Review

Aptamer-Functionalized Nanoparticles in Targeted Delivery and Cancer Therapy

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Abstract: Using nanoparticles to carry and delivery anticancer drugs holds much promise in cancer therapy, but nanoparticles per se are lacking specificity. Active targeting, that is, using specific ligands to functionalize nanoparticles, is attracting much attention in recent years. Aptamers, with their several favorable features like high specificity and affinity, small size, very low immunogenicity, relatively low cost for production, and easiness to store, are one of the best candidates for the specific ligands of nanoparticle functionalization. This review discusses the benefits and challenges of using aptamers to functionalize nanoparticles for active targeting and especially presents nearly all of the published works that address the topic of using aptamers to functionalize nanoparticles for targeted drug delivery and cancer therapy.

Keywords: aptamer; nanoparticle; delivery; cancer

1. Introduction

The ideal cancer therapeutics should be capable of exerting maximum destruction on cancer cells while being able to keep damage to healthy tissues at a minimum. Many anticancer drugs are toxic to cancer cells and healthy cells largely non-differentially, and the major reason that they cause more damage to cancer is because the cancer cells grow/divide more quickly. Besides, most anticancer drugs are in general evenly distributed throughout the body when administered systemically and the result is that only a very small fraction of the drugs reach the diseased site. Therefore, it is not surprising that selective delivery of anticancer drugs to cancer cells has long been a vigorous pursuit of cancer scientists.

Nanoparticles have the potential to encapsulate and transport anticancer drugs to tumor tissue more effectively [1]. However, nanoparticles per se do not have specificity to cancer cells; the fact that nanoparticles accumulate preferentially in cancer sites is basically due to the enhanced permeability and retention (EPR) effect of the tumor tissue [2]. On the other hand, if nanoparticles could be functionalized by ligands capable of recognizing cancer cells specifically, they will be able to target and deliver cargoes selectively to cancer cells and thus greatly increase the therapeutic index (increasing therapeutic efficacy while reducing toxicity). To date, a number of moieties have been studied to functionalize nanoparticles for specific targeting and aptamer is one of them [3].

This paper discusses aptamer-functionalized nanoparticles in targeted delivery for cancer therapy. It first compares passive and active targeting of nanoparticles, then describes the advantages of using aptamers to functionalize nanoparticles for active targeting, explains the strategies to conjugate aptamers to nanoparticles, and summarizes nearly all of the existing aptamer-functionalized nanoparticles used thus far to study targeted delivery to cancer cells. It finally briefly discusses the challenges facing active targeting.
2. Passive vs. Active Targeting of Nanoparticles

Passive targeting of nanoparticles refers to the passive accumulation of nanoparticles in the tumor tissue, which is generally attributed to the enhanced permeability and retention effect. The concept of EPR was first introduced more than 30 years ago when Maeda and colleagues found that certain macromolecules accumulate preferentially in the tumor tissue [4]. EPR is mainly the result of leakiness of the discontinuous endothelium of angiogenic tumor vasculature combined with defective lymphatic drainage of the tumor matrix, which facilitates the extravasation and accumulation of nanoparticles in tumor. It has been shown that the number of nanoparticles accumulated in tumor tissue may be 10–200 times higher than in normal tissue as a result of EPR. The EPR effect is considered to be the primary element to improve the efficacy and safety of nanotherapeutics. In fact, most of the nanomedicines marketed thus far base their increased therapeutic index mainly on the EPR effect [5].

Nevertheless, the EPR effect alone is insufficient for adequate nanoparticle accumulation, particularly in some circumstances. The EPR effect is not effective for some cancers because of tumor heterogeneity and cancer stage, is even not applicable to some types of cancers, and it is not effective in some patients because of individual differences. A survey of the literature in this area from 2005 to 2015 that included 232 data sets showed that only a median of 0.7% of the systemically administered nanoparticle dose could reach the solid tumor in mouse models [6]; multivariate analysis of the pertinent parameters indicated that tumor type, tumor model, and nanomaterial properties are the major factors to affect the delivery efficiency of the nanoparticles. Research also found that the high interstitial fluid pressure of tumor tissue impedes the extravasation of nanoparticles [7]; some particles that have entered the tumor intercellular space via EPR effect may be forced back into the blood circulation because of the high fluid pressure within the tumor interstitium. It is manifest that blood cancers, very early stage tumors, and small metastasized cancers do not have or have only insignificant EPR effect. In addition, because of tumor heterogeneity, the EPR effect is very poor or not shown in some types of cancers and even in different regions of the same tumor [8]. Clinical observations have also indicated that the EPR effect exhibits significant individual variations among patients; the nanomedicines do not increase the therapeutic efficacy in some subpopulations of the patients [9]. Finally, and most importantly, it is now reckoned that the EPR effect chiefly works in animal models rather than in humans [10]; in patients, their effects are just uncertain (because of interpatient variability); these uncertainties pose the most serious challenge to the rationale of nanomedicine development based on the EPR effect and to the clinical translation of the nanotherapeutics. All the above problems warrant the development of a more effective way to deliver nanoparticles to the site of interest.

Active targeting, which is achieved by conjugating tumor specific ligands to the surface of nanoparticles, can provide a means to complement the EPR effect or solve the aforementioned problems. Common classes of targeting ligands that can functionalize nanoparticles include antibodies or antibody fragments, aptamers, carbohydrates, human transferrin protein, peptides, and vitamins such as folate, etc. Representative tumor biomarkers that can be recognized by the targeting ligands include epidermal growth factor receptor (EGFR), epithelial cell adhesion molecule (EpCAM), human epidermal growth factor receptor 2 (HER2), Mucin-1 (MUC1), nucleolin, platelet-derived growth factor receptor β (PGFRIIβ), prostate specific membrane antigen (PSMA), transferrin receptor, folate receptor, and so on.

The foremost advantage of actively targeted nanoparticles over passively targeted nanoparticles is that they can add on to or improve the EPR effect. An actively targeted nanoparticle can first enter the tumor tissue via the EPR effect and then target cancer cells through specific ligand recognition of the tumor biomarker. In addition, active targeting can augment the EPR effect by having more particles entering than leaving the tumor interstitium because the particles that already enter stick to the cancer cells and thus lower the concentration of the free nanoparticles in the interstitial space. Studies have already demonstrated that actively targeted nanoparticles tend to accumulate more efficiently in the tumor tissue through their selective binding to receptors on the cancer cells when they enter the tumor interstitium [11].
The ligand-mediated active targeting not only helps nanoparticles selectively reach the tumor; it may also promote cellular internalization of the nanoparticles through receptor-mediated endocytosis since some receptors have the intrinsic property to internalize when bound by a ligand. The importance of cellular internalization should be obvious when we think of the fact that most anticancer drugs exert their actions inside cancer cells. Although nanoparticles themselves can get into the cell through clathrin-mediated endocytosis or fluid-phase pinocytosis, conjugation of active ligands to them may boost the process. Receptor-mediated engulfment has already been observed in many specific ligand conjugated nanoparticles; typical examples of aptamer-mediated cellular internalization include the PSMA-targeting A10 aptamer mediated as well as the nucleolin-targeting AS1411 aptamer mediated internalizations [12,13].

Although the targeting ligands can be conjugated with the anticancer agents such as siRNAs and chemotherapeutics directly, the advantage of using nanoparticles is that they can deliver large amounts of drug payload or diversified therapeutics to cancer cells per delivery and biorecognition event [14]. Having a nanoparticle encapsulate diverse therapeutic ingredients could potentially offer synergistic tumor killing effects (e.g., combining any of these anticancer strategies like chemotherapy, gene silencing, immunotherapy, photodynamic therapy, photothermal therapy, and thermodynamic therapy, etc.). Encapsulating different therapeutics within a nanoparticle may also help to overcome or reduce multiple drug resistance (MDR) because MDR usually does not occur to different drugs at the same time or at the same degree, and the mechanisms of MDR differs with different drugs. One example is that nanoparticle-mediated combination of chemotherapy and photodynamic therapy can overcome drug resistance through invoking multiple anticancer mechanisms including cytotoxicity and significantly enhanced production of reactive oxygen species [15].

Active targeting of nanoparticles could also have additive therapeutic effects by exploiting the drug-carrying and receptor-inhibiting actions at the same time. For instance, anticancer reagent-containing nanoparticles functionalized with HER2-targeting ligand, in addition to delivering the therapeutic ingredients into the target cells can, meanwhile, inhibit the activity of the targeted receptors or remove the receptors from the cell surface by means of internalization [16].

3. Aptamer-Functionalized Nanoparticles in Actively Targeted Drug Delivery

Aptamers are short single-stranded DNA or RNA molecules with defined three-dimensional structures that can selectively bind to target molecules with high affinity [17]. Aptamers are usually produced by selecting them from a large random sequence pool with the technology systematic evolution of ligands by exponential enrichment (SELEX). In addition to their superb binding specificity and affinity, aptamers have a number of other favorable features that together make them very suitable molecules to functionalize nanoparticles for actively targeted delivery. Aptamer functionalized nanoparticles have already demonstrated their effectiveness in targeted delivery of anticancer drugs in numerous preclinical and animal studies, though none of them have as yet entered clinical trial or application.

3.1. The Advantages of Using Aptamers to Functionalize Nanoparticles

Aptamers have a very broad spectrum of target recognition and binding; they have little or no immunogenicity; they can easily be end-attached with a chemical group to conjugate nanoparticles; they are small (only a few nanometers in diameter) and will not increase nanoparticle size significantly after coupling; they are relatively easy to make and to store [17]. Those are the general properties of aptamers that make them one of the best choices to functionalize nanoparticles. Up to now, quite a few aptamers have been used to functionalize nanoparticles for targeted delivery to cancer cells (Table 1).
Table 1. Aptamer-functionalized nanoparticles designed for actively targeted drug delivery and cancer therapy in laboratory investigation stage.

| Aptamer   | Nanomaterial                  | Payload          | Conjugation       | Size (nm) | Target       | Cancer/Cell Line  | Level       | Ref. |
|-----------|-------------------------------|------------------|-------------------|-----------|--------------|-------------------|-------------|------|
| A10, DNA  | PLA-PEG-COOH                  | Rho-labeled dextran | Direct covalent   | 264       | PSMA         | Prostate cancer    | in vitro    | [18] |
| A10, DNA  | PLGA-PEG-COOH                 | Docetaxel        | Direct covalent   | 168       | PSMA         | Prostate cancer    | in vitro + in vivo | [19] |
| A10, DNA  | PLGA-PEG-COOH                 | Cisplatin        | Direct covalent   | 155       | PSMA         | Prostate cancer    | in vitro    | [20] |
| sgc8c, DNA| Au-Ag nanorod                 | Photothermal therapy | Direct, thiol linkage | No data  | CCRF-CEM cell | ALL               | in vitro    | [21] |
| A10, DNA  | SPION                         | Doxorubicin      | Direct, covalent  | 66.4 ± 1.5| PSMA         | LNCaP cell line    | in vitro    | [22] |
| sgc8c, DNA| PAMAM dendrimer               | None             | Direct covalent   | 8         | CCRF-CEM cell | ALL               | in vitro    | [23] |
| AS1411, DNA| Liposome                      | Cisplatin        | Covalent, to cholesterol | 200       | Nucleolin    | MCF-7 cells        | in vitro    | [24] |
| S2.2, DNA | PLGA-COOH                     | Paclitaxel       | Covalent, DNA spacer | 225.3     | Macin-1      | Breast cancer      | in vitro    | [25] |
| AS1411, DNA| PEG-PLGA                      | Paclitaxel       | Direct, covalent  | 156 ± 54.8| Nucleolin    | Glioma            | in vitro + in vivo | [26] |
| No name, DNA| DNA icosahedra                | Doxorubicin      | Direct, covalent  | 28.6 ± 5.0| Macin-1      | MCF-7 cells        | in vitro    | [27] |
| A9, RNA   | SPION                         | Doxorubicin      | ONT linker, base pairing | 65 ± 12   | PSMA         | LNCaP cell line    | in vitro + in vivo | [28] |
| A9, RNA   | ONT-PAMAM dendrimer           | Doxorubicin      | ONT linker, base pairing | No data  | PSMA         | Prostate cancer    | in vitro + in vivo | [29] |
| No name, RNA| DNA                           | siRNA            | Chimeric with siRNA | 66.3-76.5 | PSMA         | C4-2B cells        | in vitro    | [30] |
| XEO2mini, RNA| Hybrid lipid-polymer          | Docetaxel        | Direct, covalent  | 50-100    | PC3 cells    | Prostate cancer    | in vitro    | [31] |
| AS1411, DNA| PLGA-lectin-PEG               | Paclitaxel       | Covalent, to PEG  | 60-110    | Nucleolin    | GI-1 and MCF-7 cells | in vitro | [32] |
| AS1411, DNA| PLGA                         | Paclitaxel       | Direct, amide linking | 200       | Nucleolin    | GI-1 cells         | in vitro    | [33] |
| AS1411, DNA| PEG-PCL                      | Docetaxel, DiR, coumarin-6 | Direct, covalent | 170.6     | Nucleolin    | bEnd.3 and C6 cells | in vitro + in vivo | [34] |
| AS1411, DNA| Mesoporous silica            | Gold nanorods *  | ONT linker, base pairing | 60        | Nucleolin    | MCF-7 cells        | in vitro    | [35] |
| CMT8, DNA | PEG-PCL                      | Docetaxel        | Direct, covalent  | 111.9 ± 64.2| U87 cells | glioblastoma       | in vitro + in vivo | [36] |
| AS1411, DNA| Gd-Hap nanorod               | Docetaxin        | Direct, covalent  | 153       | Nucleolin    | MCF-7 cells        | in vitro    | [37] |
| AS1411, DNA| Mesoporous silica            | Docorubicin      | Electrostatic binding | 140       | Nucleolin    | MCF-7 cells        | in vitro    | [38] |
| AS1411, DNA| Mesoporous silica            | Fluorescein      | Sulfo-GMBS linker | 190       | Nucleolin    | MDA-MB-231         | in vitro    | [39] |
| Sgc8, DNA | Mesoporous silica            | Doxorubicin      | Avidin-biotin interaction | 150       | PTK7         | CEM cells          | in vitro    | [40] |
| AS1411, DNA| Liposome                      | Doxorubicin      | Covalent, to cholesterol | 200       | Nucleolin    | MCF-7 breast cancer cells | in vitro + in vivo | [41] |
| A10, RNA  | H40-PLA-PEG                   | Doxorubicin      | Covalent, to PEG  | 69        | PSMA         | CWR22Rv1 cells     | in vitro + in vivo | [42] |
| STR1, DNA | SPION                         | Epirubicin       | Direct, covalent  | 57        | Macin-1      | carcinoma C26 cells | in vitro    | [43] |
Table 1. Cont.

| Aptamer | Nanomaterial | Payload | Conjugation | Size $^1$ (nm) | Target | Cancer/Cell Line | Level | Ref. |
|---------|--------------|---------|-------------|----------------|--------|------------------|-------|------|
| No name, RNA | Hollow gold nanosphere | Doxorubicin | Direct, thiol–Au bonds | ≈42 | CD30 | Lymphoma | in vitro | [44] |
| sgc8c, DNA | Aptamer DNA | Antisense ONT to P-gp | Direct, covalent | 218 | CCRF-CEM cell | ALL | in vitro | [45] |
| Sgc8, DNA | DNA nanotrains | Gold, DOX, DNIR, and EPI | Direct, covalent | No data | PTK7 | ALL | in vitro + in vivo | [46] |
| No name, DNA | Dextran–ferric oxide | None (HIT) | PDPH linker | ≈70 | HER2 | SK-BR3 cells | in vitro | [47] |
| AS1411, DNA | PLGA-PEG | Vinorelbine | Direct, covalent | <200 | Nucleolin | MDA-MB-231 cells | in vitro | [48] |
| No name, DNA | Liposome | TSP | Avidin-biotin interaction | No data | PDGFR | Breast cancer cells | in vitro | [49] |
| AS1411, DNA | PEGylated liposome | Anti-BRAF siRNA | Via PEG linker | ≈150 | Nucleolin | A375 tumor xenograft | in vivo | [50] |
| No name, RNA | PLGA-lecithin-PEG | Curcumin | Direct, covalent | 90 ± 1.9 | EpCAM | HT29 cells | in vitro | [51] |
| AS1411, DNA | pPEGMA-PCL-pPEGMA | Doxorubicin | Direct, covalent | ≈140 | Nucleolin | MCF-7 and PANC-1 cells | in vitro | [52] |
| AS1411, DNA | Gold nanoparticle | Doxorubicin or AZD8055 | Dithiolane linker | No data | Nucleolin | MCF-7, e202 and OMM1.3 | in vitro | [53] |
| A10, RNA and Duf-1 | PEG-gold nanostar | None (PTT) | Direct, di- sulfide bonds | 61.90 ± 1.61 | Prostate cell | Prostate cancer | in vitro | [54] |
| No name, DNA | Chitosan | SN38 | Tethered by linker DNA | ≈200 | Mucin-1 | Colon cancer HT-29 cells | in vitro | [55] |
| AS1411, DNA | Gold nanoparticle | Doxorubicin or TIP42 | Tethered by 21 bp DNA | 38.7 ± 1.4 | Nucleolin | HeLa and MCF-7R cells | in vitro | [56] |
| No name, RNA | Liposome | Doxorubicin | Tethered by linker DNA | 90–100 | PSMA | LNCAp cells | in vitro + in vivo | [57] |
| No name, DNA | Gold nanoparticle | Protein | With a His-tag | 85.0 ± 1.3 | His or GST | HeLa and A431 cells | in vitro + in vivo | [58] |
| A10-3.2, RNA | PEG-PAMAM | MicroRNA | Direct, covalent | 177 ± 17.5 | PSMA | Prostate cancer | in vitro + in vivo | [59] |
| A10-3.2, RNA | Atelocollagen | MicroRNA | Direct, covalent | 221 ± 6.9 | PSMA | Prostate cancer | in vivo | [60] |
| AS1411, DNA | PF127-β-CD-PEG-PLA | Doxorubicin | Covalent, to PF127 | ≈39.15 | Nucleolin | MCF-7 cells | in vitro + in vivo | [61] |
| No name, RNA | PLGA | Nutlin-3a | Direct, covalent | 292 ± 10 | EpCAM | ZR751, MCF-7, SKOV3 | in vitro | [62] |
| No name, RNA | PLGA-PEG | Doxorubicin | Direct, amidine linking | 136 ± 0.21 | EpCAM | Non-small cell lung cancer | in vitro + in vivo | [63] |
| No name, RNA | PEI | EpCAM siRNA | Electrostatic interaction | 198 ± 14.2 | EpCAM | MCF-7 and WERI-Rb1 cells | in vivo | [64] |
| HB5, DNA | Mesoporous silica-carbon | Doxorubicin | thiol-amine link to PEG | ≈140 | HER2 | SK-BR-3 cells | in vivo | [65] |
### Table 1. Cont.

| Aptamer | Nanomaterial | Payload | Conjugation | Size \(^1\) (nm) | Target | Cancer/Cell Line | Level | Ref. |
|---------|--------------|---------|-------------|-----------------|--------|------------------|-------|------|
| No name, DNA | Au–GO | None (PTT) | Direct, Au–S bond | No data | Mucin-1 | MCF-7 cells | in vivo | [65] |
| sgc8c, DNA | Gold nanorod | Hyperthermia therapy | Direct, Au–S bond | No data | CCRF-CEM cell | ALL | in vitro | [66] * |
| No name, RNA | PEG–PLGA | Doxorubicin | Direct, covalent | \(136 \pm 0.21\) | EpCAM | MCF-7 cells | in vitro | [67] |
| AS1411, DNA | MOF shell, UCNP core | Doxorubicin | Direct, covalent | \(\approx 140\) | Nucleolin | MCF-7 and 293 cells | in vitro | [68] |
| No name, RNA | GPN | Gefitinib | Direct, covalent | No data | Ets1 | H1975 cells | in vitro + in vivo | [69] |
| No name, DNA | Hyaluronan/Chitosan | 5-fluorouracil | Direct, covalent | 181 | Macin-1 | Colorectal cancer | in vitro | [70] |
| Cy5.5-AS1411 | GO and MSN | Doxorubicin | Non-covalent | No data | Nucleolin | MCF-7 cells | in vitro | [71] |
| A15, RNA | PLGA–PEG–COOH | Salinomycin | Direct, covalent | 159.8 | CD133 | Osteosarcoma CSCs | in vitro + in vivo | [72] |
| S2.2, DNA | Graphene oxide-gold | Doxorubicin | Thiol–Au bonds | No data | Mucin-1 | A549 and MCF-7 cells | in vitro | [73] |
| A15, CL4; RNA | PLGA | Salinomycin | Direct, covalent | 139.7, 141.9 | CD133, EGFR | Hepatocellular carcinoma | in vitro + in vivo | [74] |
| S2.2, DNA | ZnO nanoparticle | Doxorubicin | APTES linkage | 5–10 | Macin-1 | MCF-7 cells | in vitro | [75] |
| SRZ1, DNA | DOTAP:DOPE liposome | Doxorubicin | No data | \(=100\) | 4T1 cells | 4T1 cells | in vitro + in vivo | [76] |
| AS1411, DNA | Tocopheryl PEG–P\(\beta\)AE | Docetaxel | No data | 116.3 \(\pm\) 12.4 | Nucleolin | SKOV3 ovarian cancer cells | in vitro | [77] |
| No name, DNA | Chitosan and HA | SN38 | Direct, covalent | 129 \(\pm\) 3.2 | Mucin-1 | HT29 cells | in vitro | [78] |
| S6, DNA | Dendrimer | MicroRNA | Direct, covalent | 100–200 | AS49 cells | NSCLC cells | in vitro | [79] |
| AS1411, DNA | PLL–alkyl-PEI | shRNA | Electrostatic coupling | 168–183 | Nucleolin | AS49 cells | in vitro | [80] |
| AS1411, DNA | GQD–FMSN | Doxorubicin | Direct, amide bond | 72.5 | Nucleolin | HeLa cells | in vitro | [81] |
| KW16–13, DNA | PEG-gold nanorod | None (PTT) | Direct, covalent | No data | MCF10CA1h cell | Human breast duct carcinoma | in vitro | [82] |
| No name, DNA | Au–SPION | Gold for PTT | Thiol–Au interaction | \(\approx 39\) | Mucin-1 | Colon cancer | in vitro | [83] |
| MA3 | Iron | None (HIT) | Streptavidin-biotin, direct | \(\approx 296\) | Mucin-1 | MCF-7 cells | in vitro | [84] |
| No name, RNA | Albumin | Cisplatin | Direct, amide bond | \(\approx 40\) | EGFR | Hela cell line | in vitro + in vivo | [85] |
| No name, DNA | Human IgG | miR29b | Indirect, C12 spacer | 595.9 \(\pm\) 43.1 | Mucin-1 | A549 cells | in vitro | [86] |
| sgc8c and AS1411 | Gold | Daunorubicin | Direct, covalent | No data | ALL and nucleolin | Molt-4 cells | in vitro | [87] |
| No name, RNA | Gold | Antisense ONT | Spacer, covalent | \(<50\) | CD33, CD34 | AML-M2 | in vitro | [88] |
| No name, DNA | Mesoporous silica | Doxorubicin | Direct, covalent | 181 \(\pm\) 6 | EpCAM | SW620 colon cancer cells | in vitro | [89] |
| Aptamer  | Nanomaterial                  | Payload      | Conjugation            | Size \(^1\) (nm) | Target      | Cancer/Cell Line              | Level            | Ref.  |
|---------|-------------------------------|--------------|------------------------|------------------|-------------|-------------------------------|------------------|-------|
| TSA14, RNA | PEGylated-liposome            | Doxorubicin  | Direct, covalent       | 118 ± 2.2        | TUBO cells  | Breast cancer                 | in vitro + in vivo | [90]  |
| DNA-RNA hybrid | SPION                        | Doxorubicin  | DNA linker, streptavidin-biotin | No data          | PSMA        | Prostate cancer               | in vitro         | [91]  |
| AS1411, DNA | GC-rich dsDNA                 | Doxorubicin  | Direct, covalent       | 6.1 ± 0.7; 7.4 ± 0.4 | Nucleolin  | Drug-resistant MCF-7 cells    | in vitro         | [92]  |
| AS1411, DNA | PEG-PLGA                      | Gemcitabine  | Direct, covalent       | 128 ± 5.23       | Nucleolin  | A549 cells                    | in vitro         | [93]  |
| AS1411, DNA | HPABG                         | Doxorubicin  | Direct, covalent       | 93.7             | Nucleolin  | MCF-7 and L929 cells         | in vitro         | [94]  |
| No name, DNA | DNA dendrimer                | Epirubicin   | No data                | 36.4             | MUC1, AS1411| MCF-7 and C26 cells         | in vitro + in vivo | [95]  |
| A10, RNA | PLGA                          | Triplex forming oligonucleotide | Direct, covalent       | No data          | PSMA        | LNCaP cells                   | in vitro         | [96]  |
| No name, RNA | PLGA-PEG                     | Docetaxel    | Direct, covalent       | 93.6             | PSMA        | LNCaP cells                   | in vitro + in vivo | [97]  |
| AS1411, DNA | M-PLGA–TPGS                  | Docetaxel    | Direct, covalent       | 130.1 ± 2.9      | Nucleolin  | HeLa cells                    | in vitro + in vivo | [98]  |
| Endo28, DNA | 3WJ-RNA                      | Doxorubicin  | Direct, covalent       | 8.1 ± 1.5        | Annexin A2 | Ovarian cancer                | in vitro + in vivo | [99]  |
| No name, DNA | HAS-CS                       | Paclitaxel   | Acrylate spacer        | 170 ± 4          | Mucin-1    | MCF-7 and T47D cells         | in vitro         | [100] |
| AS1411, DNA | PEG-PAMAM dendrimer          | 5-fluorouracil | Covalent, to PEG      | No data          | Nucleolin  | Gastric cancer                | in vitro         | [101] |
| Two, DNA | DGL-PEG                       | Doxorubicin  | Covalent, to PEG       | ≈38              | Nucleolin, Cyt c | Nucleolin+ HeLa cells | in vitro + in vivo | [102] |
| No name, DNA | Iron oxide                   | None (HTT)   | No data                | No data          | FGFRI      | Human osteosarcoma            | in vitro         | [103] |
| A10, RNA | Liposome                      | CRISPR-Cas9 plasmid | Covalent, to DSPE-PEG | =150             | PSMA        | Prostate cancer               | in vitro + in vivo | [104] |
| AS1411, DNA | PEG-PAMAM dendrimer          | Camptothecin | Covalent, to PEG       | =18              | Nucleolin  | HT29 and C26 cells           | in vitro + in vivo | [105] |
| A6, DNA | Lipid-polymer liposome        | siRNA        | Direct, covalent       | 270 ± 10; 237 ± 12 | HER2       | SKBR-3 and 4T1-R cells      | in vitro         | [106] |
| No name, DNA | Chitosan- liposome            | Erlotinib    | Direct, covalent       | 179.4 ± 1.16     | EGFR       | EGFR-mutated cancer cells     | in vitro         | [107] |
| AS42, DNA | Gold                          | None (PTT)   | No data                | =37              | Ehrlich’s ACC | Ehrlich carcinoma            | in vivo          | [108] |
| No name, DNA | MCS nanogel                  | Doxorubicin  | Direct, covalent       | 15–25            | NLCaP cell | Prostate cancer               | in vitro         | [109] |
| AS1411 + S2.2, DNA | Gold-coated liposome       | Docetaxel    | through 5-Au bond      | =200             | Mucin-1, Nucleolin | MCF-7 cells | in vitro + in vivo | [110] |
| 5TR1, DNA | PLGA-chitosan                 | Epirubicin   | Electrostatic coupling | ≈222.7           | Mucin-1    | MCF-7 and C26 cells          | in vitro + in vivo | [111] |
| AS1411, DNA | Alkyl PAMAM dendrimer        | Bel-XL shRNA | Covalent and non-covalent | 148–230          | Nucleolin  | A549 cells                    | in vitro         | [112] |
Table 1. Cont.

| Aptamer | Nanomaterial | Payload | Conjugation | Size $^1$ (nm) | Target | Cancer/Cell Line | Level | Ref. |
|---------|--------------|---------|-------------|----------------|--------|------------------|-------|------|
| Gint4.T | PLGA-PEG-COOH | P3K-mTOR inhibitor | Direct, covalent | 52 ± 1 | PGFRβ | Glioblastoma U87MG cells | in vitro + in vivo | [113] |
| No name, DNA | Mesoporous silica | Epirubicin | Via disulfide bonding | 258.3 ± 20.1 | Macin-1 | MCF-7 cells | in vitro | [114] |
| No name, DNA | Aminopropyl MSN | Safranin O | electrostatic + H-bonding | ≈407 | Macin-1 | MDA-MB-231 cells | in vitro | [115] |
| No name, DNA | Chitosan- liposome | PFOB and Erlotinib | Direct, covalent | ≈180 | EGFR | NSCLC cell lines | in vitro + in vivo | [116] |
| No name, DNA | Au-Fe$_3$O$_4$ | None | Electrostatic absorption | 46 ± 3 | VEGF | SKOV-3 ovarian cancer cells | in vitro | [117] |
| No name, DNA | MPC-PAA/PEI | Doxorubicin | Anchoring via EHH | No data | Macin-1 | A549 and MCF-7 cells | in vitro | [118] |
| A15, RNA | PLGA | Propranolol | Direct, covalent | 143.7 ± 24.6 | CD133 | Hemangioma | in vitro + in vivo | [119] |
| AIR-3A, RNA | PEG-coated gold NP | None | Thiol-gold bonds | 2, 7, 36 | IL-6R | IL-6R-carrying cells | in vitro + in vivo | [120] |
| No name, DNA | PDA/PEG- coated MSN | DM1 | Direct, covalent | 203.75 ±2.37 | EpCAM | Colorectal cancer | in vitro + in vivo | [121] |
| AS-14, DNA | Gold-coated magnetic NP | None, using magnetic field | Thiolated ONT primer | 50 (GMNP) | Fibronectin protein | Ehrlich carcinoma | in vivo | [122] |
| AS1411, DNA | Chitosan-ss-PEEU | TLR4-siRNA, Doxorubicin | Direct, covalent | 124.6 ± 1.068 | Nucleolin | A549 cells | in vitro + in vivo | [123] |
| FKN-S2, DNA | PEG-aptamer micelle | ssDNA-amphiphile | No data | Fractalkine | Colon adeno-carcinoma | in vitro + in vivo | [124] |
| No name, DNA | Ursolic acid, Doxorubicin | Ursolic acid, Doxorubicin | Electrostatic interactions | ≈108.9 | HER2 | HER2-carrying cells | in vitro + in vivo | [125] |
| No name, DNA | PEG-SPION | Doxorubicin | Direct, covalent | 5–64 | Macin-1 | MCF-7 cells | in vitro | [126] |
| Two, DNA | NMOF | Doxorubicin | Hybridization | ≈130 | Nucleolin, VEGF | MDA-MB-231 | in vitro | [127] |
| STR1, DNA | PEG-Peg and Na$_2$SeO$_3$ | Epirubicin and an aptamer | Covalent, to PEG | No data | Macin-1 | MCF-7 and C26 cells | in vitro + in vivo | [128] |
| No name, DNA | Liposome | Doxorubicin | Amino- carboxyl | 170 ± 25 | HER3 | MCF-7 breast cancer cells | in vitro + in vivo | [129] |
| No name, DNA | DNA nano-ring | Doxorubicin | Incorporated in DNA ring | ≈29 (DNA ring) | Macin-1 | MCF-7 breast cancer cells | in vitro | [130] |
| A10–3.2, RNA | Cationic nanobubble | FoxM1 siRNA | Direct, covalent | 479.83 ±24.50 | PSMA | LNCaP cells | in vitro + in vivo | [131] |
| No name, DNA | DNA micelle | Doxorubicin, KLA peptide | No data | 371 | Macin-1 | MCF-7 cells | in vitro + in vivo | [132] |
| No name, DNA | Lipid-polymer | Salinomycin | Thiolated, direct | 96.3 ± 9.8 | CD20 | Melanoma stem cells | in vitro + in vivo | [133] |
| No name, DNA | Polymer-lipid | Salinomycin | Thiolated, direct | 95 | EGFR | Osteosarcoma CSCs | in vitro | [134] |
| Aptamer      | Nanomaterial                          | Payload                              | Conjugation                        | Size \(^1\) (nm) | Target          | Cancer/Cell Line                  | Level         | Ref.     |
|--------------|---------------------------------------|--------------------------------------|------------------------------------|-----------------|-----------------|-----------------------------------|--------------|----------|
| trCLN3, DNA  | Lipidated GC-rich DNA hairpin          | Doxorubicin, 2′,6′-dimethyl azobenzene | Lipid-mediated self-assembly       | 21.2 ± 1.5      | cMet            | cMet-expressing H1838 cells       | in vitro     | [135]    |
| TLS1c, DNA   | Liposome                              | Cabazitaxel                          | Avidin-biotin interaction           | 90.10 ± 2.71    | MEAR cells      | Hepatoma                          | in vitro + in vivo | [136]    |
| No name, DNA | PRABT                                 | Docetaxel                            | Direct, covalent                    | 274.7 ± 46.1    | HER2            | Epithelial ovarian cancer         | in vitro + in vivo | [137]    |
| No name, DNA | BSA-PEG-Fe\(^{3+}\)                   | Mn, Doxorubicin                       | GAG-linker, base-match              | No data         | Glut-1          | HepG-2 cells                      | in vitro + in vivo | [138]    |
| AS1411       | TD-PEC-chitosan                       | mIr-145                              | Electrostatic bonds with chitosan   | 40-270          | Nucleolin       | MCF-7 cells                       | in vitro + in vivo | [139]    |
| No name, DNA | DNA                                   | ALK-siRNA, Doxorubicin               | Direct, covalent                    | 59              | CD30            | ALCL                              | in vitro + in vivo | [140]    |
| No name, DNA | Human IgG                             | MicroRNA                             | Direct, covalent                    | 595             | Mucin-1         | Non-small cell lung cancer        | in vitro + in vivo | [141]    |
| S15, DNA     | Quantum dots                          | None                                 | Direct, covalent                    | No data         | NSCLC           | A549 cells                        | in vitro     | [142]    |
| A15, CL4; RNA| Lipid-polymer                         | Salinomycin                          | Direct, covalent                    | 110.2 ± 12.1    | CD133, EGFR     | Osteosarcoma cells and CSCs       | in vitro + in vivo | [143]    |
| No name, DNA | PEG-Au-PAMAM                          | Curcumin                             | Covalent, C6 linker                 | 5.23 ± 4.12     | Mucin-1         | HT29 and C26 cells                | in vitro + in vivo | [144]    |
| No name, DNA | Liposome                              | Docetaxel                            | Covalent, to DSPE-PEG               | 116.5 ± 9.3     | CD133           | A549 cells                        | in vitro + in vivo | [145]    |
| 5TR1, DNA    | PEGylated liposome                    | Doxorubicin                          | No data                            | 120 ± 1.8       | Mucin1          | C26 cells                         | in vitro + in vivo | [146]    |
| AS1411, DNA  | Bovine serum albumin                  | Doxorubicin                          | Direct, amidation                   | 163 ± 2.5       | Nucleolin       | MCF-7 cells                       | in vitro     | [147]    |
| No name, DNA | Copper oxide                          | mRNA 29b                             | Direct, amide linking               | ≈40             | Mucin 1         | A549 cells                        | in vitro     | [148]    |
| Sgc8c, DNA   | Fe\(^{3+}\)carbon                     | Doxorubicin                          | Direct, covalent                    | No data         | No data         | A549 cells                        | in vitro + in vivo | [149]    |
| A9, RNA      | Gold                                  | None (PTT)                           | Direct, thiol–Au bonds              | No data         | No data         | A549, MCF-7 3D cell culture       | in vitro     | [150]    |
| No name, DNA | Gold nanoshell                        | None (PTT)                           | Direct, thiol–Au bonds              | No data         | Mucin 1         | A549, MCF-7 3D cell culture       | in vitro     | [150]    |
| C10.36, DNA  | PAM (peptide + DNA ONT)               | Peptide                              | Base pairing                        | 110 ± 30        | HBLL            | B-cell leukemia cells             | in vitro     | [152]    |
| No name, RNA | LP-DNA                                | SATB1 siRNA                          | Thiolated, direct                   | 161.2 ± 11.3    | EGFR            | Choriocarcinoma                   | in vivo      | [153]    |
| AS1411, DNA  | PEGylated PLGA                        | anti-miR-21, cisplatin (CIS)         | Direct, covalent                    | 142.4 ± 5.9     | Nucleolin       | CIS-resistant A2780 cells         | in vitro     | [154]    |
| No name, RNA | Lipid-PLGA                            | All-trans retinoic acid              | Thiolated, direct                   | 129.9           | CD133           | Lung cancer initiating cells      | in vitro     | [155]    |
| S15, DNA     | PEG-PCL                               | Paclitaxel                           | Direct, amiding linking             | ≈15             | NSCLC           | A549 cells                        | in vitro     | [156]    |
| S2.2, DNA    | Elastin-like polypeptide              | Paclitaxel                           | Via gene A’ protein                 | No data         | Mucin-1         | MCF-7 cells                       | in vitro     | [157]    |
Table 1. Cont.

| Aptamer               | Nanomaterial                    | Payload                | Conjugation            | Size \(\text{\textpm}\) (nm) | Target        | Cancer/Cell Line                  | Level                  | Ref.   |
|-----------------------|---------------------------------|------------------------|------------------------|-------------------------------|---------------|-----------------------------------|------------------------|--------|
| 5TR1, DNA             | F\beta\text{AE} and PLGA       | Epirubicin, antimir-21 | Direct, covalent       | 210.4 \(\text{\textpm}10.14\) | Mucin-1       | MCF-7 cells                       | in vitro + in vivo     | [158] |
| No name, RNA          | Lipid-polymer                   | All-trans retinoic acid| Thiolated, direct      | 129.9                         | CD133         | Osteosarcoma initiating cells     | in vitro               | [159] |
| No name, DNA          | Calcium carbonate               | Epirubicin, and melittin| Avidin-biotin interaction| >300                          | Mucin-1       | MCF-7 and C26 cells               | in vitro + in vivo     | [160] |
| ACE4                  | Diacetylene-PEG                 | None                   | 31 G spacer, base pairing | ≈13                          | Annexin A2    | MCF-7 cells                       | in vitro               | [161] |
| No name, DNA          | Human IgG                       | Genistein and miRNA-29b| C12 spacer, covalent   | 598 ± 34.1                    | Mucin-1       | A549 cell line                    | in vitro               | [162] |
| No name, DNA          | Lipid-quantum dot               | siRNA                  | Direct, covalent       | No data                       | EGFR          | Triple-negative breast cancer     | in vitro + in vivo     | [163] |
| HB5, DNA              | Human serum albumin             | Curcumin               | Direct, covalent       | 281.1 ± 11.1                  | HER2          | SK-BR-3 cells                     | in vitro               | [164] |
| AS1411, DNA           | Magnetic SPION/MSN              | Doxorubicin            | Direct, covalent       | 89                            | Nucleolin     | MCF-7 cells                       | in vitro               | [165] |
| AS1411, DNA           | Albumin-IONP/GNP                | Doxorubicin            | Direct, covalent       | ≈120                          | Nucleolin     | MCF-7 and SKBR3 cells             | in vitro               | [166] |
| C2NP, DNA             | PEG-PLGA                        | Doxorubicin            | Direct, covalent       | 168.07 ± 2.72                 | CD30          | Large cell lymphoma               | in vitro               | [167] |
| AS1411, DNA           | Liposome                        | Paclitaxel and PLK1 siRNA| DSPE-PEG-MAL           | 121.27 ± 2.51                 | Nucleolin     | MCF-7 cells                       | in vitro + in vivo     | [168] |
| AS1411, DNA           | Liposome                        | Aptamer- doxorubicin   | Not Applicable         | ≈128.6                        | Nuclear nucleolin | MCF-7/Adr cells                   | in vitro               | [169] |
| AS1411, DNA           | PEGylated liposome              | 5-fluorouracil         | Via PEG linker         | 190 ± 15                      | Nuclear nucleolin | Basal cell carcinoma              | in vitro               | [170] |
| H\text{Apt}, DNA      | \beta-CD-capped MSN             | Doxorubicin            | Thiolated to \beta-CD  | 218.2 ± 6.1                   | HER2          | HER2-positive cells               | in vitro               | [16]  |
| AS1411, DNA           | SPION                           | Daunomycin, TMPyP     | Amide bond, direct     | 15–20                         | Nucleolin     | A549 and C26 cells                | in vitro               | [171] |
| S1.5, DNA             | PEGylated PLGA                  | Docetaxel              | Carbodiimide coupling  | 142.7 ± 12.3                  | HPA           | TNBC cells                        | in vitro + in vivo     | [172] |
| No name, DNA          | Mesoporous MnO\text{2}          | HMME                   | Direct, covalent       | ≈200                          | Mucin 1       | MCF-7 cells                       | in vitro + in vivo     | [173] |
| AS1411, DNA           | PLGA, PVP                       | Doxorubicin            | Direct, covalent       | ≈87.168                       | Nucleolin     | A549 cells                        | in vitro + in vivo     | [174] |
| No name, DNA          | DNA hydrogel                    | CpG ONT and Doxorubicin| Covalent, to CpG ONT   | 50.1 ± 2.82                   | Mucin-1       | MCF-7 cells                       | in vitro               | [175] |
| AS1411, DNA; (HA)     | Micro-emulsion                  | Shikonin and docetaxel| Direct, thiolated       | ≈30                           | Nucleolin; (CD44) | Gliona                           | in vitro, model        | [176] |
| No name, DNA          | Cationic liposome               | miR-139–5p             | Direct, covalent       | 150.3 ±8.8                    | EpCAM         | Colorectal Cancer                 | in vitro + in vivo     | [177] |
| Sgc8, DNA             | MSN                             | Doxorubicin            | Direct, covalent       | 103.24                        | PTK7          | CCRF-CEM cells                    | in vitro               | [178] |
| GMT8, Gint4.T; DNA    | DNA                             | Paclitaxel             | Direct, covalent       | 17.78                         | U87MG cell, PDGFRβ | Glioblastoma                     | in vitro               | [179] |
| AS1411, DNA           | Derived from erythrocytes       | Doxorubicin, siRNA     | Covalent to cholesterol via 6-A bases | ≈100            | Nucleolin | MDR MCF-7 cells                   | in vitro               | [180] |
| Aptamer | Nanomaterial | Payload | Conjugation | Size $^1$ (nm) | Target | Cancer/Cell Line | Level | Ref. |
|---------|-------------|---------|-------------|----------------|--------|-----------------|-------|------|
| TA6, DNA | DNA nanotrain | AKT inhibitor, Doxorubicin | Direct, covalent | No data | CD44 | Breast cancer stem cells | in vitro + in vivo | [181] |
| A15, RNA | Liposome | Curcumin | Direct, thiol-maleimide | 86.6 ± 4.5 | CD33 | DU145 cells | in vitro + in vivo | [182] |
| AS1411, DNA | Silver-PEG | None (irradiation) | Amide bond to PEG | 18.82 ± 2.1 | Nucleolin | Glioma | in vitro + in vivo | [183] |
| U2, DNA | Gold | None | Direct, Au-S bond | 60.23 | EGFR | Glioblastoma | in vitro + in vivo | [184] |
| M49, DNA | PEGylated liposome | Doxorubicin | Covalent, to PEG | No data | CD200R1 | 4T1/7 breast carcinoma | in vivo | [185] |
| TC01, Sgc4f, and Sgc8; DNA | DNA ONT | Doxorubicin | DNA ONT hybridization | No data | Multiple cancers and PTK7 | CCRF-CEM cells | in vitro + in vivo | [186] |
| No name, DNA | DNA origami | Antisense ONT, doxorubicin | Extended sequences | 4.17 ± 0.12 (height) | Macin-1 | HeLa/ADR cells | in vitro | [187] |
| LZH58, DNA | DNA nanotrain | Doxorubicin | Hybridization | No data | HepG2 cell | HepG2 cell line | in vitro | [188] |
| No name, DNA | SPION@SiO$_2$ | Doxorubicin | Direct, covalent | 5–27 | Macin-1 | MCF-7 cells | in vitro | [189] |
| AS1411, DNA | Upconversion nanoparticle | Protoporphyrin IX | Direct, covalent | 120 ± 4 | Nucleolin | HeLa and A549 cells | in vitro | [190] |
| AS-14, AS-42; DNA | SPMFN | Doxorubicin | Glycosidic linkages | No data | FN, HSP71 | Ehrlich carcinoma cells | in vitro + in vivo | [191] |
| AS1411, DNA | Gold | Anti-miR-155 | PolyA linker sequence | ≥30 | Nucleolin | MCF-7 cells | in vitro | [192] |
| L5, etc., DNA | PLGA | Docetaxel | Direct, covalent | 156.9 ± 42.97 | Not clear yet | HepG2 and Hub-7 cells | in vitro + in vivo | [193] |
| L5, DNA | PLGA | Docetaxel | Direct, covalent | 211.9–236.1 | TAG-72 | HepG2 and Hub-7 cells | in vitro | [194] |
| LXL, DNA | RNA hydrogel | siRNA and miRNA | No data | =200 | MDA-MB-231 cell | Triple-negative breast cancer | in vitro + in vivo | [195] |
| AS1411, DNA | CaCO$_3$ and protamine | CRISPR-Cas9 plasmid | Covalent, to HA | 230–320 | Nucleolin | H1299 cells | in vitro | [196] |
| No name, RNA | Hollow gold nanosphere | Doxorubicin | Thiolated | =42 (25–55) | CD30 | Karpas 299 cells | in vitro | [197] |
| C2NP, DNA | DNA nanotube | Doxorubicin | By extending staples | 140 × 14 (L × W) | CD30 | K299 cells | in vitro | [198] |
| No name, DNA | ssDNA-ELP | Docetaxel | Covalent, to ELP | 10–40 | Macin-1 | MCF-7 cells | in vitro | [199] |
| No name, DNA | Magnetic nanosphere | Doxorubicin | Streptavidin-biotin | No data | EpCAM | MCF-7 cells (CTCs) | in vitro | [200] |
| AS1411, DNA | DNA nanotubes | DOX, EPI, and DAU | Base pairing | No data | Nucleolin | HeLa cells | in vitro | [201] |
| No name, RNA | Protamine | Doxorubicin, ALK-siRNA | Non-covalent | No data | CD30 | ALCL | in vitro | [202] |
| Aptamer     | Nanomaterial                       | Payload          | Conjugation                      | Size $^1$ (nm) | Target             | Cancer/Cell Line                  | Level               | Ref.  |
|------------|------------------------------------|------------------|----------------------------------|----------------|--------------------|-----------------------------------|---------------------|-------|
| AS1411, DNA| TiO$_2$ nanofiber with BSA         | None             | Streptavidin-biotin              | 81.33 ± 25.70  | AS1411, DNA        | MCF-7 cells (CTCs)                | in vitro           | [203]|
| AS1411, DNA| Gold and liposome                  | Morin            | Covalent, Au-S                   | No data        | Nucleolin          | SGC-7901 cells                   | in vitro + in vivo  | [204]|
| AS1411, DNA| GO Nanosheet                       | Berberine derivative | NH$_2$-(CH$_2$)$_6$ linker      | 30–50 × 2–3    | Nucleolin          | A549 cells                        | in vitro           | [205]|
| AS1411, DNA| DNA Holliday junction              | Doxorubicin       | Phospho-diester bond             | 12.45 ± 2.16   | Nucleolin          | CT26 colon cancer cells           | in vitro           | [206]|
| Syl3c, DNA | PEGylated liposome                 | Doxorubicin       | Covalent, to PEG                 | 110 ± 5        | EpCam              | C26 Colon Carcinoma               | in vitro + in vivo  | [207]|
| No name, DNA| Ag-MOF-RBCm                       | PFK15            | Inserted into BRCm                | ≇109           | CD20               | B-cell lymphoma                   | in vitro + in vivo  | [208]|
| No name, DNA| PCL-MMA/MPEG-MASTI                | Doxorubicin       | Covalent, to NHS group            | ≇124           | EpCAM              | HT29 cells                        | in vitro           | [209]|
| AS1411, DNA| FO-loaded MOF-RBCm                | Using PDT and CD1 effects | Inserted via cholesterol        | 110–140        | Nucleolin          | KB cells                          | in vitro + in vivo  | [210]|
| MAGE-A3, DNA| NIR PLN                           | Afatinib          | By a disulfide bond               | 225            | MAGE               | NSCLC                            | in vitro + in vivo  | [211]|
| A10-3.2, RNA| Lipid-polymer hybrid              | Curcumin and Cabazitaxel | Covalent, to PEG  | 121.3 ± 4.2     | PSMA               | Prostate cancer                   | in vitro + in vivo  | [212]|
| A6, DNA    | DOTAP, Mal-PEG, cholesterol, PLGA | Pgp siRNA         | Covalent, to Mal-PEG             | No data        | HER2               | DOX-resistant 4T1 cells           | in vitro           | [213]|
| Wy5a, DNA  | PLGA-PEG-COOH                      | Docetaxel         | Amide bond with spacer           | ≇154.3         | PC-3 cell          | Prostate cancer                   | in vitro + in vivo  | [214]|

The aptamers in the table are listed in the order they appear in the literature. $^1$ Size of the nanoparticles after aptamer conjugation. For spherical nanoparticle, the number is the diameter of the particle; for nanotubes or nanosheets, the measurement uses a × symbol. $^2$ Direct conjugation means there is no bridge, spacer, or linker molecule/sequence between the aptamer and the nanoparticle. * The aptamer-conjugated gold nanorods were surface modified with BSA through electrostatic interactions.
Apart from the abovementioned characteristics, aptamers have a unique advantage that is related to their production—the establishment of the cell-SELEX technique and its improvements have made the aptamer an especially useful ligand to be used to construct the cancer-targeting nanocarriers (Figure 1).

**Figure 1.** Selection procedure of cell-internalizing DNA aptamer using cell-SELEX.

After the setting up of the prototype SELEX technology in 1990, a selection strategy known as cell-SELEX was developed in 2003 that uses whole (living) cells to select aptamers targeting cell surface molecules [215]. This technique allows for the isolation of cell-recognizing aptamers without prior knowledge of the target molecule(s). In 2006, a negative selection (or counter-selection) process was integrated into the original cell-SELEX strategy, which makes it possible to obtain cell-specific aptamers on researcher’s will [216]. In the new cell-SELEX procedure, the negative selection is performed first, wherein the negative-selection cells (these may be normal cells or any untargeted cells and several different types of cells may be used) are used to absorb the undesired or non-specific aptamers (In this step, the undesired or non-specific oligonucleotides in the pool are removed as they bind to the negative-selection cells). The negative selection is followed by positive selection that is conducted basically in the same way as the conventional cell-SELEX strategy and aims to discard the oligonucleotides that do not bind to the positive-selection cells (usually, certain types of cancer cells or any researcher-intended cells are used for this purpose). Thus, by employing the new cell-SELEX technique, one is able to generate aptamers that can specifically recognize cell surface receptors (or molecules) and thus can effectively differentiate cancer cells from normal cells. More importantly, with certain added steps, the cell-SELEX technique can still select aptamers that not only specifically recognize or target cell surface receptors but also get into the cells through receptor mediated internalization [217].
3.2. Strategies of Conjugating Aptamers to Nanoparticles

Aptamers can be conjugated to nanoparticles directly or indirectly via a linker molecule (a bridge or spacer). Both direct and indirect conjugation can be achieved either covalently or non-covalently (Figure 2).

| Direct conjugation | Indirect conjugation |
|--------------------|----------------------|
| Covalent           |                      |
| \[ \text{Polymer} + \text{NHS} + \text{Aptamer} = \text{Amide bonding} \] | \[ \text{Aptamer} + \text{Covalent bond} + \text{Polymer} \] |
| \[ \text{Au-S bonding} \] | \[ \text{Linker molecule} + \text{Polymer} \] |

| Non-covalent       |                      |
|-------------------|----------------------|
| High affinity interaction | Electrostatic interaction |
| \[ \text{Polymer} + \text{Biotin} = \text{Polymer} \] | \[ \text{Polymer} + \text{Positive charges} = \text{Polymer} \] |

Figure 2. Common strategies of nanoparticle-aptamer conjugation.

In covalent conjugation, a functional group (such as a primary amino group or a thiol group) is usually attached to one terminus of the aptamer, which can react with the functional group (such as the carboxylic acid group, the maleimide group, and the aldehyde group) on the surface of the nanoparticle or at one end of the linker molecule, or react with the gold or other metal element or inorganic molecule for inorganic nanoparticles. Common examples of covalent conjugation include the carboxylic acid group and the amino group interaction that results in an amide (or carboxamide) linkage, the carboxylic acid group and the thiol group interaction that results in a thioester bond, the carboxylic acid group and the alcohol group interaction that results in an ester bond, the primary amine group and thiol group interaction that results in a thioamide bond, the thiol group and the thiol group interaction that results in a disulfide bond, and the thiol group and the gold or silver interaction that results in a Au–S or Ag–S bond.

Non-covalent conjugation strategies include high affinity interactions and electrostatic interactions. The former includes avidin–biotin and streptavidin–biotin interactions. The latter are commonly seen...
when a linker molecule is used, in which case the opposite charges on the linker molecule and on the extended oligonucleotide sequence of the aptamer interact, but also include the using of histidine tags.

Most of the aptamer–nanoparticle conjugates reported thus far utilized the direct and covalent strategy. According to Farokhzad and colleagues [11], “covalently linked bioconjugates may result in enhanced stability in physiological salt and pH whilst avoiding the unnecessary addition of biological components (i.e., streptavidin); thus minimizing immunological reactions and potential toxicity”. Fewer studies used bridge or spacer molecule to link aptamer and nanoparticle together. These are in consideration of avoiding any possible steric or spatial restrictions on aptamer’s binding to target molecule, but an associated problem is the increased size of the conjugates. Several aptamer-nanoparticle constructions, including both direct and indirect linkage, used the avidin–biotin or the streptavidin–biotin system. These interactions are very stable but the bulk of the formulation may increase considerably and potential immunological rejection problems might also result.

3.3. Aptamer-Functionalized Nanoparticles in Pre-Clinical Studies

Up till now, quite a lot of aptamer-conjugated nanoparticles have been developed that can target specific cancer cells, deliver various therapeutic agents into cancer cells, and result in cancer cell toxicity in vitro (e.g., inhibit cell proliferation and induce apoptosis of cultivated cancer cells) and/or anticancer effects in vivo (e.g., inhibit xenograft tumor formation in nude mouse model). An inclusive list of nearly all aptamer-conjugated drug-delivering nanoparticles that have been studied thus far with their characteristics and sources is provided in Table 1. A schematic representation of the action process of aptamer-functionalized nanoparticles acting on a cancer cell is shown in Figure 3.

![Schematic representation of aptamer-functionalized nanoparticle acting on a cancer cell.](image)

**Figure 3.** Schematic representation of aptamer-functionalized nanoparticle acting on a cancer cell.

Farokhzad and Langer et al. [18] first performed the proof of concept study of using the aptamer to functionalize nanoparticles for actively targeted drug delivery in 2004. The authors synthesized the
nanoparticles of poly (lactic acid)-block-polyethylene glycol copolymer with a terminal carboxylic acid functional group (PLA-b-PEG-COOH) and encapsulated the nanoparticles with rhodamine-labeled dextran as a model drug; they then covalently attached the PSMA-targeting A10 RNA aptamer to the nanoparticles through the reaction of the amino groups on the 3′ end of the aptamers with the carboxylic acid groups on the surface of the nanoparticles. These aptamer–nanoparticle conjugates were demonstrated to be able to target the PSMA-positive prostate LNCaP cells significantly more efficiently compared with the same PEGylated nanoparticles without aptamer conjugation and could get internalized into the cells. The uptake of these conjugates was not boosted in the PC3 cells that are also prostate-derived but do not express PSMA.

A similar nanoparticle-aptamer construction, which used the same PSMA-targeting aptamer but used poly (lactic-co-glycolic acid)-block-polyethylene glycol copolymer with a terminal carboxylic acid group (PLGA-b-PEG-COOH) as nanomaterial and encapsulated the anticancer drug Docetaxel within the nanoparticles, was later assessed both in vitro and in vivo by the same laboratory. The in vivo results showed that the aptamer-targeted drug-loaded nanoparticles exhibited significantly more reduced toxicity (side effects) in the nude mice as measured by mean body weight loss than non-targeted nanoparticles, and intratumoral injection of these aptamer-targeted drug-loaded nanoparticles resulted in complete tumor reduction in five of seven LNCaP xenograft nude mice compared with two of five for non-targeted nanoparticles [19].

Up to the present time, polymers, which include miscellaneous classes with PLGA-PEG being the most frequently used, remain the most used nanomaterials to construct aptamer functionalized nanoparticles to study targeted delivery for cancer therapy, followed by lipid based materials, particularly liposomes and nucleic acid based nanoparticles, including either DNA or RNA. Other organic nanomaterials that have been used include dendrimers, chitosan, proteins/peptides, or hybrids of the above. There are also many inorganic nanomaterials that have been studied in this area, including gold (Au) compounds, silver (Ag), mesoporous silica, graphene based, Calcium carbonate, ZnO, iron, etc. Other and special inorganic nanomaterials include magnetic nanomaterials, quantum dot based nanoparticles, and so on. In addition, organic and inorganic hybrids have also been used. Refer to Table 2 for a classified list of these nanoparticles and nanomaterials with their payloads, targets, related cancers, etc.
| Type of Nanoparticle | Payloads | Aptamers | Targets | Cancers | References |
|---------------------|----------|----------|---------|---------|------------|
| PLA-PEG             | Rhodamine-labeled dextran | A10      | PSMA    | Prostate cancer, lung cancer | [18] |
| PLGA-PEG            | Cisplatin, Docetaxel, Doxorubicin, Gemicitabine, Paclitaxel, Salinomycin, Vinorelbine, PDK-mTOR inhibitor, anti-miR-21, and cisplatin, | A10, A15, AS1411, CD30, CD133, EpCAM, HPA, Nucleolin, PC-3 cell, PGFRβ, PSMA | PSMA, CD133, EGFR, MUC1, Nucleolin, TAG-72 | Breast cancer, glioblastoma, glioma, large cell lymphoma, lung cancer, NSCLC, osteosarcoma, cisplatin-resistant ovarian cancer, prostate cancer, TNBC | [6, 22, 29, 35, 57, 71, 76, 81, 102, 122, 163, 176, 181, 223] |
| PLGA                | Docetaxel, Paclitaxel, Nutlin-3a, Salinomycin, Triplex forming oligonucleotide, Propranolol | A10, A15, AS1411, L5, S2.2, EpCAM-Ap | PSMA, CD133, EGFR, MUC1, Nucleolin, TAG-72 | Breast cancer, hepatocellular carcinoma, hemangioma, human glial cancer, prostate cancer | | |
| PEG-PCL             | Docetaxel | AS1411, GMT8, S15 | Nucleolin, NSCLC, U87 cells | Glioblastoma, glioma, lung cancer | [43, 45, 165] |
| H40-PLA-PEG         | Doxorubicin | A10 | PSMA | Prostate cancer | [42] |
| pPEGMA-PCL-pPEGMA   | Doxorubicin | AS1411 | Nucleolin | Pancreatic carcinoma | [52] |
| PEG-PAMAM           | MicroRNA | A10–3.2 | PSMA | Prostate cancer | [58] |
| PF127-β-CD-PEG-PLA  | Doxorubicin | AS1411 | Nucleolin | Breast cancer | [60] |
| PEI                 | EpCAM-siRNA | EpCAM-Ap | EpCAM | Breast cancer, retinoblastoma | [63] |
| GPN                 | Gefitinib | Ets1-Ap | Ets1 | NSCLC | [69] |
| PLL-alkyl-PEI       | shRNA | AS1411 | Nucleolin | Lung cancer | [80] |
| HPMAE               | Docetaxel | AS1411 | Nucleolin | Breast cancer | [94] |
| M-PLGA-TPGS         | Doxorubicin | AS1411 | Nucleolin | Cervical cancer | [96] |
| PbABT               | Docetaxel | HER2-Ap | HER2 | Ovarian cancer | [137] |
| PbAE and PLGA       | Epirubicin and antimir-21 | 5TR1 | MUC1 | Breast cancer | [158] |
| PLGA, PVP           | Doxorubicin | AS1411 | Nucleolin | Lung cancer | [174] |
| PCL-MMA/MPEG-MA     | Doxorubicin | EpCAM-Ap | EpCAM | Colorectal cancer | [209] |
| Type of Nanoparticle | Payloads | Aptamers | Targets | Cancers | References |
|----------------------|----------|----------|---------|---------|------------|
| **Lipid based nanoparticles** | | | | |
| Liposome | Curcumin, Doxorubicin, Cabazitaxel, Cisplatin, CRISPR-Cas9 plasmid, Docetaxel, Doxorubicin, Paclitaxel, and PLK1 siRNA, TSP | A10, A15, AS1411, HER3-Ap, PSMA-Ap, TLS1c | CD133, HER3, MEAR cells, Nucleolin, PSMA, PDGFR | Breast cancer, DOX-resistant breast cancer, Hepatoma, lung cancer, prostate cancer, | [33,50,58,65,113,138,145,154,178,191] |
| PEGylated-liposome | 5-FU, Doxorubicin, Anti-BRAF siRNA | 5TR1, AS1411, M49, Sy3c, TSA14, | CD200R1, EpCAM, Mucin1, Nucleolin, TUBO cells | Basal cell carcinoma, breast cancer, colon carcinoma, melanoma | [50,90,146,170,185,207] |
| DOTAP:DOPE liposome | Doxorubicin | SRZ1 | 4T1 cells | Breast cancer | [76] |
| Cationic liposome | miR-139-5p | EpCAM-Ap | EpCAM | Colorectal Cancer | [177] |
| **Chitosan based nanoparticles** | | | | |
| Chitosan | SN38 | MUC1-Ap | MUC1 | Colon cancer | [55] |
| Chitosan and HA | SN38 | MUC1-Ap | MUC1 | Colorectal adenocarcinoma | [78] |
| HAS-CS | Paclitaxel | MUC1-Ap | MUC1 | Breast cancer | [100] |
| **Dendrimer based nanoparticles** | | | | |
| Dendrimer | MicroRNA | S6, sgc8c | A549 cell, CCRF-CEM | ALL, NSCLC | [23,79] |
| ONT-PAMAM dendrimer | Doxorubicin | A9 | PSMA | Prostate cancer | [29] |
| PEG-PAMAM dendrimer | 5-fluorouracil, Camptothecin | AS1411 | Nucleolin | Colorectal cancer, Gastric cancer | [101,105] |
| DGL-PEG | Doxorubicin, ATP-aptamer | AS1411, Cyt c-Ap | Nucleolin, Cyt c | Cervical cancer | [102] |
| Alkyl PAMAM dendrimer | Bcl-xl shRNA | AS1411 | Nucleolin | Lung cancer | [112] |
| **Hydrogel based nanoparticles** | | | | |
| MCS nanogel | Doxorubicin | LNCaP-Ap | LNCaP cell | Prostate cancer | [109] |
| DNA Hydrogel | CpG ONT and Doxorubicin | MUC1-Ap | MUC1 | Breast cancer | [175] |
| RNA Hydrogel | siRNA and miRNA | LXL | MDA-MB-231 cell | Triple-negative breast cancer | [195] |
Table 2. Cont.

| Type of Nanoparticle | Payloads | Aptamers | Targets | Cancers | References |
|----------------------|----------|----------|---------|---------|------------|
| DNA icosahedra       | Doxorubicin | MUC1-Ap | MUC1    | Breast cancer | [27] |
| Aptamer DNA          | Antisense ONT against P-gp | sgc8c | CCRF-CEM cell | ALL | [45] |
| GC-rich dsDNA       | Doxorubicin | AS1411 | Nucleolin | Drug-resistant breast cancer | [92] |
| DNA dendrimer        | Epirubicin | MUC1-Ap, AS1411-Ap | MUC1, AS1411 | Breast and colon cancers | [95] |
| 3WJ-RNA             | Doxorubicin | Endo28 | Annexin A2 | Ovarian cancer | [99] |
| DNA nano-ring        | Doxorubicin | MUC1-Ap | MUC1 | Breast cancer | [130] |
| Lipidated GC-rich    | Doxorubicin and 2′,6′-dimethyl-azobenzene | trCLN3 | cMet | cMet-expressing lung cancer | [135] |
| DNA hairpin          | ALK-siRNA, Doxorubicin, Paclitaxel | CD30-Ap, Gint4.T, GMT8, Sgo4f, Sgo8, TO1 | cancer cells, CD30, PDGFRβ, PTK7, U87MG cell | ALCL, ALL, Glioblastoma | [140,179,186] |
| DNA origami          | Antisense ONT, doxorubicin | MUC1-Ap | MUC1 | MDR cervical cancer | [187] |
| DNA nanotube         | Doxorubicin | C2NP | CD30 | Human anaplastic large cell lymphoma | [198] |
| DNA nanotrain        | AKT inhibitor, DAU, DOX, DNR, EPI, Gold | AS1411, LZH58, Sgo8, TA6 | CD44, HepG2 cell, nucleolin, PTK7 | ALL, Breast cancer stem cell, cervical cancer, liver cancer | [46,181,188,201] |
| DNA Holliday junction| Doxorubicin | AS1411 | Nucleolin | Colon cancer | [206] |
| Albumin              | Cisplatin, Curcumin, Doxorubicin | AS1411, EGFR-Ap, HB5 | EGFR, HER2, nucleolin | Breast cancer, cervical cancer | [85,147,164] |
| Human IgG            | Genistein, miRNA-29b | MUC1-Ap | MUC1 | NSCLC | [86,141,162] |
| Elastin-like polypeptide | Paclitaxel | S2.2 | MUC1 | Breast cancer | [157] |
| Human serum albumin  | Doxorubicin, ALK-siRNA | CD30-Ap | CD30 | Lymphoma | [202] |
| Type of Nanoparticle                | Payloads                        | Aptamers                        | Targets   | Cancers                                      | References          |
|------------------------------------|---------------------------------|---------------------------------|-----------|----------------------------------------------|---------------------|
| **Polymer and lipid hybrids**      |                                 |                                 |           |                                              |                     |
| PLGA-lecithin-PEG                  | Paclitaxel, Curcumin            | AS1411, EpCAM                   | Nucleolin | Breast cancer, colorectal adenocarcinoma     | [32,51]             |
| PLGA-lipid-PEG                     | Docetaxel                       | XEO2mini                        | PC3 cells | Prostate cancer                              | [31]                |
| Lipid-polymer liposome             | sRNA                            | A6                              | HER2      | Breast cancer                                | [106]               |
| Polymer-lipid                      | All-trans retinoic acid, Curcumin and Cabazitaxel, Salinomycin | A10-3.2, A15, CD20-Ap, CD133-Ap, CL4, EGFR-Ap | CD20, CD133, EGFR, PSMA | Melanoma, osteosarcoma, prostate cancer | [133,134,143,159,212] |
| Lipid-PLGA                         | All-trans retinoic acid         | CD133-Ap                        | CD133     | Lung cancer                                  | [155]               |
| DOTAP, PLGA, cholesterol, Mal-PEG  | P-gp siRNA                      | A6                              | HER2      | DOX-resistant breast cancer                  | [213]               |
| **Polymer and chitosan hybrids**   |                                 |                                 |           |                                              |                     |
| PLGA-chitosan                      | Epirubicin                      | STR1                            | MUC1      | Breast cancer, colon carcinoma              | [111]               |
| Chitosan-ss-PEEUAA                 | TLR4-siRNA, Doxorubicin         | AS1411                          | Nucleolin | Lung cancer                                  | [123]               |
| Chitosan-liposome                  | Erlotinib                       | EGFR-Ap                         | EGFR      | EGFR-mutated cancer cells                    | [107]               |
| Chitosan-liposome                  | PFOB and Erlotinib              | EGFR-Ap                         | EGFR      | NSCLC                                        | [116]               |
| KL-DNA micelle                     | Doxorubicin+KLA                 | MUC1-Ap                         | MUC1      | Breast cancer                                | [132]               |
| PAM (peptide +DNA ON)              | Peptide                         | C10.36                          | HBLL      | B-cell leukemia                              | [152]               |
| ssDNA-ELP                         | Docetaxel                       | MUC1-Ap                         | MUC1      | Breast cancer                                | [199]               |
| **Nucleic acid and peptide hybrids** |                                 |                                 |           |                                              |                     |
| Atelocollagen                      | MicroRNA                        | A10–3.2                         | PSMA      | Prostate cancer                              | [59]                |
| Tocopheryl PEG-PβAE               | Docetaxel                       | AS1411                          | Nucleolin | Ovarian cancer                               | [77]                |
| PEG-aptamer micelle                | None or Aptamer                 | FKN-S2                          | Fractalkine | Colon adeno-carcinoma                       | [124]               |
| Ursolic acid                       | Doxorubicin                     | HER2-Ap                         | HER2      | HER2-carrying cells                          | [125]               |
| TD-PEG-chitosan                    | miR-145                         | AS1411                          | Nucleolin | Breast cancer                                | [139]               |
| LP-DNA                             | SATB1 siRNA                     | EGFR-Ap                         | EGFR      | Choriocarcinoma                              | [153]               |
| Diacetylene-PEG                    | None                            | ACE4                            | Annexin A2 | Breast cancer                                | [161]               |
| Type of Nanoparticle | Payloads | Aptamers | Targets | Cancers | References |
|----------------------|----------|----------|---------|---------|------------|
| Inorganic nanoparticles |          |          |         |         |            |
| Gold                 |          |          |         |         | [15,44,53,66,82,87,88,108,120,150,151,184,192,197] |
| Mesoporous silica    |          |          |         |         | [35,38–40,89,114,178] |
| ZnO                  |          |          |         |         | [75] |
| GQD-MSN              |          |          |         |         | [81] |
| Iron                 |          |          |         |         | [84] |
| Au-Fe₃O₄             |          |          |         |         | [117] |
| Copper oxide         | mRNA 29b | MUC1-Ap  | MUC1    | Breast cancer | [148] |
| Calcium carbonate    | Epirubicin, and melittin | MUC1-Ap  | MUC1    | Breast cancer | [160] |
| Mesoporous MnO₂      | HMME     | MUC1-Ap  | MUC1    | Breast cancer | [173] |
| Silver-PEG           | Irradiation | AS1411  | Nucleolin | Glioma | [183] |
| Graphene oxide sheets| Berberine derivative | AS1411  | Nucleolin | Lung cancer | [205] |
| Quantum dots         | None     | S15      | NSCLC   | Lung cancer | [142] |
| QD-PMAT-PEI          | siRNA    | PSMA-Ap  | PSMA    | Prostate cancer | [30] |
| Lipid-quantum dot    | siRNA    | EGFR-Ap  | EGFR    | Triple-negative breast cancer | [163] |
Table 2. Cont.

| Type of Nanoparticle | Payloads | Aptamers | Targets | Cancers | References |
|----------------------|----------|----------|---------|---------|------------|
| Magnetic nanoparticles |          |          |         |         |            |
| SPION                | Epirubicin, Doxorubicin, Daunomycin and TMPyP | STR1, A9, A10, AS1411, DNA-RNA hybrid | MUC1, Nucleolin, PSMA | Colon cancer, breast cancer, lung cancer, prostate cancer | [22,28,43,91,171] |
| Dextran-ferric oxide | None     | HER2-Ap  | HER2    | Human adenocarcinoma | [47] |
| Au-SPION             | None     | MUC1-Ap  | MUC1    | Colon cancer         | [83] |
| Iron oxide           | None (HTT) | FGFR1-Ap | FGFR1   | Human osteosarcoma   | [103] |
| Gold-coated magnetic NP | None   | AS-14    | Fibronectin protein | Ehrlich carcinoma | [122] |
| PEG-SPION            | Doxorubicin | MUC1-Ap  | MUC1    | Breast cancer        | [126] |
| Fe3O4-carbon         | Doxorubicin | Sgc8c-Ap | Sgc8c   | Lung cancer          | [140] |
| Magnetic SPION/MSN   | Doxorubicin | AS1411   | Nucleolin | Breast cancer | [165] |
| SPMFN                | Doxorubicin | AS-14 and AS-42 | FN and HSP71 | Ehrlich carcinoma | [191] |
| SPION@SiO2           | Doxorubicin | MUC1-Ap  | MUC1    | Breast cancer        | [189] |
| Magnetic nanosphere  | Doxorubicin | EpCAM-Ap | EpCAM   | Breast cancer        | [200] |
| Other inorganic nanoparticles |          |          |         |         |            |
| Gd3SrHap             | Doxorubicin | AS1411   | Nucleolin | Breast cancer | [37] |
| MOF-UCNP             | Doxorubicin | AS1411   | Nucleolin | Breast cancer | [68] |
| Gold-liposome        | Docetaxel, Morin | AS1411, S2.2 | Nucleolin, MUC1 | Breast cancer, gastric cancer | [119,213] |
| Aminopropyl MSN      | Safranin O | MUC1-Ap  | MUC1    | Breast cancer        | [115] |
| MPC-PAA/PEI          | Doxorubicin | MUC1-Ap  | MUC1    | Breast cancer, lung cancer | [118] |
| PDA/P2EG- coated MSN | DM1      | EpCAM-Ap | EpCAM   | Colorectal cancer    | [121] |
| Organic and inorganic hybrids |          |          |         |         |            |
| NMOF                 | Doxorubicin | AS1411, VEGF-Ap | Nucleolin, VEGF | Breast cancer | [127] |
| PEI-PEG and Na2SeO3  | Epirubicin and an aptamer | STR1 | MUC1 | Breast cancer | [128] |
| BSA-PEG-Fe3+        | Mn, Doxorubicin | Glut-1-Ap | Glut-1 | Liver cancer | [138] |
| PEG-Au-PAMAM        | Curcumin | MUC1-Ap  | MUC1    | Colon adenocarcinoma | [144] |
| Albumin-IONP/GNP    | Doxorubicin | AS1411   | Nucleolin | Breast cancer | [166] |
| β-CD-capped MSN     | Doxorubicin | HAp      | HER2    | HER2-positive cells | [16] |
| CaCO3 and protamine | CRISPR-Cas9 plasmid | AS1411 | Nucleolin | NSCLC | [196] |
| TiO2 nanofiber with BSA | None   | AS1411   | Nucleolin | Breast cancer CTCs | [203] |
Table 2. Cont.

| Type of Nanoparticle | Payloads                  | Aptamers | Targets                  | Cancers                          | References |
|----------------------|---------------------------|----------|--------------------------|----------------------------------|------------|
| Cationic nanobubble  | FoxM1 siRNA               | A10–3.2  | PSMA                     | Prostate cancer                  | [131]      |
| Micro-emulsion       | Shikonin and docetaxel    | AS1411   | Nucleolin and CD44       | Glioma                           | [176]      |
| RBC membrane         | Doxorubicin, siRNA        | AS1411   | Nucleolin                | MDR breast cancer                | [180]      |
|                      | Protoporphyrin IX         | AS1411   | Nucleolin                | Cervical cancer, lung cancer     | [190]      |
| Ag-MOF-RBCm          | Doxorubicin               | CD20-Ap  | CD20                     | B-cell lymphoma                  | [208]      |
| FO-loaded MOF-RBCm   | Using PDT and CDT effects | AS1411   | Nucleolin                | KB Cell Line                     | [210]      |
| NIR PLN              | Afatinib                  | MAGE-A3  | MAGE                     | NSCLC                            | [211]      |

For aptamers that do not have a name, “target-Ap” is used to represent the aptamer; for example, EpCAM-Ap represents the aptamer that targets EpCAM.
4. Challenges Facing Actively Targeted Delivery

Although active targeting holds much promise, several challenges exist. These include the increased complexity of synthesis and purification, the increased cost to make the conjugants, the alterations of nanoparticle properties, choosing a suitable tumor marker or receptor to target, and so forth.

4.1. Potential Alterations of Nanoparticle and Ligand Properties after Conjugation

Ligand conjugation may alter the properties of the nanoparticle. Not only will it increase nanoparticle size; it can also change the charge and modify the conformation of the nanoparticle. The change of nanoparticle size is likely to affect their pharmacokinetics; the change of nanoparticle charge will probably complicate their cellular uptake; the change of nanoparticle conformation may influence the binding feature of the attached ligand because of inadequate steric freedom or decreased orientation. All these must be taken into consideration in making actively targeting nanoparticles.

Although conjugating ligands to nanoparticles might change the pharmacokinetic property of the nanoparticles, this may not be a problem for aptamer conjugation because aptamers are very small, about 2–3 nm in length, in comparison with the drug-carrying nanoparticles, which is typically around 100 nm or larger in diameter. In fact, no literature has reported any alterations in the pharmacokinetics of nanoparticles following aptamer coupling.

Aptamers are commonly modified before therapeutic use. The purpose of modification is to increase their stability against nuclease degradation or prolong their half-life against kidney filtration. Aptamer modification can be performed during selection or after selection. The former aims at stabilizing the aptamers against nucleases. The latter aims at prolonging renal retention and is frequently done with PEGylation, covalent attachment of PEG to one end of the aptamer. Therefore, the attachment of aptamers to a nanoparticle will favorably increase their stability.

However, conjugation of aptamers to a nanoparticle might interfere with their proper folding and change their binding specificity and affinity. For example, the surface charge of the nanoparticle and the density of the attached aptamers on the nanoparticle may both affect their folding and three-dimensional structure. In addition, aptamers that are coupled directly to a nanoparticle may not recognize and bind their target effectively because there is no sufficient space (stereo-interference effect). Sometimes, the orientation of aptamer immobilization may also affect aptamer binding. All these problems should be considered by the researchers and optimum parameters or corresponding resolving measures be taken. For instance, the density and the orientation of attached aptamers can be investigated and optimized, and when stereo-interference occurs, the researchers can consider the use of a spacer molecule.

4.2. Selection of Suitable Tumor Marker or Receptor

The ideal receptor for targeted therapy is one that is exclusively presented on the tumor cells but not on the healthy cells. However, such a receptor may not exist in reality. What we can do is to choose the receptors that have a higher expression level on tumor cells than on healthy cells. The expression of the target receptors on healthy cells, though at a lower level, still carries a potential risk of off-target binding. What is more, binding to these receptors may consume or waste the therapeutic nanoparticles and lower its concentration to reach the tumor.

4.3. The “Binding Site Barrier” Effect

Aside from the challenges mentioned above, there may also be the “binding site barrier” problem, which refers to a situation wherein high affinity binding to target cells prevents in-depth and uniform penetration of the targeted therapeutics into the tumor tissue. This phenomenon was first observed by Weinstein and colleagues [218,219] with antibodies, which showed that (1) antibody–antigen binding in tumor-retarded antibody percolation and (2) high antibody affinity had a tendency to decrease antibody percolation. The explanation to the phenomenon that higher-affinity antibodies penetrate the tumor
tissue less efficiently than lower-affinity antibodies is that during tissue penetration, the higher-affinity antibodies bind tightly to the cells they first meet and so there are fewer free antibody molecules available; in contrast, lower-affinity antibodies tend to bypass these target cells and can penetrate deeper. Although the “binding site barrier” was originally demonstrated in antigen-antibody interaction, it may be reasonably extrapolated to the actively targeted nanoparticles and a similar phenomenon has in fact be observed by Miao et al. [220] using anisamide ligand targeted lipid-coated calcium phosphate nanoparticles. Therefore, it is essential to seek a balance between the affinity of active tumor targeting and the depth of nanoparticle penetration; trial and error may be necessary [221].

5. Conclusions

The first nanotechnology-based anticancer medicine was approved by the United States Food and Drug Administration (FDA) in 1996, which used PEGylated liposomes to encapsulate the chemotherapeutic drug doxorubicin. Today, about ten nanoparticle based medications are on the market (approved by FDA or other agencies) for cancer therapy [14,222]. All of them are non-targeted or passively targeted. These nanodrugs could delay the clearance or prolong the half-life of the drugs and reduce side-effects to a certain degree. However, only a modest increase in therapeutic efficacy could be observed and the undesired off-target problem still exists, which calls for the development of active targeting of nanoparticles. At the present time, more than a dozen nanoparticles for cancer therapy are undergoing clinical trials [2], of which several are actively targeted, but none of them are aptamer-functionalized. Actively targeted, especially aptamer-functionalized, nanoparticles hold great promise for future nanodrug development and applications. Therefore, more efforts are needed to further the investigation in this area, to refine the experiments and overcome the obstacles for clinical translation. Some obstacles for developing aptamer conjugated-nanoparticles into clinical use include insufficient data about their off-target effects and toxicity either in animals or in human. Venditto and Szoka once notified in their review paper titled Cancer nanomedicines: so many papers and so few drugs published in 2013 that “if we are truly interested in bringing more drugs into the clinic we should focus less on our publication record and more on devising scientific progress that translates into patient treatment” [223]. The same situation exists in the investigation of aptamer-functionalized nanoparticles when we take notice of the fact that more than two hundred papers have been published so far but none of the aptamer-functionalized nanoparticles have entered clinical trials, not to mention clinical application.

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**Abbreviations**

| Acronym | Definition |
|---------|------------|
| 3WJ-RNA | a highly stable three-way junction (3WJ) motif from phi29 packaging RNA |
| 5-FU | 5-fluorouracil |
| ALCL | anaplastic large cell lymphoma |
| ALK | anaplastic lymphoma kinase |
| ALL | acute lymphoblastic leukemia |
| AML-M2 | acute myeloid leukemia subtype 2 |
| APTES | (3-aminopropyl) triethoxysilane |
| BSA | bovine serum albumin |
| cMet | hepatocyte growth factor receptor |
| COOH | (terminal) carboxylic acid group |
| CSC | cancer stem cell |
| CTC | circulating tumor cell |
| CUR-NP | curcumin-loaded lipid-polymer-lecithin hybrid nanoparticle |
| Cyt c | cytochrome c |
| DAU | daunorubicin |
| DGL | dendrigrift-poly-L-lysines |
| DOTAP | 1,2-dioleoyl-3-trimethylammonium-propane |
| Abbreviation | Full Name |
|--------------|-----------|
| DNR          | daunorubicin |
| DOX          | doxorubicin |
| dsDNA        | double-stranded DNA |
| DSPE         | 1,2-distearoyl-sn-glycero-3-phosphoethanolamine |
| EGFR         | Epidermal growth factor receptor |
| EHH          | electrostatic adsorption, hydrogen bonding, and hydrophobic interaction |
| Ehrlich’s ACC | Ehrlich’s ascites carcinoma cell |
| ELP          | elastin-like polypeptide |
| EpCAM        | epithelial cell adhesion molecule |
| EPI          | epirubicin |
| FGFR1        | fibroblast growth factor receptor type-1 |
| FMSN         | fluorescent mesoporous silica nanoparticle |
| FN           | fibronectin |
| FO           | Ferric oxide |
| FoxM1        | Forkhead box M1 |
| Gd:5rHap     | gadolinium-doped luminescent and mesoporous strontium hydroxyapatite |
| GMNP         | gold-coated magnetic nanoparticle |
| GNP          | gold nanoparticle |
| GO           | Graphene oxide |
| GPN          | gefitinib-loaded poly (lactic co-glycolic acid) nanoparticle |
| GQD          | graphene quantum dot |
| GST          | glutathione S-transferase |
| HA           | Hyaluronic acid |
| HAS-CS       | human serum albumin coated with chitosan |
| HBLL         | human B cell leukemia and lymphoma |
| HCC          | Hepatocellular carcinoma |
| HER3         | human epidermal growth factor receptor 3 |
| His          | hexahistidine |
| HMME         | is a photosensitizer |
| HPA          | heparanase |
| HPAEG        | poly(2-((2-(acryloyloxy)ethyl)disulfanyl)ethyl)poly(ethylene glycol) methacrylate |
| HSP71        | heat shock cognate 71 kDa protein |
| HTT          | hyperthermia therapy |
| IL-6R        | interleukin-6 receptor |
| IONP         | Iron oxide nanoparticle |
| KG6E         | glutamic acid-modified dendritic poly(L-lysine) system |
| KLA          | (KLAKLAK)2 peptide |
| LP-DNA       | liposome-polycation-DNA |
| MAA          | methacrylamide |
| MAGE         | melanoma-associated peptide antigen |
| MAL          | maleimide |
| MASI         | N-(methacryloy)succinimide |
| MCS          | Myristylated Chitosan |
| MMA          | methyl methacrylate |
| MOF          | (mesoporous) metal-organic framework |
| MPC          | mesoporous carbon |
| MPEG         | Poly(ethylene glycol) methyl ether |
| M-PLGA       | mannitol-functionalized poly(lactide-co-glycolide) |
| MNOP         | Mesoporous silica nanoparticle |
| mTEC         | mouse tumor endothelial cell |
| MDR          | multiple drug resistance |
| MUC1         | Mucin-1 |
| NHS          | N-hydroxysuccinimide |
| NIR PLN      | near infrared-persistent luminescence nanomaterials |
| NMOF         | amino-triphenyl dicarboxylate-bridged Zr4+ metal-organic framework nanoparticle |
| NP           | nanoparticle |
| NSCLC        | non-small cell lung cancer |
| ONT          | oligonucleotide |
| PAA          | polyacryllic acid |
| PAM          | Peptide amphiphile micelle |
| PAMAM        | polyamidoamine |
| PBABT        | poly (butylene adipate-co-butylene terephthalate) |
| PCL          | poly(ε-caprolactone) |
PDA hydrochloride dopamine
PDGFR platelet-derived growth factor receptor
PEC polyelectrolyte complexe
PEEUA polyethylenimine-urocanic acid
PEG polyethylene glycol
PEI polyethylene imine
PF127 Pluronic F127
PFK15 1-(4-pyridyl)-3-(2-quinoline)-2-propyl-1-one (an aerobic glycolysis inhibitor)
PFOB Perfluorooctylbromide
PGFRβ platelet-derived growth factor receptor β
P-gp P-glycoprotein
PLA poly(lactic acid)
PLGA poly(lactic-co-glycolic acid)
PLL poly (L-lysine)
PEMMA-PCL-pPEGMA poly(poly(ethylene glycol) methacrylate)-poly(caprolactone)-poly(poly(ethylene glycol) methacrylate)
PLK1 Polo-Like Kinase 1
PMBc red blood cell membrane
PTK7 protein tyrosine kinase-7
PVP Poly (N-vinylpyrrolidone)
Pβ-AE poly (β amino ester)
QD quantum dot
SABT1 special AT-rich sequence binding protein 1
SPION superparamagnetic iron oxide nanoparticles
TAG-72 tumor-associated glycoprotein 72
TD thiolated dextran
TiO₂ titanium dioxide
TLR Toll-like receptor TLR4-siRNA
TM-JM transmembrane-juxtamembrane 1/2 domain
TMPyP 5,10,15,20-tetra (phenyl-4-N-methyl-4-pyridyl) porphyrin
TMPyP4 5,10,15,20-tetrakis(1-methylpyridinium-4-yl) porphyrin
TNBC triple-negative breast cancer
TPGS D-α-tocopheryl polyethylene glycol 1000 succinate
TSP thermosensitive polymer
UCNP up-conversion luminescent
NaYF₄ Yb(3⁺)/Er(3⁺) nanoparticle
VEGF vascular endothelial growth factor
β-CD β-cyclodextrin

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