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Functionalized liposomes as drug nanocarriers for active targeted cancer therapy: A systematic review

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Abstract

Cancer is a broad term used to describe a group of diseases that have more than 270 types. Today, due to the suffering of patients from the side effects of existing methods in the treatment of cancer such as chemotherapy and radiotherapy, the employment of targeted methods in the treatment of this disease has been received much consideration. In recent years, nanoparticles have revolutionized in the treatment of many diseases such as cancer. Among these nanoparticles, liposomes are more considerable. Active targeted liposomes show an important role in the selective action of the drug on cancer cells. Until now, a variety of anti-cancer agents have been reported for targeted delivery to cancer cells using liposomes. The results of *in vitro* and studies *in vivo* have been shown that selective action of the targeted liposomes is increased with reduced side effects and toxicity compared with free drugs or non-targeted liposomes. This systematic review expresses the reports of this type of drug delivery system. Search terms were searched through several online databases including PubMed, Scopus, and Science Direct from 1990 to 2019 and the quality evaluation was performed. Out of 11,676 published articles, 196 articles met the inclusion criteria. The current report reviews developments in the liposomes targeted with aptamer, transferrin, folate, and monoclonal antibodies.

Keywords: Liposome, Active targeting, Cancer therapy, Aptamer, Transferrin, Folate, Monoclonal antibodies.

1. Introduction

Duo to the high side effects of the common cancer therapies (chemotherapy, radiation therapy and surgery) such as damage to healthy cells, the targeted therapy with different mechanisms of action are attracted more attention [1]. Today, the use of nanostructures as a system for targeted drug delivery has been widely considered [2]. Nano-systems are able to use the structural features of tumor tissue for passive targeting. A free drug may be released non-specifically, while a nanostructure can be inserted into tumor tissue through enhanced permeability and retention (EPR) effect *via* leaky blood vessels. Increased permeability of blood vessels in tumors causes the accumulation of nanoparticles and release of drugs in the vicinity of tumor cells [3-6]. However, the reduction of drug toxicity and increase the therapeutic index can be obtained by the site-specific delivery. In addition to reach tumor microenvironment passively through the EPR effect, the surface engineered nano-systems can target specific cancer cells by binding to the receptors over-expressed in cancer cells including fibroblast growth factor, epidermal growth factor, folate (FA), transferrin (Tr), and nuleolin receptors. Targeting these overexpressed receptors accumulates the anticancer agent in cancer microenvironment and increases the uptake of the agents by cancer cells [7]. Among these nanosystems, liposomes are the most common nanocarriers owing to their inherent advantages such as high biocompatibility, cell-like membrane, low immunogenicity and toxicity, ability to protect drugs from hydrolysis, and prolong their biological half-life. Liposomes are microscopic vesicles containing a phospholipid bilayer that surrounds a fluid space. Due to the amphipathic properties liposomes can encapsulate hydrophilic and hydrophobic drugs [8,9]. Surface modification of liposomes was firstly implemented with monoclonal antibodies with capability of binding to specific tumor antigens. In addition to monoclonal antibodies (mAbs), other molecules such as transferrin, folate, and new agents so called aptamers have been conjugated with liposomes to construct active targeting agents (Fig. 1) [10-12]. The main objective of this systematic review is to present an overview of studies on the use of aptamers as new functionalizing agents for construction of targeted liposomes as well as summarizing the studies on the functionalized liposomes with the conventional ligands.

2. Methods

2.1. Study selection and Data sources

This systematic review was conducted by searching through PubMed, Scopus, and Science Direct databases from 1990 to 2019. The selected search keywords were liposome, targeted therapy, liposome encapsulated, folic acid, monoclonal antibodies, transferrin, and aptamer. The medical subject headings (MeSH) terms including: transferrin AND liposome AND cancer therapy AND folic acid OR folate AND targeted AND monoclonal antibodies AND Functionalized liposomes AND aptamer OR oligonucleotide NOT photodynamic therapy NOT photothermal therapy were used for detection of articles. It is noteworthy that due to the large amount of data in this field, except in case of aptamer functionalized liposomes, the other articles from 2015 to 2019 in the main text and the articles from 1990 to 2014 are provided in the supplementary material. The search in databases was conducted by four independent researchers, and the results were checked by the fifth researcher.

2.2. Study eligibility

Articles with insufficient data for extraction as well as review and duplicate articles were excluded from this analysis**.** The included articles were those contained liposomes with the intended ligands for the treatment of cancer and published in English language.

2.3. Collection and extraction of data

Firstly, the specified keywords were searched in the desired databases to obtain the articles. After exclusion of duplicate publications, the remaining articles were further studied for defined eligibility criteria according to their titles and abstracts. Then, the full texts of original articles were carefully evaluated for extraction of the specified data. The studies in functionalized liposomes were separately categorized based on type of ligand. In each case, the type and size of liposome, the type of loaded drug and receptor/antigen, the clinical application, and the type of study were determined.

2.4. Screening and selection results

A total of 11,676 potentially relevant articles were identified by searching through the databases. After removing duplicates publications, review articles, and those were not related to the cancer therapy, the titles and abstracts of 295 remaining articles were screened according to eligibility criteria. In this step, 82 records were excluded from the analysis because of including of other ligands, photo-thermal and photodynamic effects or other reasons. In addition, 18 articles were removed duo to combined function of ligand with another agent and the negative results. Finally 195 full text articles were included in qualitative assessment and data extraction. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the search process is illustrated in Fig. 2.

3. Results

3.1. Liposome functionalized with Aptamer

The recent drug discovery approaches try to design the molecules that are able of modulating the activity of biological targets. Today, new methods have been developed for the synthetic drugs production and biological ligands such as SELEX (Systemic Development of Ligands with Rich Enrichment). Aptamers are artificial single-stranded and short-chain oligonucleotides derived from RNA or DNA and they can be produced by the *in vitro* SELEX method (Fig. 3) [13]. These emerging ligands have been known as alternative to antibodies. They can be easily conjugate with the variety of functional groups, biomolecules and dyes without losing their activity (unlike antibodies) [14]. Also, the much more stability of aptamers than antibodies make them suitable for difficult conditions such as high temperatures. Conjugating aptamers with therapeutic agents for targeted drug delivery have received much attention today. Aptamers have been more considered for targeting liposomes due to their low molecular weight, non-immunogenicity, better tumor penetration and targeting, and no change in affinity by chemical modification. Moreover, aptamers have unique 3D structure that is affected by their sequence. Aptamers have been screened for a wide variety of the disease-related biomarkers such as epidermal growth factor receptor (EGFR), prostate-specific membrane antigen (PSMA), human epidermal growth factor receptor 2 (HER2), protein tyrosine kinase (PTK7), and vascular endothelial growth factor

(VEGF). The aptamer attachment to the target is highly selective and with a high binding affinity. In recent years, aptamers have been emerged as a new and advanced generation of promising targeted ligands, especially in the field of drug delivery systems for cancer therapy [15, 16].

Yu et al. developed a method for prepare aptamer-functionalized cationic liposomes. They used the aptamer by sequence 5 -HS-(T) 10 GGTGGTGGTGGTTGTGGTGGTGGTGG-3 (AS1411, nucleolin aptamer). The liposomes were loaded with Paclitaxel (PTX) and Polo-like kinase1 targeted siRNA, and functionalized with aptamer. The AS1411 ligand makes the liposome selectively targeted MCF-7 cells *in vitro* and *in vivo*. This formulation enhanced the apoptotic cell death and reduced angiogenesis. They concluded that the using AS1411 aptamer functionalized liposomes can be served as a promising platform for treatment of breast cancer [17].

Aptamer-functionalized liposomes for treatment of cell carcinoma were developed by Cadinoiu et al. The liposomes were prepared by film hydration technique and conjugated with aptamers for enhancing active targeting. AS1411 aptamer conjugation increased liposome size and the negatively charged DNA aptamer enhanced the surface potential of the liposomes. The *in vitro* release of 5-Fluorouracil (5-FU) showed that after 24 h, a small amount of drug was released from targeted liposomes. *In vitro* anti-tumor studies indicated that the aptamer functionalized 5-FU encapsulated liposomes induced a significant cytotoxic effect on cancer cells. Therefore, it was concluded that the formulation could be effective in cancer treating [18].

In 2015, Alshaer et al. developed the liposome functionalized with anti-CD44 aptamer for targeting cancer cells. CD44 receptor protein is overexpressed in many cancer cells. They used aptamer with sequence 5'GGGAUGGAUCCAAGCUUACUGGCAUCUGGAUUUGCGCGUGCCAGAAUAA GAGUAUAACGUGUGAAUGGGAAGC UCGAUAGGAAUUCGG-3'. Zeta potential of both Mal-Lip and Apt1-Lip was −17.5 ± 0.9 mV, n=6 and −31.0 ± 2.3, n=6. They also evaluated the cellular uptake by Flow-cytometer and confocal imaging using the two $CD44^+$ cell lines; human lung cancer cells (A549), human breast cancer cells (MDA-MB-231), the $CD44^-$ cell line, and mouse embryonic fibroblast cells (NIH/3T3). The results showed that this formulation was more sensitive to cancer cells [19].

Aptamer-targeted liposomes for the treatment of breast cancer have been prepared by Xing et al. Firstly; liposomes containing doxorubicin (DOX) were prepared and functionalized with AS1411 nucleolin aptamer. Then, the efficacy of the liposomes was evaluated *in vitro* and *in vivo*. The findings exhibited that AS1411 aptamer-conjugated liposomes increased more cellular internalization and DOX cytotoxicity on breast cancer cells than non-targeting liposomes. In conclusion, this formulation could recognize nucleolin overexpressed on breast cancer cells surface and enabled drug delivery with high specificity and selectivity [20].

These results also agree with findings of Li et al. which formulated DOX containing liposome targeted with AS1411 aptamer for breast cancer treatment. According to their results, targeted liposome increased cellular uptake and cytotoxicity of the drug through aptamer-mediated drug delivery which preventing drug efflux and enhancing therapeutic effect [21].

Duan et al. in 2018 described vincristine-loaded and sgc8-modified liposomes for treating acute lymphoblastic leukemia (Fig. 4). Sgc8 aptamer binds specifically to PTK7 which is a transmembrane receptor protein tyrosine kinase and a potential biomarker for T-ALL. The particle size, zeta potential, PDI, encapsulation efficiency, and drug loading of this formulation were 110.37 nm, −14.37 mv, 0.201, 90.63% and 9.38%, respectively. They also evaluated the binding properties of sgc8/VCR-Lipo which are critical for its specificity and efficacy. The IC_{50} value for sgc8/VCR-Lipo was 8.2-fold cytotoxic than that of VCR-Lipo after 24 h. According to the results, intravenous injection could specifically deliver sgc8/VCR-Lipo into the local tumor which indicated the efficacy of targeted liposome in the treatment of cancer [22]. All the reported research works in aptamer-functionalized liposomes are summarized and given in Table 1.

3.2. Liposomes functionalized with Folic acid (FA)

As mentioned, the higher overexpression of some receptors in cancer cells than in healthy cells can be considered in choosing the suitable ligand to conjugate with the liposome for targeted drug delivery system. The folate receptor (FR) belongs to the family of glycoproteins known as FRa, FRb, and FRg isomers. The FRa isomer has the greatest potential for targeted cancer treatment. In cancers including breast, lung, kidney, ovarian, colorectal, and brain, the folate receptor is highly expressed [53]. However, sarcomas, lymphomas, pancreas, testicles, bladder, prostate, and liver cancers often do not show a high level of folate receptor. FA is widely used

tumor-targeting ligand with the stability over a wide range of temperatures and pH that can bind specifically to the folate receptor [54]. This ligand is a small, hydrophilic, non-toxic, inexpensive, and stable circulating molecule that makes it useful for targeted transfer [55]. FA increases treatment efficacy, decreases drug dosage and reduces toxicity of therapeutic agents to healthy tissues [56-58].

5F-U liposome targeted with folic acid was designed by Handali et al. for drug delivery to the colon cancer. In this work, the cytotoxicity of formulation against HT-29, Caco-2, CT26, HeLa and MCF-7 cell lines was determined by MTT assay. They used the response surface methodology (RSM) method to optimize the formulation condition. The optimal formulation showed 39.71% encapsulation efficiency. The mechanism of cell death was also investigated through the production of reactive oxygen species (ROS), change in mitochondrial membrane potential ($\Delta\Psi m$), cytochrome c release and activity of caspase 3/7. The results showed selective delivery and higher toxicity of targeted liposomes in comparison to free drug [59].

In 2018 combination of Celastrol and Irinotecan were encapsulated in FA conjugated liposomes by Soe et al. These nanocarriers were prepared by the thin-film hydration technique. The formulation showed higher drug release profiles for both drugs and higher cellular uptake and increased apoptosis in FA receptor-positive breast cancer cells. Besides, *in vivo* studies showed efficient drug delivery of the targeted formulation by specific targeting of cancer cells and minimizing systemic adverse effects (Fig 5) [60].

Min et al. reported the synthesis and evaluation of a drug delivery system to FR overexpressing mouse origin breast cancer cells. In this work, the FA coated liposomes encapsulated with both gold nanorods and DOX were prepared. The results showed that when liposomes were exposed to an 880-nm NIR laser, the release of DOX was increased. NIR laser also increased the toxicity of the formulation to the cancer cells. Therefore, the use of this drug delivery system was suggested as an effective strategy for treating the cancer cells that have a high expression of folate receptors [54].

FA conjugated cationic liposomes loaded with Bis-arylidene Oxindole (NME2) were developed by Elechalawar et al. The mole percentage of targeting ligand (FA) in the formulation was > 11%, which is typically well above (3-4 times) the ligand percentage used in conventional

practice. The ligand-targeted liposomes triggered up-regulation of caspase-8 in FA receptor-moderately expressing melanoma cells. In this formulation, the combination treatment of targeted FA-liposomes and NME2 could induce caspase-8 through activation and consequent cleavage of receptor interacting protein kinase-1 (RIP-1) [61].

The folate-conjugated pH-sensitive liposomes containing DOX for treatment of breast cancer have been designed by Silva et al. According to the results, targeted formulation exhibited higher cellular uptake and anti-cancer activity than free DOX. Moreover, encapsulation of DOX in liposomes significantly decreased DOX cardiotoxicity and pulmonary metastasis [62]. All the reported researches in FA conjugated liposomes are summarized and given in Tables 2 and S1.

3.3. Liposomes functionalized with Transferrin (TF)

Another ligand used for targeting of liposomes is TF. Transferrin receptor (TFR) is a membrane glycoprotein which mediates iron acquisition by most cells in the organism. Malignant cells such as cancer cells require high levels of iron, so this receptor is much more expressed [78, 79]. This receptor has been regarded as an important tool for targeted transmission (Fig. 6).

Plumbagin liposomes functionalized with TF have been described by Sakpakdeejaroen et al. They showed that the loading of plumbagin in Tf-bearing liposomes significantly enhanced plumbagin uptake by cancer cells, resulting in an improvement of the anti-proliferative (by up to 4.3-fold) and apoptosis efficacies (by up to 5.5-fold) compared with the drug solution. *In vivo*, the intravenous injection of Tf-bearing liposomes entrapping plumbagin led to tumor suppression for 10% of B16-F10 tumors and tumor regression for a further 10% of the tumors [80].

Jhaveri et al. described TF receptor targeted liposomes for Resveratrol (RES). They showed that compared to free RES or RES-L, the TF-RES-Ls were significantly more cytotoxic and induced higher levels of apoptosis through the activation of caspases 3/7 in GBM cells. The therapeutic efficacy of this formulation was studied in a subcutaneous xenograft mouse model of GBM. Tf-RES-Ls showed more tumor growth inhibition than free drug and non-targeted RES liposomes [81].

In 2017 BI et al. developed TF-conjugated liposomes for targeted drug delivery to cancer cells. The mean size, zeta potential, and drug encapsulation efficiency of liposomes were 125.3 nm,

+2.9±2.4 mV, and 65.3%, respectively. Free cordycepin suspension released about 85% within 4 h; however, liposome-cordycepin and TF-liposome-cordycepin released about 80% after 24 h. The IC_{50} value for TF-liposome cordycepin in HepG2 cells was 31 μM at 24 h. As a result, TF-modified liposomes exhibited an increased cytotoxicity on the cancer cells [82]. All the reported researches in TF-conjugated liposomes are summarized and given in Tables 3 and S2.

3.4. Liposomes functionalized with Monoclonal antibodies (mAbs)

One of the important ways to treat cancer is to use formulations that deal directly or indirectly with the immune system. Today, antibody-antigen reactions are widely used to diagnose and treat many diseases. mAbs are antibodies produced by B cells. In contrast to polyclonal antibodies, mAbs are mono-specific and homogeneous [93]. Purified antibodies have more tendencies for binding to the antigens and as a result, the reactions are more sensitive. Until now various types of antibody fragments such as anti-CD20 monoclonal antibody, anti-CD47 monoclonal antibody, EGFR antibody, and anti-Fas monoclonal antibody have been used as targeting agents [94]. mAbs can strengthen the immune system's attack to cancer cells by binding to cancer cell surface antigens. The conjugation of antibodies to liposomes leads to improve the cancer cellular uptake and enhances the cytotoxic activity of the drugs [95, 96]. All the reported researches in mAbs conjugated liposomes are summarized and given in Tables 4 and S3.

Arabi et al. developed anti-CD44 liposomes of DOX. The liposome size was 90.1 ± 2.1 nm with PDI of 0.14 ± 0.01 and zeta potential of -18 ± 0.01 before coupling to antibody, which partly increased to 107 ± 3.1 nm with PDI of 0.26 ± 0.02 and zeta potential of -15.6 ± 0.03 after the conjugation. In this study, the results of flow cytometry analyses and confocal laser scanning microscopy indicated the enhanced cellular uptake of this formulation in CD44-positive C-26 cells compared to free drug. Moreover, CD44-DOX-L at doses of either 10 or 15 mg/kg resulted in superior tumor growth inhibition. The authors suggested that CD44-DOX-L formulation can be exploited in targeted therapy for a variety of tumors [97].

In 2018, Anti-GD2 liposomes loaded with Sepantronium bromide (YM155) were prepared by drug/lipid film hydration and extrusion method. Immuno-liposomes had zeta potential of -10 mV, with an antibody coupling efficiency of 60% and YM155 encapsulation efficiency of14%. An *in-vitro* toxicity study showed the less toxicity for immune-liposomes as compared to free

drug. However, *in vivo* pharmacokinetic evaluation showed the prolonged blood circulation and increased half-lives of the targeted liposomes [98].

The anti-CD44 immuno-liposomes encapsulating glycosylated PTX were developed in 2019 by Khayrani et al. They found that the overexpression of CD44 was only in SK-OV-3 cell lines and therefore, they considered it as representative of CD44-positive cells. The IC_{50} values of the cell lines were in the range of 15–20 nM, which means that the cells are sensitive adequate to give the feasibility of using the targeted formulation for ovarian cancer treatment. They also evaluated the anti-tumor effects of the prepared formulation *in vivo* with repeated administration at a total dose of 300 mg/kg of PTX. It was found that targeted liposomes exhibited higher cytotoxicity in SK-OV-3 cells than glycosylated paclitaxel liposomes and glycosylated paclitaxel. Moreover, targeted liposomes showed most effective anti-tumor activity without adverse effects. It was concluded that this formulation has a potential for targeted drug delivery to the cell surface molecules specifically to ovarian cancer cells [99].

It was found that targeted liposomes exhibited higher cytotoxicity in SK-OV-3 cells than glycosylated paclitaxel liposomes and glycosylated paclitaxel. Moreover, targeted liposomes showed most effective anti-tumor activity without adverse effects.

In another study, Lin et al. prepared four anti-HER2 monoclonalantibody and purified them *via* active and refolding method. Cationic immuno-liposomes of Curcumin/DOX/Herceptin were functionalized with an anti-HER2 monoclonalantibody and targeted against HER2-overexpressing cells. The binding efficiency of these nanoparticles to MDA-MB-231, MCF-7, SKBR3 and Hs578 cell lines was examined. The results indicated receptor-specific binding of targeted liposomes to SKBR3 and cell lines. In this research, oligoclonal nanoparticles exhibited more cytotoxicity effect in comparison to non-targeted liposomes against HER2-positive tumor cells (Fig. 7) [100].

4. Future prospective of active targeted liposomes

So far, only a few targeted liposomal formulations have been entered to clinical trials, though many of them have shown more efficiency in animal and in vitro studies [101]. Many problems have to be solved in order to achieve their successful clinical use. In addition, a number of factors influences on the function of targeted liposomes, including : (i) liposome size for cellular uptake of various cancer cells; (ii) charge of liposomes; (iii) ligand amount on the surface of liposomes; (iv) penetration through body tissues from biological barriers to reach the tumor site; (v) elimination of surface modified liposomes by the body immune system; and (vi) binding between the ligands and the serum proteins in the blood circulation [101, 102]. Formation of protein corona atmosphere around the targeted liposome when they are introduced in blood-stream prevents the proper function of the liposomes [103, 104]. On the other hand, when the functionalized liposomes are exposed to the tumor micro environment, they may bind to tumor surface receptors and cannot be able to penetrate into the tumor [105]. Further, the Reticuloendothelial System (RES) uptake of targeted liposomes can be affected by the existence of target on their surface. These are some reasons which can be responsible for the clinical failure of the targeted liposomes. In spite of the existence of huge challenges for clinical use and scaling up the laboratory based targeted liposomal formulations, however, several clinical trials on them are currently underway [106].

5. Conclusion

In recent years, nanoparticles have been extensively considered as drug carriers. Nanoparticles improve the pharmacokinetic properties of the drug by improving the drug's performance and reducing its side effects. Moreover, they increase the permeability of drug and make it suitable for the targeted drug delivery system. Surface modification of liposomes as nano-delivery systems can be performed to obtain the nanocarriers with distinctive features such as attachment to the receptors existing on the surface of cancer cells. With the modified liposomes, the ranges of their applications in modern drug delivery systems have greatly expanded. The liposomes surface can be modified with different types of ligands such as aptamer, folate, transferrin and monoclonal antibodies to improve the selectivity of drug uptake by cancerous cells. These

active targeted liposomes have several advantages including enhancement of selectivity of drugs to cancer cells for decreasing side effects to normal cells, increasing drug accumulation on cancer cells, and efficiency in the control of drug release. In this review, active targeted liposomes have been demonstrated in various studies both *in vitro* and *in vivo*. Limitation of these nanocarriers to only certain types of cancer that express specific receptors on the cell surfaces are the disadvantages of active targeting liposomes. Furthermore, there is huge challenge in their clinical translation, and further research is required for developing their application in the treatment of cancer.

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Table 1. Summary of research articles in liposomes functionalized with aptamer for active targeted cancer therapy

Liposome type	Size (nm)	Ligand	Receptor/ Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
PEGylated	292.00	CD133 Apt.	CD133	Propranolol	HemSCs	*In vitro* and *in vivo*	Remarkable decrease in hemangioma volume, weight and microvessel density	[23]
Cationic	150.3± 8.8	EpCAM Apt.	EpCAM (+)	miR-139-5p	HCT116, HCT8, SGC7901 and HeLa	*In vitro* and *in vivo*	Significant tumor suppressive effect on subcutaneous HCT8 colorectal tumor	[24]
PEGylated	145	Endoglin Apt.	Endoglin	mIP-10 plasmid	B16,mTEC, 293T-mE and 293T	*In vitro* and *in vivo*	Enhancement in the recruitment of CTLs and showing anti-tumoral effect	[25]
Cationic	121.2± 2.5	AS1411	Nucleolin	PTX / siRNA	MCF-7	*In vitro* and *in vivo*	Increased number of apoptotic cells and reduced angiogenesis	[17]
PEGylated	190 ± 15	AS1411	Nucleolin	5-FU	TE 354.T	*In vitro*	Increased stability of the liposomes by aptamer moieties and acting act as steric barrier	[18]
PEGylated	175.5 ± 9.0	EGFR Apt.	EGFR	siRNA/QDs	MDA-MB-231 and MDA-MB-453	*In vitro* and *in vivo*	competitive *in vivo* delivery and therapeutic efficacy	[26]
PEGylated	128.6	AS1411	Nucleolin	DOX	MCF-7/Adr	*In Vitro*	Efficient accumulation in the nuclei	[21]
PEGylated	110.37	sgc8 Apt.	PTK7	Vincristine	CCRF-CEM	*In vitro* and *in vivo*	Significant inhibition of proliferation of cancer cells in vitro and tumor growth in vivo	[22]
PEGylated	161.2 ± 11.3	EGFR Apt.	EGFR	SATB1 RNA	(BeWo, JEG-3 and JAR	*In vitro* and *in vivo*	Striking tumor weight inhibitory rate and increased drug delivery	[27]
Cationic	119.5 ± 12.7	CD133 Apt.	CD133	PTX / siRNA	U251	*In vitro* and *in vivo*	Persistent target ability to bind glioma cells and brain microvascular endothelial cells	[28]
PEGylated	~ 137	CD-44 Apt.	CD-44	siRNA	MDA-MB-231-Luc2-GFP	*In vitro* and *in vivo*	Efficient gene silencing in CD44-expressing tumor cells	[29]
PEGylated	170±25	HER3 Apt.	HER3	DOX	293T, 293E, MCF-7 and BT474	*In vitro* and *in vivo*	Greater tumor suppression and alleviated side effects like weight loss, low survival rate, and organ injury	[30]
PEGylated	~120	T1 Apt.	PMN-MDSCs	DOX	4T1, MDA-MB-231, MDA-MB-468, MCF-7 …	*In vitro* and *in vivo*	Cytotoxic and immunomodulatory effects and superior therapeutic efficacy	[31]
PEGylated	178.7 ± 3.1	AS1411	Nucleolin	HMME / Acriflavine	SKOV-3 and HL-7702	*In vitro* and *In vivo*	Enhancement of sonodynamic therapy and precise tumor targeting and magnetic resonance imaging	[32]

PEGylated	100–120	CD133 Apt.	CD133	Docetaxel	A549	*In vitro* and *in vivo*	Significant antitumor activity with a very low systemic toxicity	[33]
PEGylated	120 ± 1.8	5TR1 Apt.	Mucin1	DOX	C26	*In vitro* and *in vivo*	Increased selective delivery of drug to tumor tissue,significant deceleration in tumor growth and enhanced survival	[34]
PEGylated	100-780	LC09 Apt.	VEGFA	CRISPR/Cas 9	K7M2	*In vitro* and *in vivo*	Selective distribution, effective genome editing in tumor, inhibited OS malignancy and lung metastasis, reduced angiogenesis and bone lesion with no detectable toxicity.	[35]
PEGylated	184.8 ± 5.87	EGFR Apt.	EGFR	O2 / Erlotinib	EGFR-negative, A549, H1975 and PC-9	*In vitro* and *in vivo*	Desired physicochemistry, good bio-stability and controlled drug release, and facilitated uptake	[36]

Table 1. Continued

Liposome type	Size (nm)	Ligand	Receptor/ Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
PEGylated	200-270	A6 Apt.	HER-2	siRNA	MDA MB-231, MCF-7, 4T1-R, SKBR-3and 4T1-S	*In vitro*	Significant increase in cell transfection with No significant cellular toxicity	[37]
PEGylated	179.4 ± 1.16	EGFR Apt.	EGFR	Erlotinib	Helf, PC-9 and H1975	*In vitro*	Facilitated uptake of liposomes by specific binding and causing apoptosis in cells	[38]
Cationic	~150	A10 Apt.	PSMA	CRISPR/Cas 9	PC, LNCap and PC-3	*In vitro* and *in vivo*	Significant cell- type binding specificity	[39]
PEGylated	150 ± 20	IL-4Rα Apt.	IL-4Rα	CpG	CT26	*In vitro* and *in vivo*	Enhanced anti-tumor activity	[40]
PEGylated	118 ± 2.2	TSA14	HER2	DOX	TUBO	*In vitro* and *in vivo*	Improved selectivity and therapeutic efficacy of liposomes	[41]
PEGylated	138.7-146.8	SZTI01	PSMA	TPEN Zinc chelator,	C4–2 and PC3	*In vitro* and *in vivo*	Specific delivery to targeted cells and reduced tumor growth of prostate cancer	[42]
DOTAP/DOPE	~100	AS1411	4T1 cell	DOX	4T1, 4TO7 and 67NR	*In vitro* and *in vivo*	Enhanced drug accumulation in tumor tissue, sup-ressed tumorgrowth and increased survival rate	[43]
PEGylated	115.1-122.7	GBI-10	Tenascin-C	Gadolinium	C6 and NIH 3T3	*In vitro*	Increased cellular binding of liposomes to tumor cells	[44]
PEGylated	140 ± 6	CD44 Apt.	CD44	Rhodamine	A549, NIH 3T3 and MDA-MB-231	*In vitro*	Higher sensitivity and selectivity for Apt-Liposome compared to the blank liposomes	[19]
PEGylated	172.2 ± 43.9	AS1411	Nucleolin	DOX	MCF-7 and ADR	*In vitro* and *in vivo*	Accumulation of drug in tumor tissues, inhibiting tumor growth and reducing side effects	[45]
Thermo	-	PDGFR	PDGFRs	DOX	MDA-MB-	*In vitro*	Higher binding an toxicity to	[46]

sensitive		Apt.			231, MCF-7, HepG2 and WiDr		tumor cells compared to blank liposomes	
PEGylated	90–100	PSMA Apt.	PSMA	DOX	LNCaP and PC3	*In vitro and in vivo*	Significant enhance in cellular binding and uptake, and selective retention in tumor tissue	[47]
Cationic	~150	AS1411	Nucleolin	Anti-BRAF siRNA	A375, HEK293, MCF-7, AML12 and C2C12	*In vitro* and *in vivo*	Much higher accumulation and significant silencing activity in tumor cells	[48]
PEGylated	-	AraHH001	mTEC	Rhodamine	OS-RC-2 cells)	*In vitro* and *in vivo*	Higher accumulation on tumor vasculature compared to blank liposomes	[49]
PEGylated	210 ± 20	AS1411	Nucleolin	DOX	MCF-7	*In vitro* and *in vivo*	High specificity and selectivity in drug delivery	[20]
PEGylated	119.3 ± 0.9	ESTA Apt.	ESTA	Cy3	HUVEC	*In vitro* and *in vivo*	Efficient and rapid uptake	[50]
PEGylated	~200	sgc8 Apt.	CEM-CCRF	Fluorescein-dextran	CEM-CCRF	*In vitro*	High specific targeting with excellent efficiency	[51]
PEGylated	200	AS1411	Nucleolin	Cisplatin	MCF-7 and MDAMB-231	*In vitro*	Highly specific and significant killing of the target cancer cells	[52]

Table 2. Summary of research articles in liposomes functionalized with folic acid for active targeted cancer therapy								
Liposome type	**Size (nm)**	**Ligand**	**Receptor/ Antigene**	**Drug/agent**	**Application or Cell line**	**Study type**	**Outcome**	**Ref**
PEGylated	184.2 ± 9.16	FA	FA receptor	Oleuropein	22Rv1	*In vitro* and *in vivo*	Increase bioavailability, tumor suppression, weight loss resistance, and survival probability	[63]
PEGylated	~ 140	FA	FA receptor	Arsenic Trioxide	HeLa, KB and HT-3	*In vitro*	Superior selectivity and efficiency in inducing higher cell apoptosis	[64]
long-circulating and pH-sensitive	123 ± 6	FA	FA receptor	DOX	4T1	*In vitro* and *in vivo*	Higher tumor uptake and antitumor activity	[62]
PEGylated	156.7± 0.63	FA	FA receptor	Rapamycin	Human 5637, HT1376 and MBT2	*In vitro* and *in vivo*	Enhanced retention and FR-targeting	[65]
PEGylated	154	FA	FA receptor	Gold nanorods and DOX	4T1) and NIH3T3	*In vitro* and *in vivo*	Enhanced toxicity and effective growth inhibition towards cancer cells	[54]
PEGylated	105-120	FA	FA receptor	Mitomycin C / DOX	LNCaP and KB	*In vitro*	Significant enhance in cytotoxic activity	[66]
Temperature-Sensitive/Magnetic	140.9 ± 8.1	FA	FA receptor	17-AAG	SKOV3 and MCF7	*In vitro* and *in vivo*	Inhibition in proliferation of cancer cells witheffective targeting to tumor tissues	[67]
PEGylated	114.0 ± 4.58	FA	FA receptor	5-FU	CT26	*In vitro* and *in vivo*	Higher cellular uptake, lower IC50 and higher ROS production compared to free drug	[68]
PEGylated	205 ± 2.2	FA	FA receptor	Nitrooxy/ DOX	MCF10A, MCF7, SKBR3, T74D, MDA-MB-231, U-2OS and JC	*In vitro* and *in vivo*	Maximal anti-tumor efficacy against FAR positive/Pgp positive cells	[69]
PEGylated	~190	FA	FA receptor	Celastrol / Irinotecan	MCF-7, MDA-MB-231 and A549	*In vitro* and *in vivo*	High uptake, selective targeting, enhanced apopto -sis in cancer cells and minimized adverse effects	[60]
PEGylated	174	FA	FA receptor	5-FU	HT-29, Caco-2, CT26, HeLa and MCF-7	*In vitro* and *in vivo*	Reduced tumor volume in comparison to free 5-FU	[61]
PEGylated	~100	FA	FA receptor	Bleomycin	HeLa and MCF-7	*In vitro*	Effective induction in apoptosis and cell-cycle arrest and increased liposomal uptake	[70]
Cationic	200 ± 5	FA	FA receptor	Bis-arylidene Oxindole	A549, B16F10, NIH3T3, SKOV-3 and CT26	*In vitro* and *in vivo*	Induced potent caspase-8 up-regulation even in FR-moderately expressing melanoma cells	[61]
PEGylated	222±8	FA	FA receptor	Betulinic acid	HepG2 and A549	*In vitro*	Selective up takeand enhanced cytotoxicity	[71]

PEGylated	~500	FA	FA receptor	Oridonin	HepG-2 and A549	*In vitro* and *in vivo*	Higher binding to cancer cells and improved antitumor activity	[72]
PEGylated	94.2	FA	FA receptor	Mitomycin C	KB, IGROV-1, T-24, J6456, M109 and C26	*In vitro* and *in vivo*	Increased cellular uptake and cytotoxic activity	[73]
cationic	95.3	FA	FA receptor	HIF-1α siRNA	A375	*In vitro*	Significant enhance in anti-melanoma activity	[74]
PEGylated	150	FA	FA receptor	C6 ceramide / DOX	A2780-ADR,HeLa and H69-AR	*In vitro*	Significantly higher cell death	[75]
PEGylated	200	FA	FA receptor	metabolite of norcantharidin	H22	*In vitro* and *in vivo*	Increased tumor-targeting, cellular apoptosis in the tumors and antitumor activity	[76]

Table 3. Summary of research articles in liposomes functionalized with transferrin for active targeted cancer therapy								
Liposome type	**Size (nm)**	**Ligand**	**Receptor/ Antigene**	**Drug/agent**	**Application or Cell line**	**Study type**	**Outcome**	**Ref**
PEGylated	113 ± 2	TF	TF receptor	Plumbagin	A431, T98G and B16-F10	*In vitro* and *in vivo*	Increased drug uptake by cancer cells and antiproliferative efficacy and apoptosis activity	[80]
PEGylated	-	TF	TF receptor	Resveratrol	U-87 MG, Astrocytoma, LN-18 and glioblastoma	*In vitro*	Enhanced uptake by cells and increased activation of caspases 3/7	[83]
PEGylated	211.2 ± 0.8	TF	TF receptor	Resveratrol	U-87	*In vitro* and *in vivo*	Enhanced growth inhibition and activation of caspases 3/7	[81]
PEGylated	107	TF	TF receptor	5-FU	HT-29	*In vitro*	Increased cytotoxic activity and inducing apoptosis via mitochondria signaling pathway	[84]
PEGylated	180	TF	TF receptor	Dopamine	hCMEC/D3	*In vitro*	The absence of toxicity and decreasing complications to patients	[79]
PEGylated	103.4± 2.8	TF	TF receptor	Dihydroquinol-in derivatives	Hep G2, 6HEK-293T and HeLa	*In vitro*	Enhanced ROS level and improved cell uptake	[85]
PEGylated	157	TF	TF receptor	Zoledronica cid	4T1	*In vitro*	Improved anticancer activity	[86]
PEGylated	109.01 ± 1.33	TF	TF receptor	Vincristine/ tetrandrine	C6	*In vitro* and *in vivo*	Prolonged circulation time and accumulate in tumor l site leading to robust anticancer efficacy	[87]
PEGylated	125.3	TF	TF receptor	Cordycepin	PLC/PRF/5 and HepG2	*In vitro*	Enhanced cellular uptake	[82]
PEGylated	86	TF	WT1	WT1 shRNA	B16F10	*In vitro* and *in vivo*	Reduced tumor size and increased survival	[88]
PEGylated	< 200	TF	TF receptor	Docetaxel / quantum dots	Brain cancer	*In vitro* and *in vivo*	Improved and prolonged brain targeting of drug	[89]
PEGylated	416 ± 95	TF	TF receptor	Artemisinin	HCT-8	*In vitro*	Enhanced delivery of drug	[90]
PEGylated	138.6 ± 6.65	TF	TF receptor	Nitrocamptothecin/cyclodextrin	HepG2, A2780 and L02	*In vitro* and *in vivo*	Enhanced cytotoxicity to tumor cells, improved efficiency of targeted drug delivery	[91]
PEGylated	144.5± 1.7	TF	TF receptor	Isoquinoline Derivative	HeLa, HepG2 and HEK-293T	*In vitro*	Superior antitumor activity compared to non targeted controls and the free drug	[92]

Table 4. Summary of research articles in liposomes functionalized with monoclonal antibodies for active targeted cancer therapy								
Liposome type	**Size (nm)**	**Ligand**	**Antigene**	**Drug/agent**	**Application or Cell line**	**Study type**	**Outcome**	**Ref**
Immunoliposomes	100	Anti-CD44	CD44	Glycosylated PTX	SK-OV-3 and OVK18	*In vitro* and *in vivo*	Enhancedcytotoxicity, reduced tumor volume and increased the therapeutic efficacy	[99]
cationicImmunoliposomes	250	Anti-HER2/neu	HER2/neu	Curcumin/DOX/Herceptin	MDA-MB-231, MCF-7, SKBR3 and Hs578	*In vitro* and *in vivo*	Specific binding and targeting to surface of cells and increased cytotoxic activity	[100]
Immunoliposomes	140	Anti-EGFR	EGFR	DOX	MDA-MB-468	*In vitro*	Increased cytotoxicity and therapeutic window of drug	[107]
Immunoliposomes	100	MM-302	HER2	DOX	MDA-MB-453 and MDA-MB-231	*In vitro* and *in vivo*	Enhanced drug delivery as a result of targeting	[108]
Immunoliposomes	80- 100	scFvG8 / Hyb3	MAGE-A1/ HLA-A1	DOX	MZ2Mel43, G43, Mel78and Mel2A	*In vitro* and *in vivo*	Enhanced tumor cell kill, accumulation of targeted liposomes and cytotoxicity	[109]
Thermal-sensitive multifunctional	185.7 ±51.48	Anti-EGFR	EGFR	DOX / Gold nanorods	A431 and A549	*In vitro* and *in vivo*	Selective targeting and noo signs of major morphological damages to the normal tissues	[110]
Immunoliposomes	115.5 ± 3.1	Anti-CD123 /anti-CD33	CD123/ CD33	DOX	HL-60 and THP-1	*In vitro*	Increased cellular uptake and enhanced antitumor effects	[111]
Immunoliposomes	109.5 ± 3.42	Anti-EGFR	EGFR	Afatinib	A549 and H1975	*In vitro* and *in vivo*	Enhanced drug delivery, growth inhibition and cellular internalization rate	[112]
Immunoliposomes	110-190	Anti-PD-L1	PD-L1	Calcein	B16OVA, B16,BSF, LLC and C26	*In vitro* and *in vivo*	Increased accumulation and cytotoxicity providing tumor shrinkage	[113]
Immunoliposomes	106.7-102.4	Anti-HER2	HER2	DOX	BT474, SKBR3 and MCF10A	*In vitro*	Efficient binding and enhanced cytotoxicity	[107]
Immunoliposomes	102–106	Anti-HER2	HER2	DOX	MCF10A, SKBR3 and BT474	*In vitro*	More cytotoxicity effect in comparison to non-targeted liposomes	[114]
Immunoliposomes	120 ± 5	Anti-HER2	HER2	Methotrexate	BT-474, SKBR-3 and MDA-MB-231	*In vitro*	High target-binding avidity and efficient cytotoxicity	[116]
Immunoliposomes	140±3.4	Anti-HER2	HER2	Trastuzumab/ Docetaxel	MDA-MB-453 and MDA-MB-231	*In vitro* and *in vivo*	Efficient drug delivery with higher efficacy and prolonged survival	[117]
Immunoliposomes	127.0 ± 2.0	MEM-102/MEM-43/5	CD48 / CD59	Fluor 647	$CD48^{+}$, $CD59^{+}$ and BW5147 cells	*In vitro* and *in vivo*	Specific recognition of antigen-positive cells and efficient drug delivery	[118]
Immunoliposomes	140–190	Anti-CD20	CD20	Superparamagnetic iron oxide	Granta and Z138C	*In vitro* and *in vivo*	Induced cell internalization and apoptosis effect	[119]

Immunolipo somes	170	Anti-GD2	GD2	Sepantroniu m bromide	IMR32 and KCNR	*In vitro* and *in vivo*	Prolonged blood circulation, increased half-lives and tumor accumulation	[98]
Immunolipo somes	< 100	Anti-DR5	DR5	-	Jurkat, COLO205, WiDr, A2058, BxPC-3 …	*In vitro*	Enhancing the anti-cancer apoptosis	[120]

Table 4. Continued

Liposome type	Size (nm)	Ligand	Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
Immunolipo somes	80-100	Anti-EGFR	EGFR	Porphyrin	CT26-fLuc	*In vitro* and *in vivo*	More effective against tumor growth	[121]
Immunolipo somes	138.2 ± 5.9	trastuzuma b	HER2	Rapamycin	MDA-MB-231and SK-BR-3	*In vitro*	Enhanced cytotoxicity	[122]
Immunolipo somes	160.1 ± 0.9	Anti- CA IX	CA IX	Triptolide	A549	*In vitro* and *in vivo*	Restrainingtumor growth and showing prolonged life-span	[123]
Immunolipo somes	<180	Anti-EGFR	EGFR	5-FU	A431	*In vitro*	Decreased IC_{50}	[124]
Immunolipo somes	140.3	Anti-HER2	HER2	PTX/ Rapamycin	4T1 and SKBR3	*In vitro* and *in vivo*	Increased cytotoxicity, enhanced uptake and controlled tumor growth	[125]
Immunolipo somes	80- 95	Anti-MAGE A1	MAGE A1	-	MZ2Mel43, G43, Mel78 and Mel2A	*In vitro*	Promoting internalization of nanoparticles	[126]
Temperature - sensitive	219 ± 29	Herceptin	HER2	Gemcitabine	K-BR-3	*In vitro*	Increased cytotoxicity and improved drug delivery	[127]
Immunolipo somes	180	Anti-EGFR	EGFR	-	LS180	*In vitro* and *in vivo*	Improved survival and cure rates	[128]
Immunolipo somes	107 ± 3.1	Anti-CD44	CD44	DOX	C-26 and NIH-3T3	*In vitro* and *in vivo*	Superior tumor growth inhibition and higher inclination to tumor	[97]
Immunolipo somes	112.1± 0.5	Anti-VEGF165	VEGF165	PTX	SGC-7901	*In vivo*	Carrying anticancer drugs to the interior of solid tumors and effective inhibition of tumor growth	[129]
Immunolipo somes	>100	Anti-CD20	CD20	Antisense gene	Jurkat T, HL60, HEL, CCL-213, and CCL-86	*In vitro* and *in vivo*	Selective and effective reduced the expression of *BCL2* in target cells	[130]
Immunolipo somes-ICG	189.1 ± 4.8	Anti-MUC-1	MUC-1	DOX	4T1 and HT-29	*In vitro* and *in vivo*	Rapidaccumulation	[131]

Stealth PLGA	193.5± 12.5	Anti-CAGE scFV	CAGE scFV	Recombinant methioninase	SGC-7901	*In vitro* and *in vivo*	Increased cell uptake and more effective in inhibiting tumor growth	[132]
Immunolipo somes	120	Anti-EGFR	EGFR	Celecoxib	HT-29, SW620, MDA-MB-468 and HCT-116	*In vitro*	Enhanced selective uptake and toxicity	[133]

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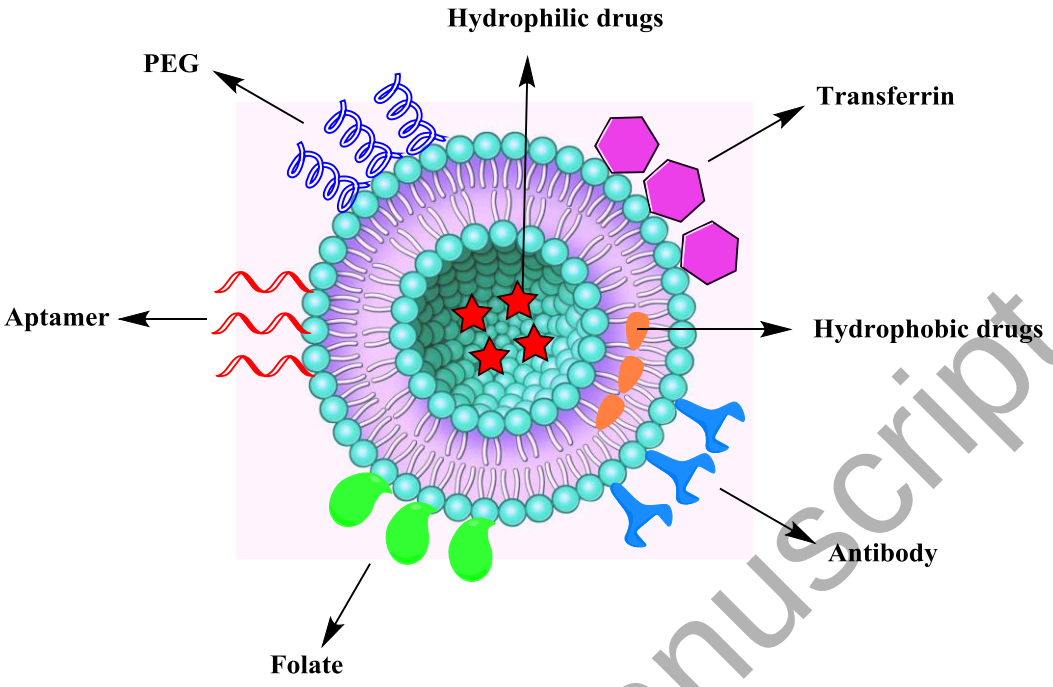

Fig. 1: Targeting of liposome with various ligands

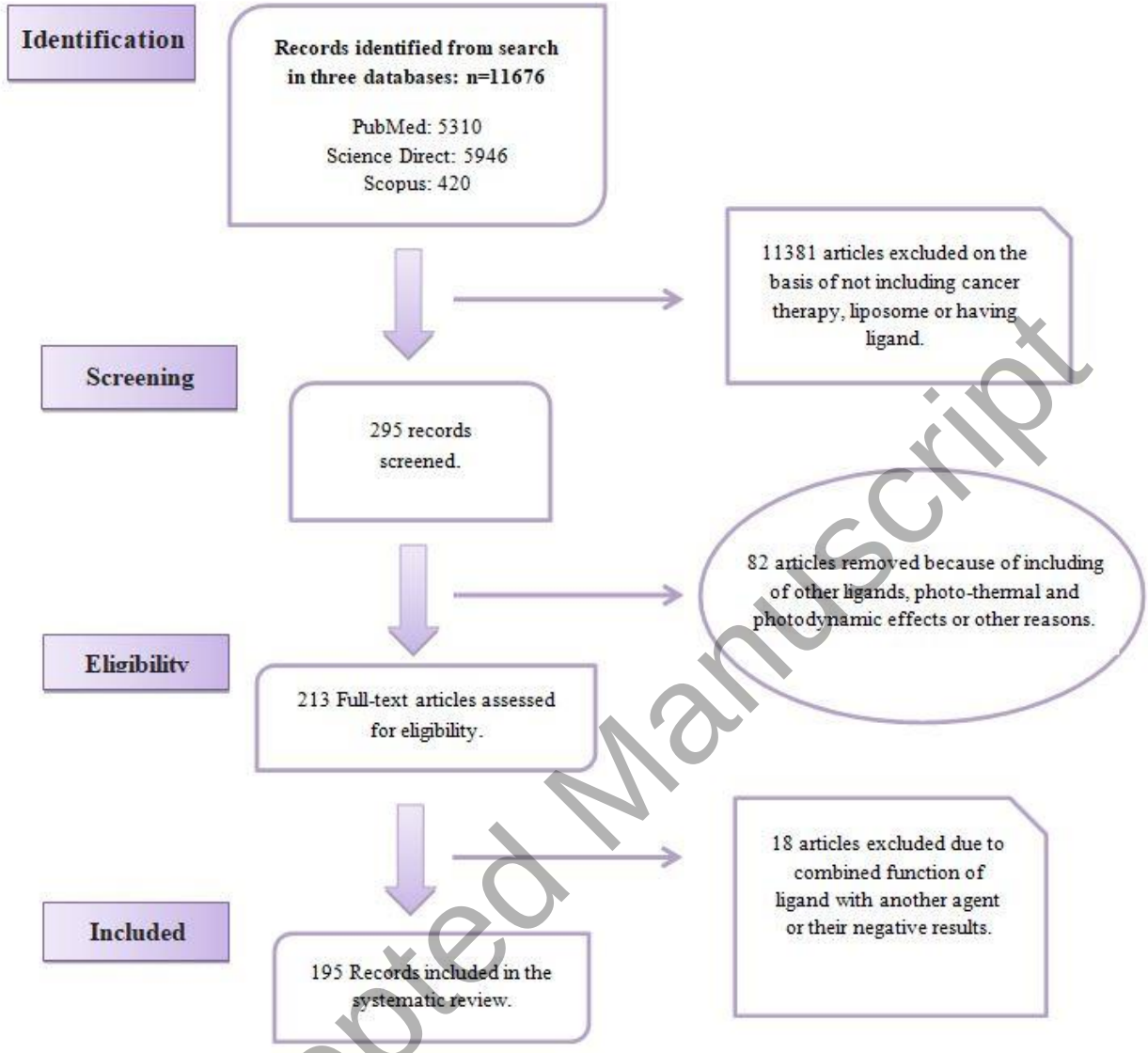

Fig. 2: PRISMA flow diagram.

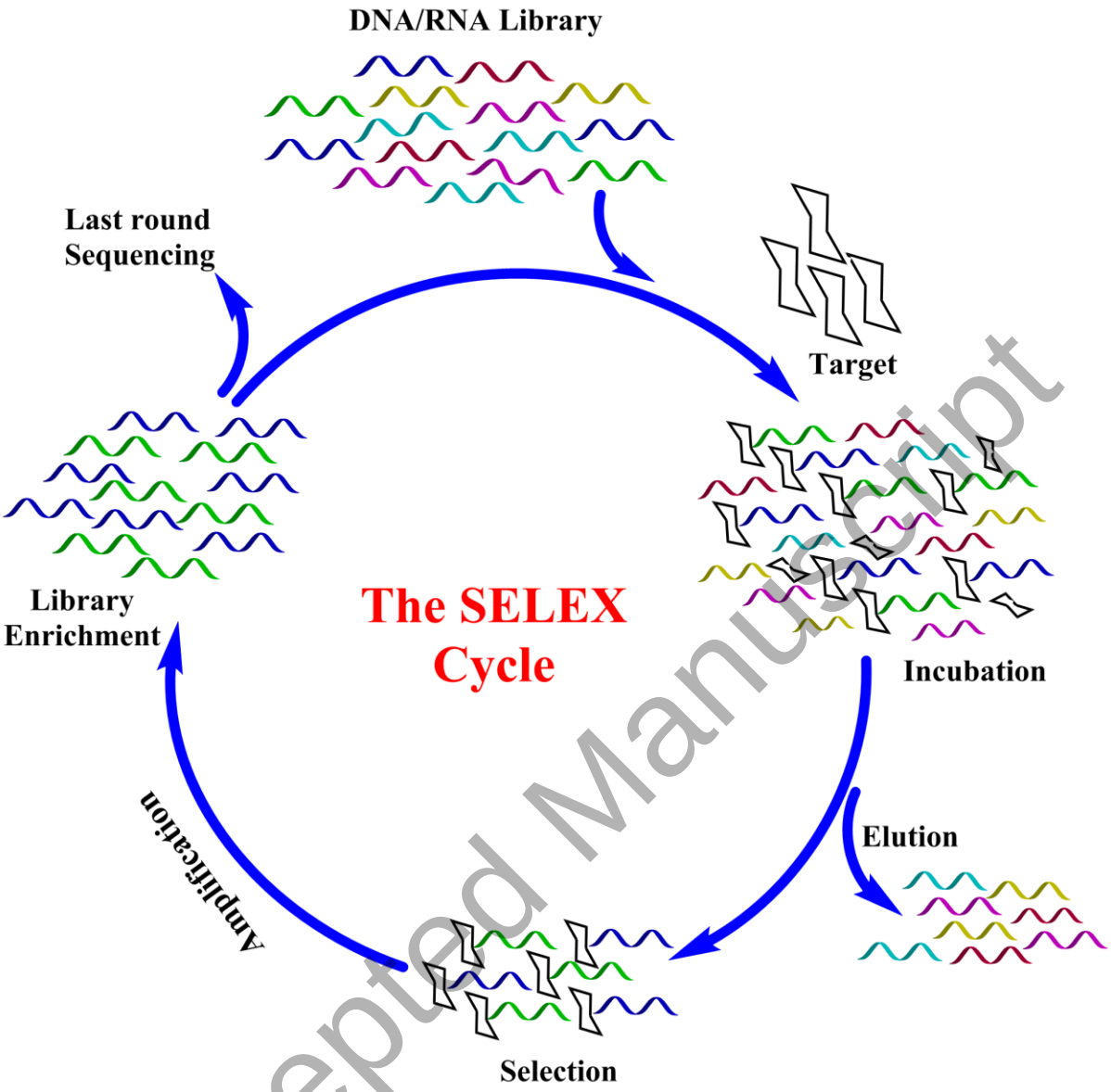

Fig. 3: Schematic illustration of SELEX process

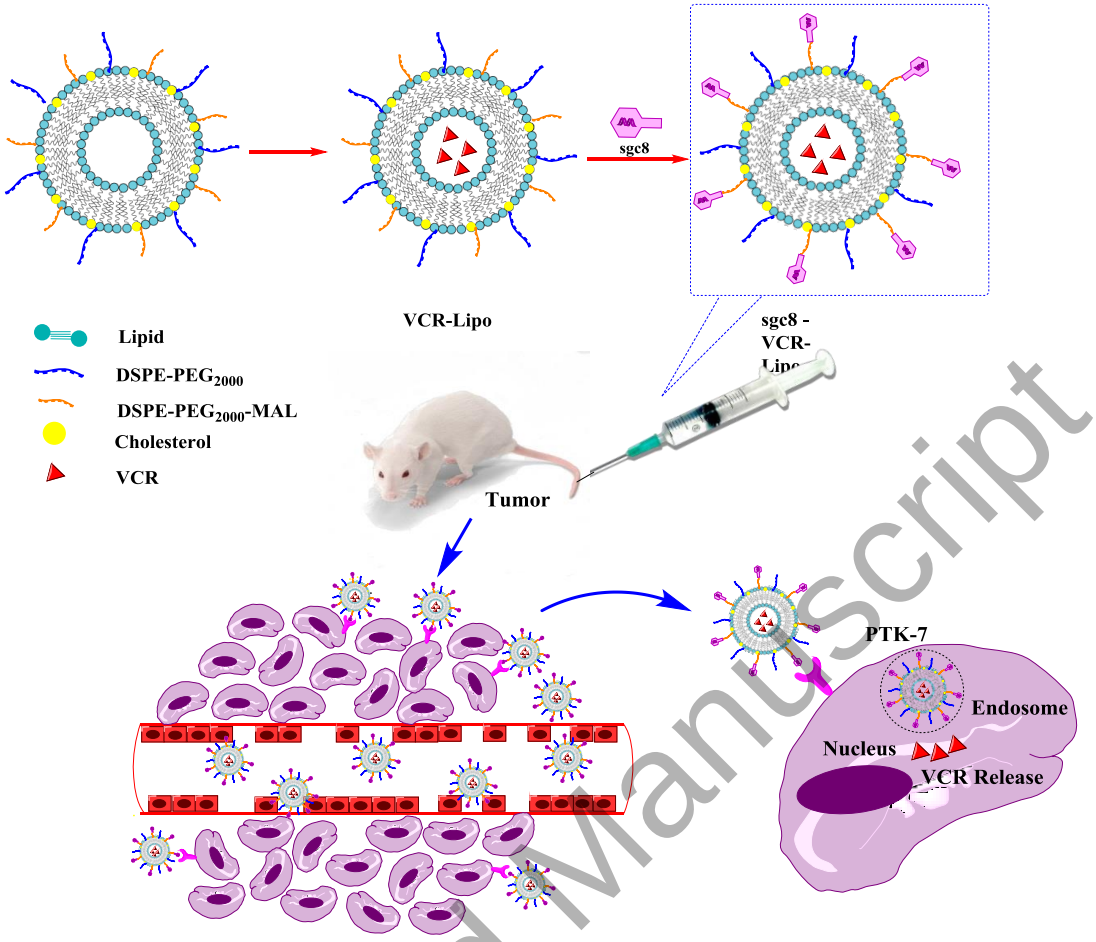

Fig. 4: Graphical illustration of sgc8/VCR-Lipome function [19].

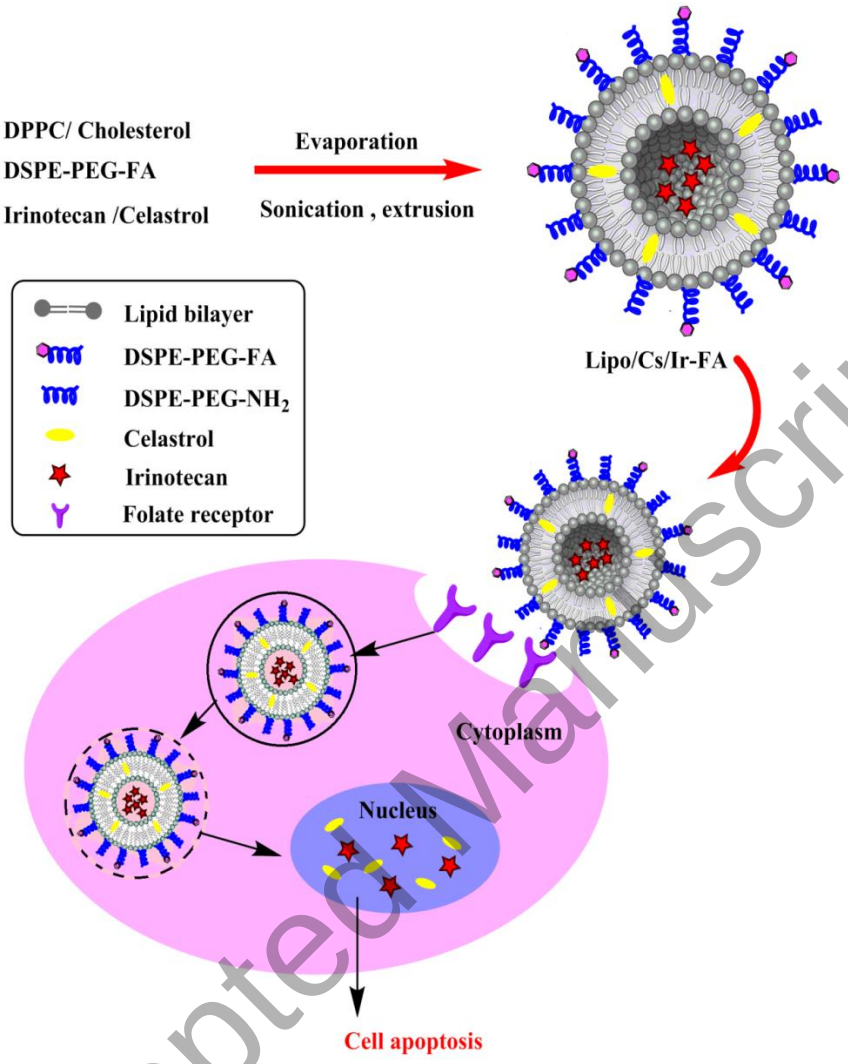

Fig. 5: Schematic illustration of the folate functionalized liposomes for breast cancer therapy [57].

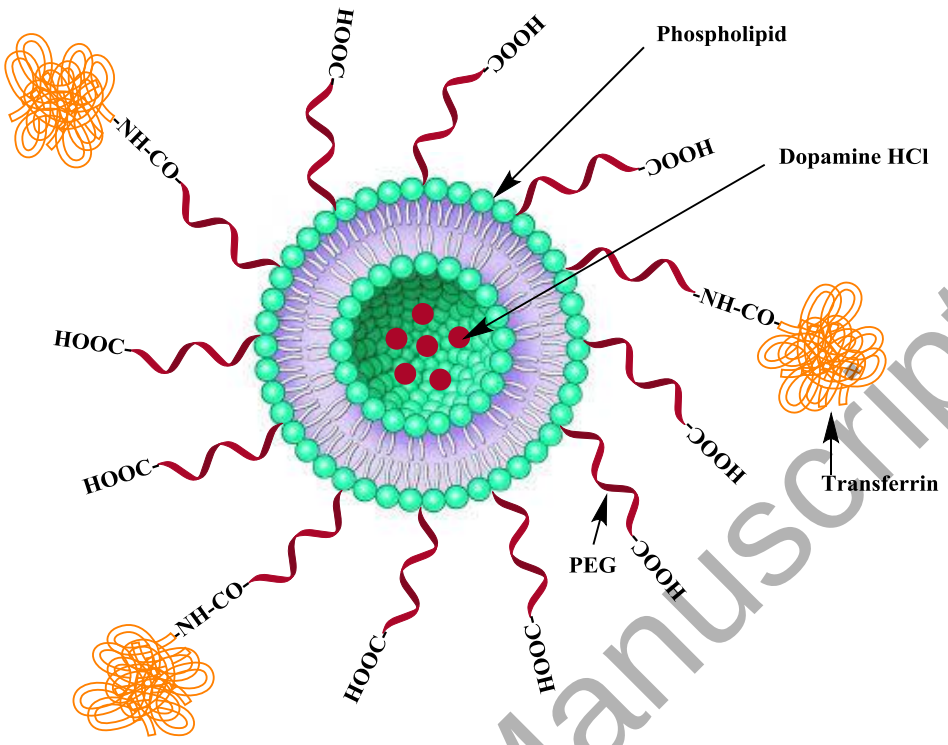

Fig. 6: Graphical representation of the hydrophilic drug dopamine-hydrochloride into the Tf functionalized liposomes [76].

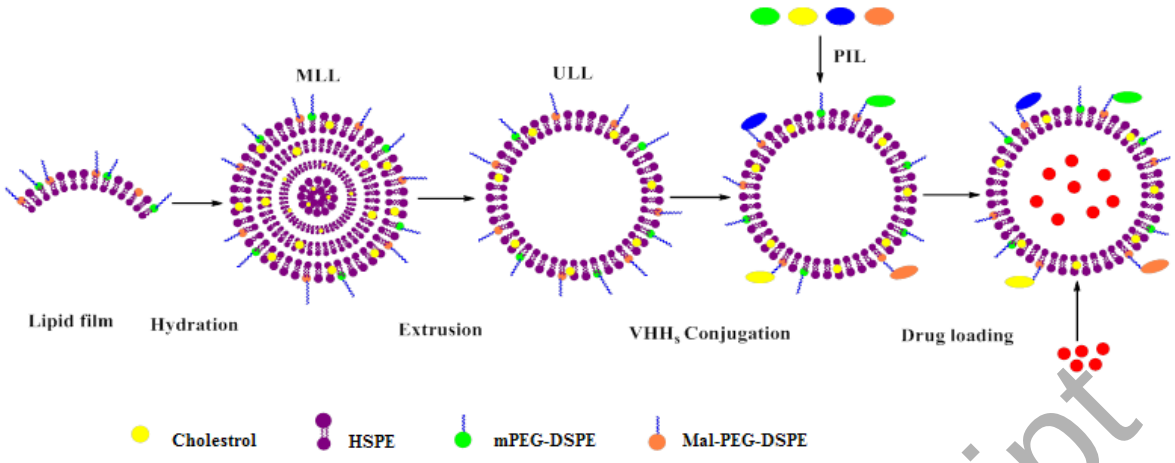

Fig. 7: Schematic representation of the preparation of heavy chain antibodies targeted liposomes [97].

Table S1. Summary of research articles in liposomes functionalized with folic acid for active targeted cancer therapy

Liposome type	Size(nm)	Ligand	Receptor/ Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
PEGylated	130	FA	FA receptor	Oligonucleotide	B16F10	*In vitro*	Higher cellular uptake	[1]
PEGylated	143.5	FA	FA receptor	Imatinib	HeLa and A549	*In vitro*	Promising strategy in cervical cancer therapy	[2]
PEGylated	129.8	FA	FA receptor	DOX / Bmi1 siRNA	HeLa, KB, Hep3B, A549, Huh7, MCF-7 and LO2	*In vitro* and *in vivo*	Higher accumulation in tumor cells	[3]
PEGylated	137.0±0.9	FA	FA receptor	DOX	HeLa and KB	*In vivo*	Selectively take up of the liposomes	[4]
PEGylated	160.1	FA	FA receptor	Ursolic acid	KB	*In vitro* and *in vivo*	More toxicity and apoptosis	[5]
PEGylated	197.8±4.58	FA	FA receptor	Irinotecan	S180	*In vivo*	More drug distribution, superior anticancer activity and lower toxicity	[6]
PEGylated	100–110	FA	FA receptor	Carboplatin	CB-17	*In vitro* and *in vivo*	Significant improvement in therapeutic efficacy of the drug	[7]
PEGylated	100–120	FA	FA receptor	DOX	KB	*In vitro* and *in vivo*	Enhancement in the delivery of anticancer drugs	[8]
PEGylated	76.0 ±35.5	FA /CHEMS	FA receptor	Daunorubicin	L1210JF and KB	*In vitro* and *in vivo*	Increased drug release in the tumor	[9]
Cationic/magnetic	174 ± 53	FA	FA receptor	DOX	HeLa and ZR-75-1	*In vitro*	Surface binding in cells with high folate receptor expression	[10]
PEGylated	110-130	FA /polymer	FA receptor	Docetaxel	MCF-7 andA-549	*In vitro* and *in vivo*	Greater accumulation of the drug in tumor tissue	[11]
PEGylated	110 ± 10	FA	FA receptor	Ricin	KB	*In vitro*	Enhancement in cytotoxicity	[12]
Cationic	~150	FA	FA receptor	Ct DNA/DOX	KB, L1210JF and RAW264.7	*In vitro* and *in vivo*	Selective uptake, tumor growth inhibition and increased cytotoxicity	[13]
PEGylated	120	FA	FA receptor	DOX / ATRA	MV4-11 AML and KB	*In vitro*	Higher cytotoxicity than non-targeted liposomes	[14]
Thermosensitive-magnetic	361±20	FA	FA receptor	DOX	KB and HeLa	*In vitro*	Enhanced uptake into tumor cells and increased cytotoxicity	[15]
PEGylated	-	FA	FA receptor	DOX	KB, KB-V and J6456	*In vitro* and *in vivo*	Therapeutic improvement	[16]
Cationic	163.5	FA	FA receptor	Calcein	MCF-7	*In vitro*	Significant higher uptake	[17]
PEGylated	100–110	FA	FA receptor	Zoledronic acid	Fibroblasts, J774, M109 and	*In vitro*	More efficient intracellular delivery of the drug	[18]

					M109R			
PEGylated	115 ± 20	FA	FA receptor	Arsenic trioxide	KB,HeL and MCF-7	*In vitro*	Improvement in the drugefficacy	[19]
PEGylated	110 - 120	FA	FA receptor	Docetaxel	KB	*In vitro*	Enhancement in tumor cell uptake and antitumor efficacy	[20]
PEGylated	130	FA	FA receptor	Mitoxantrone	KB and A549	*In vitro*	High levels of cytotoxic activity	[21]
PEGylated	120±20	FA /CHEMS	FA receptor	DOX	KB and HeLa	In vitro	Taken upselectively by cancer cells and greater cytotoxicity	[22]

Table S1. Continued

Liposome type	Size (nm)	Ligand	Receptor/ Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
PEGylated	~100	FA	FA receptor	DOX	KB and A549	*In vitro* and *in vivo*	Significantly higher antitumor effect	[23]
PEGylated	110 - 130	FA	FA receptor	DOX	MV4-11	*In vitro* and *in vivo*	High efficiency of cellular uptake and cytotoxicity	[24]
PEGylated	124 - 163	FA	FA receptor	5-FU	B16F10	*In vitro* and *in vivo*	Enhanced drug uptake by tumor cells	[25]
PEGylated	100	FA	FA receptor	DOX	L1210JF	*In vivo*	Better anticancer effectiveness	[26]
PEGylated	70 - 90	FA	FA receptor	-	J6456	*In vitro*and *in vivo*	Increased drug levels in tumor cells	[27]
Cationic	80 - 90	FA	FA receptor	Oligodeoxy-ribonucleotide	KB	*In vitro*	Enhancement in drug uptake by cells	[28]
PEGylated	97.1	FA	FA receptor	PTX	KB	*In vitro*	Enhanced cytotoxicity	[29]
PEGylated	100	FA	FA receptor	Daunorubicin	L1210JF	*In vivo*	Significant increase in drug uptake by cells and tumor inhibition	[30]
PEGylated	65 - 90	FA	FA receptor	Calcein	IGROV	*In vivo*	Enhanced uptake into cells	[31]
PEGylated	70 - 90	FA	FA receptor	DOX	J6456	*In vivo*	Alternation in liposome bio-distribution	[32]
PEGylated	90 - 110	FA	FA receptor	Oligonucleotide	KB	*In vitro* and *in vivo*	Increase in drug delivery	[33]
PEGylated	130	FA	FA receptor	DOX	KB and C6	*In vitro*	Increase in drug uptake	[34]
PEGylated	~100	FA	FA receptor	DOX	KB	*In vitro* and *in vivo*	Increase in tumor growth inhibition	[35]
Cationic	100–200	FA	FA receptor	DNA	M109	*In vitro* and	Increased tumor-association of drug	[36]

						in vivo		
PEGylated	~200	FA	FA receptor	Boron	KB	*In vitro*	Enhanced uptake and subcellular distribution	[37]
Cationic/pH-sensitive	-	FA	FA receptor	AraC / Calcein	KB	*In vitro*	Facilitated endocytosis into cells and enhanced cytotoxicity	[38]
PEGylated	70–100	FA	FA receptor	DOX	M109	*In vitro* and *in vivo*	Rapid internalization of drug into cells and higher cytotoxicity	[39]
PEGylated	130	FA	FA receptor	DOX	KB, HeLa, WI38 and fibroblast	*In vitro*	Enhancement in cytotoxicity and specificity	[40]
PEGylated	-	FA	EGF receptor	Oligodeoxy-ribonucleotid	KB	*In vitro*	Efficient and tumor specific delivery	[41]

Table S2. Summary of research articles in liposomes functionalized with transferrin for active targeted cancer therapy

Liposome type	Size (nm)	Ligand	Receptor/ Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
PEGylated	124.1 ± 6.5	TF	TF receptor	Docetaxel	A2780	*In vitro* and *in vivo*	Enhanced targeting ability, decreased side effects and improved anti-tumor efficacy	[42]
PEGylated	189.5 ± 69.9	TF	TF receptor	Zoledronic acid	MDA-MB-231	*In vitro*	Enhancement in the anti-cancer effect	[43]
PEGylated	294	TF	TF receptor	Cisplatin	C6	*In vitro*	Higher transport efficiency to cells	[44]
PEGylated	< 200	TF	TF receptor	DOX	ATCC HTB-177	*In vitro* and *in vivo*	Improving the aerosol treatment	[45]
PEGylated	115 ± 20 107 ± 14	TF	TF receptor	Ceramides	HeLa, A2780 and HUVEC	*In vitro* and *in vivo*	Strong antitumor and pro-apoptotic effect	[46]
PEGylated	118.3 ± 12.7	TF	TF receptor	DOX	KB	*In vitro*	Enhanced in vitro cytotoxicity	[47]
PEGylated	175.5 ± 7.28	TF	TF receptor	siRNA	K562, LAMA-84 and BJ	*In vitro*	Combining molecular and cellular targeting	[48]
PEGylated	75.6±3.2	TF	TF receptor	Docetaxel	K562and KB	*In vitro*	Efficient uptake and greater cytotoxicity	[49]
PEGylated	70 ± 19	TF	TF receptor	DOX	HepG2	*In vitro* and *in vivo*	Significant increase of drug in tumor cells	[50]
PEGylated	< 100	TF	TF receptor	Sodium borocaptate	U87Δ	*In vitro* and *in vivo*	Selective and high concentration drug delivery	[51]
PEGylated	180	TF	TF receptor	Oxaliplatin	Colon 26	*In vitro* and *in vivo*	Enhanced extravasation of liposomes into tumors	[52]
PEGylated	110	TF	TF receptor	DOX / Verapamil	K562	*In vitro*	Effective in overcoming drug resistance in cells	[53]
PEGylated	135.80 ± 2.76	TF	TF receptor	DOX	A549, 16HBE14o and Calu-3	*In vitro*	Increased levels of cytotoxicity	[54]
PEGylated	146	TF	TF receptor	AlPcS4	AY-27	*In vitro* and *in vivo*	Selective delivery of photosensitizers to tumor cells	[55]
PEGylated	122.8 ± 31	TF	TF receptor	BSH	Colon 26	*In vitro* and *in vivo*	Enhanced accumulation of ^{10}B into the cells	[56]
PEGylated	180-220	TF	TF receptor	Endostatin	HUVEC	*In vitro* and *in vivo*	Inhibition of angiogenesis and promotion of apoptosis	[57]
Cationic	584.2 ± 8.8	TF	TF receptor	DDAB	HeLa	*In vitro*	Efficient DNA delivery into the cells	[58]
PEGylated	146	TF	TF receptor	AlPcS4	HeLa	*In vitro* and *in vivo*	Selective uptake and high intracellular concentration	[59]
PEGylated	180–200	TF	TF	Cisplatin	MKN45P	*In vitro*	Significant high uptake and	[60]

			receptor				increase in drug level in cells	
PEGylated	100–140	TF	TF receptor	-	Colon 26	*In vivo*	Specific receptor-mediated endocytosis to target cells	[61]
PEGylated	122	TF	TF receptor	DOX	C6	*In vitro*	Significantly increased drug uptake	[62]

Table S3: Summary of research articles in liposomes functionalized with monoclonal antibodies for active targeted cancer therapy

Liposome type	Size (nm)	Ligand	Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
Immunoliposomes	405.1±2.74	Anti-ITGB6	ITGB6	5-Fluorouracil	SW480 and HT-29	*In vitro* and *in vivo*	Higher drug induction of cellular apoptosis rate and reduction in IC_{50}	[63]
Temperature-sensitive	130.1 ± 1.3 128.2 ± 1.6	Anti-MUC-1	hCTMO1	DOX	MDA-MB-435, MCF-7 and C33a	*In vitro* and *in vivo*	Increased accumulation of targeted liposomes in the tumor	[64]
Immunoliposomes	About 100	2C5	nucleosome	DOX	SKOV-3	*In vitro* and *in vivo*	A significant reduction in tumor growth and enhanced therapeutic efficacy of drug	[65]
Immunoliposomes	107 ± 2	Anti-PSMA	PSMA	^{225}Ac	LnCaP, Mat-Lu, HUVEC, BT474 and MDA-MB-231	*In vitro*	Selective binding, internalization, and killing PSMA-expressing cells	[66]
Cationic	185.7	Anti-CAGE	CAGE	rMETase	SGC-7901	*In vitro*	Significant cellular accumulation in the cytoplasm	[67]
Immunoliposomes	~100	anti-HER2	Anti-HER2	Curcuminand Resveratrol	MCF7 and JIMT1	*In vitro*	Increase of therapeutic effect and enhancement of cytotoxic effects	[68]
Immunoliposomes	87.4 ± 2.6	Anti-CD30	CD30	DOX	KARPAS 299 and SUP-M2	*In vitro* and *In vivo*	Significant inhibition in tumor growth, higher binding affinity to cells and lower IC_{50}	[69]
Immunoliposomes	107 ± 25 114 ± 33	Trastuzumab	Her-2+	Bleomycin	BT-474, SKBR-3, MCF-7, Her18, HCC-1954 and MDA-453	*In vitro*	Decreased tumor cell growth, cell viability, and side effects	[70]
Multifunctional immunoliposome	~ 180	Anti-Mesothelin	Mesothelin	DOX / USPIOs	Panc-1	*In vitro* and *in vivo*	Selective accumulation and higher inhibitory effect on tumor growth	[71]
Immunoliposomes	-	anti-c-Met	c-Met scFvs	DOX	H1993, H520, H460, H441,A549, and	*In vitro* and	Selective and increased accumulation of the drug, and enhancement in its antitumor	[72]

		scFvs			293T	*in vivo*	activity	
Immunoliposomes	-	Milatuzumab	anti-CD74	-	B cells	*In vitro*	Promoting accumulation of CD74 on the surface of B cells and more cytotoxicity	[73]
Immunoliposomes	194.47 ± 3.20	Anti-HER2	HER2	PE38KDEL	SK-BR3, MDA-MB-231and MCF-7	*In vitro*	Specific binding and internalization into cells, and more cytotoxic effect	[74]
pH-sensitive	160	Anti-CD33	CD33	Ara-C	HL60, KG-1 and THP-1	*In vitro*	The highest cytotoxicity against cells	[75]
Immunoliposomes	100	2C5	Nuclesome	Doxil	4T1, C26 and PC3	*In vivo*	Enhanced accumulation in tumors	[76]
Immunoliposomes	-	Anti-HER2	HER2	Magnetite NPs	BT474 and SKOV3	*In vivo*	Accumulation in tumor cells	[77]
Immunoliposomes	90-110	Anti-TAG-72	TAG-72	pDNA	CHO, WiDr and LS174 T	*In vivo*	Efficiently localized in the tumor tissues	[78]
Immunoliposomes	~ 200	Anti-HER2	HER2	PTX	BT-474 and SK-BR-3	*In vitro*	Higher cellular uptake	[79]
Immunoliposomes	87.0±10.87	2C5	Nucleosome	DOX	U-87 MG	*In vitro* and *in vivo*	Significantly higher accumulation in tumor	[80]
Immunoliposomes	90 - 120	2C5	Nucleosome	DOX	LLC, 4T1, C26, BT-20, MCF-7 and PC3	*In vitro*	Specific internalization of drug into cytosol	[81]

Table S3. Continued

Liposome type	Size (nm)	Ligand	Antigene	Drug/agent	Application or Cell line	Study type	Outcome	Ref
Immunoliposomes	100 to 120	Anti-CD166	CD166	Topotecan, DOX and Mitoxantrone	PC3, Du-145 and LNCaP	*In vitro*	Improved cytotoxic activity andefficient intracellular delivery of drug,	[82]
Immunoliposomes	<200	Herceptin	HER2	PTX	BT-474 and SK-BR-3	*In vitro* and *in vivo*	Increased cellular uptake, tumor tissue distribution and superior antitumor efficacy	[83]
Immunoliposomes	90 - 110	Anti-HER2	HER2	ADS645WS and gold	BT-474 and MCF-7	*In vivo*	Intracellular drug delivery and accumulation within cancer cells	[84]
Immunoliposomes	-	IgM	PSMA	Suicide gene	LNCaP, PC-3, DU145 and T24	*In vitro*	Selective delivery of gene to the cancer cells	[85]
Immunoliposomes	110±15	2C5	Nucleosome	DOX	LLC and BT-20	*In vitro*	Specific binding to various tumor cells	[86]
Immunoliposomes	100 ± 10 120 ± 10	Anti-CD19 / anti-CD20	CD19 and CD20	DOX / vincristine	CB17 and FMC63	*In vitro* and *in vivo*	Improved therapeutic outcome	[87]
Immunoliposomes	-	Anti-GD2	GD2	CpG-myb	14.G2a	*In vitro* and *in vivo*	Improved antitumor effect	[88]
Immunolipos	100-200	GAH	Cell	DOX	MKN1, MKN45,	*In vitro and*	Bounding to the surface of cancer cells and internalization	[89]

omes			surface		MKN74, HSC-3, C-1, HT-29, LoVo, ….	*in vivo*	by the cells	
Immunoliposomes	143	GAH	Cell surface	DOX	WiDr-Tc and SW837	*In vitro and in vivo*	Significantly superior antitumor effects against GAH-positive cancer cells	[90]
Immunoliposomes	90 - 120	Anti-MUC-1	MUC-1	DOX	GZHI and 4T1-MUC1	*In vitro* and *in vivo*	Effective in treating early lesions in both the pseudo-metastatic and metastatic models	[91]
Immunoliposomes	-	Anti-TF	TF	DOX	K562 and K562/ADM	*In vitro*	Accumulation and internalization of the drug in in drug-resistant cells	[92]
Immunoliposomes	~ 250	OV-TL3	OA3	DOX	NIH:OVCAR-3	*In vitro* and *in vivo*	superior target cell binding and cell growth inhibition of the drug	[93]
Immunoliposomes	52 ± 20	DAL K29	Cell surface antigene	Methotrexate	Caki-1 and ATCC TlB9	*In vitro* and *in vivo*	More tumor inhibition	[94]

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