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Aptamer Mediated Polymeric System in Cancer - Targeted Drug Delivery System - A Review

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ABSTRACT

Cancer is one of the main causes of death far and wide the world. Targeted drug delivery to the tumor is one of the major areas in tumor or cancer research. Aptamers are oligonucleotides with flexible three dimensional structures that identify and link to the specific targets, which includes tumor receptors, in same manner and greater attraction. Aptamers discover many capable of properties for tumor targeted drug delivery, because of their selection, synthesis, steep binding affinity and specificity, synthetic accessibility, low immunogenicity Due to their unique properties, aptamer mediated nano vehicles have been developed to transfer drugs to the tumors to reduce systemic toxicity and hence the permeation is improved. From last few decades, aptamers have all of a sudden become a new class of targeting materials for drug delivery. Aptamers are single stranded, produced by a complicated, technique known as SELEX (Systematic Evolution of Ligands by Exponential enrichment).When the technology of aptamer selection was developed almost 25 years ago, it was said to be that it will be one of the revolutionary start into solve many problems associated with cancer and many other diseases. This review is majorly discussed about the aptamers and their current concepts in the tumorigenesis and implications for aptamers relate Chemotherapy, clinical studies of aptamers, and patents on aptamers so far.

Keywords: Aptamers; Systematic evolution of ligands by exponential enrichment; Targeted drug delivery system; Chemotherapy

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INTRODUCTION

There are various extensive health issues in recent years, and one of them is cancer. Due to the changes in the molecular level of the cells and genetically influences on the cells leads to cancer, this process may involves many factors like viral infection, environmental factors, and abnormal. Hence, it takes a great challenge and efficiency to recognize and to overcome that a desired tool is required for histopathological notice to avoid the prolongation growth of tumor cells among healthy cells [1]. Cell surface receptors differ tumor cells from healthy cells. Cancer is the one of main causes of death by far and wide. It was estimated that about 14.1 million cancer cases and 8.2 million cancer deaths in 2012. Among these, about 56% of the cases and 64% of the deaths occurred in the economically developing world. In the United States, cancer is the second leading cause of death. By 2030, the global exercise is approaching to climb to 21.7 million new cancer cases and 13 million cancer deaths gradually due to the expansion and aging of the population [2]. A collection of 1,529,560 new cancer cases and 5,69,490 deaths from cancer were, recorded in last 20 years, a lot of economics and effort has been adopted against cancer. Cancer is now become a top most precedence in pharma industry and National Institutes of Health. Aptamers, originally generated over SELEX, have abruptly developed as new and rugged class cancer treatments. These DNA/RNA oligonucleotides can transform into definite 3dimentional configurations and tie up to the specific target particles with affinity and specificity [3,4]. To this point aptamers are selected at variance with varied chain of targets like,

sugars**,** nucleic acids, phospholipids, proteins, entire cells. Since aptamers gets easily degraded by nucleases, hence many strategies have been adopted to overcome degradation of aptamers by enhancing in stability, chemical modification of oligonucleotides and others [5].

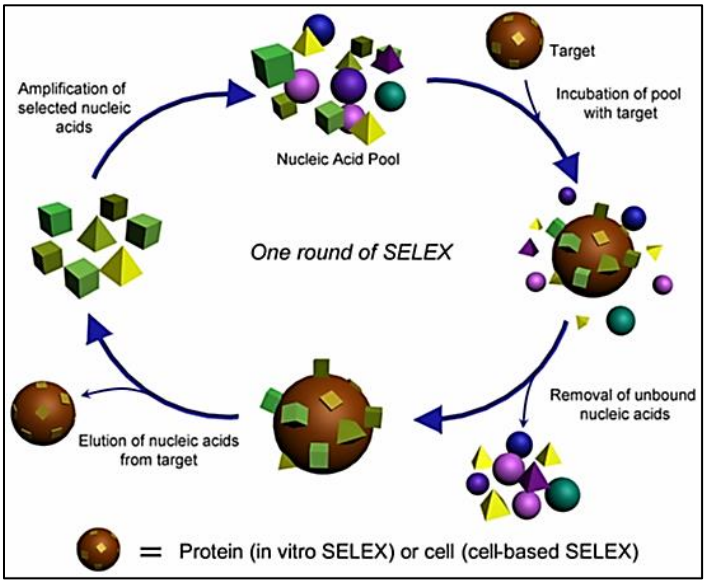

Figure 1: A schematic representation of SELEX [3]

Aptamers (*Aptus + Meros)*

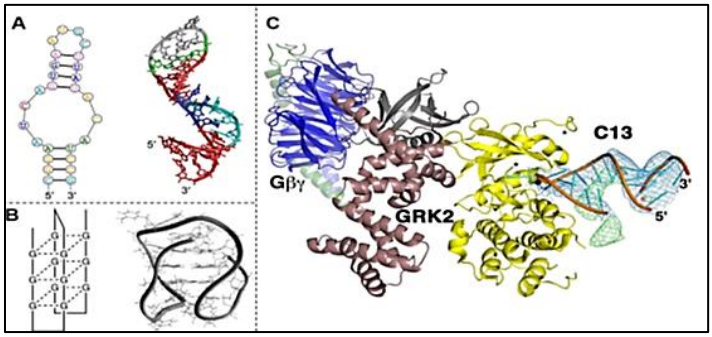

Figure 2: (A) Subordinate assembly and the progressive conformation of the commercial aptamers product macugen; (B) Molecules of the qua druplex DNA (aptamers AS1411) and schematic designs; (C) The arrangement of the RNA aptamers C13 and its receptor, G protein attached receptor kinase 2(GRK2). C13positions and a denine nucleotide in the of GRK29, which stabilizes a GRK2 in a unique and remodeled conformation. The stem of the aptamers in directly subsidizes to its affinity [1]

Aptamers are short single stranded nucleic acids (30-70 nucleotides in length) in, 1990 by Andrew Ellington, it was derived from the Latin and Greek word i.e. aptus means 'to fit', and meros means 'part. They are basically 3Dstructures and they have high affinity and specificity hence they binds to the targets at the end for the better sequence for primer binding amplification with Polymerase Chain Reaction (PCR) [6]. Larry Gold and Craig Tuerk have enhanced the process of selecting RNA ligands on bacteriophage T4 DNA polymerase, binds to its specific target protein From then, the use of aptamers in targeting the protein and to study the interaction of the protein application were rebounded. It's also used to study the interaction between molecular pathways, study the biochemical expression, which could solve many diseases [7]. The innovation of aptamers is considered as a merit in improvement of screening of oligonucleotide using Systematic Evolution of Ligands by Exponential enrichment (SELEX) (Figure 1). In this technique, extended progressions, nucleotide ligand were occupied and they made to undergo various processes of selection, amplification and sterilization until it shows high specificity with different target [8]. Remarkably SELEX generated with a selections of 1013-1015 oligonucleotides randomly, which are developed chemically in the form of DNA materials. These oligonucleotides which are chemically developed have structures of indiscriminately qualified in the innermost region with 5 and 3 bases of nucleotide at both the ends [9]. The difficult situation of the collections increases by all of the indiscriminate of the nucleotide sequences. By Krylov and others developed an aptamer which was assigned based on Non Equilibrium Capillary Electrophoresis of

an Equilibrium Mixture (NECEEM). This helped in the selection of the aptamers with high affinity by reducing the time consumption when compared to conservative SELEX [10].

SELEX

Combination of chemistry is one of the applicable device for developing new particles or molecules which promote research and development in various pharmaceutical corporations. Due to their secondary and tertiary structures, nucleic acids are well suitable for combinational chemistry [11]. SELEX has much advantage over polymerized chain reaction (PCR) stratagem, effortlessly. Aptamers are generated using SELEX as a basic tool, for targeting the various molecular nucleic acids is one of the better options so for. A chemically synthesized complex contains about 10 molecules of oligonucleotides in specific sequences, and, from these complex formations, the molecules shows and can be utilized for the distinct functions. The development of aptamers *in vitro*, by SELEX primarily the process includes in the aseptic condition of an indiscriminate DNA matrix which are intended for proteins, viruses, bacteria, metal ions, amino acids, antibiotics, peptides, organic dyes and finally the entire cells. Later, the structures have been altered for the specific targets and are processed by PCR (DNA-SELEX) or reverse transcription (RT)-PCR. Further the process is followed till the structures have specificity against its host cells. The specificity of the SELEX along with oligonucleotides is determined on various aspects, such as concentration of the target, at the starting point random DNA moiety is used for the process, equal ratio between the target and oligonucleotides is maintained. To conclude, these complex structures with high specificity with its targets were cloned into bacteria. The clones with better action are utilized for the sequencing process which finally leads to the formation of well-defined structure of an aptamer [12,13].

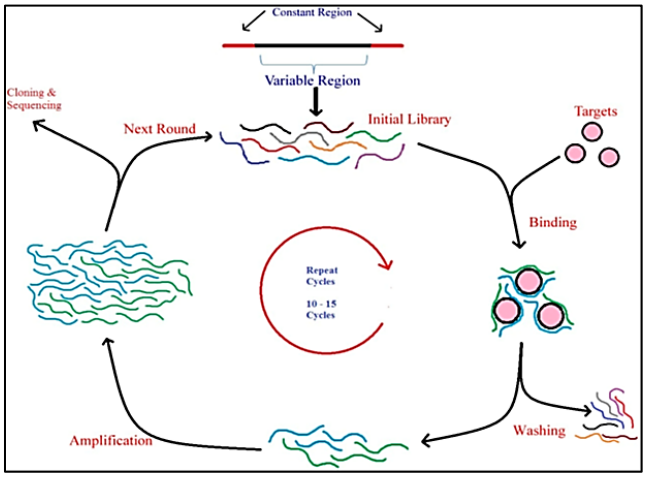

Figure 3: Schematic representation of SELEX process [5]

General Profile of Aptamers

Bunka DH and Stockley PG have discussed the general profile of the aptamers according to their study, aptamers are short single stranded, and well-formed 3 dimentional configured DNA or RNA ligands (Figure 2). Aptamers generally binds to those molecules which has high affinity and specificity e.g. proteins, iron channels, phospholipids, nucleic acids, and entire cells. Aptamers are oligonucleotides it also known as smart ligands because of their small size, flexibility, and selective internalization and intra tumoral penetration. The syntheses of aptamers are easy and inexpensive and show low antigenic and immunogenic intensity, and chemical modifications for distinctive applications. Aptamers are synthesized, from oligonucleotide by systematic evolution of ligands by exponential enrichment (SELEX) one of the techniques used for the production of oligonucleotides, in which binds to a specific ligands. Various techniques have been utilized to develop to overcome the stability of the aptamers and they have succeeded in it. PEG (poly ethylene glycol) and others are freely binds with aptamers and these chemical compounds helps in modifying the aptamers as per required targets and also to strengthen the pharmacokinetic properties and bioavailability [7,14].

Interaction of Aptamers with Cancer Cells

Lennarz S et al. are briefly discussed about the distant interaction of aptamers in cancer. Aptamers acts as a vehicle which directs the drug to a specific sites of tumor cells and its achieved by developing a molecular model to recognize and binds to a required receptors [15]. Aptamers are unique and are capable of modifying their own 3D

structures as per the specific receptors (Figure 2). Human tumor cells shows different pathological actions over administrations of the drugs treat tumor inhibition in the body but the aptamers are very sensitive action in isolating the tumor cells in the specific sites. To overcome this disadvantage of the aptamers various strategies have employed i.e. by improving the diagnosis, therapeutic action of it and by reducing the toxicity in various cancer patients. On these parameters, it is a great challenge to develop a aptamers which bind to a specific target, easily identify the very sensitive region of the tumor site and also to develop a aptamers which targets the nonspecific plasma membrane antigens [16-18].

Aptamers –Based Therapy

Monsuez JJ et al. are mentioned in their review article that, cancer therapies involves photodynamic, radiotherapy, chemotherapy, and photo thermal therapy which may cause toxicity and infect the healthy cells. To overcome this effect, antibody based drugs were used to design a targeted therapies. The antibody design have higher effect but it also shows some side effects like, the production of these therapy is very limited because of very high production cost this particular therapy involving aptamers are being developed to substitute the antibody therapy due to their limitation in the field of cancer treatment. Recent study shows that aptamers with the combination with nucleic acid is very significant and effective in cancer treatment [19] (Figure 3).

Aptamers with Nucleic Acid

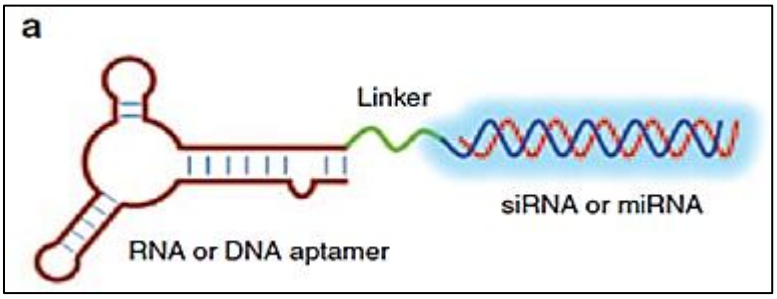

Figure 4: (a) Schematic of the first generation aptamers (RNA or DNA)-siRNA /miRNA chimera

Gene silencing devices, such as small interfering RNA (siRNA) and microRNA (miRNA), are the latest applications in therapeutics where aptamers are guides the molecules to deliver the drug to the various cell or tissue accurately. Thus, the combination of aptamers and nucleic acid will enhances the ability of targeting to a specific towards siRNA/miRNA with respect to the oncogene and inhibits it by over expressing genes in tumor cells [20-22].

Aptamers –siRNA Therapy

McNamara et al. were the researchers to develop the aptamer-siRNA chimera, relating to target cell. PSMA was targeted by an altered form of A10 RNA aptamer, which was bounded with Bcl2 (B-cell lymphoma 2) siRNA or Plk1(polo-like kinase1) siRNA were utilized. The aptamer siRNA has its specificity towards cells which have expressions PSMA leads to the silencing of Plkl1or Bcl2 gene expression and inhibiting tumor growth. In a same way Thiel et al. showed an HER2, linked with Bcl2 siRNA was targeted by RNA aptamer. HER2 expressing cancer cells were targeted by HER2-Bcl2 siRNA along with the chimera specially and stimulates down regulation of the Bcl2 gene. Recent study conducted by Wullner et al. explained the binding of two divergent aptamers, targeting a particular cells or tissue, binding to siRNA, forms a bivalent chimera. It contains of two similar RNA aptamers which targets PSMA and also bounded to eukaryotic elongation factor 2 (EEF2) siRNA. On comparisons of bivalent PSMA aptamer-EEF2 siRNA was found more efficient than monovalent aptamers in aspects like enhancing half-life and facilitated inhibition of tumors [23,24].

Aptamers mi-RNA Therapy

Dai et al. and Esposito et al. have done their search on two different aptamers using mi-RNA, according to their research work it states that miRNA is one of the advanced technique which are used treat cancer using aptamers targeting a specific cancer cells or tissues. Dai et al. created a hybrid complex having an aptamer with MUC1 and miRNA-29b, targets ovarian carcinoma cells. The miRNA-29b consolidation was bind to the specific sequences of MUC1 aptamers was grown in an aseptic conditions with MUC1 expressing OVCAR-3cells (Ovarian

Adenocarcinoma). miRNA and aptamer complex was down regulating the DNA methyl transferase gene expression. These restores PTEN (Phosphatase and tensin homolog) expression, that caused programed cell death [25,26].

Current Concepts in Tumorigenesis

Tumor heterogeneity:

Van Allen EM et al., Hoffman RM et al. and Denison TA et al. and many scientists and research scholars have performed various research work tumorology using aptamers. Some of the general information on their work is mentioned here [26]. One of the problem facing in many research and development program is that various drug delivery vectors are bring cleared in preclinical development but failed in evaluations of clinical development [27,28]. At present tumor heterogeneity is one of the important and effective causes for chemoresistance and cancer relapse. Due to the increasing cases of cancer the collective evidences shows that tumor heterogeneity generally established in 3 different manner, (1) tumor cells including heterogeneous cell with different phenotypic activity leads to malignancy. (2) pathological expansions of tissue within the tumor is observed and it may have many different types of cancer mainly breast cancer cells due to the variation in the receptors. (3) the original tumor cells are compared with the extracted cancer cells from metastatic region. Due to their ability to determine toxicity of the cancer model heterogeneity becomes an advanced challenge in targeting delivery, and these models are do not contains biomimetic niches and different variability [1,29]. Howeover, many of the aptamer mediated nano vehicles only binds to a specific receptor, and other tumor cells within, hence they does not show the greater action of drug within the tumor cell and will easily acquire MDR. Chimerization or multi conjugation technique is one of the main aspects of combinational aptamers in cancer treatment [30,31]. This was demonstrated in many preliminary studies, which includes the generation of monovalent aptamers sgc8 and sgd5a based on various aspects. These monovalent aptamers have ability to locating and destroying different tumor cells, which includes CEM, Toledo, and Ramos cells [32]. Various other research have processed on various cancer cells, antibodies i.e. anti-HER2 antibody and S6 RNA aptamer with GNPs detects different breast cancer cells and a dual aptamer SPIO-NP system combines with the A10 and DUP-1 peptide aptamers, which includes both PSMA (+) and PSMA (-)cancer cells based on their drug delivering effect and selective uptake of cells [33-35] (Figure 4).

Hypoxia induced aberrant EPR and MDR:

Borden MA et al., Livney YD et al. and Denison TA et al. have discussed the beneficial and drawback of the hypoxia induced cancer therapy. In this particular topic the issues and the benefit effect of hypoxia is briefly discussed as per their review on the area. Frequently discussed problems in oncology are the involuntary growth of cancer cells and the regions facing hypoxia [36]. Hypoxia is mainly inhibits tumor therapies by decreasing flow of drug in to the cells, enhancing drug release from the cell, increasing anticancer metabolism with drug, leads to alteration of the DNA repair and cell death [37]. Tumor heterogeneity and stemness, hypoxia initiatives on impaired EPR and MDR, which of aptamer mediated nano vehicles based on the following mechanisms: (1) due to the poor formation of diffusion and vasculature, barrier container which transfer the drug containing nanovehicle into the origin of the cancer cells, then it leads to EPR impairing and decreased cytotoxicity in hypoxic regions [18,38]. Because most of the aptamers mediated nano vehicles are administered systemically through intravenous routes the drug reach the site of action through the blood stream. The route of administration of drugs can be given by regional release and local delivery with the help of situ forming gels [38,39]. This may benefited to decreasing in the availability of drug systemically and to enhances the concentration tumor within, by utilizing strong aptamer receptor binder. Chemotherapeutic removal of tumor cell can be enhanced by injecting through central hypoxic region of the infected site using ultrasonic radiographic. It can also be given by locoregional regimens-in the form of aerosols or by transcatheter arterial administration.(2) cancer cells has greater oxygen saturated conditions due to their high glycolytic rate [40]. This metabolic process, known as the Warburg effect and hence considered as most important contribution to chemoresistance [41]. The process is regulated by hypoxia inducible factors 1 and 2 these factors modulates tumor glycolysis, metabolism of lipids and affect the processes of vascularization and angiogenesis [42,43]. Hence, hypoxia inducible factors -1 and hypoxia inducible factors -2 along with their target genes i.e. pyruvate dehydrogenase kinase (PDK), are targeted by hypoxic antagonist, and cytotoxin with the help of Aptamer mediated nano vehicles, this gradually increases the effect of targeted hypoxia therapies (Figure 1). On bases, many studies has proposed that it is it becomes very important reverse the Warburg effect and to reduce metabolic flexibility in order to improve sensitivity of chemotherapeutic by inhibiting hypoxia inducible factors using NSC-134754, echinomycin, tirapazamine and cetuximab and others [44,45]. (3) in particular, Chen et al. demonstrated, using ATP binding cassette genes, and by increases the activity of efflux transporters like, multidrug resistance protein 1 (MRP1), glycoprotein (P-gp), thus, hypoxia upregulates and leads to ATP dependent cellular

uptake reduction and failed to cure. Latest development in nanomedicine have shown that by the inhibition of the interpretation of the mRNAs of MDR efflux pump proteins (MDR1 or MRP1), by using antisense oligonucleotides or siRNA or using chemo sensitizers (e.g. verapamil) or by blocking MDR efflux proteins, antibodies, small molecule compounds to overcome MDR. Therefore, prohibitions of the target genes using united aptamer mediated nanovehicles that gives a pharmacologic antagonist or single or multiple siRNAs, that improves the sensitivity of chemotherapy (Figure 1) [28,46-48].

Tumor stroma interaction microenvironment:

Capulli M et al., Xiao et al. and Hale MD et al. and many others have given a review on the tumor stroma as per their review, to enable cancer progression just the phenotypic and genetic properties of cancer cells are not enough it also requires support of microenvironment [49]. In detail, for the controlled process of tumorigenesis, the tumor cells and their stromal partners contributes in many process. This two way discussion was completely reproduced in a prostate cancer model and further promoted by the cancer associated stroma (CAS) that gives evidence for the development or progression of growth of the healthy cell to specific bone metastasis [50]. In particular the changes of genetic and phenotypic in the cancer cells were noted when CAS cells were mutually developed i.e. macrophages and fibroblasts [51]. Likewise, cancer associated with fibroblasts increases the secretion of stromal cell derived factor-1, transforming growth factors-β1, matrix metalloproteinase 9 and interleukin-6 to accelerate the separation and attack of tumor cells [52,53]. Moreover, to stimulate angiogenesis by expressing vascular endothelial growth factor (VEGF), these cells also produce tumor necrosis factor (TNF), epidermal growth factor (EGF) and other, contribute to breakdown of surrounding substances and cancer cell motility, anti-apoptotic and providing proliferative support hypoxia hire macrophages that provide above trophic functions [54,55]. These researches recommend that the neglected CAS is most required therapeutically target for aptamer mediated Nano vehicles (Figure 1) [56]. Moreover, the prostate cancer and its ability to spread into bone tissue made the researchers to reveal the involvement of extracellular matrix (ECM). Some study shown that, type I collagen (COL-I) showed enhanced chemotactic migration hence cancer cells derived from LNCaP prostate cancer cells which was overexpressed by integrin α2β1. The activation of the suppressor gene BRCA2, is achieved by inhibiting the bone protein, thereby upregulating the reduction of E-cadherin and expression the Akt or PI3K pathway. The ECM shows a crucial role in the EMT (epithelial mesenchymal transition). Hence, entire cell identifying aptamer mediated Nano vehicles binding to COL-I secreting cells, aptamers targeting and integrin α2β1 which is a cancer cells is overexpressed and this may be the alternative for therapeutics for the collision in the progression of the EMT [57,58] (Table 1).

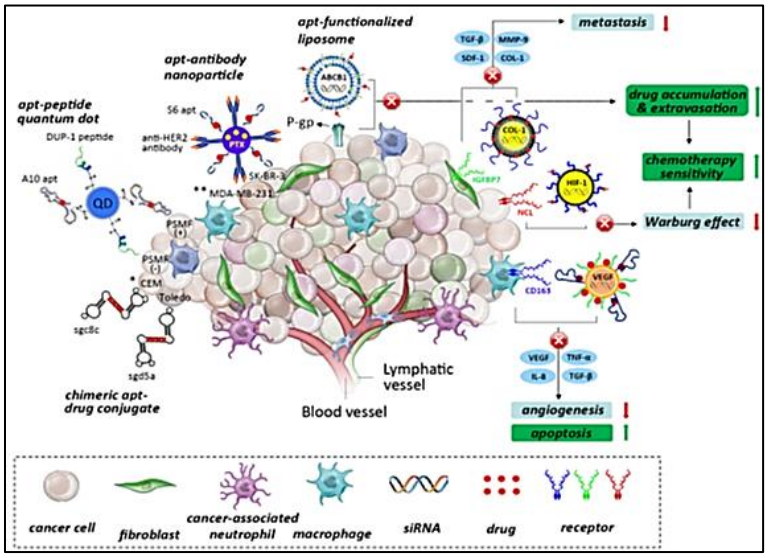

Figure 4: The role of the tumor niche influencing tumor heterogeneity, tumor stroma interactome and hypoxic aberrancy [1]

Table 1: Aptamers and their applications (58)

Receptor	Applications of the aptamers	RNA/DNA
Tenascin-C	Tumor imaging	RNA
Nucleolin	Photodynamic therapy	DNA
	Tumor imaging	
Prostate Specific	siRNA ,cytotoxin Chemotherapeutic drug delivery	RNA
Membrane Antigen		
(PSMA)		
gp120	siRNA delivery	RNA
Transferrin receptor	Protein targeting to lysosome	RNA/DNA
Mucin-1 (MUC-1)	Radionuclide delivery	DNA
	Photodynamic therapy	
Protein tyrosinekinase-7	Chemotherapeutic drug delivery	DNA
Immunoglobin heavy	Micelle nanoparticles for drug delivery	DNA
Muchain (IGHM)		
Epidermal growth	Nanoparticle drug delivery	RNA
factor receptor (EGFR)		

Clinical Studies of Aptamers

Aptamer production:

The enzymatic production of aptamers during the selection process still remains as a most important, in order to generate large amounts of material for clinical testing, and for large scale production, enzymatic synthesis is simply not applicable. A first key step in the discovery process of any aptamer is the identification of a core and minimal functional sequence, which can be generated synthetically by solid phase synthesis [7]. Aptamer are typically between 70 and 90 nucleotides in length including the constant regions. Following selection, aptamers are analyzed by comparing sequence composition and identifying sequence by comparing two dimensional folds using well developed algorithms to identify common structural design allowing for minimization. In general, shorter molecules are better for chemical synthesis, as each unnecessary nucleotid both reduces yields and enhances manufacturing costs. However, in some clinical aptamers, for example Fovista, this has led the replacement of loop residues with flexible polyethylene glycol (PEG) linkers resulting in a savings of four coupling steps (see below).

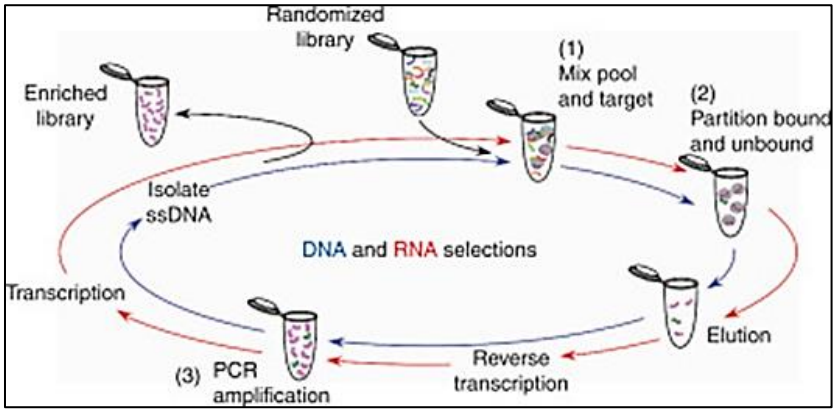

Figure 5: A schematic of the selection process for DNA and RNA aptamers libraries. Starting with randomized library incubated with the target (1), bound species and partitioned and stringently washed (2), followed by elution of desired of species. For RNA selections, recovered material must be reverse transcribed by polymerase chain reaction(PCR) amplification (3)and transcription back into RNA to generate the library for the next round. DNA selection however, are ready for PCR amplification after elution (3), but afterwards must be separated from the complement strand before the resulting ssDNA pool can be used for the next round

For research and development process, minimized aptamers 20 to 50 nucleotides in length can be generated in individual labs using lab scale DNA or RNA synthesizers (e.g. Expedite 8909, ABI394) or by the many oligonucleotide synthesis companies. Depending on oligonucleotide length and the modifications present, synthesis at the 1 µmole scale typically yields 1 mg of material, which is often sufficient for hundreds of *in vitro* experiments and sufficient to perform preclinical analyses in small animal (mouse) models [7]. Machines are capable of scaling to 10 to 15 µmole, but for larger synthesizes, equipment capable of generating gram scale quantities of aptamers can be readily obtained (e.g. the AKTA oligopilot plus 100 can scale from 250 µmole to 4 µmole). The synthesis ranging

from 50 nmoles to 4 mmoles and beyond can also be out sourced to a number of commercial sources that offer large-scale R&D grade materials. However, while the exact synthesis method for clinically evaluated aptamers, to our knowledge, are not publically available, the synthesis methods all rely on standard solid phase phosphoramidite chemistry.

Clinical application of aptamers in cancer:

Aptamers obtained by SELEX shows the specificity and greater sensitivity which required for the process of diagnosis of cancer. With these high affinity and specific target ability makes aptamers unique and they have ability to clearly differentiate between all the different cancer cells. Howover, aptamers targets various receptors have been highly adapted for disease diagnosis and the delivery of therapeutic moiety into cells. Aptamer mediated targeting delivery helps to detect and delivery to the site, enhances the early diagnosis and positive prognosis, by reducing treatment costs due to the reduced incidents of late stage of cancers and enhancement in the therapeutic options, will reduce the side effects [59]. Some of the clinical application of aptamers is given in Tables 2 and 3 gives the information about the aptamers which are undergoing clinical studies. There are many aptamers being developed for various types of diseases worldwide some of the aptamer undergoing clinical studies are, given in the below table [60,61].

Table 2: Clinical application of apatmers [59]

APTAMERS	TARGETS	NUCLEIC ACID	CLINICAL USES
A9,A10	PSMA	RNA	Prostatecancer therapy and imagining
NOX-A12	CXCL12	RNA	Hematological tumor therapy
AptA,AptB	Mucin 1	DNA	Cancer therapy and imagining
AS1411	Nucleolin	DNA	Cancer therapy and imaging
TTA1	Tenascin C	RNA	Cancer imaging

Table 3: Clinical application of apatmers [60]

Aptamer design for	Code Names of aptamers
Aptamers therapeutics for muscular degeneration and mascular edema	Pegaptanid (macugen)
	E10030(Fovista)
	ARC1905
Therapeutic aptamers for hemostasis	RB006
	ARC1779
	NU172
	ARC19499
Therapeutic aptamers for cancer	AS1411
	NOX-A12
Therapeutic aptamers for diabetes mellitus	NOX-E36

Patents on aptamers:

Aptamer patents are mainly classified in two categories: (1) which includes methods of inventions and modification in them; (2) based on their applications. In this review I have collected all the important patents on therapeutic aptamers. During these collections of patents on aptamers, we found more patent on aptamers specifically on protein, which is based on new process for the production, modification in the process. Some of the patents based on therapeutic aptamers along with the inventor information's are given below in the (Tables 4 and 5) [58].

Table 4: List aptamers undergoing clinical trials [58]

Aptamer	Molecular target	Sponsor	Medical indications	Status
ARC1779	Activated von Willebrand Factor (vWF)	Archemix Corporation	Purpura; Thrombotic Thrombocytopenic; Von Willebrand Disease Type-2b	Phase 2 completed
ARC1905	Complement factor C5	Ophthotech Corporation	Age-Related Macular Degeneration	Phase 1 completed
ARC19499	Tissue Factor Pathway Inhibitor	Baxter Healthcare Corporation	Hemophilia	Phase 1 terminated
AS1411	Nucleolin	Antisoma Research	Leukemia, Myeloid Phase 2 completed	Phase 2 completed
			Metastatic Renal Cell Carcinoma	Phase 2 status is unknown
E10030	Platelet-derived growth factor	Ophthotech Corporation	Age-Related Macular Degeneration	Phase 3 recruiting Participants
NOX-E36	Monocyte Chemoattractant Protein-1 (MCP-1)	NOXXON Pharma AG	Type 2 Diabetes Mellitus; Albuminuria	Phase 2 completed
NOX-A12	Stromal Cell-Derived Factor-1	NOXXON Pharma AG	Multiple Myeloma; Chronic Lymphocytic Leukemia	Phase 2 recruiting Participants
NOX-H94	Hepcidin	NOXXON Pharma AG	Anemia of Chronic Disease	Phase 2 completed
NU172	Thrombin (Factor IIa)	ARCA Biopharma	Heart Disease	Phase 2 status is unknown

Table 5: Patents on Modification in SELEX Procedure [59]

Patent information	Year	Content of patents on SELEX	Inventor/Applicant
US5580737	1996	Counter SELEX	Jenison R et al. Nexstar Pharma.Inc
WO9833941	1998	Flow cell SELEX	Gold LS et al. Nexstar Pharma. Inc
WO0056930	2000	Truncation SELEX	Pagratis N et al. Nexstar Pharma. Inc.
US5683867	1997	Blended SELEX	Biesecker G et al. Nexstar Pharma. Inc.
US20026387620	2002	Transcription Free SELEX	Smith JD et al. Gilead Sciences Inc.
US5567588	1996	Solution SELEX	Gold L et al. Uni. Res. Corp.
WO9604403	1996	Chimeric SELEX	Ringquist S et al. Uni. Res. Corp.
US20026376474	2002	Tissue SELEX	Heilig JS et al. Gilead Sciences, Inc
US6001577	1999	Photo SELEX	Willis M et al. Nexstar Pharma. Inc.
US20077312325	2007	Toggle SELEX	Sullenger BA et al. Duke University
EP1386972	2004	Mirror image SELEX Spiegelmers	Kleinjung F et al.
US5763595	1998	Covalent SELEX or Chemi SELEX	Eaton BS et al. Nexstar Pharma. Inc.

CONCLUSION

An impending human catastrophes was anticipated by the world health organization, according to WHO and other health organizations that cancer cases are estimated to flood by 56% in next 20 years and may rise up to 21.7 million. Therefore, advanced techniques are to conquer cancer hence aptamers are the one of the advance technique to treat cancer. Since their first discovery in 1990 aptamers have attracted a growing interest as novel targeting molecules. These aptamers are easily select against any particular targets for the great therapeutic and diagnostic filed because of their high specificity low toxicity and internalizing properties. Till today a various types of anti-cancer agents are successfully used in the therapies of cancer cells *in vitro*. However, the successful administration of aptamers to the cancer cells and the results of its therapeutical index has only been obtained in only one report. Hence much more research and developments needs to be done before aptamer drug delivery can reach management and clinical trials of cancer patients. The development and improvements in the selection and methods to improve the conjugation of the aptamers are very much required for potential clinical developments. With the involvement of many various companies and academics in the area of research, the development of aptamer will speed up and aptamers will find their desired place in treatment of cancer and bring uprising development in targeted drug delivery and also in cancer diagnosis. Based on various research, researchers have successfully developed a n aptamers having high affinity which are made to target protein, which involves cell-adhesion molecules, proteases, cytokines, kinases, and cell-surface receptors others. Since aptamers can be selected against the various proteins, the therapeutic index of the aptamers was found to be very significant. When aptamers on systemic administration they tend to show toxicity poor pharmacokinetics. Although aptamers are unlikely to illegitimate an immune response, the safety profile of each individual aptamer conjugate must be examined carefully. The effect on non-target cells due to activation or inhibition of proteins needs to be empirically evaluated because aptamers binding action will significantly differ for each protein moiety. Aptamers are the versatile tool for the cancer therapy, these aptamers

have given a very new ways of detecting the cancer or tumor cell in the body in the primary stage and treatments for the earlier development of tumor cell because of high affinity against tumor cell. Aptamers were conjugated with conventional anti-cancer drugs for the anticancer therapy, thus aptamers helps to drive therapeutics to the specific site.

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