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REVIEW ARTICLE **OPEN ACCESS**

Multi therapeutic and drug delivery approaches of aptamers

Satya Lakshmi S, Ramya R*, Srinivasa Rao Y
Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Duvvada, Visakhapatnam-530049, India.
***Corresponding author's :** E mail: satyalaxmi148@gmail.com

ABSTRACT
In Greek "meros" means "part [smallest unit of repeating structure]" and in latin "aptus/apto" means "to fit. Aptamers are single stranded nucleic acid molecules that bind and inhibit proteins and are commonly produced by systemic evolution of ligands by exponential enrichment [SELEx]. Aptamers undergo pharmacological revesion, and aptamers undergo specific affinity, and therapeutic half life. Modify each drug for a selected clinical trials need. 25 years ago, primarily therapeutic aptamer was described. Now single apatamer has been accepted by by FDA for clinical use. Various others are in clinical or preclinical enlargement. Aptamers are mostly created by selecting them from a large random sequence pool, but natural aptamers also obtain in ribo-switches. With reference to therapeutics in terms of synthetic accessibility and size modified by medicinal chemistry. Aptamers shows important advantages. Although these properties, aptamers are slow to succeed the market place, with just one aptamer based drug receiving recognition earlier. Different types of apatemers presently in beforehand which will helps to changes how DNA therapeutics is noticed. It is subjected to future apatamers will progressively find usage together with other therapeutic molecules. During this review, the overall properties of aptamer, the benefits and limitations of aptamers, the principle and procedure of SELEX, and aptamers in therapeutics and drug delivery are summarized.
KEY WORDS: *Aptamers, SELEX, Drug delivery, Riboswitches, Targeted therapy*

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INTRODUCTION

Therapeutic agents accepted by food and drug administration for the treatment of various human pathologies show reduced therapeutic index and producing significant toxicity and side effects associated to the non-specific bio-distribution within the body because of non selectivity for diseased cells. Therefore, the research of strategies for therapeutic targeted delivery has become one among the foremost important challenges field. The essential thought is to use targeting ligands and specifically recognizes diseased cells .and they act as carriers for therapeutics. So as to enhance the efficacy and therefore the suitability for the treatment. [1, 2].

Aptamers differ from antibodies, but they impersonate properties of antibodies during a sort of diagnostic format. antibodies have made contributions towards the advance of diagnostic assays and in most diagnostic tests commonly used in clinics now a days. Aptamers are receiving attention for their novel properties, like highly selective and specific target recognition and binding [3].

General properties of aptamer

1. Binding affinity in low nanomolar to picomolar range.
2. Entire selection is a chemical process carried out in vitro and can therefore target any protein.
3. Can select few ligands under a verity of conditions for in vitro diagnostics.
4. Iterative rounds against known target, limit screening process.
5. Invariable activity regardless of batch synthesis.
6. Pharmacokinetic properties can change on demand.
7. Target site of protein is determined by investigator.
8. Wide varieties of chemical modifications to the molecule for diverse functions.

Merits of aptamers

1. Stable products are produced.
2. Aptamers penetrate tissues and cells.
3. It performs simple chemical modifications.
4. It generates enzymatic aptamers.

5. It is non immunogenic targets.

Drawback of aptamers

1· Pharmacokinetic and systemic properties are inconsistent and they hard to predict.
2· Small size aptamers are permitting to renal filtration.
3. Aptamers have a shorter half life.
4· Unmodified aptamers are sensitive to serum degradation

Aptamers, originated from the start of the 1990s, are single-stranded DNA or RNA with the power to bind to non-nucleic acid target molecules, like peptides, proteins, drugs, or maybe whole cell with high specificity and high affinity [4]. As we all known, antibodies, peptides, small molecules and aptamers can all play the role of ligands. The enzymatic degradation of peptides resists their own in vivo application [5]. Compared with the ligands above, the aptamers display a better binding affinity to targets with equilibrium constant (Kd) values within the nanomolar range [6].

SELEX approach in aptamer identification

SELEX technology is an in vitro process wont to identify aptamers from large pools of diverse oligonucleotides, which may function as specific ligands for a given target [7] un systemically sequence oligonucleotide library is synthesized during a typical SELEX experiment that period 20-100 residues long .The pool has usually contain between 1×10^{13} to 1×10^{15} members, even though its assert that even less diverse pools will given useful aptamers [8]. Single stranded RNA molecules is ready by the in vitro transcription of double stranded DNA templates in RNA SELEX by Using a recombinant T7 RNA polymerase [9]. Usually library of single stranded DNA molecules is prepared by the strand separation of double stranded PCR products in DNA SELEX [10].

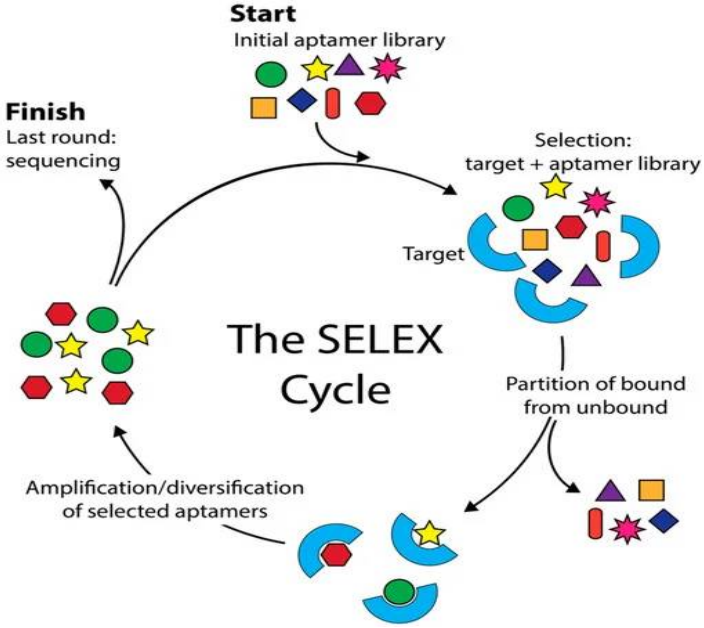

Fig. 1: Schematic representation of SELEX (Systematic Evolution of Ligand by Exponential enrichment)

APPLICATIONS OF APTAMERS

a. Aptamers potential applications in nanotechnology

The ability of RNA or DNA aptamers in targeted drug delivery because these molecules assembled with therapeutic agents. Early diagnosis of disease depends on the specificity of the molecular probes and but also on the detection sensitivity. Their predictable functional groups and structures for the chemical modification, aptamers can be used in advance signalling mechanism mainly development of diagnosis and disease treatments. Some cancer cells, especially those within three earlier stage and disease development, may have a really low density of targeting on the cell surface and available for detection. Aptamers have the ability to target the tumor cells and to transport small molecules, like proteins, drugs or siRNA, through the microvasculature or the tumor interstitial tissue because of their smaller molecular size [11, 12]. Additionally, by taking advantages of straight forward synthesis and their chemical modification, these aptamers are often conjugated to functional group with relative ease enabling there use as effective.

b. Aptamers as potential therapeutic agents [13]

Aptamers are effectively used for therapeutic application like neoplastic diagnostics and cell detection [14] and targeted therapy [15] also as sorting and enrichment [16]. The generation of a group of DNA

aptamers for various sorts of cancer cells these were employed in treatment of various carcinomas including small-cell lung, non-small-cell lung (NSCLC), acute myelogenous leukemia (AML), liver and carcinoma, also as virus-infected cells [17]. Employing a similar strategy, DNA aptamers for mesenchymal stem cells [18] and live bacterial cells has been developed by research groups during past 2years. Because of superior targeting performance aptmers and aptamer assemblies are validated as essential molecular tools in the areas of anti-cancer, anti-infectives, anticoagulation, anti-inflammation, anti-angiogenesis, anti-proliferation, and immune therapy [19, 20]. Pfizer's Macugen® (pegaptanib), an aptamer-based anti-VEGF treatment for age-related degeneration, was approved by USFDA in 2004 supported findings from two clinical trials involving 1200 patients and every one subtypes of neovascular AMD [21]. Finally this review summarizes an inventory of therapeutic aptamer targets that are currently in clinical or pre clinical studies and offers optimism that the long term potential of aptamers therapeutics remains bright.

Cancer

Targeted therapy by various inhibitors such as antibodies and small molecular substances is most common in treatment of cancer Aptamers are terminal in targeted therapy with reference to specificity. Within the early years of aptamers, few aptamers were generated against cell surface proteins [22]. Aptamers that have shown promise anti-cancer therapeutics are summarized below.

Prostate-specific membrane antigen

The fascinating attribute of a cancer target is specificity, and one among the simplest examples is prostate specific membrane antigen (PSMA), a surface protein expressed in healthy prostate, prostatic adenocarcinoma, and therefore the vasculature of a spread of solid tumors. PSMA has been studied broadly as a tumor marker also as a target for imaging and therapy. PSMA is a folate hydrolase, considered as a prostatic adenocarcinoma marker, but a current study approved that an optimized, truncated version of the A9 aptamer inhibited prostatic adenocarcinoma invasion and migration in in vitro [23]. Daily injection of aptamer inhibited the event of bone metastases during a mouse model in which PSMA- expressing cells were deposited by intra-cardiac injection. Most studies using the PSMA aptamer, however, have exploited the very fact that PSMA is internalized. The PSMA aptamer has been conjugated on to the peptide toxin gelonin [24] and to Dox, which is understood to intercalate into DNA [25] for delivery and PSMA-expressing cells were killed. To extend the quantity of payload which will be delivered, PSMA aptamers are conjugated to varied nanomaterials, including quantum dots, iron oxide nanoparticles, and polymeric (PLGA-block-PEG) nanoparticles [26]. The PSMA aptamer was also deliver sRNA targeting nonsense-mediated messenger RNA increase antigen expression and presentation in prostatic adenocarcinoma cells and inhibit tumor growth in immuno-competent mice [27].

MUC1

Aberrantly glycosylated sorts of the mucin glycoprotein family are a crucial class of tumor surface markers, and MUC1 especially is over expressed on several epithelial cancer cells but not normal cells. DNA aptamers are developed that bind MUC1 glycoforms, one among which was conjugated to the photodynamic therapy agent chlorin e6. The aptamer delivered the agent to a spread of MUC1 + neoplastic cell lines, including breast, colon, lung, ovarian, and pancreatic cancers, which were killed by light activation *in vitro*. MUC1 has also been labeled with 99mTc for molecular imaging. When imaged by autoradiography, the MUC1 aptamers penetrated xenograft tissue quickly and uniformly but had relatively short t½ values, which can get to be improved if this approach is employed for radionuclide therapy [28].

Human epidermal growth factor receptor 2

Another well-known cancer target is that the EGF receptor family member human epidermal growth factor receptor 2 [HER-2 (erbB2)], which is amplified and over expressed during a significant proportion of breast cancers also as other epithelial tumors. HER-2 monoclonal antibodies, like trastuzumab, are widely used clinically. The higher characterized family member EGFR is overexpressed in many solid tumors and has also been targeted by monoclonal antibodies, like cetuximab. Both HER-2 and EGFR have also been utilized in receptor mediated endocytosis for antibody-drug conjugates. A DNA aptamer generated to bind HER-2 inhibits growth of gastric cancer cells *in vitro*, and intra-peritoneal delivery in mice of a trimeric version of an equivalent aptamer (but not the monomer) inhibited growth of equivalent cells as xenografts [30].

(ii) Eye disorders

Vascular endothelial growth factor

Neovascularization may be a pathologic process seen in age-related degeneration (AMD), retinopathy of prematurity and diabetic retinopathy. Vascular endothelial growth factor (VEGF) is up-regulated altogether three diseases. Three RNA aptamers were isolated against VEGF165 with binding affinities (Kd) between 5 and 50 pM. *In vivo* experiments in adult guinea pigs determined that the aptamer could inhibit VEGF mediated capillary leakage by 58%. Pharmacokinetic experiments were performed in rhesus

monkeys by conjugating the 5'-end of the aptamer to a 40-kD PEG molecule. This optimized aptamer, renamed as NX-1838, determined t½ of 9.3 h and reaches peak concentrations of 4.9 μg/ml at 8-12 h. During a rat model of retinopathy of prematurity, NX-1838 reduced retinal neovascularization by 80% [31]. Phase I studies demonstrated no significant risks with one intravitreal administration of the aptamer. Furthermore, evaluation of patients with diabetic retinopathy 3 months after injection revealed no deterioration in vision and, in fact, a 27% improvement in vision of three lines or greater when examined by the first Treatment of Diabetic Retinopathy Study (ETDRS) chart [31]. The clinical test (phase II) clinical trial was a multi-injection study with or without photodynamic therapy, which was the quality of care treatment at the time. of these treated with NX-1838, now called pegaptanib, 87.5% had stable vision or improved vision and 25% demonstrated 3 lines or greater improvement by ETDRS. Of these patients who received both pegaptanib and photodynamic therapy, 60% had a 3 lines or greater visual improvement by ETDRS at 3 months [32].

The beneficial effect of pegaptanib was seen as early as 6 weeks after treatment compared to negative controls [33]. Side effects of pegaptanib noted within the clinical trials included endophthalmitis, increased pressure , and rare cases of anaphylaxis and anaphylactoid reactions [34]. These results led to pegaptanib being the primary aptamer-based drug to receive approval from the FDA to treat degeneration in 2004. Since then, pegaptanib has been largely replaced by the antibody-based therapy ranibizumab that recognizes more isoforms of VEGF. However, it's important to recognize that pegaptanib recommended for intraocular antiangiogenesis treatment and validated aptamer-based drug therapy.

More recently, two additional targets are validated to treat AMD. Pegpleranib may be a platelet-derived protein DNA aptamer that has been tested clinically with ranibizumab, an anti-VEGF antibody. A phase I clinical trial study demonstrated improved vision compared to ranibizumab alone. A phase II clinical trial dose escalation study of the 2 drugs showed similar results [34].

(iii) Aptamers as delivery agents

Aptamers are often designed as targeting ligands, particularly when generated by cell-based SELEX, and may differentiate diseased cells from healthy cells, thus enabling the selective delivery of therapeutic compounds to focus on cells. The emerging integration of aptamers with nanotechnology and chemical biology is envisioned to supply more versatile target-specific molecules, stimulate further new diagnostic and therapeutic nanotechnologies, and supply significant potential for several research and clinical applications within the near future. Compared to applications of antibodies, aptamer research remains in its beginning, but developing at a fast pace [35].

(iv) Aptamer based NPs for targeted drug delivery applications

The SELEX method is an efficient affinity selection technique and considered as a combinatorial identification methodology. Recent studies have mentioned that the cell-specific markers comprise membrane-bound molecules where they are doing not symbolize the molecular tertiary structure in membranes. Moreover, many approaches were made on recombinant cells to defeat this loop hole by over expressing marker proteins using whole cell within the procedure of SELEX, also referred to as CELL-SELEX. CELL-SELEX method which is extended from the normal SELEX procedure. Hence, selection of aptamers depends on the effectiveness of the precise separation of affinity targets. Generally, these approaches benefited with a limited number of aptamers which are used currently within the applications of targeting Tenascin-C, prostate-specific membrane antigen (PSMA), gp120, nucleolin, transferrin, mucin-1 protein, tyrosine kinase-7 (PTK-7), immunoglobulin heavy Mu chain. HIV-infected cells specific aptamers also are used for targeted drug delivery approach [36]. Within the recent literatures, new cell-specific aptamers are reported for brand new perspectives for the drug delivery applications. Hence, more number of studies is expected on several cell types' specific drug delivery applications within the near future [37].

Protein tyrosin kynase7 (PTK7)

PTK7 may be a membrane bound receptor tyrosine kinase-like molecule. It's over-expressed in colon carcinomas and is additionally referred to as colon carcinoma kinase-4. Although it contains a catalytically inactive tyrosine kinase domain, it's been suggested to retain a task as a sign transducer in some tumors types [38]. A DNA aptamer that binds to PTK7 was developed by Shangguan *et al*., [39]. Ramos (human Burkitt's lymphoma) cells were used for counter selection to stop the enrichment of DNA aptamers that would recognize common molecules present on the surface of both cell lines. A 41-nt aptamer sgc8c that demonstrated remarkable particularity in terms of binding to the CCRF-CEM cells was further characterized [39]. Using protein purification methods, the target that sure to the aptamer was isolated and subsequently identified by mass-spectrometric analysis to be PTK7 [40]. In subsequent studies done by an equivalent group. It has been demonstrated that the aptamer sgc8c is internalized into target cells [41].To construct a biodegradable drug-delivery vehicle the sgc8c aptamer was conjugated to

the surface of a viral capsid protein (MS2) by using chemo-selective oxidative coupling reaction. The inside of the viral capsid was modified and linked to the AlexaFluor 488 maleimide so as to detect it in cell-binding assays. The binding of the aptamer-cojugated viral capsid to the targeted Jurkat T leukemia cells is explained by flow-cytometric analysis. Using confocal technique it had been established that the capsids were internalized into the cells and co-localized with a lysosomal marker (Low Density Lipoprotein). As another confirmation of internalization, Kang *et al*., [42] recently used sgc8-conjugated liposome nanostructures as a platform to deliver low relative molecular mass dextran conjugated to FITC as a model drug into CEM-CCRF cells for confocal imaging. More recently, Taghdisi *et al*., [43] used the sgc8 aptamer to deliver daunorubicin, another anthracycline chemotherapeutic agent; to PTK7 expressing acute lymphocytic leukemia T cells (Molt-4). Flow cytometric analysis demonstrated that the sgc8-daunorubicin complex was internalized by the Molt-4 but not by the control U266, which is a PTK7 negative cell line. As compared to the daunorubicin, the aptamer-drug complex was less toxic to U266 cells. In yet one more application, Kang *et al*., [42] newly used sgc8-conjugated liposome nanostructures as a platform to deliver small molecule drugs into CEM-CCRF cells.

Anthracycline family-based chemotherapeutic drugs are membrane permeable and are randomly concerned by the cells through the method of passive diffusion. Conjugating them with the sgc8c aptamer restricts their entry into PTK7 expressing cells. This "sieve" mechanism should curb the non-specific uptake of chemotherapeutic drugs and minimize the toxic effects of chemotherapeutic agents on normal cells [44].

Tenascin-C

Tenascin-C (TN-C) is an extracellular matrix protein (ECM) that's implicated within the process of tissue remodeling. It's over expressed within the tumor stroma where it's thought to enlarge angiogenesis and invasion. In one among the earliest samples of "blind" cell-based SELEX for target identification, Daniels *et al*., [45] performed selection against U251 glioblastoma cells. The resulting DNA aptamer was employed for affinity purification of the target and recognized by mass spectrometric analysis as TN-C. Although this study helped to validate TN-C as an aptamer target, this particular aptamer didn't bind with high affinity to TN-C at physiologic temperatures. An equivalent group therefore performed a variety against purified TN-C employing a 2'fluoro-pyrimidine-modified RNA library [46]. A truncated version of the aptamer was further changed by replacing purines with 2'-OMe-modified purines and capping the 3' end. A 5'-amine was incorporated that was wont to conjugate the metal chelator MAG2. The MAG2-aptamer was subsequently radiolabeled with 99mTc. So as to assess the tumor uptake and bio-distribution property of the radiolabeled anti-TN-C aptamer it had been injected intravenously into mice bearing gliobastoma (U251) and carcinoma (MDAMB-435) tumor xenografts. After 18 h of injection aptamer was exclusively localized in tumors that were shown by Scintigraphic images [47]. This proof-of-principle study demonstrated that an anti-TN-C aptamer might be wont to target tumors (glioma, breast, and colon) that express high level of TN-C which aptamers, generally , may have pharmacologic properties that make them excellent agents for tumor-specific drug delivery [48].

CONCLUSION

Single-stranded RNA or DNA oligonucleotides are considered as aptamers and are generated with SELEX technology. Aptamers can form numerous specified three-dimensional structures and with high affinity and specificity they can bind with diverse target molecules. During this review, we introduce the SELEX Process which is that the beginning of the aptamers. Aptamers have promising potential applications in clinical diagnosis and therapy particularly in cancer treatment and eye disorders but aptamers have advantages in therapeutic uses mainly because they need little or no immunogenicity, which suggests the feasibility of repeat prescriptions and fewer side effects. Additionally we summarize aptamer-mediated drug delivery system. So far, variety of aptamers is developed and very few have entered clinical trials, just one aptamer has been approved by the FDA for clinical use. It'll produce more exciting leads to the targeted delivery system of tumor treatment and it might be reasonably expected that aptamer-targeted delivery system will have a bright future in few years.

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