nanocarriers. For example, a nanoplatform based on aptamer-functionalized gold NPs was developed by Huang et al for co-delivery of a photosensitizer and doxorubicin.⁶⁶ This tumor-targeted combinative therapy system resulted in significant necrocytosis of HeLa and Dox-resistant MCF-7R cell lines upon exposure to an exciting light. In addition, light-triggered release of doxorubicin resulted in enhanced cytotoxicity in target cells. To achieve controlled drug delivery and allow for radioimaging, MUC1 aptamer-capped mesoporous silica NPs (MSNs) were engineered by Pascual et al.⁶⁷ Safranin O-loaded MSNs functionalized with aminopropyl groups and gated with the negatively charged MUC1 aptamer have been intended for specific delivery to target tissues and specific release of therapeutic agents in tumor cells. Confocal microscopy showed that MUC1 aptamer-capped NPs (MUC1-apt-NPs) were internalized into MDA-MB -231 breast cancer cells overexpressing the MUC1 receptor, which resulted in pore opening and cargo release. Radio-labeling of MUC1-apt-NPs with ⁹⁹mTc resulted in tumor targeting in vivo, as evidenced using SPECT imaging in tumor-bearing Balb/c mice. Carbon NPs, which are inert, have also been evaluated in combination with functional aptamers for targeted drug delivery and bioimaging. Li et al reported use of aptamer-gated mesoporous carbon nanospheres for imaging of cellular mucin and on-demand targeted drug delivery.⁶⁸ Aptamer-coupled carbon NPs can be used for real-time switchable imaging of cellular mucin through π - π stacking, and can also be used for targeted doxorubicin release in tumors. Selenium NPs (SeNPs) have recently received attention for use in drug delivery and biomedical applications.⁶⁹ SeNPs can be functionalized with aptamers for the optimization of drug delivery. Recently, a targeted co-delivery system based on SeNPs was developed using 5TR1 aptamer as the targeting agent

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to enhance the in vitro and in vivo anti-tumor efficacy of epirubicin and NAS-24 aptamer (an apoptosis induction agent).⁷⁰ Aptamer-modified SeNPs significantly reduced toxicity in non-target cells, but reduced cell viability of the target cancer cells. The in vivo anticancer efficacy of these SeNPs confirmed that this nanosystem significantly inhibited tumor growth of tumor-bearing mice to a greater extent than treatment with epirubicin alone. In addition, other aptamer-functionalized inorganic nanocarriers, such as calcium carbonate NPs,⁷¹ and iron oxide NPs,⁷² have also been evaluated for targeted drug delivery.

Aptamer-mediated active TDDS have been shown able to induce significant antitumor activities. In addition, aptamers can be used as targeting ligands for other drug delivery to treat non-tumor diseases. Danesh et al developed aptamermodified gold NPs for targeted delivery and controllable release of daunorubicin to T-cell acute lymphoblastic leukemia.⁷³ Targeted delivery of tacrolimus using pHresponsive aptamer-chitosan-PLGA nanocomplexes to suppress immunological rejection was also investigated.⁷⁴ Besides, aptamer-functionalized lipid NPs were constructed for specific delivery of RNAi to osteoblasts to treat bone anabolic diseases.⁷⁵ In two another studies, aptamermodified nanocapsules and gold NPs were developed for targeted delivery of antimicrobial agents to bacteria via aptamer-receptor interactions to eradicate pathogens.^{76,77} Taken together, aptamers can be used to decorate a variety of drug delivery vehicles to confer targeting ability whereby to enhance the therapeutic efficacy of payloads against various diseases (Table 1). Nanocarriers solve the unmet properties of "problem" drugs by encapsulation, while aptamers push them to the endpoint of targeted therapy.

Concluding Remarks

Aptamers are pleiotropic ligands that can be chemically synthesized in large quantities and exhibit high affinity for selected targets. Aptamers that can be considered as artificial antibodies have many advantages over naturally-occurring ligands such as scalability, high specificity, and ease of conjugation to other molecules. These properties make aptamers suitable for use in theranostics, biomedical imaging, drug potentiation, and targeted drug delivery. Aptamers can act as agonists or antagonists to modulate the functions of target effectors pertinent to a disease. Aptamers can also be coupled

Table	Representative	Nanocarriers	Functionaliz	ed with a	a Specific	Aptamer	Used for	Targeted D	rug De	livery	

Nanocarrier	Aptamer	ΑΡΙ	Target	Carrier Type	Ref.
Liposomes	EGFR TLSIc 5TRI	Erlotinib Cabazitaxel Doxorubicin	EGFR-mutated cells MEAR cancer cells Mucin1 on cancer cells	Organic	60 61 78
Polymeric NPs	PSMA ASI4II	Docetaxel Cisplatin	Prostate cancer A2780 R cancer cells	Organic	62 79
Polymer-lipid hybrid NPs Micelles	EGFR MUCI	Salinomycin Doxorubicin/KLA peptide	Osteosarcoma MCF-7 cancer cells	Organic Organic	80 63
Dendrimers	ASI4II MUCI/ATP	shRNA Epirubicin	A549 lung cancer cells MCF-7/C26 cancer cells	Organic	64 81
Albumin NPs Lipopolymer Nanovesicles Gold NPs Silica NPs Carbon NPs Selenium NPs Calcium NPs SPIO NPs	ASI411 LC09 ASI411 Apt (His) EpCAM ASI411 STR1 MUC1-Dimer MUC1	Doxorubicin CRISPR/Cas9 Paclitaxel Antimicrobial peptides Doxorubicin shRNA/Dox Epirubicin/RNA Epirubicin and melittin Doxorubicin	MCF7 cancer cells Osteosarcoma MDA-MB-231 cells Salmonella SW620 colon cancer Gastric cancer cells MCF7/C26 cancer cells MCF-7/C26 cancer cells MCF-7 cancer cells	Organic Organic Biological Inorganic Inorganic Inorganic Inorganic Inorganic Inorganic	82 83 84 85 86 87 70 71 72
MOF NPs	AS1411	Doxorubicin	HeLa/HEK 293T cells	Hybrid	88

Abbreviations: API, active pharmaceutical ingredient; NPs, nanoparticles; apt, aptamer; EGFR, epidermal growth factor receptor; TLSI, an aptamer highly specific for BNL IME A.7R.1 (MEAR) cells; 5TRI, a DNA aptamer targeted to MUC1 receptors; PSMA, prostate-specific membrane antigen; MUC1, an aptamer that selectively binds to abnormally glycosylated mucin-1; AS1411, A 26-base guanine-rich oligodeoxynucleotide anti-nucleolin aptamer; LC09, an osteosarcoma cell-specific aptamer; EpCAM, epithelial cell adhesion molecule; SPIO, superparamagnetic iron oxide; MOF, metal-organic framework.

to signaling molecules for use in diagnostics. Aptamer-based biosensors, called aptasensors, can be used to detect a variety of biomarkers. Aptamers can be linked to luminophores or signal enhancers to allow for targeted imaging. Moreover, aptamers can be used as targeting ligands to functionalize non-targeted drugs, or as therapeutic molecules to potentiate the effects of other therapeutic molecules. Finally, aptamers can be used to construct intelligent drug delivery systems for the application of precision medicines. Aptamers have great potential for use in the biomedical/pharmaceutical field due to advances in the SELEX technique. Further studies may identify other potential uses of aptamers.

Although aptamers are extremely rich in resources, there are still some areas for improvement in the use of aptamers. The synthetic technology of oligonucleotides needs to be further developed so as to boost the output of aptamers. The aptamers screening technology needs to be further updated to facilitate the quick identification of target aptamers. It also requires to expand the modification strategies of aptamers to make them available for molecular coupling. Furthermore, the biological stability of aptamers in vivo should be taken into serious consideration, which is the prerequisite for the application of aptamers. We believe that these problems will be tackled properly with advances in aptamer technology.

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Disclosure

The authors declare no conflicts of interest in this work.

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