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Review

Aptamer grafted nanoparticle as targeted therapeutic tool for the treatment of breast cancer

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ABSTRACT

Breast carcinomas repeat their number and grow exponentially making it extremely frequent malignancy among women. Approximately, 70–80% of early diagnosed or non-metastatic conditions are treatable while the metastatic cases are considered ineffective to treat with current ample amount of therapy. Target based anti-cancer treatment has been in the limelight for decades and is perceived significant consideration of scientists. Aptamers are the 'coming of age' therapeutic approach, selected using an appropriate tool from the library of sequences. Aptamers are non-immunogenic, stable, and high-affinity ligand which are poised to reach the clinical benchmark. With the heed in nanoparticle application, the delivery of aptamer to the specific site could be enhanced which also protects them from nuclease degradation. Moreover, nanoparticles due to robust structure, high drug entrapment, and modifiable release of cargo could serve as a successful candidate in the treatment of breast carcinoma. This review would showcase the method and modified method of selection of aptamers, aptamers that were able to make its way towards clinical trial and their targetability and selectivity towards breast cancers. The appropriate usage of aptamer-based biosensor in breast cancer diagnosis have also been discussed.

1. Introduction

With 685,000 deaths and 2.3 million diagnosed cases in women in the year 2020, breast cancer comes under the umbrella of most common malignant disease among women. It arises from the lobules of glandular tissue and the epithelial lining of the breast. If not diagnosed at an early stage, it may invade the neighboring breast tissue spreading towards lymph nodes and finally to other organs as well [1]. The major cause of mortality is multidrug resistance and tumor metastasis [2,3]. As per World Health Organization (WHO), breast carcinoma accounts for 12% of all the new annual cases of cancer worldwide [4]. Breast carcinoma can be divided into two types, first based on histological components and the second is based on molecular characteristics. Based upon the histology, breast carcinoma is further differentiated into lobular and ductal carcinoma. Based on molecular expression of the receptor, breast cancers are further differentiated into estrogen (ER) positive breast carcinoma (PR), progesterone positive, human epidermal growth factor-2 (HER-2) positive and triple-negative breast cancer (TNBC) which is ER, PR, HER-2 negative [5–11]. Till now, the therapy of breast neoplasm relies upon systemic treatment and localized therapy. The patient at stage 0 is preferred to opt for surgical intervention while those at advanced-stage cancer are advised for chemotherapy, lupectomy or radiation therapy. For such patients, the main goal is to promote survival rate with fewer health hazards [12–16]. However, the major drawback of such therapy is the challenges imposed by metastatic and advanced cancer due to recurrent cases and resistance of therapy. For instance, chemotherapy uses cytotoxic agents for therapy that are pumped out by cancer cells, or if deposits at the site, it affects normal healthy organs as well [17]. On contrary, surgery is not a better option when cancer metastasizes to neighbouring organs like the liver or lungs. Radiotherapy, however, helps in the contraction of tumor cells but causes serious adverse effects. A monoclonal antibody-trastuzumab administered for long-duration caused severe toxicity and cardiac dysfunction in breast cancer cases [18]. Radiotherapy, although, helps in shrinking tumor size, but also damages the nearby tissues as well [19]. Hence, a ground-breaking technology that can help in shrinking the graph of breast cancer cases is required that could deliver the safe drug, obstruct relapse and metastasis and prolong the journey of cancer-free

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journey of patients.

In the revolutionized field of oncotherapy, nanoparticles have been a boon that conquers the biological hindrances, reduce the dose and intensity of chemotherapy-induced side effect. Nanotechnology could be able to target the neoplastic cells either by enhanced permeation and retention (EPR) approach or by active targeting. Since EPR relies on the leaky nature of cancer cells, only 20% of the drug could be able to transfer to the cell, while the rest is eliminated by the body [20–27]. Besides this, active targeting using ligands like folate, transferrin, aptamers could improve the cellular binding, improve cell uptake and internalization via receptor responsive endocytosis [28–37]. The pharmacologically active agent should thus be modified in a carrier to deliver to the specific region at pre-determined area. This approach of targeted delivery thus profoundly supplies the cargo only to the tumor site (in case of cancer), while the normal cells would be restricted to the influence of cytotoxic agents. In search of such novel and successful therapy, aptamers have been developed almost three decades ago using a highly effective tool called SELEX. From the pool of sequences, SELEX extracts the most appropriate aptamer with high affinity and selectivity towards the target. For example, AS1411 is under phase II trial for the treatment of acute myeloid leukemia [38]. Aptamer is single-stranded oligonucleotide that undergoes deformation and upgrades into tertiary structure enabling them to bind to the target site with high affinity [39]. The simplicity of the chemical structure of aptamer enables them to recover with full conformational structure even after chemical or thermal degradation [40] They are highly stable at a wide horizon of pH, easy to manufacture, cost-effective and non-immunogenic. Thus, normal human physiology does not consider them alien material and accepts them comfortably [41–44]. Aptamer has shown enhanced efficacy against cancer which bind with anti-cancer agents, radiopharmaceuticals, or oncogene suppressing agent. The dose of chemotherapeutics or radiopharmaceuticals thus could be reduced. For cancer cell diagnosis, aptamer act as a guide for various probes to target and detect cancer using computed tomography (CT), magnetic resonance imaging (MRI), single photon emission topography (SPECT) and ultrasonography[45]. Aptamers due to their size and charge also have the potential to bind with the nanoparticles, improves their targeting ability without affecting size up to a certain extent [46]. An aptamer drug conjugate could also be designed to specifically target certain cells and deliver anti-cancer agents directly into the lesion. The conjugate thus is composed of three moieties: aptamer, drug, and linker. It is essential to note that linkers and their conjugation chemistry should be focused that release the drug inside the tumor cells. For example, aptamer sgc8-Dox was linked with doxorubicin through an acid-sensitive hydrazone linker. As a result, the complex after internalizing into the tumor cells released the drug conditionally in the acidic environment of the tumor [47]. Using high-throughput gene sequencing tool, aptamers can be conjugated with gene therapeutics such as small hairpin RNA (shRNA), small interfering RNA (siRNA) and microRNA (miRNA). Such RNAi-based anti-cancer therapy potentially exacerbate the evolution of next generation therapy. For instance, a chimera of aptamer and siRNA to target HER-2 positive cells have been demonstrated by Yu et al. EGFR siRNA was used as inhibitory compound which was placed in between HER2 and HER3 aptamer to form chimeras. The chimera with triple hit strategy downregulated the expression of the three receptors (HER2,3 and EGFR) and promoted apoptosis. In the mouse xenograft model, the chimeras showed 6–7 times anti-tumor effect in comparison to PBS and 1.5 fold reduced tumor growth compared to those treated with a physical mixture of HER2,3 aptamer and EGFR siRNA. Thus, it was envisaged a therapy of siRNA with aptamer could be explored further to acquire adequate anti-cancer results in vivo [48].

Several aptamers are developed so far that bestowed excellent target binding effect. However, under the influence of nucleases, aptamer degrades [49]. As an alluring candidate, aptamer have been utilized as a smart system in imaging, diagnoses, and therapy of cancer. Here, in this review, we tried to extend the information of using aptamer in the therapy of breast cancer. We offered a piece of state-of-art information on the method of selection of appropriate aptamer, ongoing cancer-targeted aptamer-based clinical trial and theranostic application of aptamer grafted nanoparticle preparation, particularly against breast carcinoma.

2. Targeted drug delivery

The therapy of cancer typically employs cytotoxic agents such as microtubule inhibitors or DNA-damaging agents [50,51]. Chemotherapies are delivered at the highest possible dose which is non-toxic and corresponds to the maximum tolerated dose. However, it is well documented that conventional chemotherapy produces a negative effect on health such as hair loss, cardio and neural toxicity, hepatocellular damage, renal damage, nausea, vomiting, immunosuppressive effect, etc [52,53]. A wide variety of chemotherapeutics are available in the market, but only a few were successful to increase the survival rate of patients with metastatic cancer [54]. To compensate for the associated side effects and improve therapeutic outcome, a nanocarrier (Nc) for delivering of such cytotoxic compounds have been developed. The Nc preferentially deposit at the tumor site due to their size due to elevated permeability and retention (EPR) effect. Such preferential nanoparticle accumulation is due to the reduced lymphatic drainage and abnormal neovasculature of tumor tissue [55]. A well-known example is Doxil™ which is a pegylated liposomal preparation carrying Doxorubicin [56]. Due to inadequate lymphatic drainage and leaky vasculature, the nanoparticles were allowed to accumulate at the site of the tumor. There are other clinical examples which includes Mepact ™ [57], Myocet ™ [58], Abraxane ™ [31], DaunoXome ™.

However, only 20–30% of delivery to tumor cells could be mediated by the EPR effect. Tumor neovasculature, size, intravascular pressure and genomic makeup contribute towards tumor aggressiveness [59–62].

To establish an advanced therapeutic effect, the active targeting approach could be a boon in cancer treatment due to high uptake and enhanced retention [30,63]. Receptor-mediated targeting emerges as new therapy with advanced recognition of specific target areas to bind and spare the normal cells [37,64–71]. This could enhance the uptake, drug availability, drug retention, slow elimination, and reduced side effect. Some of the common tumor receptors are transferrin [30,72,73], integrins [74–76], folate [77–81], human epidermal growth factor 2 [82] etc. For successful internalization and endosomal escape, the target should be chosen not only upon the basis of their expression level but one that could enable rapid uptake and avoid the endosomal escape (Fig. 1).

3. Aptamer

Originating from a novel category of ligands, aptamers have emerged as next-generation therapy in the field of medicine [83], which is a key approach in emphasizing research. Under the umbrella of specialized tertiary structures, aptamers are defined as single-stranded and short oligonucleotides with discerned affinity and sensitivity towards anticipated targets such as a peptide, tissues, antibiotics, etc [84,85]. Aptamers are highly flexible compounds with the size of 10–30 kDa, non-immuno-responsive, easy to develop, chemically modifiable, and importantly highly stable in harsh environments also [86,87]. The authority of 3-D structure of aptamer allows them to strongly bind with the target due to forces in between them. Such extrapolated forces are due to salt bridges, hydrogen bonding, electrostatic interaction, Van der Waals forces, and aromatic ring stacking. The juxtaposition between antibodies and aptamer arises due to proficiency of aptamers such as small size (1–2 nm), low batch failure and ease of substitution. The aptamers are the nucleotide derivative of antibodies but are economic and more flexible versions than monoclonal antibodies [88,89]. Thus, aptamers are seen as an assortment of the arena from conventional therapy or therapy relying on antibodies. In 1990, two groups extensively studied

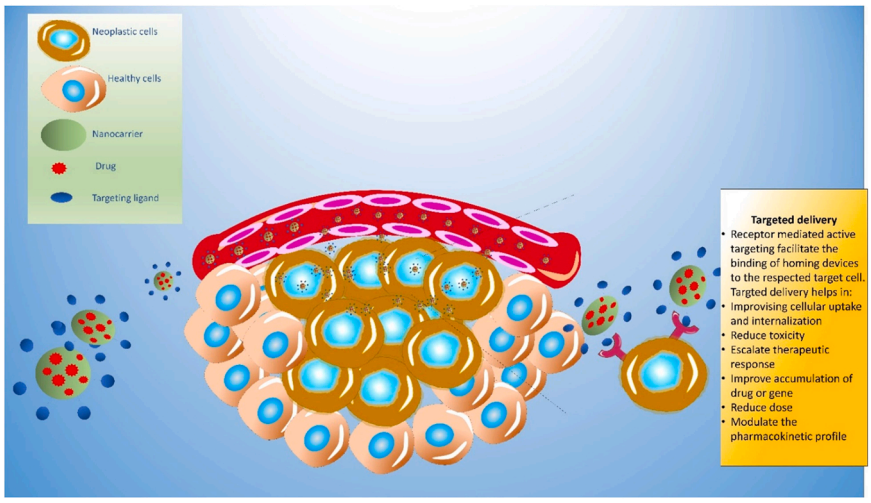

Fig. 1. Schematic representation of active targeting of nanoparticle inside and around the tumor cells.

and isolated aptamer for the first time in history using specialized tool called Systematic Evolution of Ligands by Exponential enrichment (SELEX) [90,91]. Such a simple technique can develop numerous aptamer which could fit in the pocket of the target efficiently [92].

3.1. Selection process of aptamer

As discussed, the screening of aptamer is performed using SELEX which generally depends on 4 major steps: 1. Preparation of single-stranded oligonucleotide and modulating to form 3-dimensional architecture. Incubation of target with above-mentioned assembly of 10^{14}~10^{16} random sequence of single-stranded oligonucleotides, while monitoring pH, temperature, and ionic strength keeping in mind about the applicability of target 2. Separation of bounded sequence from unbounded sequences, such filtration of bounded nucleic acid is called elution 3. Amplification using polymerase chain reaction 4. Finally, separation of single-stranded oligonucleotide with the strongest affinity towards the target. The processes are repeated multiple times (15–20 times) and selected candidates are cloned and characterized further [93] (Fig. 2). Thus, from the pool of sequence, one can assume to extract the best target to design medicine with great clinical outcomes.

3.2. SELEX methods

Using the conventional method of selection, many aptamers show no to low affinity towards the target which is mainly due to sheathing of aptamer's horizon or tumor heterogeneity. In response to this, the SELEX has been revised so to extract aptamer with property to accommodate into the cavity of a various target site. As an advanced tool, cell-SELEX could overcome the limitations of conventional SELEX. For instance, a piece of prior knowledge about the target may not be required for selecting an appropriate aptamer. Moreover, aptamers could bind the target in its native form to the cavity of the target site, thus abolishing the risk of binding failure. More advantageously, the process offers an advanced selection method to choose aptamers that do not bind to the normal cells or those aptamers that are internalized by the endocytosis mechanism [94,95]. The cell-based SELEX employs live cells to optimize the aptamers, which are utilized practically against various cancers such as cervical cancer [96,97], ovarian cancer [98,99], prostate cancer [100], breast cancer [101,102], liver cancer [103], and

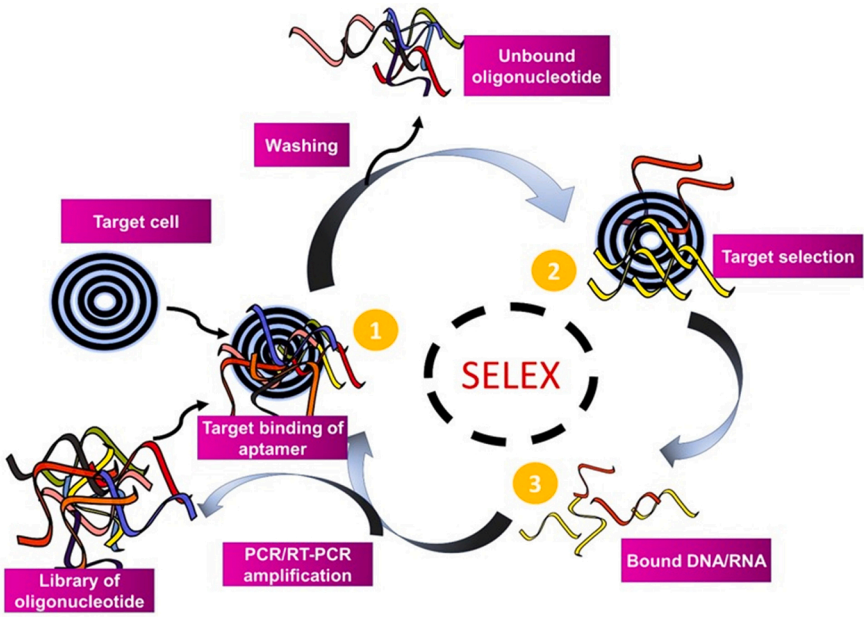

Fig. 2. Schematic illustration of in-vitro SELEX. Step 1 is the incubation of target with the pool of DNA or RNA library for ligation. Oligonucleotide with high efficiency will bind to the target cell (as seen in step 2) while those do not bind to the target cells were removed subsequently (step 3). The removal of such unbound oligonucleotide is known as elution. The selected DNA/RNA further reverse transcribed and amplified using PCR technique. The selected oligonucleotide then used in next round, cloned, sequenced and characterized.

glioma [104]. Since the cell membrane is composed of numerous metabolic components, proteins, carbohydrates, and lipids, which upon deviation from normal physiology to disease condition corresponds to structural and confirmational changes. Thus, the research group of Gold, investigated such aptamer for the first time which could bind to the red blood cells [105]. Now, tremendous research is going on to optimize the aptamers that could effectively bind to the target cells. The revelation of both positive and negative receptors and their binding affinity with aptamer is also important to be identified to obtain those aptamers sparing the normal or healthy cells. Shao et al., identified the aptamer (BC-15) using cell-SELEX approach that binds to the hnRNP A1 (protein) overly expressed on breast cancer cells [106].

Another approach is based on selecting aptamers at micro-level using a microfluidics mechanism. This method rapidly generates aptamer with high affinity and efficiency towards targeted protein involved in cardiovascular disease or carcinoma [107–110]. This technique notably involves technology such as microarray-assisted microfluidic chip [99,111], sol-gel [112], and acoustophoresis [113,114]. For example, aptamer against C reactive protein was screened out using a microfluidic system [115].

Analytical techniques have also been used to select the aptamers. Thus, SELEX based on capillary electrophoresis has been employed that separates the ions due to their hydrodynamic diameter, frictional energy and charge influenced by electrophoretic movement [42,116,117]. The unbound DNA molecules from the bound one can be separated within 2–4 rounds which is advantageous over conventional SELEX that need 15–20 rounds to optimize the desired targeting ligand. A well-known example is anti-glypican-3 aptamer (AP613–1) against hepatic carcinoma [118] and human IgE [119] and neuropeptide Y aptamer [120] (selected after 4 rounds only).

In many circumstances, a library contains hundreds and thousands of sequences from which the best aptamer is picked. However, it is not necessary to get the best performing aptamer with a high affinity towards the desired target. Thus, a highly advanced approach called high throughput screening is developed recently that differentiates the enriched sequence at a very early stage followed by avoiding PCR bias that comes across due to over selection [121,122]. Thus, the highly inventive bioinformatics tool could quantify productively and give the best target interacted aptamer. Cho and their team demonstrated a rapidly developed PDGF-BB aptamer using high throughput sequencing approach [111].

Another common SELEX method is Bead SELEX. Here, the target molecules were immobilized on a solid support comprised of Sephadex, sepharose, agarose, and magnetic bead. Resin-based solid support with the enrichment of multiple tags such as glutathione S-transferase (GST), histidine, maltose-binding protein, or biotin for streptavidin, glutathione, Nickel nitrilotriacetic acid and resin of amylose [123,124]. The solid support plays a significant role in embellishing high-affinity aptamer with even small targeted compounds, as a high concentration of target cells due to cooperative binding promotes non-specific and undesired binding with ligands [125]. Moreover, the need of solid support for the selection of aptamer is the low molecular weight of the target. Magnetic bead support offers wide advantages such as low sample requirement, modifiable surface, and importantly, ease to operate [126]. Li et al., obtained a high specific aptamer that binds with the serum of lung cancer patients. Initially, the single-stranded random DNA library was screened using agarose beads as a support system, serum as a target by SELEX and real-time quantitative polymerase chain reaction (RT-PCR) method. Successively, after 10 rounds of screening, the single-stranded DNA library was amplified to double-stranded DNA, following high throughput screening to obtain aptamer with high affinity towards tumor marker [127]. The bead-SELEX method was employed in another recent study, where a novel human epidermal receptor-3 (HER3) binding RNA aptamer was obtained which showed a dissociation constant of 700 nM. This novel aptamer in turn inhibited the interaction of heregulin and HER3, which were associated with causing resistance towards targeted therapy against HER2 receptor [128]. Various method of SELEX has been described in Fig. 3.

3.3. Modification of selected aptamer

The nucleotide backbone of aptamer, however, degrades under the influence of nuclease. RNA and DNA aptamers possess similar functions but vary in stability. The ribose sugar of RNA aptamers has a reactive hydroxyl group that get deprotonated at alkaline condition. As a result, the anionic group at 2′ positions affects the phosphorous ion causing RNA hydrolysis [129]. To provide target-related therapeutic effects, aptamers should be stable inside the body. Various structural modifications have been performed to get a highly stable aptamer. A widely used approach is ribose remodulation at 2′ position with fluoro or amino or O-methyl group to protect from nuclease effect [130]. One of the early examples of sugar modified SELEX employed 2′-aminopyrimidines that helped to prevent degradation by RNase A. However, this method is currently not utilized widely in comparison to 2′-fluoropyrimidines, due to instability of base pairing and negativity of chemical synthesis [131,132]. With growing knowledge about chemical modification, various other modifications have also been investigated. For instance, modification by 3′- biotin on DNA aptamer enhanced the half-life circulation with improved stability and protection from blood nucleases [133]. Nucleases are inherently chiral and thus can identify the stereospecific components. For aptamers to escape the nuclease recognition, they need to be in the incorrect chiral configuration in response to them. For instance, the DNA or RNA are composed of D-nucleotides, thus to hide and get protected, a conversion to L-nucleotide could be beneficial that could escape from the acknowledgment of enzymatic degradation [134]. But, till date, there is no such natural enzymatic activity developed that could boost up the mirror-image response of nucleic acid. Thus, modified SELEX has been employed to identify unnatural mirror image targets. D-aptamer (natural) optimized from libraries that could work against unnatural target bind with similar characteristics due to structural resemblance. In contrast, L-aptamer could therefore recognize the natural target. These L-nucleotides are known as spiegelmers (derived from the German name of mirror). As observed, D-adenosine targeted L-RNA spiegelmers did not exhibit any degradation even after 60 h of incubation [135]. Moreover, L-aptamer uses a methylene bridge to connect 2′-O and 2′-N forming a ribose sugar bicyclic configuration, thereby improving resistance from nuclease [136]. One of the best approaches to improve the circulation of therapeutic carriers is PEGylation. It becomes easy for the PEGylated molecule to diminish the glomerular filtration and enhance circulation. PEGylated aptamer has been in the focus of research that potentially delivered safe therapy against von Willebrand factor. von Willebrand factor is a glycoprotein in the blood that is involved in platelet aggregation and cardiovascular disease (CVD). In most CVD, the von Willebrand factor rises that signify critical cardiac events including cancer [137]. Another example of a well-known pegylated aptamer is Pegaptanib which is a marketed preparation used for age-related macular degeneration [138]. At different doses, the average life exhibited by Pegaptanib in vitreous humor was 90–99 h whilst after injection, the plasma concentration showed a half-life of about 88–102 h [139].

4. Clinical trials based on aptamer in context to cancer therapy

The therapy consisting of nucleic acid has been in the trend of research since last decades that put a positive impact on target-based delivery. Hundreds of clinical trials have been performed to date and endorsed by FDA as well to promote the market of targeted drug delivery systems. Keeping in mind the hypothesized target, various clinical trials using aptamer on carcinoma are going on around the world. In our search on https://clinicaltrials.gov/, we found 7 neoplasms, 2 tumors and 1 malignancy study completed/ongoing around the globe. The area-wise distribution has been shown in Fig. 4 and Table 1. To provide

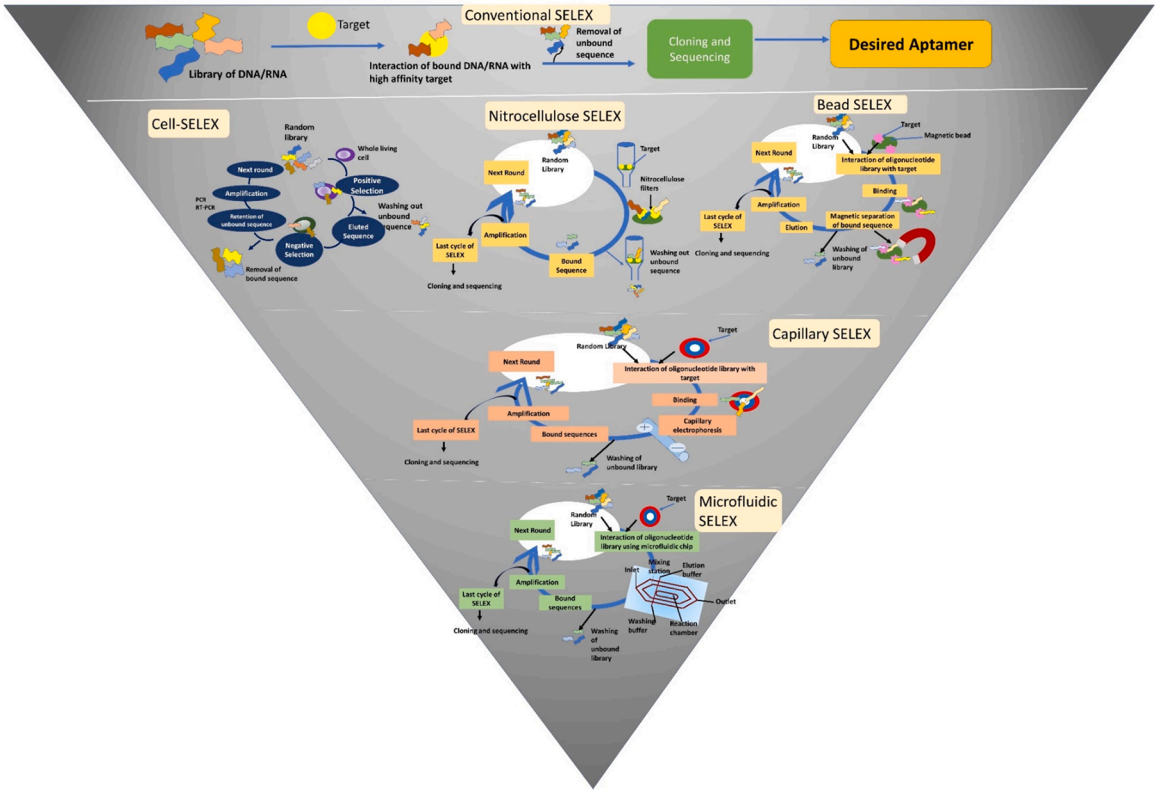

Fig. 3. Representation of various methods of SELEX.

adequate information about clinical trials utilizing aptamer as targeting ligand, all studies have been compiled in Table 2.

5. Aptamer mediated active targeted delivery of nanocarrier in breast carcinoma

Breast neoplasm is the malignant form of cancer that arises from the epithelial lining of the mammary gland [140–142]. Hormonal therapy, chemotherapy, and radiotherapy are the mainstream treatment approach against sundry cancers including breast carcinoma [143,144]. The deficiency in the clinical approach of such treatment along with multiple side effects [145], poses a burden over the healthcare system to come out with options with upgraded efficacy and importantly reduced side effects. Targeted delivery of cytotoxic agents could preferentially be useful over conventional therapy due to binding of ligands directly to the receptor promoting cell internalization; due to a mechanism called endocytosis. To follow the endocytic pathway, numerous mechanisms have been demonstrated that could escalate the internalization of aptamers: phagocytosis, micropinocytosis and clathrin/caveolin-associated pathway [146–149]. The clathrin-mediated endocytosis of aptamers was scrutinized using anti-protein tyrosine kinase 7 aptamer and Burkett's lymphoma-specific DNA aptamer [150,151]. Thus, aptamer could extend the therapeutic profile by providing targeting delivery of potent cargos (Table 3).

5.1. AS1411 aptamer

Nucleolin is a multifunction protein situated in the nucleus and overly expressed on the plasma membrane of varied cancer surfaces [152,153]. It is a protein with size of 76 kDa and is associated to carry out biological processes such as cell proliferation and the growth and regulation of transcription. AS1411 aptamer specifically binds with nucleolin that potentiate its cellular internalization reaching targeted nuclei [154,155]. The binding of nucleolin to AS1411 in tumor cells restricts Rac1 activation along with induction of methuosis, which is a unique form of nano apoptotic cell death mediated by exaggerated micropinocytosis stimulation [156,157] (Table 4).

Utilizing such profound binding and apoptosis effect of AS1411 aptamer, Abnous and the team investigated the anti-cancer effect of three different kinds of aptamer-based DNA complex. Integrin α6β4 targeted DNA aptamer (IDNAA) (aptamer that could affect the growth and migration of neoplastic cells by inhibiting the interaction of α6β4 to that of laminin), MNK2Fapt (DNA aptamer which could prevent migration, proliferation, and programmed cell death by selective inhibition of MAP kinase interacting kinase 1) and AS1411 (aptamer upon binding with nucleolin easily get internalized into the cytoplasm and target nuclei). DNA complex prepared by incubating IDNAA, MNK2Fapt and AS1411 at room temperature, showed higher internalization in 4T1 and PC 3 cells. MNK2Fapt is a therapeutically active aptamer and can profoundly hinder proliferation at low doses. However, due to the lack of specific receptors, they fail to extend into the cells. Hence, other aptamers (IDNAA and AS1411) not only improved the internalization but in together reduced the viability of cells also. Thus, such targeted therapy also opened a path of using drug-free therapy that could effectively inhibit tumor cell growth with reduced side effects [158]. There is increasing heed in DNA origami application while developing targeted therapy. So far, number of nanostructural form of DNA has been developed such as DNA nanocentipede, DNA tetrahedron structure and dendrimer nanostructure, but these designs are highly time-consuming and complicated. To have a better version, the same team proposed a novel cruciform DNA nanostructure to achieve targeted delivery of doxorubicin (Fig. 5). The novelty is composing the DNA nanostructure using two aptamers: AS1411 and FOXM1. The strategy of such a design was to reduce the dose of doxorubicin leading to less toxic effect in non-cancerous cells. The loading of drug into the novel structure was ascertained by fluorescent microscopy, which showed a reduction in fluorescence intensity after the addition of 2 μm DNA nanostructure to 7 μm doxorubicin, thereby verifying the drug-DNA nanocomplex. The

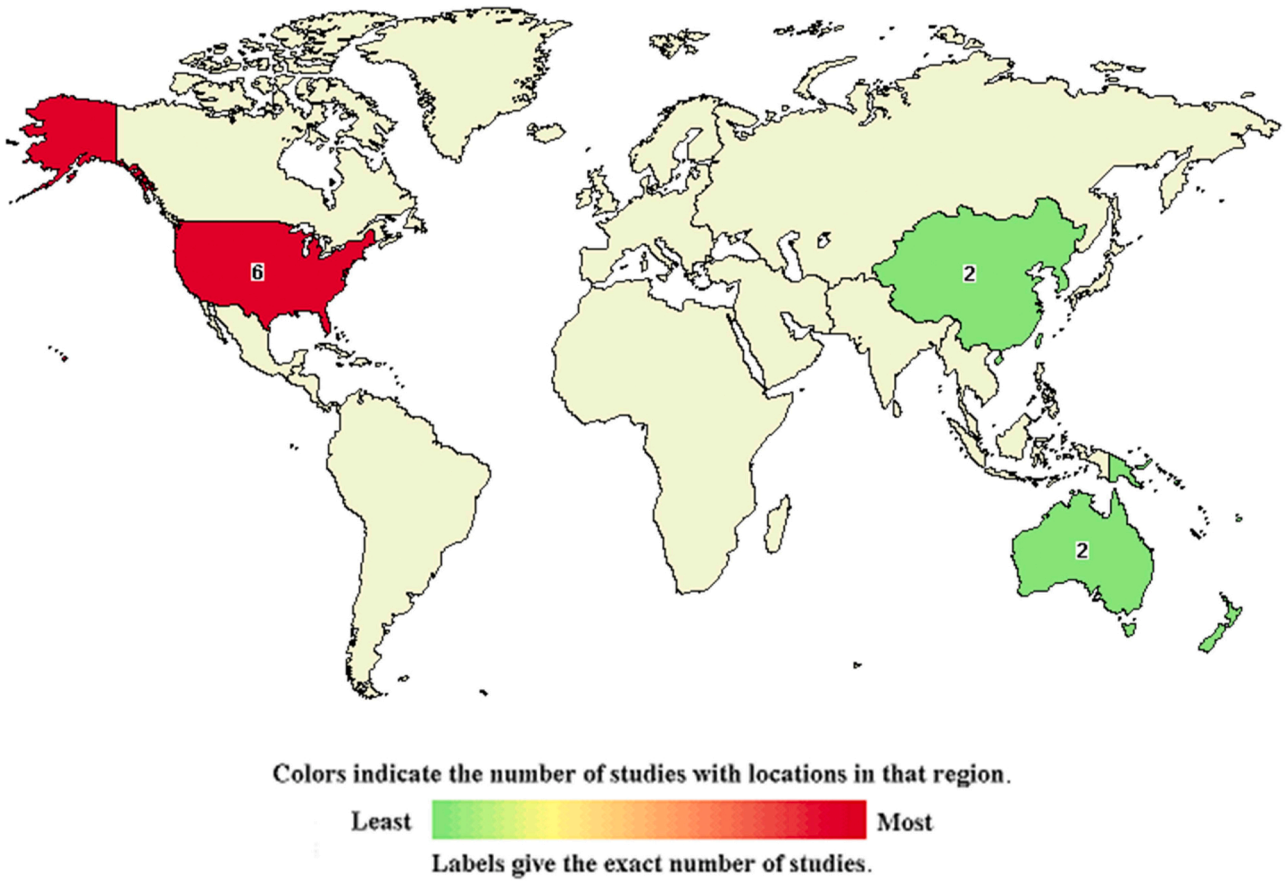

Fig. 4. Representation of country wise distribution of cancer related clinical studies using aptamer as targeting ligand. (adapted from https://clinicaltrials.gov/).

Table 1
Representation of ongoing or terminated cancer based clinical trials using aptamers.

Name of region	Number of studies	Reference
United states of America (North America)	6	[261]
East Asia and Pacifica	2	

team noted suppression of tumor growth in vivo in comparison with the DNA nanostructure group, doxorubicin treated group and the control group. Thus, the results confirm the in vivo anti-tumor efficacy of drug-DNA nanostructure with reduced concentration by elevating the targeted delivery and effect of FOXM1 aptamer as anti-cancer therapy [159]. Studies have explored the surface functionalization facility of gold nanoparticles along with their application as a drug delivery vehicle. Due to biocompatibility, non-toxicity, and small architecture they are favored in various cancer therapy [160–164]. A study potentially resolved the non-targeted effect of gold nanoparticles by attaching AS1411 aptamer on the surface of 5 nm gold nanospheres which easily get internalized into the target cell. This, in contrast to AS1411 and oligonucleotide modified gold nanospheres, facilitated a higher cytotoxic effect. Moreover, the intraperitoneal daily dose of AS1411- gold nanospheres to mouse xenograft model of breast cancer resulted in complete inhibition of tumor growth. Thus, targeting the gold nanostructure using a suitable ligand can improve anti-cancer therapy [165].

The targeting delivery of liposomes on multidrug resistant breast cancer have also been investigated in MCF-7 cells, where the doxorubicin (DOX) loaded liposome grafted with AS1411 aptamer (apt-DOX-LIP) comparatively demonstrated escalated antiproliferative activity than plain DOX and mutated aptamer conjugated liposome carrying DOX (apt/m-DOX-LIP). The IC50 value of plain DOX was less than apt-DOX-LIP and apt/m-DOX-LIP, which could be due to recognition by P-glycoprotein present over the cell membrane that pumps the DOX out before entering the cell. However, due to endocytosis, apt/m-DOX-LIP got access to cell, but P-glycoprotein's ability to recognize DOX intracellularly shows efflux of drug due to which its IC50 value retarded as compared to apt-DOX-LIP. In contrast, apt-DOX-LIP due to binding with nucleolin access to the nucleus by bypassing the pump-out effect of drug by P-glycoprotein. Thus, it was concluded a thorough information about the targeting ligand motivates the entry of nanocarrier inside the cell while overcoming the multidrug resistance by tumor cells [166].

Metal-organic framework or MOF are another subclasses of nanocarrier which are been under study due to their intrinsic porosity, modulating ability [167,168] and crystalline lattices that are applied in nanomedicine [169–172], catalysis [173–177], gas separation [178, 179] and storage along with chemical sensing [180,181]. Additionally, the MOF exceptionally allows high drug loading and their structure prevents the drug from enzymatic degradation. To further explore, scientists formulated core-shell iron oxide (Fe_3O_4)/MOF encapsulating carbon dot (to acquire fluorescence imaging) and DOX (to promote apoptosis), functionalized by AS1411 aptamer using a conjugating agent (zirconium 2-amino-1,4-benzenedicarboxylate) against triple-negative breast cancer (TNBC). TNBC is a highly aggressive disease and rely on conventional chemotherapy. Thus, the conventional delivery of drug fails to reach enough at desired tumor area and does not correspond to improved anti-cancer performance [182,183]. The formed preparation (Apt-CD-DOX-(Fe_3O_4)/MOF) showed 29% DOX release at pH 7.4 while at pH 5.5 showed 47% drug release for over 4 days. Such a prolonged release confirms the stability against serum. The TNBC positive cells (MDA-MB-231) showed more than 77% cell death after treatment with

Table 2
Clinical trial studies using aptamer for cancer therapy.

S. No.	Status	Title of study	Condition	Phase	Intervention	Total participants	Study type	Study starts	Study end	Country	Ref.
1	Recruiting	Development of detectors for diagnosis of recurrent bladder cancer.	Urinary bladder neoplasm	–	–	230	Observational	11111 june 2015	April 2022	United States	[262]
2	Not known	Assessment of Clinical Application of 68Ga Labeled ssDNA aptamer Sgc8 in Healthy group and Colorectal Patients	Colorectal cancer	Early phase I	68Ga-Sgc8	70	Interventional	11 January 2017	30 December 2019	China	[263]
3	Not known	Neoadjuvant based therapy using Abraxane against newly diagnosed breast carcinoma	Breast carcinoma	Phase II	Nab-paclitaxel	60	Interventional	April 2013	June 2020	Australia	[264]
4	Not recruiting	Investigation of proteomic biomarker for Outcome Prediction of Lipiodol TACE Treatment	Hepatocellular cancer	–	Lipiodol	60	Observational	15 September 2021	December 2024	United States 217	–
5	Active but not recruiting	Effect of Iloprost in prevention of lung carcinoma in former smokers	Lung cancer	Phase I	- Drug: Iloprost – Other: Quality-of-Life Assessment – Other: Placebo Administration – Other: Questionnaire Administration	34	Interventional	5 November 2015	–	United States	[265]
6	Withdrawn	A Phase I Study of the Combination of Alsertib (MLN8237) and Brentuximab Vedotin in Relapsedor Refractory CD30-Positive Lymphomas and Solid tumor	CD-30 positive lymphoma and Solid tumor	Phase I	– Drug: Brentuximab Vedotin – Drug: Alsertib	0	Interventional	FDecember 2015	September 2018	United States	[266]
7	Termiated	A Study of AS1411 Combined with Cytarabine for the treatment of cases with Primary Refractory or Relapsed Acute Myeloid Leukemia	Acute myeloid leukemia	Phase II	– Drug: AS1411 – Drug: Cytarabine	90	Interventional	January 2010	January 2011	United states	[267]

Apt-CD-DOX-(Fe_3O_4)/MOF, however, CD-DOX-(Fe_3O_4)/MOF and DOX-(Fe_3O_4)/MOF showed the viability of 32% and 39% respectively. Such an effect was demonstrated due to the presence of AS1411 aptamer on the surface of nanocarrier that effectively bind to the nucleolin over expressed cells and triggered the pH-responsive drug release [184] (Fig. 6).

5.2. EpCAM

The epithelial cell adhesion molecule (EpCAM) is a transmembrane glycoprotein with 314 amino acid and are majorly expressed in epithelial tissues [185]. The overexpression of EpCAM is majorly associated with deprived survival and target-based delivery [186]. The target oriented delivery of therapeutics or genes could be fruitful in binding to specific populations of cell [131,187,188]. EpCAM is one of the potent biomarkers responsible for breast cancer metastasis, which is known to be the leading cause of mortality [189]. EpDT3 is one of the best aptamers found in a study from the EpCAM aptamer family due to its high affinity towards EpCAM-expressing line Kato III cell line [190]. SYL3, another EpCAM aptamer was developed by Song and co-workers,

Table 3
Representation of aptamer mediated therapy for the treatment of breast cancer.

Aptamer	Drug/gene	Carrier	Cell line	In vivo/ In vitro	Ref.
AS1411, MNK2Fapt, IDNAA	–	–	PC-3, 4T1	In vivo	[158]
AS1411	Doxorubicin	Liposome	MCF-7	In vitro	[166]
AS1411	Doxorubicin	Metallic organic framework	MDA-MB-231	In vitro	[184]
EpCAM	siRNA	SWCNT	MCF-7	In vitro	[192]
MUC1	Paclitaxel	Albumin nanoparticle	MCF-7	In vitro	[201]
5TR1	Bcl-xL shRNA	SWCNT	MCF-7 and MDA-MB-231	In vitro	[233]
A6 aptamer	P-glycoprotein siRNA	Lipid nanoparticle	SKBR-3 and 4T1-R	In vitro	[238]

Table 4
Illustration of potential of aptasensor for detection of breast tumor cells.

Aptamer	Cell line	Outcome of study	Ref.
S6 aptamer	SK-BR-3	The formed aptasensor eliminated the normal cells and demonstrated high selectivity of anticipated biosensor.	[268]
AS 1411	MCF-7	The biopolar electrode with electrochemiluminescence was successful in detention of cancer cells	[269]
5′-amine modified aptamer	MDA-MB-231	The results explained high selectivity and sensitivity of cancer cells which detected 300cell/ml sample	[270]
AS1411 and MUC1	MCF-7	The result displayed linear aptasensor response with detection limit 6cells/ml of sample	[271]
MUC1	MCF-7	The detected cells showed a linear range of 10–1000000 cells/ml which was due to high selectivity which enable point-to-point cancer diagnosis	[272]

which was not only able to bind with EpCAM overexpressing cells but was also able to attach with EpCAM recombinant protein. The team investigated the specificity and binding ability of SYL3 on MDA-MB-231 (breast cancer cell line). Upon further optimization, SYL3C aptamer was obtained which was half the length of the original aptamer and showed a dissociation constant of 38 ± 9 nM in MDA-MB-231. The result of flow cytometry analysis indicated the cancer cell recognition ability of SYL3C aptamer with the advantage of ease synthesis, high selectivity, cancer cell imaging, and tumor detection at an early stage [191].

In another study, single walled carbon nanotube (SWCNT) conjugated with polyethylenimine/piperazine was used for targeted delivery of siRNA (SWCNT-PEI/PIPE-siRNA-Apt). To investigate whether targeted siRNA could block the expression BCL9l, MCF-7 cells were transfected with SWCNT-PEI/PIPE-siRNA-Apt and SWCNT-PEI/PIPE-siRNA. The PI staining results showed that cells treated with targeted SWCNT induced apoptosis better than non-targeted SWCNT. This efficiency of decreased level of BCL9l protein and cell death is due to the targeted delivery of aptamer [192]. In another study, human breast adenocarcinoma cells were targeted that overly express EpCAM. Such an over-expression are directly associated with poor overall survival, relapse and metastatic progression. Here in this study, EpCAM aptamer was covalently coupled with PEG-PLGA polymersomes loaded with doxorubicin by pH gradient method (Fig. 7). The nanosystem was

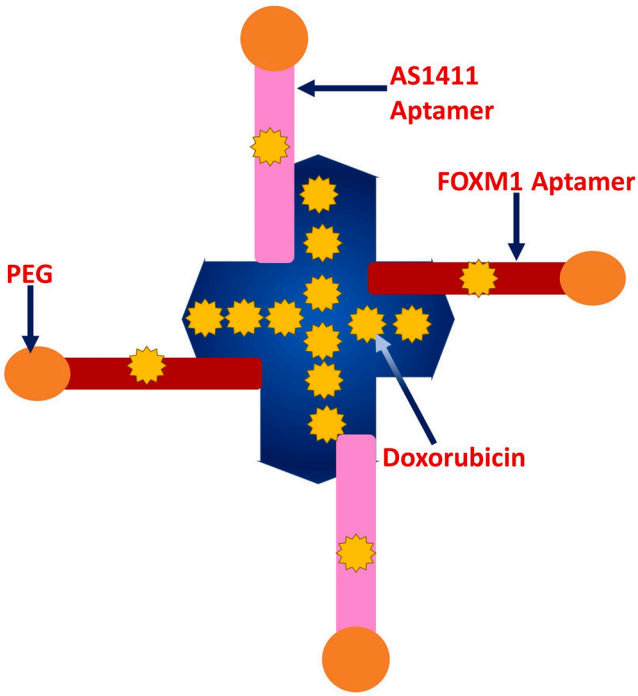

Fig. 5. Schematic representation of doxorubicin DNA aptamer nanostructure.

significantly more cytotoxic ($P < 0.01$) and exhibited higher cellular uptake and internalization in EpCAM overexpressing cells than non-targeted cell lines. The synthesized aptamer coupled nanopolymersomes offered an effective treatment strategy for the delivery of cytotoxic drugs towards the cancer cells [193].

Chemotherapy is the conventional form of anti-cancer treatment. Nutlin-3a is a murine double minute 2 (MDM2)-p53 inhibitor which acts by activating cell cycle arrest and is responsible for cancer cell apoptosis. The anti-cancer efficacy of the potent molecule has been investigated in multiple studies but low bioavailability, poor water solubility, and high drug resistance restrain its clinical use [194–196]. To overcome this, Das et al., nutlin-3a loaded multifunctional poly (D, L-lactide-co-glycolide) (PLGA) nanoparticle. To enhance the tumor-targeting benefit, the nanoparticles were functionalized with EpCAM aptamer. Moreover, the nanoparticles were also loaded with quantum dots to achieve a therapeutic plus diagnostic application of nanoparticles. This is required so to diagnose the disease at an initial stage and proving early treatment. The surface charge, particle size, and size distribution of obtained nanoparticles were measured by Zetasizer. Moreover, the surface morphology and size were further ascertained using a sophisticated instrument called atomic force microscopy (AFM) and transmission electron microscopy (TEM) as depicted in Fig. 8 **(A-C).** A broad range of in vitro studies such as cytotoxicity studies, cell uptake, apoptosis and cell cycle arrest indicated a positive anti-cancer result against breast tumor cells. Apart from this, the images of 2D monolayer and tumor spheroid obtained due to the association of quantum dots on nanoparticles suggested theranostic applicability which is better in comparison to the non-conjugated counterpart (Fig. 8**, D** and **E**). Overall, the nanosystem opened a door for cancer imaging and its therapy. However, the scientists also demanded a further in vivo investigation for its biodistribution and anti-tumor effect [197].

5.3. *MUC1*

MUC1 is a transmembrane glycosylated protein that is generally present on normal epithelial cells. Under abnormal circumstances or diseased conditions, MUC1 is overly expressed on the surface of several cancer cells such as lung, pancreatic, ovarian, and breast cancer

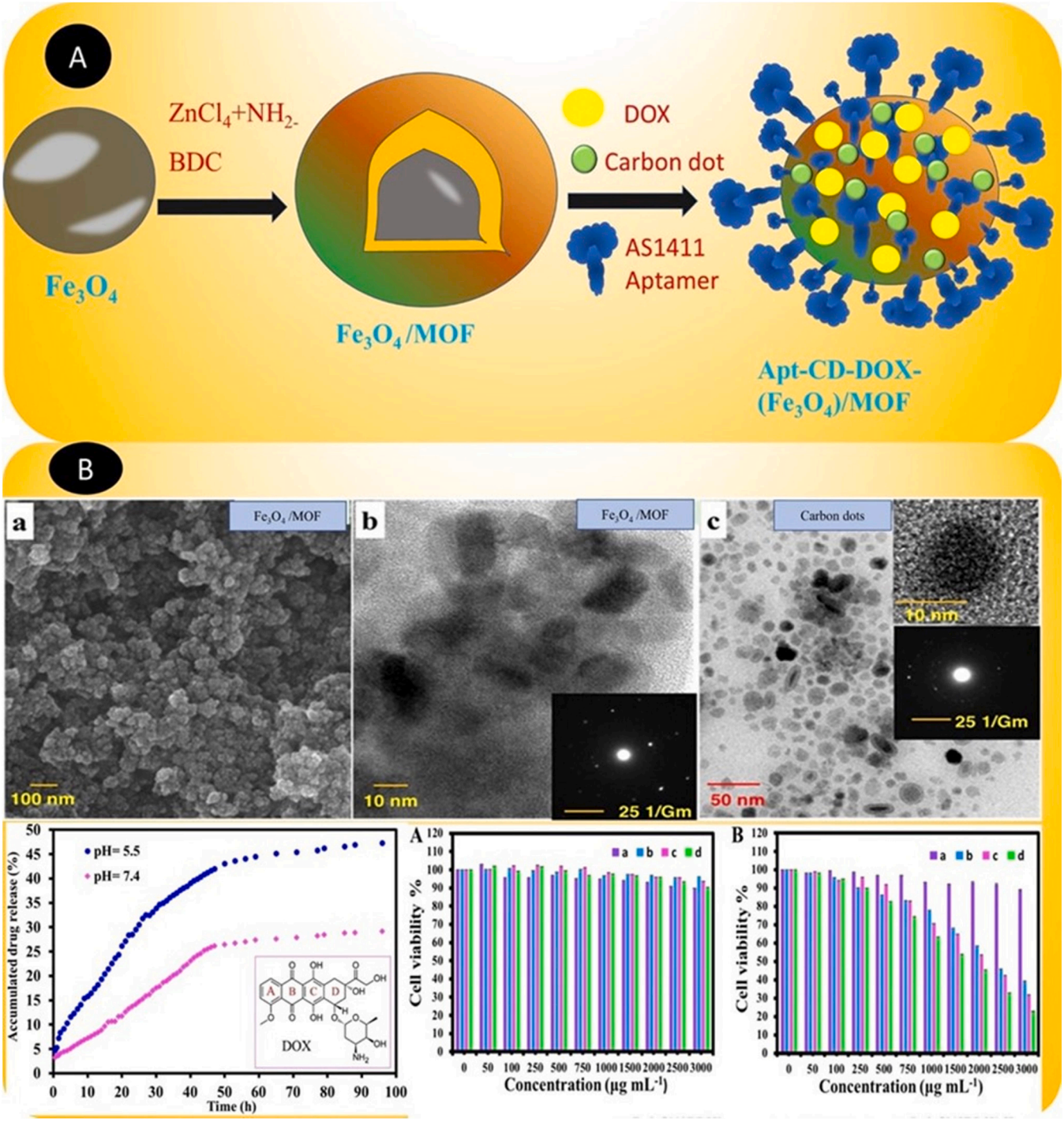

Fig. 6. A). Schematic illustration of synthesis of MOF encapsulating carbon dots and doxorubicin grafted with AS1411 aptamer against nucleolin overexpressed triple negative breast cancer cells. B). a) Field emission SEM image of Fe_3O_4/MOF b) TEM image of Fe_3O_4)/MOF c) TEM image of carbon dots, d). The release of DOX from Apt-CD-DOX-(Fe_3O_4)/MOF at pH 7.4 (pink) and 5.5 (blue), showing prolong release at acidic Ph. I: representation of cell viability of HUVEC cells incubated with a). Fe_3O_4/MOF, b). DOX-(Fe_3O_4)/MOF c).CD-DOX-(Fe_3O_4)/MOF and d). Apt-CD-DOX-(Fe_3O_4)/MOF, II: representation of cell viability of MDA-MB-231 cells incubated with a). Fe_3O_4/MOF, b) DOX-(Fe_3O_4)/MOF c).CD-DOX-(Fe_3O_4)/MOF and d). Apt-CD-DOX-(Fe_3O_4)/MOF illustrating the targeting effect of preparation on TNBC cells [184].

programmed with MUC1 gene [198–200]. In a study by Manesh et al., it was observed that paclitaxel conjugated with triphenyl phosphonium (TPP) in albumin nanoparticle decorated MUC1 aptamer (PTX-TPP-NP-MUC1) showed a strong tumor inhibitory effect at 5–200 nm on MCF-7 cells, while no uptake was observed in MDA-MB-435 cells (MUC1 under expressing cells). Such an elevated anti-tumor effect was mainly due to 3 reasons: 1) EPR effect of nanomaterial 2). TPP conjugation improved the delivery of drugs to mitochondria and 3). Selective binding of the aptamer to MUC1 over-expressing MCF-7 cells. Strikingly, TPP improved the accumulation of drug 100–500 times inside the mitochondria by decreasing the mitochondrial potential of its membrane. Thus, the preparation was found successful in the suppression of breast cancer due to the dual-targeted effect [201].

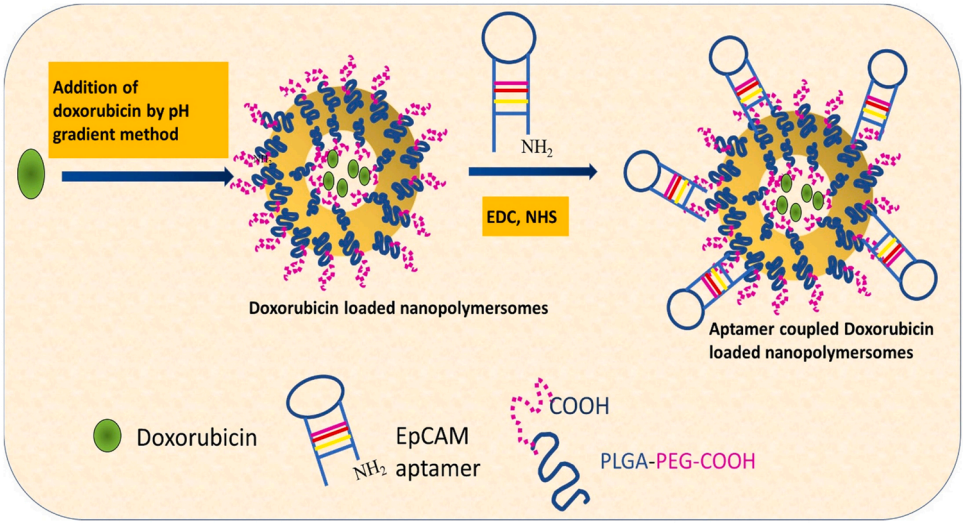

Fig. 7. Schematic representation of EpCAM aptamer grafted nanopolymersome.

The development of aptamer potentiated the mechanism of early diagnosis and therapy of cancer. Apart from being a highly sensitive and selective ligand, aptamers offer other potential benefits such as the ability to cross the barrier because of low molecular weight and ease in development and modification [202,203]. Hua et al., worked on the development of two MCF-7 cell detecting agents. In the former one, MUC1 aptamer was conjugated covalently with a magnetic bead (MUC1Apt-MB) to capture MUC1 overexpressing cancer cells. In the latter one, AS1411 was coupled to cadmium telluride quantum dots (CTQD) and decorated on the surface of silica nanoparticles (Apt-CTQD-SiNP) to form a nanoprobe. The cells were then treated with both the aptamer bound material and detected using square-wave voltametric and Photoluminescence assay. The results showed high sensitivity and specific selectivity due to signal amplification effect of quantum dots along with nucleolin and MUC1 binding affinity towards respective aptamers [204]. In another study, breast cancer was detected using nanoparticles functionalized with two different aptamers. Firstly, MUC1 aptamer (APT1) was coated on gold nanoparticle (AuNP) and then attached to ATP aptamer (APT2) functionalized CTQD via electrostatic interaction and Van der Waals forces between APT2 and AuNP forming APT1-AuNP-APT2-CTQD complex. The cells treated with dual targeted complex showed strong fluorescent intensity, which was due to the strong affinity between MUC1 receptors and its biomarker. Also, the communication between ATP molecules in the lysosome and ATP aptamer caused its dissociation from APT1-AuNP. While no fluorescence was observed in MUC1 negative cells indicating target mediated delivery of therapeutic. Thus, such an approach could be demonstrated in cancer detection and its prognosis [205].

Modulation of nanoparticles with the use of smart materials can modify the existence of the formidable disease. To this end, several varieties of nanomaterials, including metallic, magnetic, or hybridized nanoparticles and QDs played a significant role. Quantum dots (QD) have been explored widely due to their modifiable band gap energy which produces photoluminescence emission in between the wide range of wavelengths [206–209]. Navazi et al., developed a smart theranostic system by combining the use of QD and nano hydrogel loaded with paclitaxel. With a view to selectively target MCF-7 cells and eradicate their existence, the nanosystem was also loaded with sodium oxamate and lactate dehydrogenase so to inhibit pyrolysis and conversion of pyruvate to lactate and further modified with MUC1 aptamer. As a result of such treatment, the viability of the breast cancer cells reduced significantly due to higher cellular internalization and mitochondria-assisted cell death. Collectively, the smart nanocarrier could be a robust theranostic compound to detect and exterminate cancer tissues [210]. Another study observed the breast cancer targeting effect of mesoporous silica nanoparticles (MSN) loaded epirubicin, which offered a plateau of advantages in drug delivery such as amenable surface charge, controlled pore and particle size, and controlled drug release. The cellular uptake of aptamer conjugated MSN was significantly higher than free epirubicin and MSN-loaded epirubicin. The cytotoxic profile of cells treated with MUC1-MSN-Epirubicin was significantly higher than free drug and MSN-loaded epirubicin due to higher internalization into the cells. The drug lasts longer into the tumor cells and thus enables cell death. Such an effect is highly required for treatment against serious diseases like cancer [211]. MUC1 are also expressed on triple-negative breast cancer cells (TNBC) which tend to be most aggressive among breast carcinoma due to high recurrence rate and metastasis. Thus, in this regard, Carmo and the group developed PLGA nanoparticles grafted with MUC1 aptamer and labeled them with technetium-99 m to diagnose cancer. The imaging result showed higher uptake at the lesion area which is due to target mediated delivery of aptamer conjugated nanoparticles. The investigation also showed an uptake by the kidney which is due to the biodistribution of nanoparticles. Thus, it could be confirmed that the nanocarrier with ligand could be useful for cancer imaging and diagnosis [212]. A similar study was also reported by another group of researchers who investigated the capability of MUC1 capped MSN loaded with safranin-O and doxorubicin and later the nanoparticles were labeled with technetium-99 m for bioimaging. It is noteworthy that MSN-apMUC1-Tc showed relatively higher accumulation in the mouse xenograft model as observed by in vivo imaging results. The high accumulation at the cancer site was suggested to be due to the interaction of MUC1 aptamer with MDA-MB-231 overexpressing cells. Hence, aptamer could be a potential agent in both treatment, diagnosis, and imaging of cancer lesions [213].

5.4. HER-2 and ER aptamer

Investigation of cancer biomarkers sanctions the development of a therapy that works against them. The targeting ligands bind with them, inhibiting their internalization and deliver their corresponding functions. Human epidermal growth factor receptor 2 or HER-2 and estrogen receptor in combination and individual expression open a path of target mediated drug delivery system. Patients with increased expression of HER-2 demonstrate more malignant tumor, increased invasiveness, and reduction in overall survival [214]. The only treatment options available to such patients are surgical operation and chemotherapy. HER-2 monoclonal antibody called trastuzumab has been approved as first-line therapy against them however, evidence high chance of drug

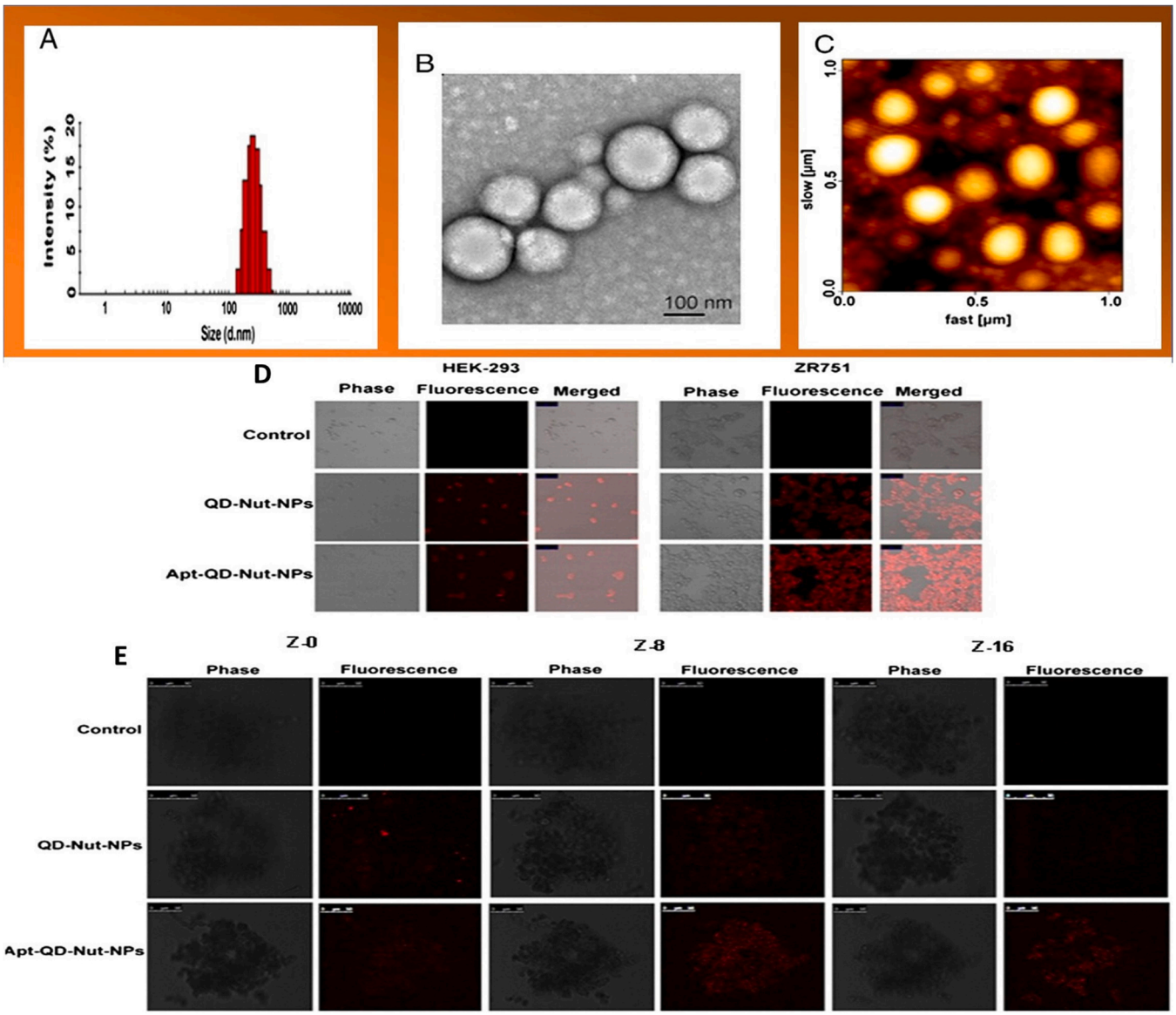

Fig. 8. Physico-chemical characterization of EpCAM functionalized nutlin-3a loaded PLGA nanoparticle (A). Particle size of nanoparticle measured by Zetasizer, (B) and (C) TEM and AFM image nutlin-3a loaded nanoparticles, (D) Confocal bio-imaging of HEK-293 and ZR751 cells grown in 2D monolayer, (E) Confocal microscopic image of ZR751 cells grown as 3D spheroid [260].

resistance [215,216]. Therefore, targeted therapy is focussed based on aptamer that directly affects the cells showing overexpression of HER-2. On this account, a HER-2 binding aptamer (HB5) was developed using SELEX that selectively targeted HER-2 peptide with *Kd* of ~19 nM. Next, doxorubicin was intercalated for targeted delivery. HB5 also strongly bind with HER-2 ECD protein with high affinity and showed no cross-reactivity to albumin and trypsin. The target binding ability of HB5 was clearly demonstrated by confocal microscopy that revealed enhanced fluorescence in HER-2 positive cells and low uptake by HER-2 negative cells [217]. Aptamers, thus are able to overcome the limitations demonstrated by antibodies, showing promising results such as better penetration due to small size and excellent stability. To explore more, aptamers in association with nanoparticles modify the therapeutic window, decrease the dose and toxicity. In another study, HER-2 aptamer was used to escort curcumin loaded albumin nanoparticle (HER-2apt-Cur-Alb Np) against cancer showing overexpression of HER-2 receptors. It is noteworthy that curcumin showed 0% release in the first 3 h at pH 7.4 that increased up to 6% after 48 h of study. However, from Cur-Alb Np, a little release was reported which mimics the biological environment and hence causes no side effect at normal physiological condition. However, at acidic pH containing GSH, the nano preparation showed an increase in release pattern from 48% to 58% after 48 and 72 h, respectively. Such a pattern of release is required to release the drug at the tumor microenvironment as well as at endosomal compartments. However, at the same condition, the release of plain curcumin was comparatively low. The conjugation of nanoparticles with aptamer was ascertained by Fourier transform infrared spectroscopy and gel electrophoresis that revealed successful conjugation of aptamer with nanoparticles. To evaluate the anti-tumor efficacy of targeted preparation in vitro, MTT assay was done. The three preparations (free curcumin, targeted nanoparticle and non-targeted nanoparticle) showed concentration and time dependent toxicity. No significant toxicity was observed within 24 h of study with either of the preparation, however after 72 h of study, the cell (SK-B3-HER positive cells) viability was 50%, 60% and 69% after treatment with HER-2apt-Cur-Alb Np, Cur and Cur-Alb Np, respectively. This is due to target mediated delivery that extensively affected HER2 cells sparing the normal cells [218]. Hence, aptamer based therapeutics should be

investigated more because it has the potential to reach the clinical market, enhance patient compliance, reduce drug dose, and thus associated side effects. A6, ECD-APT1 and HB5 are some aptamers that show strong binding affinity towards HER2 positive cells [219,220].

In similarity, estrogen receptors are also overexpressed on certain breast cancer cells. However, aptamer to target such cells have not been investigated much. Estrogen receptor basically contains three domains known as C terminal ligand binding domain, N-terminal domain and central binding domain. The binding of estrogen with its receptor encourages its release and initiates signals that encourages cancer metastasis and progression [221,222]. Thus, it becomes essential to not only treat such cancer but also diagnose them at an early stage. Sett and group devoted their time to the development of a DNA aptamer (ER-Apt) based probe for selective detection of estrogen receptor-positive cancer cells. A DNA aptamer was screened out via SELEX when ERα+ cells were used as a target. The histogram result of flow cytometry showed a shift in fluorescence signal in MCF-7 (ERα+) cells after incubation with ER-Apt while no such result was exhibited by MDA-MB-231 cells (ER- cells). The results thus indicated binding of the aptamer to its target only. The FAM-labeled aptamer (FAM- ER-Apt) made the nucleus appear green as observed by immunofluorescence study. Both ER-Apt and scrambled aptamer showed cytotoxicity at higher concentrations but not at a lower concentration. However, no such result was demonstrated in ER-ve cells [223]. Hence, all studies established one common fact, that aptamers can selectively bind to their target cells and spare the normal cell or untargeted cells. To increase the therapeutic and diagnostic window of therapeutic chaperons, such target-mediated therapy is required.

5.5. Other aptamer

Aptamers are designed according to the structural outlook of the target and its cellular localization. Intracellular or extracellular oncoproteins drive the ability of the cell to become tumorigenic which could be besieged by aptamers to stimulate anti-cancer pathways antagonizing the effect [224]. The main concern while intracellular delivery of aptamer is maintaining the structural integrity, nonetheless, many groups were successful in the delivery of completely functionalized aptamer [225–232]. In a study, SWCNT was conjugated with polyethyleneimine and modified with 5TR1 aptamer for the delivery of short hairpin RNA or shRNA to the breast cancer cells. Gene therapy put a good impression in cancer treatment as the expression of an oncogenic gene can be suppressed. SWCNT formulated its way towards cytoplasm through the nano-needle technique without causing any disturbance to the membrane. While polyethyleneimine derivative facilitated the endosomal release of polyplex through 'proton sponge effect', thus prevented from lysosomal degradation. The results exhibited the great potential of targeted gene delivery causing apoptosis of cancer cells (Fig. 9) [233].

The major impediment for an effective anti-cancer regimen is multidrug resistance (MDR) [234]. However, it is still unclear about the main reason behind resistance towards anti-cancer therapy. Extrinsic and intrinsic, both the mechanisms have been considered as a possible way of drug resistance by breast tumors [235,236]. One of the major investigated causes of MDR is overexpression of ATP-binding cassette transporters, among which P-glycoprotein is the culprit of anti-cancer treatment. P- glycoproteins do not allow the entry of drugs inside the cell keeping their level beneath the therapeutic verge. Thus, the frequency of research focussing on MDR increased. Wu and their team used siRNA to restrain the activity of P-glycoprotein, thus escalating the sensitivity of anti-cancer therapy [237]. Utilizing such a technique, Powell along with other scientists developed A6 aptamer grafted hybrid nanoparticle encapsulating P-glycoprotein siRNA to overcome the resistance mediated effect. Due to the effect of targeted therapy, the expression of P-glycoprotein was successfully reduced following higher accumulation of drug inside the breast cancer cell's nuclear compartment. Hence, aptamers elicit a promising approach not only in the treatment of confined cancer but also help in overcoming the resistance offered by tumorigenic cells [238]. Another glycophosphoprotein called osteopontin (Opn) is mainly secreted by metastatic cancer cells [239–245]. They are overly expressed on several cancers and protect cells from apoptosis, induce the formation of the colony, escalate metastasis and migration. Clinical studies confirmed the association of Opn with a malignant tumor and meagre patient outcomes [246–248]. In this regard, RNA aptamer targeting Opn has been developed and

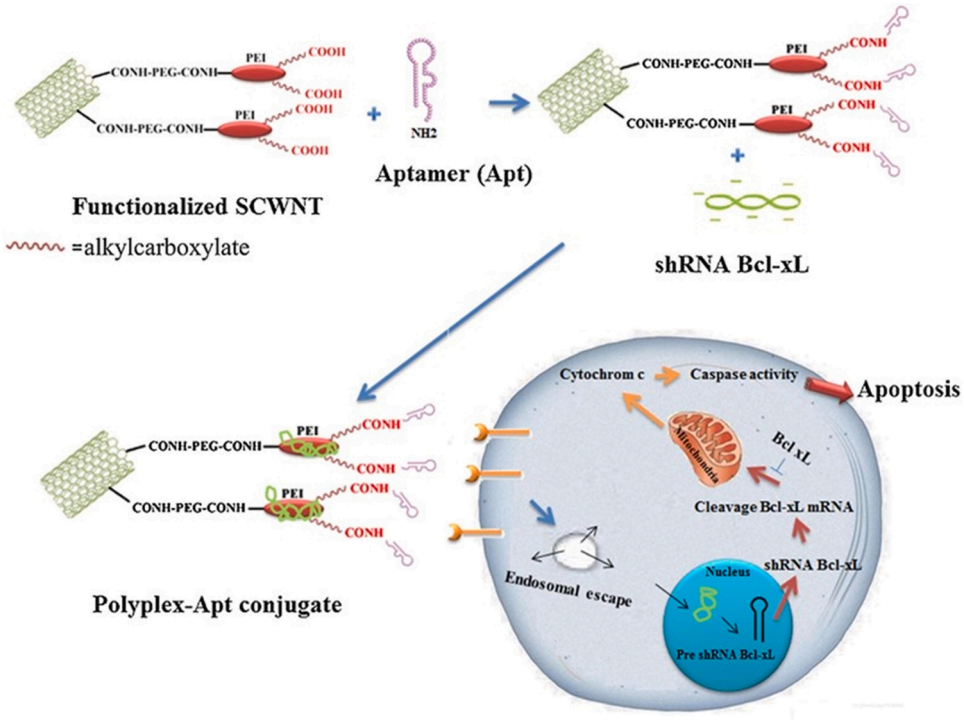

Fig. 9. Schematic illustration of delivery of aptamer conjugated SWCNT for the delivery of shRNA [233].

studied which showed targeted delivery on MDA-MB-231 cells liberated relevant metastatic cancer growth suppression [249]. Since, chemotherapy, radiotherapy and surgery impose a burden of side effects on patients, photothermal therapy is being presented as star treatment due to high sensitivity and accuracy, ease to operate, and importantly shows minimal side effects. Still photothermal and photodynamic therapy is under controversy due to the non-recognition of tumor cells. Photodynamic therapy can activate photosensitizers within the tumor cells to persuade chemical damage and cell death. Since the aptamer can selectively target the cancer cells, albumin modified molybdenum disulfide nanosheets were fabricated and surface modified with nucleic acid aptamer. After combination with laser irradiation of 808 nm, subcutaneous tumor progression was inhibited with a continuous rise in mice's body mass. Hence, it was evidenced, photothermal therapy using targeting ligand possesses effective and precise treatment of breast cancer.

6. Current challenges and possible solutions

Aptamers demonstrate excellent performance in vitro, however, still there are various bottlenecks in their clinical use. The most frequently encountered hurdle of using aptamers is the nuclease degradation in blood and biological fluid. The aptamers degrade in blood within a few minutes (approximately 10 min) [250], which is insufficient for any therapy to reach up to the mark [251]. Thus, several methods have been developed to protect aptamer from nuclease degradation (Fig. 10). Two methods are in current clinical practice, which uses a modified form of aptamers. One is an in-SELEX method and the second is the post-SELEX method; in the former one, aptamers with predefined structure and compatibility with DNA polymerase could be directly isolated from DNA or RNA library. Modifications such as 2′-fluoropyrimidines [131], 2′-aminopyrimidines [252], and 2′-O-methyl nucleotides [253] have been included in SELEX procedure. Macugen is the best clinical example obtained using this modification [254]. However, the success of such modifications is very low as the affinity and specificity of aptamer get affected. In post SELEX approach, modifications are introduced during solid-phase chemical synthesis to the pre-selected aptamer, for example at the base, phosphate group, sugar ring or 2′-positions. However, such modification of pre-selected aptamer could also affect the binding affinity with the target [255]. Hence, aptamers should be tailored in a way that could have no impact on its selectivity and specificity.

Aptamers with molecular weight ranging from 5 to 20 kDa are easily removed via renal filtration as kidney can easily remove compounds with a molecular weight below 50 kDa. One of the best approaches to overcome such limitation is a conjugation of aptamer with polyethylene glycol. The PEGylated aptamer remains in the bloodstream for several days without losing its efficacy [256,257].

Aptamers also recognize several targets that bind to the molecules with similar configuration. Gening et al., developed aptamer against DNA polymerase β, but it also inhibited DNA polymerase κ, which are another class of DNA polymerase family [258]. Such cross-reactivity causes side effects by affecting other metabolic responses. However, such limitations could be conquered by introducing a negative selection step in the SELEX procedure [259].

7. Concluding remark

With a surge of scientifically advanced tools and novel technology, we have reached an era to cure diseases based upon their biological characteristics. Aptamers are today widely used technique due to employability in identification, internalization, and safe delivery of therapeutics or nanotherapeutics. However, to date only one kind of aptamer-based therapy, Macugen, got the nod to be placed in the market. It should, however, be noted that any effective therapy requires several research years before its placement into phase IV clinical trial. Aptamers being extraordinary candidates degrades by nucleases and hence withdraw their targeting ability. This is one of the reasons, why aptamer fails to acquire a successful position. However, with little modification, the feasibility of aptamers can be upgraded. Their high target binding nature, excellent tolerability, improved shelf life and non-immunogenic nature continuously bring the eye of many scientists and investors. Aptamers escort the carrier directly to the nucleus via receptor-mediated endocytosis, thus can escape the endosome. It is noteworthy that aptamer-based therapy was able to overcome the MDR barrier eliciting an effectively upgraded treatment effect. Cytotoxic drugs, genes that silence the oncogenes and diagnostic agent can be delivered successfully to appropriate and pre-determined cells; such that only cancerous or diseased cells will react after their delivery while normal cells will remain confined and protected from targeted therapy. While reviewing, only few studies demonstrated animal study, while the others used only cell lines. To the best of our knowledge, aptamers have been extensively utilized in multiple studies against breast cancer.

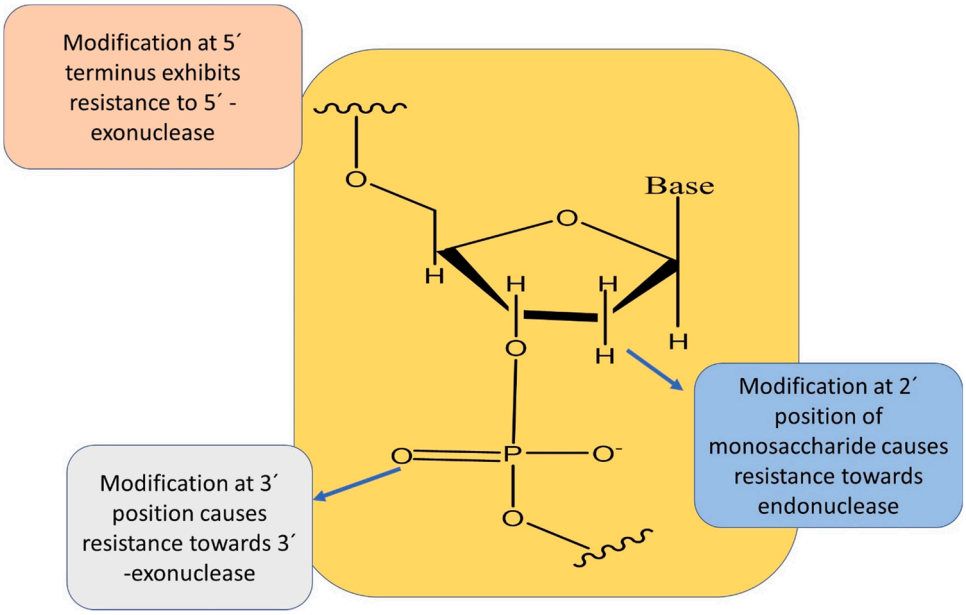

Fig. 10. General modifications of oligonucleotides against nuclease degradation.

Moreover, for the first time, a review on aptamer-based targeted therapy for breast cancer has been demonstrated which makes this article novel. To come up and combat the deadliest disease, one must establish a 'proof-of-concept' to provide the application of smart therapies. Scientists should also examine the in-vivo targeting and anti-cancer activity. Hybrid materials, dual-targeted therapy, therapy mimicking the tumor microenvironment along the employability of aptamer will motivate safe and effective delivery of therapeutics towards cancers including breast neoplasm. Such next-generation remedial strategy and early diagnosis is extremely required to relish healthy life under diseased condition.

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CRediT authorship contribution statement

All authors contributed equally and significantly to complete this manuscript.

Conflict of interest statement

There is no conflict of interest and disclosures associated with the manuscript.

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