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Review Article

APTAMERS: NANOMATERIALS AS A POTENTIAL AGENT FOR ANTIVIRAL THERAPEUTIC DRUG DELIVERY DEVELOPMENT: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Chemotherapeutic experts have been utilised to cure a variety of disorders, but their practical application is restricted due to their regrettable selectivity and outrageous fundamental optional effects. Short single-stranded DNA or RNA oligonucleotides known as aptamers are released from randomised libraries and have strong propensity and differentiation towards targets like antibodies as well as characterised structures and ties to targets like proteins. They commonly suppress protein interactions while restricting proteins, which may elicit positive effects like threat. Aptamers have recently demonstrated their amazing promise for use in medicines, biosensors, and bioimaging thanks to a number of advantages, such as minimal immunogenicity, simplicity of giant degree blend, low pack to-bunch collection, genuinely substance modification, and programmability. At any rate, the steady for the most part accomplishment speed of aptamer is far from being brilliant, despite everything needs to overwhelm the gigantic obstruction in propensity, constancy for utilitarian application, explicit illness cell affirmation. The sensible method of controlling the binding execution of aptamers and dealing with their show in the practical application is of great significance and these single-abandoned DNA or RNA aptamers could outline with astoundingly poisonous chemotherapy drugs, hurts, strong RNAs or different particles as novel aptamer-drug structures, which are prepared to do endlessly out working on the obliging plentifulness and decreasing the critical danger of solutions and have unprecedented possible in living spaces for appointed ailment treatment. In this survey, we have extensively covered and summarised the ongoing improvements in the aptamer-drug structure philosophy for designated drug transport in the assessment methodologies of aptamers for unambiguous disease biomarkers. A modified strategy utilising aptamers could be a reliable system for quick and precise advancement of biopharmaceutics for use in infection-related treatment, especially in light of the enormous advances in modernised thinking for protein and RNA structure conjectures. Additionally, the likelihood of future conception is also summarised.

Keywords: Cancer, SELEX, Targeted drug delivery, Nanoparticle, Therapy, Aptamer

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INTRODUCTION

For the best clinical applicability, proper evaluation must be followed by effective treatment. Researchers have been actively pursuing the specific delivery of anticancer drugs to malignant development cells for a long time. Nanoparticles may more efficiently encapsulate and deliver anticancer drugs to tumour-growing tissue [1]. Despite this, nanoparticles as such are not specific to cancerous development cells; rather, the increased permeability and retention (EPR) effect of the cancer tissue is what causes nanoparticles to aggregate, particularly in disease locations [2, 3]. However, if ligands with the ability to recognise malignant growth cells specifically could be added to nanoparticles, they would actually want to target and deliver cargoes to disease cells specifically, greatly increasing the restorative record (expanding helpful viability while reducing harmfulness). Aptamer is one of the molecules that have been studied so far to explicitly functionalize nanoparticles for focusing [4]. Small single-stranded DNA or RNA oligonucleotides known as aptamers, have the ability to generate secondary and tertiary structures. Similar to antibodies, which are essentially made of nucleic acid with high affinity to specific targets like ions, entire cells, peptides, proteins, bacteria, viruses, and other cellular targets, etc., antigens are separated from randomised libraries and exhibit high affinity and specificity towards targets. These nucleic acid aptamers, which typically vary in size from 20 to 80 nucleotides, first appeared in the 1990s and exhibit binding properties [5, 6]. The Aptamer, a medicinal drug created by Nexstar and NeXagen, exhibits perfect analogies to antibodies. NX1838, now known as Macugen (Pegaptanib sodium), was the first Aptamer to be used in a clinic setting (and the first FDA-approved Aptamer). NX1838 functions as a vascular endothelial antagonist [7, 8].

Due to aptamers' remarkable potential, such as their potent anti-tumor activity, excellent circulation stability, biocompatibility, multimodal diagnostic functionalities, high loading efficiency, and ability to treat bacterial or viral infections, the field of aptamers research is expanding [9]. The issues of aptamer degradation, metabolic clearance, renal filtration, regulation of the duration of action, cross-reactivity, and irreversible tissue uptake remain despite aptamers' potential for theranostic and bioimaging applications [10]. Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is an *in vitro* selection process for aptamers that is used to find the best aptamer for a given target. It comprises of the three main phases of library formation, binding/separation, and nucleotide amplification [11]. The use of aptamer-conjugated nanoparticles (NPs) and their theragnostic applications in a variety of diseases, such as oncology, inflammatory, and viral diseases, with their *in vitro* selection procedure and their applications along were discussed, are presented in this review.

In vitro screening of aptamers with drug delivery potential

Systematic Evolution of Ligands by Exponential Enrichment (SELEX), an iterative process of exponential enrichment, is typically used to manufacture aptamers. In this procedure, aptamers are screened from a randomised ssDNA or RNA library. It is utilised to choose the aptamer from roughly 1012-10-15 combinatorial oligonucleotide libraries [12, 13] that has a high affinity towards the particular target. It consists of the three main phases depicted in fig. 1, which are the creation of the library, binding/separation, and nucleotide amplification. As indicated in table 1, SELEX methods based on proteins, cells, and animal models are currently often used to select the aptamers with drug delivery potential.

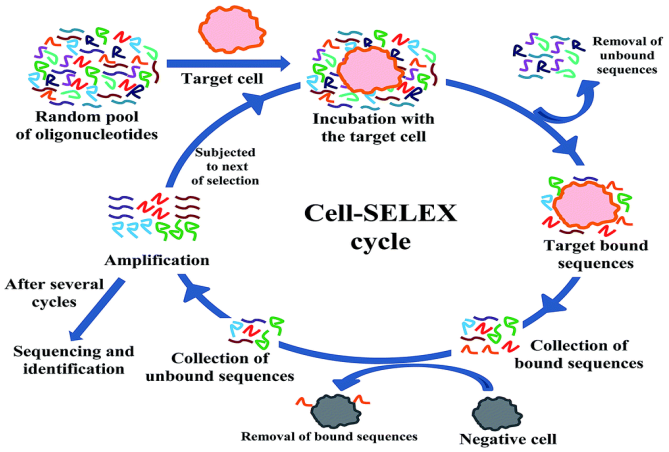

Fig. 1: Schematic illustration of SELEX protocol for aptamer identification (Reprinted from [13] with permission (RSC 2015))

Table 1: Comparison of the advantages and disadvantages between three SELEX approaches

Model	Protein-based selex	Cell-based selex	*In vivo* selex	References
Target	Purified proteins	Live cells	CDX or PDX models	[33]
	All types of proteins	Membrane protein	Membrane protein	[33]
Advantages	Wide range of target	Recognition of target with native form; without the prior knowledge about target proteins	High biostability; high specificity; suitable for cancer metastasis model; capable of crossing the blood-brain barrier	[34, 35]
Disadvantages	Time-consuming, vague, and ineffective in recognising targets in their natural conformations	Time consuming; failure for *in vivo* use	High cost	[33, 39, 40]

The food and drug administration approved only one aptamer (Pegaptanib, Macugen®) to date for the treatment of age-related macular degeneration (AMD) [15]. Pegaptanib is an RNA aptamer that specifically recognises and inhibits the human vascular endothelial growth factor (VEGF165) with high affinity (Kd 50 pM) [16]. Current studies describe the developments of these aptamer nanomedicines in clinical trials [17, 18]. Other therapeutic aptamers are currently being assessed in a variety of clinical trials, spanning from phase one to three. Here, a variety of SELEX techniques have been used to produce aptamers with efficient cell-targeting and internalising capabilities. The majority of these methods reflect one of two basic strategies: classic protein-based SELEX for binding to isolated membrane proteins or live cell-based SELEX [19, 20]. Several of the most used aptamers for cancer antigens are listed in table 2.

Table 2: Aptamers that bind cell-surface markers selected by protein-SELEX or cell-SELEX

Aptamer library	Name of the aptamer	Biomarker	Type of SELEX	References
RNA, DNA	FB4, GS24 (DW4)	mTfR	Protein-SELEX	[107]
2'F-RNA	A9, A10 PSMA	PSMA	Protein-SELEX	[106]
DNA	Sgc8	PTK7	Cell-SELEX	[109]
2'F-RNA	E07	EGFR	Protein-SELEX	[110]
Thio-DNA	TA1-TA6	CD44	Protein-SELEX	[111, 104]
2'F-RNA	c2, Waz	CD71 (hTfR)	Hybrid SELEX[1]	[115]
DNA	AS1411	Nucleolin	screening of G-rich oligos in cell lines	[117, 118]
2'F-RNA	GL56	Insulin receptor	Cell-SELEX	[119]
2'F-RNA	B1, C1, E1	HER2	Cell-SELEX	[113]
DNA	C10, C10.36	CD19 (+) Burkitt lymphoma	Cell-SELEX	[121]

Hybrid SELEX = combination of protein-and cell-based SELEX.

As a result, with the introduction of SELEX, the invention technique has changed and improved in terms of efficiency and time-cost optimisation. Aptamers have had a lot of success, but they have some drawbacks that prohibit them from being widely used in many applications, especially in the biomedical sciences. The primary issue is aptamer degradation by nucleases in biological media. Modified nucleotides before or after the SELEX round, mirror image aptamers, and aptamer displacement screening are frequently employed to address this problem.

For instance, altering the 20-amino pyrimidine nucleoside sugar position, 20-fluoropyrimidine nucleosides [20-23], 20-O-methyl purine, and 20-O-methyl pyrimidine nucleosides or 30-and 50-nucleotides, located L-ribose or L deoxyribose in oligonucleotide backbone and displace aptamer with low-molecular-weight compound from the binding site of a target molecule, improve pharmacokinetics of the aptamer in blood. Regarding the second issue, increasing the size of the aptamer by conjugation with polyethylene glycol (PEG) and renal aptamer filtration is an effective technique to lengthen the bloodstream circulation period. The usage of polycationic biopolymers like porphyrin and converting an inactive aptamer to an active form are the most popular solutions to the third challenge linked to controlling the activity duration of aptamers [24, 25]. Furthermore, Cell-SELEX and *in vivo* SELEX negative selection [26], automated SELEX and CE–SELEX were used to avoid aptamer generation with purified target molecules, cross-reactivity of aptamer, and automation of aptamer generation limitations, respectively [27], SELEX has often been carried out on pure proteins, and it may be difficult to purify cell surface receptors in their correctly folded and changed conformations as a result, not many aptamers that bind cell surface receptors have been produced. Most surface receptors are actively internalised in response to ligand contact, and all cell surface proteins cycle intracellularly to some extent. Subsequently, various payloads have been conveyed into cells utilizing aptamers that tight spot cell surface receptors displayed in table 3.

Table 3: Cell surface protein aptamers and their applications

Receptor name	RNA/DNA	Choice technique	Delivery usage	Reference
Mucin-1 (MUC-1)	DNA	Recombinant peptides	Photodynamic therapy (PDT) Radionuclide delivery	[123]
Prostate-specific membrane Antigen (PSMA)	RNA	Purified extracellular domain of PSMA	siRNA delivery, cytotoxin delivery, Chemotherapeutic drug delivery and cellular imaging	[124-128]
Immunoglobin heavy mu chain (IGHM)	DNA	Cell SELEX using Burkitt's lymphoma cell line (Ramos)	Micelle nanoparticles for drug delivery	[129]
Tenascin-C (TN-C)	RNA	Purified TN-C	*In vivo* tumor imaging	[130]
Nucleolin	DNA	Not applicable	Photodynamic therapy (PDT) tumor imaging	[156]
Protein tyrosine kinase-7 (PTK7)	DNA	Cell SELEX using T-cell acute lymphoblastic leukemia (ALL) cell line	Chemotherapeutic drug delivery	[147]
gp120	RNA	Purified recombinant gp120	siRNA delivery	[141]
Epidermal growth factor receptor (EGFR) RNA	RNA	Purified extracellular domain of EGFR	Nanoparticle delivery	[155]
Transferrin receptor (TfR)	RNA/DNA	Purified extracellular domain of mouse TfR	Protein targeting to lysosome	[164]

CE microfluidic chips

The target molecules are incubated with a library of ssDNA. Binding sequence separation is accomplished via capillary electrophoresis. By using PCR to purify and amplify binding nuclear acids, an enriched pool of ssDNA is produced that is ready for additional rounds of selection. After two to four rounds of selection, high-affinity aptamers are frequently obtained [30, 31]. Additionally, the CE-SELEX approach has a higher partitioning efficiency than the conventional SELEX method, which reduces the number of rounds of SELEX to one to three [32]. The CE-SELEX typically takes less than an hour to incubate at room temperature. The targets' activity is also maintained during the brief incubation period [33].

Sol-gel microfluidic chips for screening of aptamers

A microfluidic device is used to incubate a library of ssDNA with protein sol-gel arrays in order to effectively select ssDNA aptamers against target molecules [34]. The number of selection cycles required to manufacture high-affinity aptamers was significantly decreased thanks to the sol-gel microfluidic devices. As a result, it may help enhance the selection of aptamers for these particular proteins and enable the separation of aptamers unique to many of the target proteins [35].

Magnetic-bead-based microfluidic chips for screening of aptamers

The random ssDNA library is first incubated with target proteins attached to magnetic beads in the microfluidic selection procedure. After incubation, the microfluidic chip performs the partitioning process to separate the target-bound aptamers from the unbound nuclear acids [36]. To continually elute weakly-and unattached nuclear acids from the microfluidic chip, strict washing conditions are established in the microchannel [37]. The external magnets are taken out following the separation, and the beads containing the chosen aptamers are liberated from the apparatus. On the chip, the full separation procedure, including bead elution, washing, and trapping, is carried out. The chosen Aptamers are then amplified by PCR. The SELEX technique has become more effective because to the use of magnetic beads to choose aptamers in a microchannel [38].

Cell selex

The cell SELEX involves the same procedures as a regular SELEX, including incubation, partitioning, and amplification. Both positive and negative selection are part of the crucial cell SELEX process. Negative selection is a crucial phase in the process since it helps the candidate Aptamer become more specific by removing the sequence that binds to healthy cells [39]. Various modified cell SELEX procedures have been developed over the past few years in an effort to increase the efficacy [40] and enrich the aptamer screening depicted in fig. 2.

Fluorescence-activated cell sorting SELEX [FACS-SELEX]

In this method, a cytometry device is used to separate the cell [target] which is bound to Aptamer, from the unbound Aptamer, which is based upon the principle of fluorescence and scattering. This technique developed in which the isolation and identification of the bound Aptamer to the target is carried out by using FACS device [41].

Cell internalization SELEX

The primary benefit of this approach, which is supported by numerous research, is that the aptamer is carried inside the cells as well as bound to the cell surface [42-44].

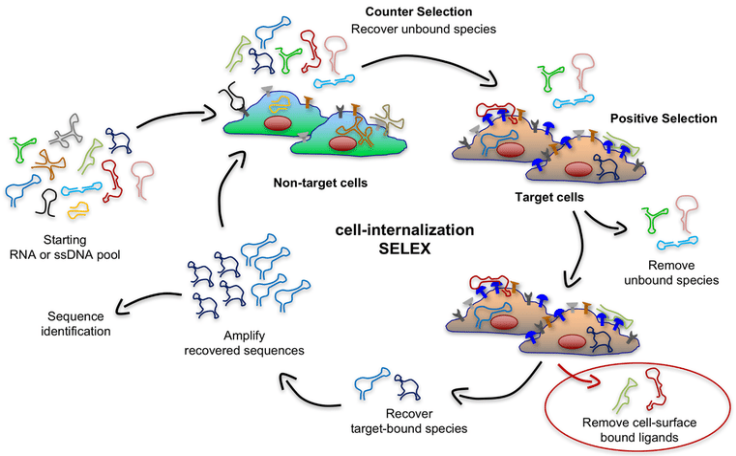

Fig. 2: Schematic illustration of the cell-SELEX. This procedure consists of four main steps for each round of selection: (i) counter-selection by incubating the nucleic acid library with negative cells (green cells) that do not express target antigens, (ii) a positive selection by incubating recovered unbound sequences with positive cells (tan cells) expressing cell-surface antigens (depicted in blue), (iii) recovery of target-bound sequences, and finally (iv) re-amplification of recovered species. (Reprint with permission from (44) Biomedicine 2017)

3D cell SELEX

This process, which is utilised to create the proper Aptamer against the target molecule, combines the three-dimensional [3D] cell culture and cell SELEX methods. Since 3D cell culture replicates or offers the natural cellular environment in which the cell grows, it is used in this method because it creates a physiologically acceptable setting that will aid in the improvement of the research and drug discovery processes. With the aid of magnetic levitation technology, the two-dimensional cell cultures are transformed into the three-dimensional cell structures [45].

Ligand gaided selection [LIGs]

Using this technique, an aptamer is created against a target cell's expressed epitope of interest [46].

Cross over SELEX

The Hicke's laboratory created this technique with the primary goal of creating aptamers with increased efficiency and avoiding creating aptamers against molecules or biomarkers expressed on target cells [47].

Counter SELEX

Negative SELEX and counter SELEX serve comparable functions, however, counter SELEX uses related target compounds as incubation subjects. Jenison *et al.* created the counter SELEX technique in 1994 to increase the specificity of aptamers [48]. Counter SELEX, in contrast to conventional SELEX, includes an additional phase that involves using structurally-similar targets to incubate with aptamers in order to successfully distinguish non-specific oligonucleotides [49, 50]. It should be noted that the usage of various incubation items is the primary distinction between counter SELES and negative SELEX [51].

Capillary electrophoresis SELEX

In general, it takes about more than 15 rounds to obtain aptamers using the conventional SELEX method, which is labor-intensive and time-consuming. In 2004, a modified SELEX method called capillary electrophoresis SELEX (CE-SELEX) was developed [53, 54]. CE-SELEX separates the target bounded sequences from unbound sequences by the difference in electrophoretic mobility, which is a highly efficient separation method.

***In vivo* SELEX**

An *in vivo*-based SELEX technique was created by researchers to produce tissue-penetrating aptamers inside of animal models of the target disorders. Mi *et al.* attempted to choose aptamers inside a tumour of a living organism for the first time in 2010 [55]. With the exception of the selection target, the process for this *in vivo* SELEX is comparable to that of regular SELEX. In mice suffering intrahepatic tumours, a library of RNA aptamers modified with 2'-fluoropyrimidine was administered into the tail vein. The aptamers were then taken out of the liver tumours, amplified, and injected again into more mice carrying the same tumour. They were successful in choosing aptamers against the RNA helicase and p68 that had Kd values in the nano-molar range. Cheng *et al.* injected a 2'-fluoropyrimidine-modified RNA library into the mice in an effort to find aptamers that can cross the blood-brain barrier [56]. Fig. 3 shows the aptamers that were discovered using this method to adhere to brain capillary endothelia and enter the parenchyma.

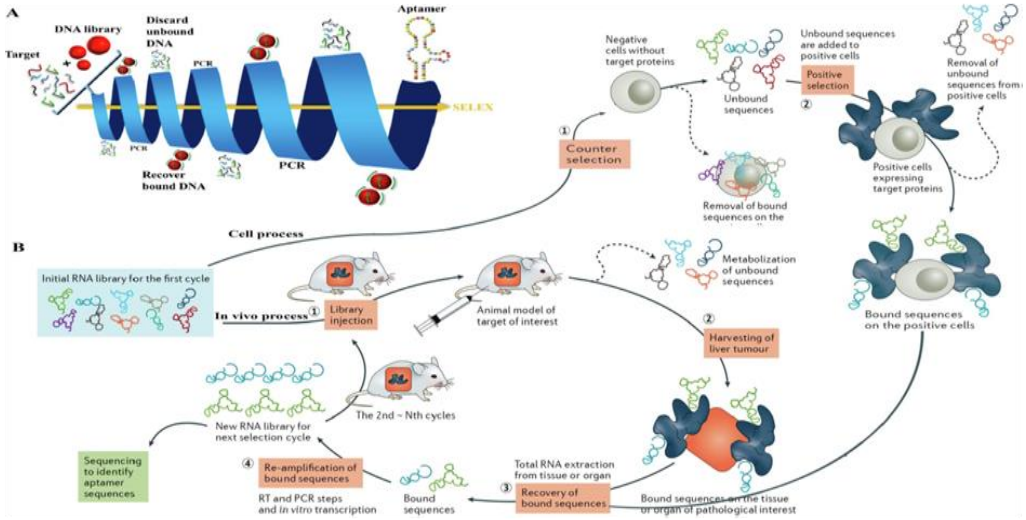

Fig. 3: A) Schematic representation of the SELEX method. An initial DNA library (of typically 10^{14} molecules) is incubated with the solid support-bound target. Unbound DNA molecules are discarded while the active species are recovered, amplified by PCR, and injected into subsequent rounds of selection. The stringency of the selection protocol can bemodulated by altering physicochemical parameters such as concentration, pH, temperature, or buffer composition. At the end of the protocol, the enriched population is sequenced and the individual aptameric sequences evaluated for their capacity at binding to the target (10). B) Cell-process: Step 1 involves counter selection by incubating the RNA library with negative cells that do not express the target protein. Step 2 involves positive selection by incubating recovered unbound sequences with positive cells expressing the target protein. Step 3 involves recovery of target-bound sequences. Step 4 involves re-amplification of recovered species and generation of a new RNA pool for the next selection round. *In vivo* process: After intravenous administration and circulation of an RNA library in the animal model (step 1), the tissue or organ of pathological interest is harvested (step 2) and the bound sequences are extracted (step 3). Subsequently, the recovered RNA sequences arere–amplified to make a new RNA library for the next selection cycle (step 4) (30). Copyright 2018, reprinted with permission from Elsevier, (10) and Copyright 2017, Macmillan Publishers Limited, part of Springer Nature (30)

High-throughput sequencing SELEX

Up until now, traditional sanger sequencing analysis has been the primary technique for determining each individual sequence in the final enriched library. The finished library typically contains thousands of sequences, making it challenging to determine which one is the greatest aptamer. Additionally, the sequences with the highest affinity and specificity are not usually the ones that are most numerous in the final selection phase. The SELEX technique recently adopted High-Throughput Sequencing (HTS) technology [57, 58]. The first feature of HTS-SELEX that stands out is the ability to sequence the library during each round of selection. As a result, enriched sequences are evident at

a much earlier round, saving time. Additionally, fewer selection rounds prevent the potential over-selection-related PCR bias [59]. Cho M *et al.* carried out the first high-throughput sequencing application in SELEX in 2010. Within three rounds, they found aptamers with Kd 3 nM that specifically bind to the PDGF-BB protein. After five rounds of selection, Berezhnoy *et al.* (2012) also used HTS-SELEX to find high-affinity aptamers against the IL-10 receptor [60, 61].

Aptamer based sensor

The aptasensor, which acts as a recognition site and is present over the aptamer, can be created using a variety of techniques and methodologies [62].

Electrochemical biosensors

The electrochemical aptasensors' primary benefits include their high sensitivity, compatibility with cutting-edge microfabrication techniques, intrinsic miniaturisation, and low cost. The manufacturing of electrochemical aptasensors employs a variety of techniques. Some of these include DPV (Differential Pulse Voltammetry), ETS (Electrochemical Impedance Spectroscopy), ECL (Electrogenerated Chemiluminescence), and Potentiometry using ISEs (Ion Selective Electrodes) [63-68]. It is simple to employ aptamers, which are oligonucleotides, as targeted agents in medicine administration [69] and even in the creation of biosensors to identify infectious agents. Aptamers can also target viral proteins linked to various viral infection phases, as illustrated in table 4.

Table 4: Summary of aptamers used in inflammatory and viral disease

S. No.	Aptamer	Target	Action	Reference
1.	Spiegelmers NOX 2149	ORL-1R	Decrease in pain and stress	[66]
2.	DEK-binding	Nuclear chromatin protein	DEK Juvenile idiopathic arthritis	[64]
3.	20–NH2-30-ligand	(RNA) IFN-a	Immunoregulatory	[69]
4.	SE RNA	Hepatitis C virus NS3	Viral proliferation in chronic hepatitis	[71]
5.	DD7, ED1 (RNA)	hNE-specific ligand A	Anti-inflammatory	[69]
6.	LIGAND	1.1 HIV-1	RT Anti-HIV	[64]
7.	Aptamer M. G (RNA)	Acetylcholine receptors	Control of myasthenia gravis	[77]
8.	CD4-specific aptamer 14 (RNA)	Antigen-presenting cells	Immunosuppressant	[79]
9.	ADR58 (RNA)	gp130 receptor	Control of rheumatoid arthritis	[66]
10.	D7, ED1 (RNA)	hNE-specific ligand	Anti-inflammatory	[77]
11.	DEK-binding	Nuclear chromatin protein	DEK Juvenile idiopathic arthritis	[78]
12.	IGEL1.2 and D17.4 (DNA)	Human IgE	Antiallergic response	[78]

Optical biosensors

Fluorescence-based APTA sensors

A fluorophore or nanoparticle that has been combined serves as the common foundation for this optical biosensor. For example, the cocaine-specific Aptamer was able to detect the target by using FRET [Fluorescence Quenching/Fluorescence Resonance Energy Transfer signal between fluorescence and DABCYL moiety [A Quencher] in this method for the fluorescence detection [74].

Colorimetric-based APTA sensors

This approach uses a unique color-changing reagent known as a colorimeter, such as AUNPs or another polymer [75]. In addition to the sensor mentioned above, other sensors, such as those used for SAW (Surface Ascoustic Wave), QCM (Quartz Crystal Microbalance), and microchannel cantilever sensor, have been utilised in conjunction with other types of analytical equipment [76-81].

Characterization of aptamers kinetics

Isothermal Titration Calorimetry (ITC), an approach based on thermodynamics [82], Microscale Thermophoresis Using surface plasmon resonance (SPR) technology, it is possible to characterise the aptamer and its target's affinity and kinetic characteristics in high throughput, real-time, and label-free manners [83]. The laser-based technique known as flow cytometry is frequently used to identify the binding properties of aptamers and entire cells. It can characterise the binding properties of aptamers and targets [84]. A fluorescent dye, such as FITC dye, is used to label the aptamer library before it is combined with the target cell. The level of fluorescence reveals how well the aptamer binds to the selected cell [85]. The ability to examine how aptamers bind to their targets is one of flow cytometry's most notable features.

Diagnostics or bio-sensing potential of aptamers

Bruno *et al.* created the first aptamer utilised as a diagnostic tool in 1999. To find anthrax spores, they used the aptamer chosen against Bacillus anthracic spores [86]. Aptamers have been extensively used to diagnose ophthalmology, cardiovascular illnesses, and cancer diseases up to this point. For instance, Wan *et al.* used aptamers against the common oncogene epidermal growth factor receptor (EGFR), which is overexpressed in many cancer types, to recognise cancer cells [87]. They immobilised anti-EGFR RNA aptamers on the surface of modified glass and discovered that these aptamers could highly precisely and sensitively trap glioblastoma cells. These findings suggested that aptamers could be employed for the early detection of cancer metastasis or for the detection of tumour cells. Two domains are present in the aptamer-based diagnostic tools: the targeting domain (aptamer) and the signalling domain (radionuclide or fluorescence). A DNA aptamer (XL-33) with a Kd value of 0.7 nM that might target metastatic colon cancer cells was chosen by Li *et al.* [88]. To visualise the cancer tissue, they further shortened the aptamer and added fluorescein amidite (FAM) to it [89]. Some example aptamers are sequentially given in table 5 to illustrate the features of recently created aptamers as diagnostic tools for biomedical usage.

Table 5: Examples of recently developed aptamers for the diagnosis of human diseases

Name	Target	Kd (nM)	Sensitivity	Specificity	Reference
Cancers					
SYL3-C	Solid cancer epithelial cell adhesion molecule (EpCAM)	22.8	60%	100% (n = 3)	[68]
XL-33	Metastatic colon cancer cells (SW620) 66.7% (n = 18 non-metastatic colon cancer tissues)	0.7	81.7% (n = 71) metastatic colon cancer tissues)	66.7% (n = 18 non-metastatic colon cancer tissues)	[66]
LXL-1	Metastatic breast cancer cells (MDA-MB-231)	44.0	76% (n = 34)	100% (n = 8 cancer cell lines)	[93]
GMT3	Glioblastoma multiforme cells (A172)	75.3	-	87.5% (n = 8 cancer cell lines)	[69]
yl19	Cholangiocarcinoma cells (QBC-939)	42.4	-	100% (n = 6 cancer cell lines)	[65]
Cardiovascular diseases					
Myo 040-7-27	Myoglobin	4.93	10 pm	-	[27]
Infectious diseases					
2008s	Plasmodium falciparum lactate dehydrogenase	42–59	57 ng/ml	No human LDH recognition	[71]
LmWC-25R and LmHSP-7b/11R	Leishmania promastigote and hydrophilic surface protein	-	100 ng (parasite protein)	-	[72]

Because of its ease of use, sensitivity, and abundance of fluorophores and nucleic acid quenchers, allosteric aptamer-based fluorescence resonance energy transfer (FRET) for the detection of molecular targets represents a superb option. According to a study, a secondary antibody tagged with an easy-to-measure dye or enzyme can be linked to an RNA aptamer identified against the biomarker for inflammation, sepsis, and tissue necrosis known as C reactive protein [90, 91]. With an aptamer-based sandwich immunoassay, it is possible to identify C reactive protein in serum samples from both high-risk (>500 mg/l) and low-risk (1e3 mg/l) patients [92]. Sandwich immunoassays based on aptamers have evolved into high-throughput microarray-based diagnostics through innovation and the development of automated high-throughput aptamer separation [93, 94].

Rationale therapeutics of aptamers targeted drug delivery

The dynamic application of nanoparticle-aptamer technology goes beyond diagnostics to include targeted medicine administration. Delivering medications to cancer cells specifically using nanoparticle aptamer bioconjugates, is one of their most popular applications. Aptamers are being developed as therapeutics for a number of diseases, including cancer treatment, the prevention of Alzheimer's disease-related proteins [95, 96], protection against the pathological prion protein isoforms that cause Creutzfeldt-Jakob disease [97, 98]. Mycobacterium tuberculosis, and the treatment of hepatitis C virus (HCV). The most advanced aptamer in the potential treatment of cancer is AS1411. AS1411 aptamer binds nucleolin on the surface of cancer cells and induces apoptosis [99-102].

An further aptamer known as SM20, which was identified against the plasminogen activator inhibitor-1, has shown *in vitro* therapeutic promise as an antimetastatic drug and may be utilised as an adjunct to conventional chemotherapy for breast cancer [103]. Aptamer nanomaterials have also emerged as promising nanoplatforms for accurate ovarian cancer diagnosis by recognising pertinent biomarkers in the serum and on the surface of tumour cells. Aptamers have been recently isolated for the potential treatment of other cancers such as glioblastoma, T cell leukaemia, and epithelial cancer cells in the breast, colon, lung, ovaries, and pancreas [104, 105]. Additionally, for efficient ovarian cancer inhibition by target protein blocking on tumour cells and focused administration of different therapeutic agents, a list of diagnosis agents and treatments is provided in table 5.

Aptamer-short molecule conjugated systems

An aptamer-doxorubicin physical conjugate was created by Bagalkot *et al.* because doxorubicin can intercalate into aptamers [106]. They employed a prostate-specific membrane antigen (PSMA)-targeting 2'-fluoropyrimidine-modified RNA aptamer, which is mostly expressed on the surface of human prostatic adenocarcinoma (LNCaP) cells. They demonstrated that this combination has great specificity and affinity for PSMA-expressing LNCaP cells. The sgc8c DNA aptamer, which particularly targets T-cell acute lymphoblastic leukaemia cells, and doxorubicin were covalently joined together by Huang *et al.* [107]. As a result, the cellular toxicity of the sgc8c-Dox conjugates to non-target cells was decreased. A doxorubicin conjugated aptamer complex (TLS11a-GC-Dox) against HepG2 cells was recently created by Deng *et al.* [108].

Aptamer-nanomaterial conjugated systems

For targeted drug delivery, Luo *et al.* created an aptamer/hairpin DNA-AuNPs combination as a smart drug carrier. The protein tyrosine kinase 7 (PTK7) DNA aptamer sgc8c was initially assembled onto the surface of the AuNPs. Then, they added more doxorubicin, an anticancer medication, to the hairpin DNA's repeating d (CGATCG) sequence on the surface of the AuNPs. Such a conjugated compound might increase anti-tumor activity while reducing toxicity. A gold nanostar core and an AS1411 anti-nucleolin aptamer make up the nanoconstruct that Dam *et al.* created [109, 110]. Such a nanoconstruct accumulates five times more in invasive breast cancer tumours than in fibrosarcoma tumours in a tumor-specific way and without any acute harm. In 2009, Cao *et al.* created the first aptamer-liposome delivery method [111]. The anti-nucleolin aptamer sequence was originally given a 12-thymine spacer at the 3' end. The chemotherapeutic drug cisplatin (to induce anti-proliferation activity) or the hydrophilic dye calcein (to monitor internalisation) were encapsulated into the liposome core after the spacer was further attached with a cholesterol tag for the immobilisation on a PEGylated liposome hydrophobic surface [112, 113]. They discovered that this combination could administer cisplatin in a way that was particular to cancer cells. Other nanomaterials being utilized in blend with aptamers for designated organization incorporate block polymeric nanoparticles, carbon nanotubes, gold-attractive nanoparticles, Quantum Spot (QD) serum egg whites nanoparticles, and dendrimers displayed in table 6.

5.3. aptamer-RNA conjugated systems

For the purpose of delivering these functional RNAi to the target site, aptamers to be associated with microRNA (miRNA), small interfering RNA (siRNA), and short hairpin RNA (shRNA) have been widely investigated. Mcnamara *et al.* proposed the first aptamer-siRNA chimaera in 2006 [114]. They covalently joined therapeutic siRNAs that target the two survival genes PLK1 and BCL2, which are overexpressed in many patient malignancies, to an RNA aptamer against human PSMA (dubbed A10). The "GL21. t-let" aptamer-miRNA conjugate was created by Esposito *et al.* [115]. The oncogenic receptor tyrosine kinase Axl and the human let-7g miRNA, which functions as a gene-silencing moiety, could both be selectively bound to and antagonised by the aptamer (GL21. t) [116]. To target the suppression of Nonsense mRNA-Mediated Decay (NMD), Soldevilla *et al.* first discovered high-affinity aptamers against CD40 and then coupled CD40 agonist aptamer-shRNA chimaera. Additionally, Fernando Pastor *et al.* [117] demonstrated that costimulatory ligands can be delivered to tumour cells in situ by bi-specific oligonucleotide aptamer conjugates (4-1BB aptamer ligand-PSMA aptamer conjugates).

The advantages of using aptamers to functionalize nanomaterials for combination therapy

Aptamers are particularly ideal molecules to functionalize nanoparticles for actively targeted administration due to their excellent binding specificity and affinity as well as a number of other advantageous characteristics. Although none of the aptamer functionalized nanoparticles have yet been used in a clinical trial or application, multiple preclinical and animal studies have already shown their efficacy in the targeted delivery of anticancer medicines The proof-of-concept study of employing the aptamer to functionalize nanoparticles for actively targeted drug delivery was initially carried out by Farokhzad and Langer *et al.* in 2004 [118]. As a model drug, the authors created poly (lactic acid)-block-polyethylene glycol copolymer nanoparticles with a terminal carboxylic acid functional group (PLA-b-PEG-COOH). After encasing the nanoparticles in rhodamine-labeled dextran, the authors covalently attached the PSMA-targeting A10 RNA aptamer to the nanoparticles.

Zhen *et al.* created an aptamer-functionalized-liposome-CRISPR/Cas9 against Polo-like kinase 1 in prostate tumour cells using a post insertion method [119]. Similar to this, Liang *et al.* chose an aptamer that was unique to osteosarcoma cells and attached it to PEG-PEI-Cholesterol (PPC) lipopolymer that contained plasmids coding for CRISPR/Cas9 and VEGFA gRNA sequences [120]. They demonstrated cell-specific gene editing and tumour reduction. Dendrimers, chitosan, proteins/peptides, or hybrids are examples of other organic nanomaterials that have been applied. Numerous inorganic nanomaterials have also been investigated in this field, including calcium carbonate, zinc oxide, iron, graphene-based materials, gold (Au) compounds, silver (Ag), mesoporous silica, and others. Magnetic nanomaterials, quantum dot-based nanoparticles, and other unique inorganic nanomaterials are examples. Hybrids of organic and inorganic compounds that have been summarised have also been used. Table 7 provides a categorised list of these nanoparticles and nanomaterials together with information on their payloads, targets, associated tumours, etc. [121].

Table 6: Summary of aptamers used in nano-carriers for the treatment of malignant tumour

Nanomaterials	Drug	Aptamer	Target cell lines	Cancer type	Therapy method	Imaging	Reference
Exosomes	Doxorubicin	sgc8	Ramos cells and CEM cells	Lymphoblast	Chemotherapy	Fluorescence	[158]
Organic							
CA-PLGA-b-TPGS NPs	Docetaxel	AS1411	MCF-7	Breast cancer	Chemotherapy	Fluorescence	[145]
$Ru(bpy)_3^{2+}$-SiO2 NPs	miRNA-21	AS1411	MCF-7	Breast cancer	Chemotherapy	Fluorescence	[148]
Poly (ethylene glycol)-poly (caprolactone) NPs	Docetaxel	AS1411	GMT8 U87 cells	Drain glioblastoma	Chemotherapy	Fluorescence	[20]
Poly (ethylene glycol)-poly (caprolactone) NPs	Docetaxel	AS1411	C6 cells	Brain glioma	Chemotherapy	Fluorescence	[21]
Inorganic							
CdTe/CdS quantum dots	Doxorubicin	MUC1	MCF-7	Breast cancer	Chemotherapy	Fluorescence	[157]
Silver (Ag) nanocluster	miR-34a	MUC1	MCF-7	Breast cancer	-	Fluorescence	[158]
Gold (Au)	-	AS1411	A375	Skin cancer	Photothermal therapy (PTT)	Fluorescence	[153]
Mesoporous SiO2 NPs	Doxorubicin	MUC1	MDA-MB-231 Cells	Breast cancer	Chemotherapy	SPECT	[161]
Fe3O4	Doxorubicin	PSMA	LNCaP cells	Prostate-cancer	Chemotherapy	MRI	[161]
Au@ c-Fe2O3 NPs	-	MUC-1aptamer	L929 CHO HT-29	Colon cancer	PTT	MRI	[166]
Fe3O4–Au Nanocomposite	Epirubicin	MUC-1 aptamer	MCF-7 and HT-29	Breast and colorectal cancer	Chemotherapy	Fluorescent imaging	[163]
Fe3O4@carbon	Doxorubicin	sgc8c aptamers	A549	Lung cancer	Chemo–PTT	MRI imaging	[164]
Fe3O4 co-loaded (PEG-PLGA) NPs	Doxorubicin	AS1411	C26 cells	Colon carcinoma cancer	Chemotherapy	MRI	[165]
Au@Ag/–S6 Aptamer		S6 aptamer	A549	Lung cancer	PTT	Fluorescence	[160]
Au nanocage/SiO2		AS1411	MCF-7	Breast cancer	PTT	SERS imaging	[161]

Table 7: Aptamer-mediated functionalized nanoparticles classified by nanomaterials and payloads

	Type of nanoparticles	Payloads	Aptamers	Targets	Cancers	Reference
Lipid based Nanoparticles	Liposomes	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	[162, 131, 164-170]
	PEGylated-liposome	5-FU, Doxorubicin, Anti-BRAF siRNA	5TR1, AS1411, M49, Syl3c, TSA14,	CD200R1, EpCAM, Mucin1, Nucleolin, TUBO cells	Basal cell carcinoma, breast cancer, colon carcinoma, melanoma	[170, 172, 175, 177-178]
	Cationic liposome	miR-139–5p	EpCAM-Ap EpCAM	EpCAM	Colorectal Cancer	[179]
	DOTAP: DOPE liposome	Doxorubicin	SRZ1 Breast cancer	4T1 cells	Breast cancer	[180]
Hydrogel based nanoparticles	MCS nanogel	Doxorubicin	LNCaP-Ap	LNCaP cell	Prostate cancer	[181]
	RNA Hydrogel	siRNA and miRNA	LXL	MDA-MB-231cell	Triple-negative breast cancer	[182]
	DNA Hydrogel	CpG ONT and Doxorubicin	MUC1-Ap	MUC1	Breast cancer	[183]
Chitosan based nanoparticles	Chitosan	SN38	MUC1-Ap	MUC1	Colon cancer	[184]
	Chitosan and HA	SN38	MUC1-Ap	MUC1	Colorectal adenocarcinoma	[179]
	HAS-CS	Paclitaxel	MUC1-Ap	MUC1	Breast cancer	[188]
Dendrimer based nanoparticles	PEG-PAMAM dendrimer Nucleolin	5-fluorouracil, Camptothecin	AS1411	Nucleolin	Colorectal cancer, Gastric cancer	[191]
	DGL-PEG	Doxorubicin, ATP-aptamer	AS1411, Cyt c-Ap	Nucleolin, Cyt c	Cervical cancer	[189]
	ONT-PAMAM dendrimer	Doxorubicin	A9	PSMA	Prostate cancer	[194]
	Dendrimer	MicroRNA	S6, sgc8c	A549 cell, CCRF-CEM	ALL, NSCLC	[193]
	Alkyl PAMAM dendrimer Bcl-xL shRNA AS1411 Nucleolin Lung cancer	Bcl-xL shRNA	AS1411	Nucleolin	Lung cancer	[195]
Polymer based nanoparticles	PF127-_-CD-PEG-PLA	Doxorubicin	AS1411	Nucleolin	Breast cancer	[196]
	pPEGMA-PCL-pPEGMA	Doxorubicin	AS1411	Nucleolin	Pancreatic carcinoma	[197]
	PLL-alkyl-PEI	shRNA	AS1411	Nucleolin	Lung cancer	[198]
	PEI	EpCAM-siRNA	EpCAM-Ap	EpCAM	Breast cancer, retinoblastoma	[199]
	PLA-PEG	Rhodamine-labeled dextran	A10	PSMA	Prostate cancer	[201]
	PCL-MMA/MPEG-MASI	Doxorubicin	EpCAM-Ap	EpCAM	Colorectal cancer	[200]
	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	[20,42,191,203,204]
	H40-PLA-PEG	Doxorubicin	A10	PSMA	Prostate cancer	[202]
	PLGA-PEG	Cisplatin, Docetaxel, Doxorubicin, Gemcitabine, Paclitaxel, Salinomycin, Vinorelbine, PI3K-mTOR inhibitor, anti-miR-21, and	A10, A15, AS1411, C2NP, EpCAM-Ap, Gint4. T, PSMA-Ap, S1.5, Wy5a	CD30, CD133, EpCAM, HPA, Nucleolin, PC-3 cell, PGFR_, PSMA	Breast cancer, glioblastoma, glioma, large cell lymphoma, lung cancer, NSCLC, osteosarcoma, cisplatin-	[72,194,206, 182]

	Type of nanoparticles	Payloads	Aptamers	Targets	Cancers	Reference
		cisplatin,			resistant ovarian cancer, prostate cancer, TNBC	
	PF127-β-CD-PEG-PLA	Doxorubicin	AS1411	Nucleolin	Breast cancer	[200]
	PEI EpCAM-siRNA	EpCAM-siRNA	EpCAM-Ap	EpCAM	Breast cancer retinoblastoma	[203]
	PEG-PCL	Docetaxel	AS1411, GMT8, S15	Nucleolin, NSCLC, U87 cells	Glioblastoma, glioma, lung cancer	[210, 211, 214]
	HPAEG	Doxorubicin	AS1411	Nucleolin	Breast cancer	[212]
	PβAE and PLGA	Epirubicin and antimir-21	5TR1 MUC1 Breast cancer	MUC1	Breast cancer	[200]
	PBABT	Docetaxel	HER2-Ap	HER2	Ovarian cancer	[202]
	PLGA, PVP	Doxorubicin	AS1411	Nucleolin	Lung cancer	[209]
	M-PLGA–TPGS	Docetaxel	AS1411	Nucleolin	Cervical cancer	[218]
Protein/peptide based nanoparticles	Protamine (HSA)	Doxorubicin, ALK-siRNA	CD30-Ap	CD30	Lymphoma	[219]
	Elastin-like polypeptide	Paclitaxel	S2.2	MUC1	Breast cancer	[221]
	Albumin	Cisplatin, Curcumin, Doxorubicin	AS1411, EGFR-Ap, HB5	EGFR, HER2, nucleolin	Breast cancer, cervical cancer	[147, 85, 240]
	Human IgG	Genistein, miRNA-29b	MUC1-Ap	MUC1	NSCLC	[222, 223
Nucleic acid based nanoparticles	Lipidated GC-rich DNA hairpin	Doxorubicin and 2',6',-dimethyl-azobenzene	trCLN3	cMet	cMet-expressing lung cancer	[224]
	Aptamer DNA	Antisense ONT against P-gp	sgc8c	CCRF-CEM cell	ALL	[212]
	DNA dendrimer	Epirubicin	MUC1-Ap, AS1411-Ap	MUC1, AS1411	Breast and colon cancers	[225]
	DNA nanotube	Doxorubicin	C2NP	CD30	Human anaplastic large CD30 cell lymphoma	[241]
	DNA icosahedra	Doxorubicin	MUC1-Ap]	MUC1	Breast cancer	[26]
	DNA nanotrain	AKT inhibitor, DAU, DOX, DNR, EPI, Gold	AS1411, LZH5B, Sgc8, TA6	CD44, HepG2 cell, nucleolin, PTK7	ALL, Breast cancer stem cell, cervical cancer, liver cancer	[227, 228, 188, 192]
	3WJ-RNA	Doxorubicin	Endo28	Annexin A2	Ovarian cancer	[229]
	DNA Holliday junction	Doxorubicin	AS1411	Nucleolin	Colon cancer	[220]
	DNA	ALK-siRNA, Doxorubicin, Paclitaxel	CD30-Ap, Gint4. T, GMT8, Sgc4f, Sgc8, TC01	Cancer cells, CD30, PDGFR_, PTK7, U87MG cell	ALCL, ALL, Glioblastoma	[231, 238]
	DNA nano-ring	Doxorubicin	MUC1-Ap	MUC1	Breast cancer	[232]
	DNA origami	Antisense ONT, doxorubicin	MUC1-Ap MUC1 MDR cervical cancer	MUC1 MDR	cervical cancer	[187]
Nucleic acid and peptide hybrids	PAM (peptide +DNA ON)	Peptide	C10.36	HBLL	B-cell leukemia	[236]
	KLA-DNA micelle	Doxorubicin+KLA	MUC1-Ap	MUC1	Breast cancer	[132]
	ssDNA-ELP	Docetaxel	MUC1-Ap	MUC1	Breast cancer	[216]
Chitosan and lipid hybrids	Chitosan-liposome	Erlotinib	EGFR-Ap	EGFR	EGFR-mutated cancer cells	[213]
	Chitosan-liposome	PFOB and Erlotinib	EGFR-Ap	EGFR	NSCLC	[238]
Polymer and chitosan hybrids	PLGA-chitosan	Epirubicin	5TR1	MUC1	Breast cancer, colon carcinoma	[110]
	Chitosan-ss-PEEUA	TLR4-siRNA, AS1411 Nucleolin	AS1411	Nucleolin	Lung cancer	[240]
Polymer and lipid hybrids	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	[216]
	PLGA-lecithin-PEG	Paclitaxel, Curcumin	AS1411, EpCAM	Nucleolin	Breast cancer, colorectal adenocarcinoma	[52]
	DOTAP, PLGA, cholesterol, Mal-PEG	P-gp siRNA	A6	HER2	DOX-resistant breast cancer	[241]
	Lipid-PLGA	All-trans retinoic acid	CD133-Ap	CD133	Lung cancer	[150]
	PLGA-lipid-PEG	Docetaxel	XEO2 mini	PC3 cells	Prostate cancer	[243]
	Lipid-polymer liposome	siRNA	A6	HER2	Breast cancer	[244]
Quantum dot based nanoparticles	QD-PMAT-PEI PSMA	siRNA	PSMA-Ap	PSMA	Prostate cancer	[18]
	Quantum dots	None	S15	NSCLC	Lung cancer	[159]
	Lipid-quantum dot	siRNA	EGFR-Ap	EGFR	Triple-negative breast cancer	[145]
	PEG-aptamer micelle	Aptamer	FKN-S2	Fractalkine	Colon adeno-carcinoma	[123]
Other organic Nanoparticles	Atelocollagen	MicroRNA	A10–3.2	PSMA	Prostate cancer	[58]
	Diacetylene-PEG	None	ACE4	Annexin A2	Breast cancer	[56]
	Ursolic acid	Doxorubicin	HER2-Ap	HER2	HER2-carrying cells	[125]
	Tocopheryl PEG-PβAE	Docetaxel	AS1411	Nucleolin	Ovarian cancer	[75]
	TD-PEC-chitosan	miR-145	AS1411	Nucleolin	Breast cancer	[139]
	LP-DNA	SATB1 siRNA	EGFR-Ap	EGFR	Choriocarcinoma	[151]
Inorganic Nanoparticles	Silver-PEG	Irradiation	AS1411	Nucleolin	Glioma	[246]
	ZnO	Doxorubicin	S2.2	MUC1	Breast cancer	[90]
	Gold	Anti-miR-155, Antisense ONT, Daunorubicin, Doxorubicin, TMPyP4, PTT	A9, AIR-3A, AS1411, As42, CD30-Ap, CD33/CD34-Ap, KW16–13, UC1-Ap, sgc8c, U2	CCRF-CEM, CD30, CD33/CD34, EGFR, Ehrlich's ACC, IL-6R, MCF10CA1h, MUC1, nucleolin, PSMA	ALL, AML, breast cancer, cervical cancer, Ehrlich carcinoma, glioblastoma, human breast duct carcinoma, lymphoma, lung cancer, prostate cancer	[245, 129, 87]
Other inorganic nanoparticles	Gd: SrHap	Doxorubicin	AS1411	Nucleolin	Breast cancer	[236]

	Type of nanoparticles	Payloads	Aptamers	Targets	Cancers	Reference
Organic and inorganic hybrids	BSA-PEG-Fe3+	Mn, Doxorubicin	Glut-1-Ap	Glut-1	Liver cancer	[131]
	MOF-UCNP	Doxorubicin	AS1411	Nucleolin	Breast cancer	[213]
	Aminopropyl MSN	Safranin O	MUC1-Ap	MUC1	Breast cancer	[246]
	PDA/PEG-coated MSN	DM1	EpCAM-Ap	EpCAM	Colorectal cancer	[221]
	Gold-liposome	Docetaxel, Morin	AS1411, S2.2	Nucleolin, MUC1	Breast cancer, gastric cancer	[247, 239]
	Albumin-IONP/GNP	Doxorubicin	AS1411	Nucleolin	Breast cancer	[133]
	CaCO3 and protamine	CRISPR-Cas9 plasmid	AS1411	Nucleolin	NSCLC	[248]
	NMOF	Doxorubicin	AS1411, VEGF-Ap	Nucleolin, VEGF	Breast cancer	[249]
	β-CD-capped MSN	Doxorubicin	HApt	HER2	HER2-positive cells	[133]
	TiO2 nanofiber with BSA	None	AS1411	Nucleolin	Breast cancer CTCs	[206]
	PEG-Au-PAMAM	Curcumin	MUC1-Ap	MUC1	Colon adenocarcinoma	[191]
	MPC-PAA/PEI	Doxorubicin	MUC1-Ap	MUC1	Breast cancer, lung cancer	[221]
	Aminopropyl MSN	Safranin O	MUC1-Ap	MUC1	Breast cancer	[160]
Others type	Ag-MOF-RBCm	Doxorubicin	CD20-Ap	CD20	B-cell lymphoma	[250]
	Micro-emulsion	Shikonin and docetaxel	AS1411 and HA	Nucleolin and CD44	Glioma	[180]
	Upconversion nanoparticle	Protoporphyrin IX	AS1411	Nucleolin	Cervical cancer, lung cancer	[251]
	RBC membrane	Doxorubicin, siRNA	AS1411	Nucleolin	MDR breast cancer	[252]
	FO-loaded MOF-RBCm	Using PDT and CDT effects	AS1411	Nucleolin	KB Cell Line	[253]
	NIR PLN	Afatinib	MAGE-A3	MAGE	NSCLC	[254]
	Cationic nanobubble	FoxM1 siRNA	A10–3.2	PSMA	Prostate cancer	[74]

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.

Future perspectives

Significant challenges that these restorative techniques face are discussed below for clinical interpretation. The limited choice of aptamers for clinical usage is one issue right away. Aptamers are single-stranded, short nucleic acids that have a propensity to debase in a nuclease-containing physiological environment. Meanwhile, *in vitro* selection was used to create the majority of aptamers in the literature. The likelihood of losing their affinity in the physiological milieu *in vivo* is high. As a result, novel SELEX procedures and aptamer stabilisation techniques are urgently required. Additionally, nothing is known about the *in vivo* pharmacokinetics, pharmacodynamics, and off-target consequences of aptamer-conjugated medicinal compounds.

Aptamer-functionalized systems are likely to acquire novel properties in size, structure, and surface charge compared to conventional materials-based nanomedicines. These traits could affect cellular uptake, biodistribution, metabolism, and excretion *in vivo*. Only a small number of studies have, to date, evaluated these therapeutic systems *in vivo*, and different experimental paradigms for the same nanocarriers have produced inconsistent results [122]. As a result, trustworthy and uniform animal models ought to be developed to enable systematic and widespread *in vivo* assessments of treatment candidates with aptamers attached [123].

Prior to conducting clinical trials, the biosafety issue around aptamer-based nanomedicines needs to be resolved. As aptamers for foreign nucleic acids may carry some hazards of genome insertion, it is important to comprehend immunological reactions. Additionally, some materials that have been functionalized by aptamers have cytotoxicity built right in. Systematic toxicity analyses of potential aptamers-integrated therapeutics must be carried out to guarantee biosafety for clinical trials, whereas artificial intelligence (AI), which includes machine deep-learning techniques, may be a useful tool for overcoming the aforementioned issues in the near future [124, 125]. Whatever the challenges, efforts are being undertaken to solve many of these problems. For example, researchers developed a number of material change and circularization techniques for aptamers that are susceptible to nuclease corruption in order to improve their serum strength, some of which essentially stabilised aptamers for lengthy *in vivo* research. With *in vivo* advancement techniques, progress has also been made in identifying potent aptamers.

Inferences of aptamers in clinical trials

Pegaptanib, which has been used to treat age-related macular degeneration, is the first commercial and therapeutic example of the usage of aptamers [126]. Antagonising vascular endothelial growth factor is what this aptamer does. Clinical models, however, have demonstrated that this aptamer has no significant impact on oncology applications. However, effective aptamers have been created for the treatment of cancer, such as NOXA12 and AS1411, which target nucleolin and have good clinical activity [262]. Due to its excellent nuclear resistance, the NOX-A12 aptamer with L-form also has a good half-life after 4 to 6 mo of treatment [128, 129]. The aptamer NOX-A12's clinical activity in the treatment of hematologic malignancies demonstrates that it not only decreased the receptivity of multiple myeloma cells to the bone marrow niche microenvironment but also successfully prevented their chemotaxis towards CXCL12 and decreased drug resistance by mediating cancer cell adhesion [130]. The effectiveness of this aptamer in combination with pembrolizumab for the treatment of metastatic colorectal and pancreatic cancer is still being investigated. Table 9 includes a summary of clinical activities involving aptamers that have been approved.

Table 9: Advance aptamers in clinical and preclinical trials

S. No.	Aptamer	Nucleotide	Target	Disease	Reference
1.	BT200	RNA	vWF, Factor VIII	von Willebrand disease Hemophilia A	[263]
2.	NU172	DNA	Thrombin	Heart	[261]
3.	EYE001	RNA	VEGF	Macular degeneration	[261]
4.	Zimura	RNA	Anti-c5	Age-Related Macular (pre-clinical	[256]
5.	Pegnivacogen	RNA with 50 -PEG and 30 inverted dT	Coronary artery disease Phase III completed Regado Biosciences	Phase III completed Regado Biosciences	[258]
6.	68Ga-Sgc8	DNA	PTK7 (CCK4)	Colorectal cancer	[264]
7.	ARC1779	DNA	vWF	Thrombotic thrombocytopenic purpura	[260]
8.	REG1	RNA	Coagulation Factor IX	Coronary Artery	[263]
9.	NOX-E36	RNA	CCL2	Type 2 Diabetes mellitus	[257, 262]
10.	AS1411	DNA	Nucleolin Acute myeloid leukemia (AML)	Nucleolin Acute myeloid leukemia (AML)	[262]
11.	E10030	DNA	PDGF	PDGF Age-Related Macular	[258, 259]

CONCLUSION

Despite some gaps in their development for clinical applications, aptamers will be widely used in virus detection and therapy in the near future thanks to the development of new tools and the fusion of high-throughput sequencing with high-throughput binding analysis. Aptamers with high affinity and specificity for clinical use will also become more and more accessible and quick. A good targeting ligand for targeted therapy is an aptamer because of its high affinity and specificity. Different aptamer-based drug delivery techniques have been created, such as aptamer-chemotherapy agents, aptamer-siRNA/shRNA/miRNA, aptamer-antibody, aptamer-enzyme, and aptamer-nanoparticles, to deliver the drug precisely to the expected sites, reducing the risk of side effects brought on by the off-target effects.

ABBREVIATIONS

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, PGFR-platelet-derived growth factor receptor, P-gp P-glycoprotein, PLA poly (lactic acid), PLGA poly (lactic-co-glycolic acid), PLK1 Polo-Like Kinase 1, PLL poly (L-lysine), pPEGMA-PCL-pPEGMA poly(poly(ethylene glycol) methacrylate)-poly(caprolactone)-poly(poly(ethylene glycol) methacrylate), PTK7 protein tyrosine kinase-7, PTT Photothermal therapy, PVP poly (N-vinylpyrrolidone), QD quantum dot, RBCm red blood cell membrane, SATB1 special AT-rich sequence binding protein 1, SPION superparamagnetic iron oxide nanoparticles, SPMFN Superparamagnetic Ferroarabinogalactan Nanoparticles, TAG-72 tumor-associated glycoprotein 72, TD thiolated dextran, TiO2 titanium dioxide, TLR Toll-like receptor TLR4-siRNA, TM-JM1/2 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-_-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-cyclodextrin, 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, also known as T-cell 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 dendrigraftpoly-L-lysines, DOTAP 1,2-dioleoyl-3-trimethylammonium-propane, 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, FGFR1 fibroblast growth factor receptor type-1, FMSN fluorescent mesoporous silica nanoparticle, FN fibronectin, FO Ferric oxide, FoxM1 Forkhead box M1, Gd: SrHap 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 heparinase, HPAEG poly(2-((2-(acryloyloxy)ethyl)disulfanyl)ethyl4-cyano-4-(((propylthio)carbonothioyl)-thio)-pentanoate-co-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-(methacryloxy)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), MSN Mesoporous silica nanoparticle, mTEC mouse tumor endothelial cell, MDR multiple drug resistance, ONT oligonucleotide, PAA polyacrylic acid, PAM Peptide amphiphile micelle, PAMAM polyamidoamine, PBABT poly (butylene adipate-co-butylene terephthalate), PCL poly (ε-capro-lactone), MUC1 Mucin-1, NHS N-hydroxysuccinimide, NIR PLN near infrared-persistent luminescence nanomaterials, NMOF amino-triphenyl dicarboxylate-bridged Zr4+metal-organic framework nanoparticle, NSCLC non-small cell lung cancer.

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AUTHORS CONTRIBUTIONS

All authors are contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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