International Journal of Pharmaceutics: X 11 (2026) 100483

Contents lists available at ScienceDirect

International Journal of Pharmaceutics: X

journal homepage: www.sciencedirect.com/journal/international-journal-of-pharmaceutics-x

Ligand-modified liposomes as drug delivery systems for the active targeting of pancreatic cancer

Yerin Jang [a,1], Jaehee Jang [a,1], Jaewoo Son [b], Hee-Young Lee [c,d,*], Jonghoon Choi [a,d,e,*]

[a] School of Integrative Engineering, Chung-Ang University, Seoul, 06974, Republic of Korea
[b] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA, USA
[c] Department of Chemical Engineering, Kumoh National Institute of Technology, Gumi 39177, Republic of Korea
[d] Feynman Institute of Technology, Nanomedicine Corporation, Seoul 06974, Republic of Korea
[e] Feynman Institute of Nanomedicine, Nanopeutics Inc., Lewes, DE 19958, USA

ARTICLE INFO

Keywords:
Liposome
Pancreatic Cancer
Active targeting
Drug delivery system

ABSTRACT

Pancreatic cancer is among the most fatal malignancies worldwide. The aggressive nature of this disease, coupled with late-stage diagnosis and limited therapeutic options, highlights the urgent need for innovative treatment approaches. Targeted therapy has emerged as a promising strategy to enhance therapeutic efficacy while minimizing systemic toxicity. Liposomes, as versatile nanoparticles, have shown significant potential to contribute to the develpment of drug delivery system. These lipid-based vesicles encapsulate chemotherapeutic drugs, shield them from degradation, and promote greater accumulation within tumor cites. Furthermore, liposomes can be surface-modifed with various ligands to improve their specificity and cellular uptake. Research on liposome-based targeted chemotherapy for pancreatic cancer has explored useful ligand-based strategies to enhance drug delivery to pancreatic cancer cells. In this review, liposome-based targeted strategies for pancreatic cancer are classified by ligand type, including antibodies, aptamers, carbohydrates, proteins and peptides, and integrates case studies to demonstrate how different targeting approaches translate into improved cellular uptake, therapeutic efficacy, and antitumor effects. In addition, emerging formulations such as dual-targeting liposomes are described, highlighting their potential to further strengthen treatment performance. The review summarizes the current research landscape of liposome-based targeted drug delivery systems for pancreatic cancer, providing insights into promising biomarkers and ligand-mediated targeting strategies. It further discusses broader opportunities for target exploration and liposomal design optimization, as well as future research directions aimed at overcoming existing limitations and improving therapeutic outcomes.

1. Introduction

Cancer is one of the leading causes of mortality worldwide, and the development of effective therapeutic strategies has long been a crucial challenge. A paradigm shift has moved from traditional cytotoxic chemotherapy toward targeted therapies, aiming to improve therapeutic efficacy while minimizing systemic toxicity(Anand et al., 2023). Among various cancers, Pancreatic cancer stands out as an especially critical focus for drug delivery research. Its rapid progression, fibrotic stromal environment, and poor response to conventional chemotherapies make it one of the deadliest malignancies (Liu et al., 2017; Hu and O'Reilly, 2024). These features limit the therapeutic benefit of existing cytotoxic agents. Consequently, the development of targeted therapeutic strategies is essential to enhance treatment precision and efficacy in this challenging disease.

In recent years, nanomedicine has provided promising solutions to these limitations. Among various nanocarriers, liposomes have attracted particular attention due to their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic drugs, and favorable pharmacokinetic profiles(Raza et al., 2023). However, challenges, such as rapid removal, insufficient penetration through dense substrates, and potential off-target effects, remain unresolved(Olajubutu et al., 2023). To

* Corresponding authors.
E-mail addresses: lhysshr@kumoh.ac.kr (H.-Y. Lee), nanomed@cau.ac.kr (J. Choi).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ijpx.2026.100483
Received 15 October 2025; Received in revised form 30 December 2025; Accepted 1 January 2026
Available online 2 January 2026

address these limitations, surface modifications of liposome have been explored, and novel liposome platforms are being developed. Liposome-based chemotherapy delivery studies for pancreatic cancer have also actively explored, utilizing various tumor-specific molecules, to enhance drug delivery to pancreatic tumor cells(Yang et al., 2011; Wang et al., 2021).

In this review, we highlight recent advances in ligand-modified liposome strategies for pancreatic cancer chemotherapy. Specifically, we categorize and summarize the use of different classes of ligands—including antibodies, aptamers, carbohydrates, proteins, and peptides—and evaluate their impact on targeting efficiency and therapeutic outcomes. We focus on how these ligands have been employed to design liposome-based drug delivery systems and review representative approaches that illustrate their therapeutic potential.

2. Study Selection

To investigate current research trends in liposome-based drug delivery systems for pancreatic cancer treatment, a literature search was conducted using electronic databases including Web of Science, Science Direct, and PubMed etc. The search included studies published from 2012 to 2025, utilizing combinations of key terms such as “Pancreatic cancer,” “Liposome,” “Chemotherapy,” and “Drug delivery.” Studies focusing primarily on drug resistance or combination therapies were excluded from this review.

A total of 348 records were initially identified through database searching. Following the initial identification, 280 records were screened based on their titles and abstracts. During this process, 238 records were excluded as they did not meet the inclusion criteria. Subsequently, the full texts of the remaining 42 articles were assessed for eligibility. Upon detailed review, 34 articles were excluded due to the following reasons: being review articles ($n = 13$), lack of relevance to the study topic ($n = 17$), or insufficient detail ($n = 4$). Ultimately, 8 studies were included in the final review (Fig. 1).

3. Pancreatic cancer and challenges in drug delivery

Pancreatic cancer is one of the lethal malignancies, with a 5-year survival rate of less than 10 %(Hu and O'Reilly, 2024). In addition to the aggressive nature of this disease, late-stage diagnosis and limited treatment options have increased the need for innovative approaches. Chemotherapy remains the cornerstone treatment for patients with pancreatic cancer(du Toit-Thompson et al., 2025; Reiss et al., 2025). Chemotherapy for pancreatic cancer initially relied on gemcitabine monotherapy, which provided only limited benefit(Nabyla Paixão and José Raimundo, 2018). The introduction of combination regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel significantly improved survival outcomes and established them as the current standard first-line treatments(Saung and Zheng, 2017).

Despite advancements in cancer therapy, effective treatments for pancreatic cancer are lacking. Pancreatic cancer therapies have shown limited success in improving patient outcomes, highlighting the urgent need for novel therapeutic approaches(du Toit-Thompson et al., 2025). Given the limitations of the conventional treatments for pancreatic cancer, more effective and less toxic therapeutic approaches are required.

Targeted therapies are designed to selectively attack cancer cells while sparing normal cells, thereby reducing adverse effects(Victoir et al., 2024). Incorporating nanoparticle-based delivery systems, particularly liposomes, further enhances this selectivity by improving drug stability, circulation time, and tumor accumulation(Wang et al., 2023). By directing therapeutic agents to specific molecular pathways involved in cancer growth and progression, targeted nanocarrier systems can help overcome resistance mechanisms that limit the efficacy of standard chemotherapy(Tarannum and Vivero-Escoto, 2022). In addition, this approach facilitates more personalized and precise therapeutic strategies tailored to the molecular profiles of individual tumors, paving the way for improved outcomes in pancreatic cancer.

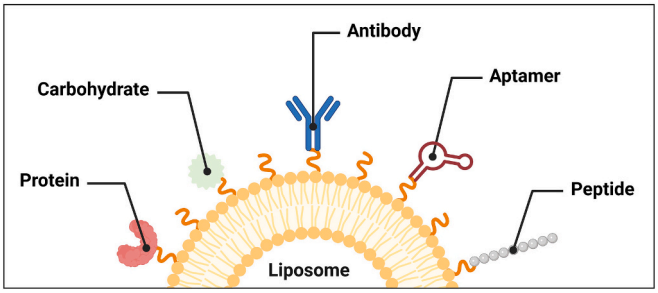

Fig. 1. PRISMA flow diagram of study selection process

4. Liposomes

4.1. Overview of liposomes

Liposomes are spherical nanoparticles composed of a phospholipid bilayer surrounding an aqueous core(Akbarzadeh et al., 2013). The sizes of these particles typically range from nanometers to micrometres. Liposomes are formed by the self-assembly of phospholipids when hydrated in an aqueous solution(Large et al., 2021). The hydrophilic head groups are oriented toward the aqueous phase both inside and outside the liposome, resulting in a bilayer structure within the solution (Khan et al., 2020). The characteristics of liposomes, including lipid composition, surface charge, size, and fabrication method, vary depending on their design and preparation processes(Akbarzadeh et al., 2013).

Liposomes are high-potential drug delivery systems capable of targeted and controlled drug release, owing to their biocompatibility, biodegradability, non-toxicity, and non-immunogenic properties. Liposomes can encapsulate both hydrophilic and hydrophobic drugs, which make them suitable carriers for a wide range of therapeutic agents (Agarwal et al., 2024). Liposomes improve bioavailability by protecting encapsulated drugs and enhancing their absorption across biological barriers(Alavi et al., 2017; Lin et al., 2022). The lipid bilayer structure facilitates sustained and controlled drug release, potentially enhancing therapeutic outcomes(Liu et al., 2022). Encapsulation within liposomes minimizes the exposure of normal tissues to toxic substances, thereby reducing their toxicity and side effects. Furthermore, surface modifications allow liposomes to be designed to target specific tissues or cells, increasing their therapeutic efficacy while minimizing adverse systemic effects (Akbarzadeh et al., 2013; Guimarães et al., 2021).

4.2. Passive targeting of liposomes

Passive targeting of liposomes to tumors is related to the leaky architecture of tumor-associated blood vessels. Depending on the type of cancer, the gap between endothelial cells in tumor capillaries is 100–780 nm, compared to 4–10 nm in the normal endothelium(Zhang et al., 2021). This enhanced permeability and retention (EPR) effect results in the effective delivery of liposomes to the tumor site (Sawant and Torchilin, 2012; Wu, 2021). Therefore, an ideal passive targeting strategy is possible if liposomes are formulated to an acceptable size that enables them to leak out of cancerous tissues (Khan et al., 2020). However, the limitations of EPR effect are evident in pancreatic cancer. The heterogeneity of the pancreatic tumor microenvironment, stemming from factors such as thick tumor stroma, high tumor interstitial fluid pressure(IFP), and non-leaky dominant vascular structures, negatively impacts the EPR effects (Liu et al., 2019).

4.3. Surface modification and active targeting of liposomes

Liposome technology has undergone continuous evolution since its introduction. Conventional liposomes, first studied clinically in the 1990s, reduced systemic toxicity, but their rapid clearance from the bloodstream limited therapeutic efficacy(Sercombe et al., 2015). To overcome this, PEGylated liposomes were developed, in which a polyethylene glycol (PEG) coating provides steric stabilization, prolongs circulation time, and enhances drug accumulation at pathological sites (Gregoriadis, 2016). Building upon this, ligand-targeted liposomes emerged, incorporating antibodies, peptides, or carbohydrates on the surface to achieve active recognition of disease-specific receptors and improve delivery precision. Liposomal surfaces have been modified with protein, carbohydrate, antibody, aptamer, and peptide (Fig. 2) (Khan et al., 2020). The usefulness of surface-modified liposomes has been demonstrated in various applications, most notably as an innovative way to overcome the limitations of conventional drug delivery systems (Riaz et al., 2018).

5. Ligand-based active targeting approaches for pancreatic cancer

Passively targeting liposomes has several limitations. Passive targeting does not recognize specific receptors, which can lead to accumulation in normal tissues and potential off-target toxicity(Olajubutu et al., 2023). Furthermore, tumor heterogeneity renders the EPR Effect inconsistent, causing heterogeneous distribution of liposomes within the tumor(Golombek et al., 2018). Active targeting of liposomes is a novel strategy for overcoming these limitations. Actively targeted liposomes are manufactured by incorporating targeting moieties onto the surface of particles designed to reduce off-target effects. To target liposomes to cancer cells, attaching sufficiently specific targeting moieties is important to achieve effective affinity for target molecules.

Cancer-targeting strategies can be classified into two main categories. The first approach targets cell surface receptors expressed on cancer cells(Riaz et al., 2018). This involves the delivery of drugs via liposomes with specific ligands for receptors that are overexpressed in cancer cells compared to normal cells. Examples of such receptors that are used as biomarkers include folate receptors, transferrin receptors, and epidermal growth factor receptor (EGFR). The second strategy is targeting the tumor microenvironment(Riaz et al., 2018). The main components of the tumor microenvironment (TME) include tumor cells, immune cells, fibroblasts, stromal cells, blood vessels, and the extracellular matrix. Typical examples include VEGF, VCAM, and B-RAF (Yang et al., 2011; Khan et al., 2020; Raza et al., 2023). In Table 1, studies targeting FAP (Lin et al., 2022) and P-selectin (Swami et al., 2024) represent strategies targeted at the tumor microenvironment, whereas the other studies focus on cell surface receptors expressed on cancer cells. To target these biomarkers, researchers have frequently used ligands such as folic acid, transferrin, and VEGF antibodies.

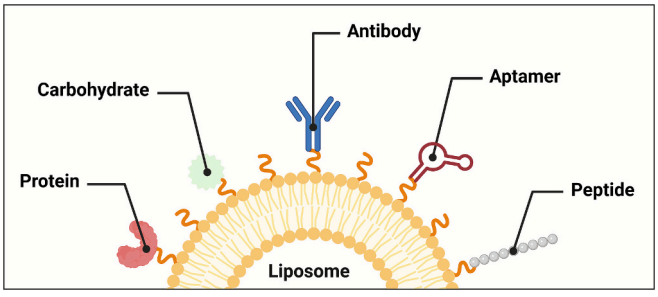

Fig. 2. Modification of the liposome surface with various ligands, such as protein, carbohydrate, antibody, aptamer, and peptide. Created in BioRender. NML, C. (2026) https://BioRender.com/4yfrc71

Recently, there has been growing interest in identifying new biomarker candidates and expanding the range of ligands applied for targeted delivery(Yan et al., 2024).

5.1. Antibodies

Antibodies, also known as immunoglobulins, are specialized proteins produced by the B cells of the immune system in response to antigens(Di et al., 2020). Antibodies exhibit a variable region at the end that binds specifically to antigens, and this ability of antibodies can be utilized as a therapeutic strategy. Antibodies are widely utilized as representative cancer-targeting agents due to their high specificity and precision. More than 50 antibody-based therapeutics have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and many additional candidates are currently under development(Paul et al., 2024). In addition, as natural components of the immune system, antibodies are highly biocompatible and possess the ability to simultaneously target multiple antigens, making them suitable for dual targeting (Sorbara et al., 2022). However, Antibodies as ligands still encounter several limitations, including their large molecular size, high production costs, and the risk of immunogenicity(Paul et al., 2024).

Recent advancements in targeted drug delivery systems using antibodies have shown promising results for the treatment of pancreatic cancer. A novel approach involving antibody fragment (AF)-conjugated liposomes (AF-GPL) loaded with gemcitabine (GEM) and paclitaxel (PTX) was developed (Yang et al., 2018). This nanoparticle was designed to selectively bind to tissue factor overexpressed in pancreatic cancer cells using AF. These nanocarriers, with an average size of approximately 168 nm, were suitable for enhanced tumor penetration. The AF-GPL system exhibited exceptional drug encapsulation efficiency exceeding 95 % for both GEM and PTX, while maintaining controlled release profiles for the encapsulated drugs. Notably, compared to their non-targeted counterparts, AF-GPL exhibited a twofold increase in cellular uptake and significantly enhanced cytotoxicity. The IC50 value was reduced to 0.45 μg/mL, demonstrating substantial improvement relative to GPL (1.92 μg/mL). Furthermore, AF-GPL induced a notably higher proportion of late apoptosis, approximately 45 %, in pancreatic cancer cells, highlighting the synergistic effect of the dual-drug and active targeting strategy.

This study presents the development and evaluation of a novel multifunctional nanoimmunoliposome system (M-PLDU) for the targeted diagnosis and therapy of pancreatic cancer(Deng et al., 2012). Mesothelin is highly overexpressed on the surface of pancreatic cancer cells, and to target this receptor, M-PLDUs were created by encapsulating ultrasmall superparamagnetic iron oxides (USPIOs) and doxorubicin (DOX) in PEGylated liposomes and then conjugating anti-mesothelin (MSLN) antibodies to the surface. Liposomes were prepared using a transient binding and reverse-phase evaporation method, achieving high encapsulation efficiencies of USPIOs (40.8 %) and DOX (68.5 %). The resulting M-PLDUs had a mean size of 175–185 nm and maintained the integrity of the anti-MSLN antibodies. Confocal microscopy and flow cytometry revealed a 1.4-fold higher cellular uptake of M-PLDUs in MSLN-expressing Panc-1 cells compared with non-targeted liposomes. The IC50 values were 1.95 μM for M-PLDU and 3.5 μM for PLDU, respectively. In vivo, the MRI signal attenuation was markedly greater for M-PLDU (145.98) than for PLDU (75.69). M-PLDU treatment resulted in a more pronounced inhibition of tumor growth than free DOX or non-targeted liposomes. Moreover, biodistribution studies have revealed higher accumulation of DOX in tumors and lower accumulation in the heart for M-PLDUs than for free DOX. These results suggest that this MSLN-targeted immunoliposomal formulation is promising for both targeted chemotherapy and early MRI diagnosis of pancreatic cancer. This system combines the benefits of targeted drug delivery, enhanced tumor accumulation, and improved MRI contrast, potentially offering a theragnostic approach for the management of pancreatic cancer (Deng et al., 2012).

Table 1
Liposome-based targeted drug delivery systems for pancreatic cancer therapy.

Name	Ligand		Receptor	Drug	EE%	Advantages	Ref.
AF-GPL	Antibody	Anti-tissue factor antibody	Tissue factor	Gemcitabine, Paclitaxel	95	• 2-fold higher cellular uptake compared to GPL • IC50: GPL 1.92μg/mL, AF-GPL 0.45μg/mL	(Yang et al., 2018)
M-PLDU		Anti-mesothelin antibody	Mesothelin	Doxorubicin	68.5	• 1.4-fold higher cellular uptake than PLDU • IC50: PLDU 3.5uM, M-PLDU 1.95uM	(Deng et al., 2012)
APTA-12	Aptamer	G-quadruplex	Nucleolin	Gemcitabine	–	• Binding affinity: AS1411 16.36 nM, APTA-12 14.37 nM • IC50 reduced by 43-fold compared to AS1411	(Park et al., 2018)
FU-psLs-GEM	Carbohydrate	Fucoidan	P-selectin	Gemcitabine	86.3	• 100 % release within 6 h at pH 5.0 • Enhanced cellular uptake at pH 5.0	(Zhou et al., 2024)
D@C-LP	Protein/ Peptide	SPE17	CLDN-4	Doxorubicin	87–88	• In $CLDN^+$ cells, D@C-LP demonstrated increased cellular uptake and cytotoxicity	(Bang et al., 2023)
GE-SML/ siRNA		GE11	EGFR	Gemcitabine	–	• IC50: GML 7.45μg/mL, GE-GML/siRNA 0.42μg/mL • Late apoptosis 23 %	(Liu et al., 2019)
BS-lipoIRI	Dual targeting	Anti-EGFR/Anti-FAP bispecific antibody	EGFR FAP	Irinotecan	70–80	• 1.6-fold higher intratumoral accumulation of irinotecan with BS-lipoIRI • 46.2 % reduction in tumor volume	(Liu et al., 2022)
Aptm[DOX/ IDO1]		Anti-CD44 aptamer	CD44	Doxorubicin	–	• Enhanced internalization in $EpCAM^+$ cell • 3.8-fold higher apoptosis	(Kim et al., 2022)

5.2. Aptamers

Aptamers are short synthetic DNA or RNA molecules that bind to specific targets with high affinity and selectivity. When conjugated to liposomes, they can enhance tumor targeting and drug delivery. The key advantages of aptamers include their small size, simple synthesis, low immunogenicity, high affinity, selectivity, and stability under various conditions(Moosavian and Sahebkar, 2019). Membrane anchoring and post-insertion methods are the two main methods for conjugating aptamers to liposomes. Major factors affecting the efficiency of aptamer-functionalized liposomes include conjugation chemistry, spacer structure, aptamer characteristics (length, modifications, etc.), and aptamer surface density. Maintaining the aptamer structure and binding ability after conjugation, optimizing the spacer length to properly expose the aptamers, and balancing the aptamer density to improve targeting without compromising liposome properties are important considerations. Although aptamer-functionalized liposomes show promise for targeted drug delivery in vitro, their in vivo performance can be more complex owing to their interactions with biological systems. The formation of a protein corona in vivo may reduce the targeting efficiency. Careful optimization is required to translate the benefits of aptamer targeting to clinical applications (Moosavian et al., 2023).

Researchers developed APTA-12, a gemcitabine-incorporated G-quadruplex aptamer targeting nucleolin, which is overexpressed in pancreatic cancer cells (Fig. 3) (Park et al., 2018). APTA-12 was designed by modifying AS1411 and incorporating gemcitabine into its

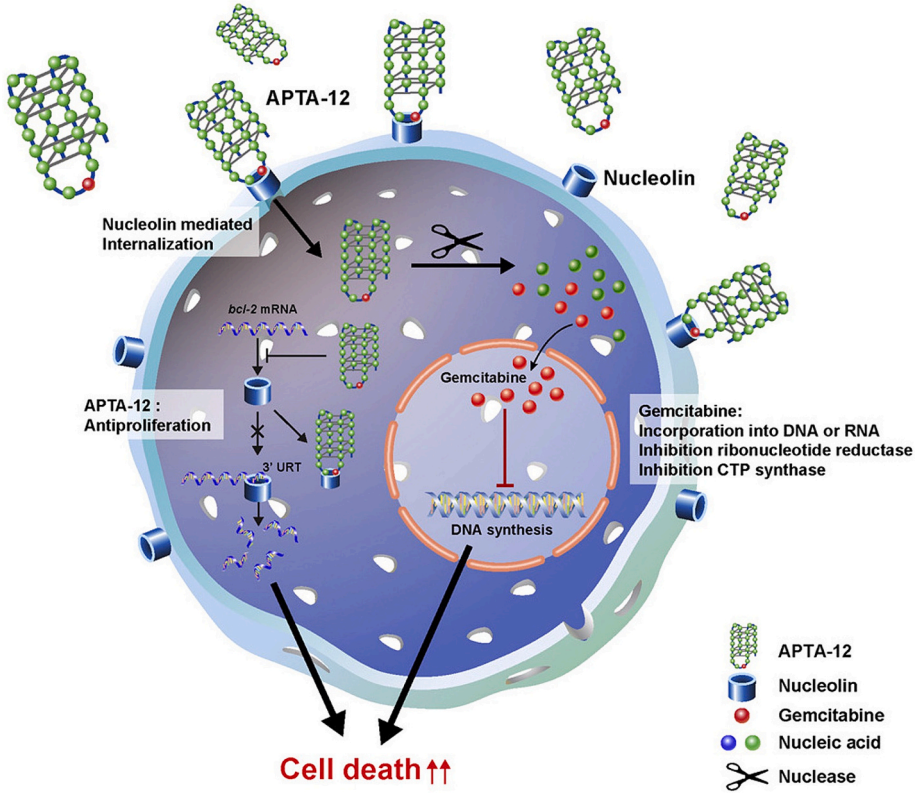

Fig. 3. Mechanism of action of APTA-12 and gemcitabine in pancreatic cancer cells. Reproduced with permission from (Park et al., 2018). Copyright 2018, Elsevier.

loop to preserve its structural integrity and binding affinity. In vitro studies have demonstrated that APTA-12 selectively binds to nucleolin-positive pancreatic cancer cells (Capan-1, AsPC-1, and MIA PaCa-2), while sparing normal cells (H6c7). It exhibited superior cytotoxicity compared with AS1411 alone, demonstrating a 43-fold reduction in IC50 values in cancer cells. In vivo experiments using Capan-1 tumor xenografts showed that APTA-12 achieved 93.4 % tumor growth inhibition and 42.5 % tumor shrinkage compared to the controls. Histological analysis revealed increased apoptosis and reduced proliferation of treated tumors. Importantly, APTA-12 displayed minimal toxicity, with no significant changes in body weight or hematological or biochemical parameters in mice. These findings suggested that APTA-12 offers a promising targeted therapeutic strategy for pancreatic cancer, combining enhanced efficacy with a favorable safety profile (Park et al., 2018).

5.3. Carbohydrates

Carbohydrates play an significant role in the regulation of various physiological processes, including cell adhesion, migration, signal transduction, and pathogen interactions(Agwa et al., 2023). Carbohydrates are abundantly available natural substances with significant economic benefits and high biocompatibility and stability. Various carbohydrate ligands are available, including fucose, mannose, galactose, and hyaluronic acid. These carbohydrates can selectively bind to specific receptors that are overexpressed on the surface of cancer cells to support efficient drug delivery. However, there is a risk of nonspecific interactions, and owing to the heterogeneity of cancer, the expression levels of carbohydrate ligands and their specific receptors can vary, making consistent targeting difficult (Swami et al., 2024). Carbohydrate ligands have the potential to overcome the limitations of conventional anticancer therapies, and further research may lead to the development of more precise and effective nanotherapeutics.

A recent study developed a novel drug delivery system for pancreatic cancer therapy using pH-sensitive cationic liposomes coated with fucoidan (Fu-pSLs-GEM) and loaded with gemcitabine (GEM) (Fig. 4A) (Zhou et al., 2024). It achieved 100 % release within 6 h at pH 5.0, demonstrating a faster release rate compared with pH 7.4. The fucoidan coating was designed to target tumor cells by binding to P-selectin, which is often overexpressed in cancer tissues (Fig. 4B). These nanoparticles demonstrated promising characteristics, with a particle size of 171 nm and a high drug encapsulation efficiency of 87.3 %. The Fu-pSLs-GEM system exhibited enhanced stability under acidic conditions, which is particularly relevant for targeting the tumor microenvironment. Importantly, the pH-sensitive nature of these liposomes facilitated faster drug release under acidic conditions than at normal pH, potentially improving drug delivery to cancer cells (Fig. 4C). In vitro studies revealed that Fu-pSLs-GEM exhibited stronger and more rapid anticancer effects than free GEM or uncoated liposomes (Fig. 4D,E). This enhanced efficacy could be attributed to the targeted delivery mechanism and pH-sensitive release profile of the nanoparticles. These findings suggest that Fu-pSLs-GEM represents a promising approach for

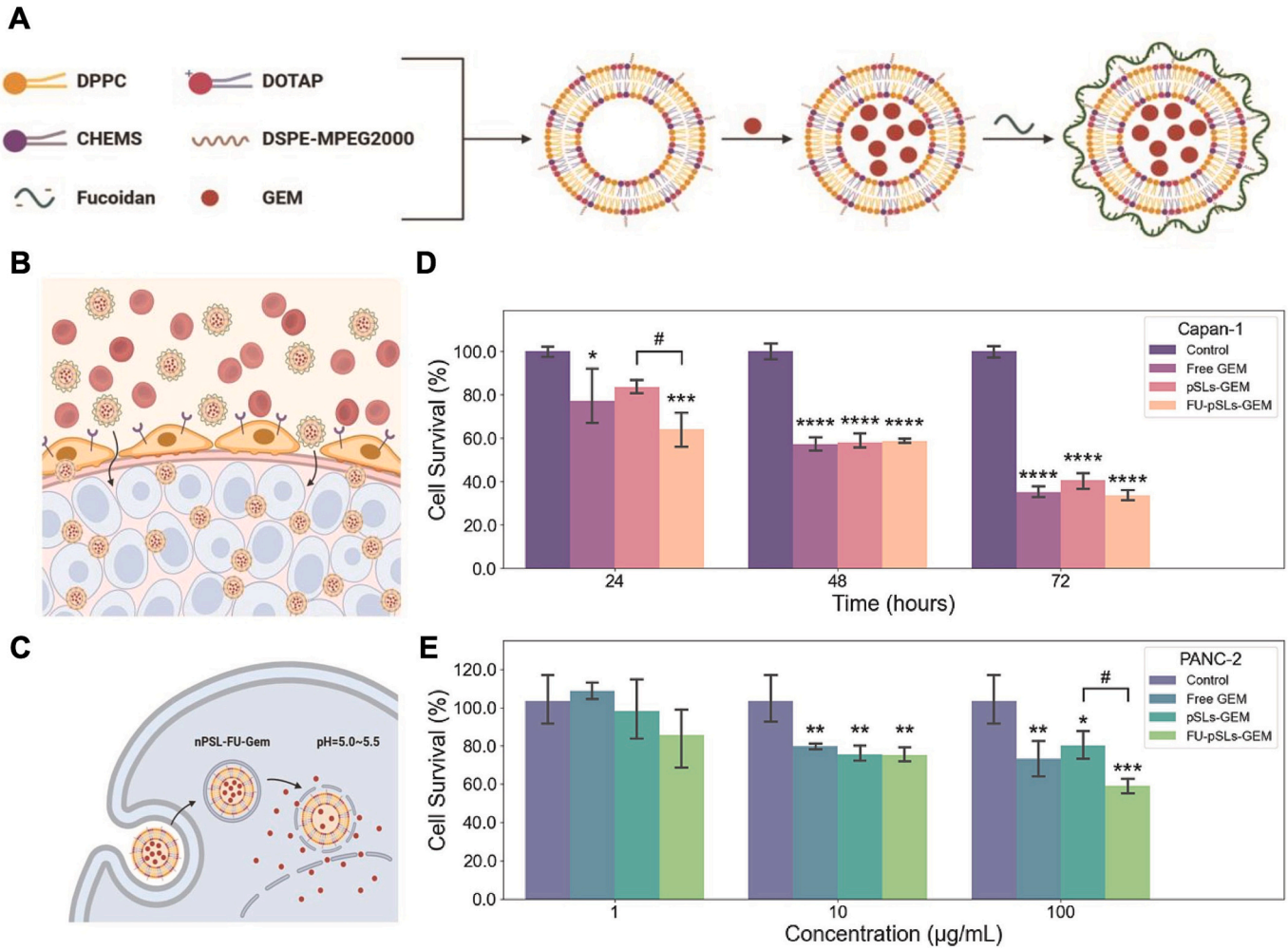

Fig. 4. (A) Preparation of Fu-psLs-GEM. (B, C) Mechanism of FU-pSLs-GEM binding to P-selectin. The anti-tumor effect of FU-pSLs-GEM to (D) Capan-1 and (E) PANC-2. Reproduced with permission from (Zhou et al., 2024). Copyright 2024, Elsevier.

improving the delivery and efficacy of gemcitabine in pancreatic cancer treatment.

5.4. Proteins and peptides

Proteins and peptide ligands occupy a size range between that of smaller molecules and antibodies. Proteins and peptides exhibit high affinity and specificity and form large binding interfaces with receptors through protein–protein interactions(Spicer, Jumeaux et al. 2018). They also have low immunogenicity and excellent cost-effectiveness, making them easy-to-use and economical options for large-scale synthesis. This scalability is critical for the commercial viability of protein–peptide-based therapeutics. However, the extremely short half-life of peptides in plasma, along with their rapid enzymatic degradation, remains one of the most significant limitations(Cheetham et al., 2016). The abundance of chemical groups in proteins and peptides allows for a wide range of modifications, facilitating the fine-tuning of properties such as stability and target specificity (Jiang et al., 2019).

A recent study explored the potential of CLDN4-targeted liposomes as a novel therapeutic approach for pancreatic cancer (Fig. 5A) (Bang et al., 2023). Researchers developed liposomes loaded with doxorubicin and conjugated them to CPE17, a peptide derived from *Clostridium perfringens* enterotoxin that specifically binds to CLDN4 (Bang et al., 2023). This strategy leverages the overexpression of CLDN4 on the surface of pancreatic cancer cells, which occurs due to the disruption of tight junctions in these malignant cells. The engineered liposomes, termed D@C-LP, demonstrated promising physicochemical properties, with a particle size of approximately 210 nm and a high drug encapsulation efficiency of 87 %–88 %. In vitro studies revealed an enhanced uptake and cytotoxicity of D@C-LP in CLDN4-positive pancreatic cancer cells compared to CLDN4-negative cells, highlighting the potential of this targeted approach (Fig. 5B-E). This innovative strategy builds on previous research demonstrating the efficacy of targeting CLDN4 in various cancers, including pancreatic cancer. By combining the specificity of CLDN4 targeting with the established cytotoxic effects of doxorubicin, this approach represents a promising avenue for improving pancreatic cancer treatment outcomes.

A recent study developed liposomes co-loaded with gemcitabine and HIF-1α siRNA, conjugated with GE11 peptide to target pancreatic cancer cells overexpressing EGFR (Lin, Hu et al. 2019). GE11-conjugated liposomes (GE-GML/siRNA) had a particle size of approximately 166 nm. GE11 significantly enhanced cellular uptake in Panc-1 human pancreatic cancer cells, resulting in a reduced IC50 value (0.42 μg/mL for GML/siRNA vs. 7.45 μg/mL for the non-targeted GML) and an increased late apoptosis ratio of 23 %. The in vivo results demonstrated a remarkable fourfold reduction in tumor size compared to the control group, highlighting the potential of this targeted delivery system in pancreatic cancer treatment. This approach combines several promising cancer therapeutic strategies. The use of the GE11 peptide for EGFR targeting has been shown to improve the specificity and efficacy of various nanocarrier systems. The co-delivery of gemcitabine and HIF-1α siRNA addresses both chemotherapy resistance and the hypoxic tumor microenvironment, which are significant challenges in pancreatic cancer treatment.

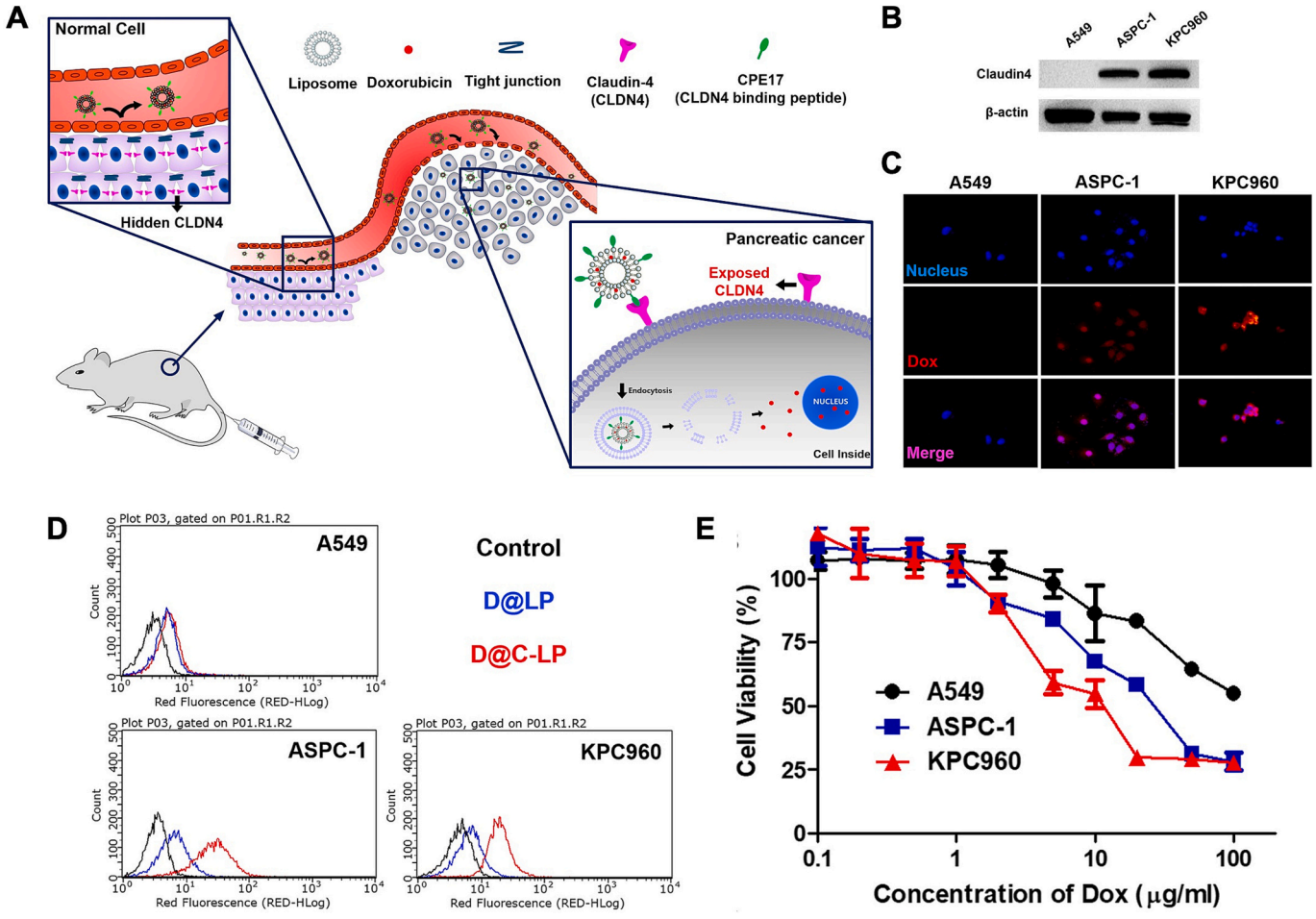

Fig. 5. (A) Design of D@C-LP to target exposed CLDN5 on pancreatic cancer cells. (B) Western blot analysis of CLDN4 expression in A549, AsPC-1 and KPC960. (C) Confocal microscopy images and (D) flow cytometry showing cellular uptake of D@C-LP. (E) The anti-tumor effect of D@C-LP. Reproduced with permission from (Bang et al., 2023). Copyright 2023, Springer Nature.

5.5. Dual targeting

There are two main approaches to achieving dual targeting. One targets the same receptor on two different cell types with a single ligand, and the other uses two ligands to target two different receptors on the same or different cells (Taghipour et al., 2022). Dual targeting is a promising strategy to overcome the difficulties of conventional targeting strategies, such as the low tumor site penetration of nanoparticle-based drug delivery systems and limited penetration due to pathological barriers. Dual targeting offers precise tumor targeting, enabling efficient drug delivery and enhanced therapeutic efficacy by targeting unique receptors and markers specific to cancer cells(Taghipour et al., 2022).

A novel approach for pancreatic cancer treatment has been developed utilizing bispecific antibody-conjugated liposomal irinotecan (BS-LipoIRI), which simultaneously targets the epidermal growth factor receptor (EGFR) on pancreatic cancer cells and fibroblast activation protein (FAP) on cancer-associated fibroblasts (Lin, Liang et al. 2022). BS-LipoIRI exhibits a size range o-f 12–130 nm and a drug encapsulation efficiency of 70 %–80 %. Compared with non-targeted LipoIRI, BS-LipoIRI demonstrated enhanced cellular uptake and cytotoxicity against pancreatic cancer cells. In vivo studies revealed that BS-LipoIRI exhibited a prolonged circulation time and increased accumulation in tumors.

Another study presents a novel approach for cancer therapy using aptamer-conjugated nanoliposomes (Aptm[DOX/IDO1]) that deliver doxorubicin (DOX) and IDO1 siRNAs to breast cancer cells (Fig. 6A) (Kim et al., 2022). This targeted delivery system induces immunogenic cell death and reverses immunosuppression in the tumor microenvironment, leading to enhanced antitumor effects in breast cancer models. Researchers have demonstrated that Aptm[DOX/IDO1] specifically binds to cancer cells, effectively delivers its payload, and synergistically suppresses tumor growth by increasing cytotoxic T-lymphocyte infiltration and reprogramming the immunosuppressive tumor microenvironment in vivo (Fig. 6B).

6. Limitations and future perspectives, and clinical trials

Liposome-targeted chemotherapy for pancreatic cancer is promising; however, several limitations hinder its efficacy. Pancreatic cancer exhibits significant intratumoral and intertumoral heterogeneity, hindering the treatment of all cancer cells with a single targeted therapy. The complex genetic landscape and diverse cell populations within tumors contribute to variable drug responses and the development of resistance mechanisms. Targeting a single molecular pathway is often insufficient

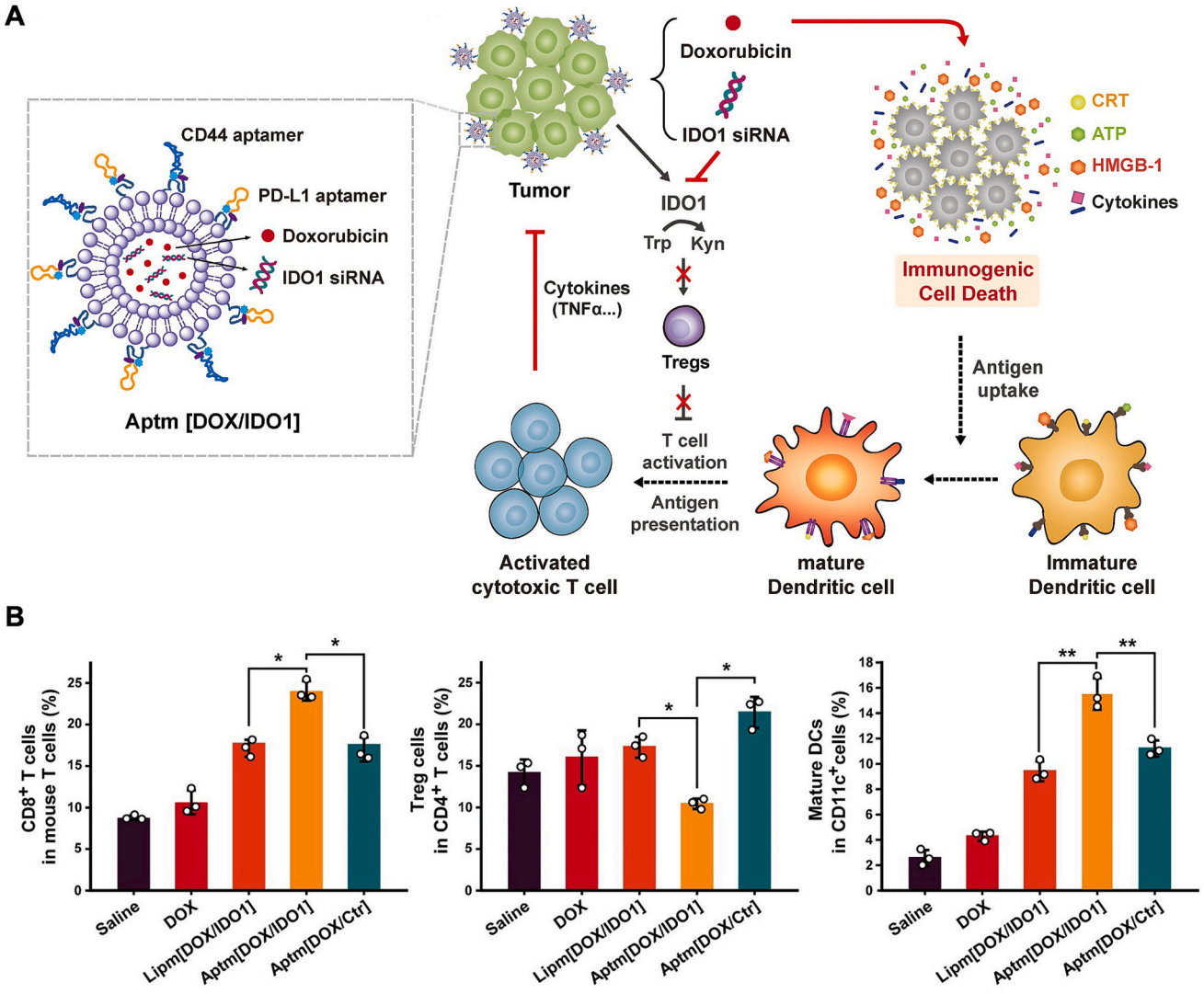

Fig. 6. (A) Schematic illustration of Aptm[DOX/IDO1] co-delivering DOX and IDO1 siRNA via anti-CD44/PD-L1 aptamer. (B) Flow cytometry of tumor-infiltrating $CD8^+$ cytotoxic T lymphocytes (CTLs), $FoxP3^+$ regulatory T cells (Tregs), and $CD80^+/CD86^+$ mature dendritic cells (DCs) in tumor tissues. Reproduced with permission from (Kim et al., 2022). Copyright 2022 Elsevier.

due to the adaptability of cancer cells. Moreover, pancreatic tumors can activate alternative signaling pathways or upregulate compensatory mechanisms, limiting the long-term effectiveness of single-target liposomal therapies.

The lack of reliable biomarkers for patient stratification and treatment response monitoring poses a challenge in optimizing targeted liposomal therapies. Identifying biomarkers is crucial for developing personalized treatment approaches and enhancing overall efficacy. In conclusion, while liposomal-targeted chemotherapy holds promise for pancreatic cancer treatment, addressing these limitations is crucial for improving therapeutic outcomes. Future research should focus on establishing precise targeting strategies, designing patient-specific liposomes, and identifying predictive biomarkers to enhance the efficacy of liposomal drug delivery systems in pancreatic cancer.

Liposome-based drug delivery systems for PDAC therapy remain extremely limited in clinical evaluation. Currently, the only liposomal formulation approved for pancreatic cancer treatment is nanoliposomal irinotecan, commercially known as Onivyde(Hu and O'Reilly, 2024). A liposomal formulation under clinical investigation is thermosensitive liposomal doxorubicin (ThermoDox®), which encapsulates doxorubicin in a heat-responsive liposomal carrier designed to release the drug locally at the tumor site upon exposure to ultrasound-induced hyperthermia(Agarwal et al., 2024).

7. Conclusion

Ligand-modified liposomes have emerged as a promising nanoplatform for targeted chemotherapy in pancreatic cancer. By conjugating specific ligands such as antibodies, aptamers, carbohydrates, proteins, and peptides, these liposomes enable selective drug delivery to cancer cells or tumor microenvironment, thereby enhancing therapeutic efficacy and minimizing systemic toxicity. Despite these advances, liposome-based chemotherapy for targeting pancreatic cancer remains challenging due to the remarkable intra- and intertumoral heterogeneity, adaptive resistance mechanisms, and the lack of reliable biomarkers for patient stratification and therapeutic monitoring. These factors contribute to limitation of drug responses and decrease the efficacy of single-target strategies. To overcome these challenges, future research should focus on developing precision-targeted strategies, designing patient-specific liposome system, and identifying predictive biomarkers to optimize treatment outcomes.

CRediT authorship contribution statement

Yerin Jang: Writing – original draft, Visualization, Software, Resources, Project administration, Investigation, Formal analysis, Data curation. **Jaehee Jang:** Writing – original draft, Software, Resources, Project administration, Formal analysis, Data curation, Conceptualization. **Jaewoo Son:** Validation, Software, Methodology, Investigation. **Hee-Young Lee:** Writing – original draft, Visualization, Supervision, Methodology, Formal analysis. **Jonghoon Choi:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Dr. Jonghoon Choi is the CEO and the Founder of the Feynman Institute of Technology at the Nanomedicine Corp, Seoul, Republic of Korea and of the Feynman Institute of Nanomedicine at the Nanopeutics Inc., Lewes, DE, USA. Dr. Hee-Young Lee is the CSO of the Feynman Institute of Technology at the Nanomedicine Corp, Seoul, Republic of Korea.

Acknowledgements

This research was supported by the National Research Foundation of Korea(NRF) funded by the Korea government(MSIT) (RS-2024-00459728, RS-2024-00343605, and 2025-RISE-01-024-05).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpx.2026.100483.

Data availability

No data was used for the research described in the article.

References

Agarwal, H., Bynum, R.C., Saleh, N., Harris, D., MacCuaig, W.M., Kim, V., Sanderson, E. J., Dennahy, I.S., Singh, R., Behkam, B., Gomez-Gutierrez, J.G., Jain, A., Edil, B.H., McNally, L.R., 2024. Theranostic nanoparticles for detection and treatment of pancreatic cancer. WIREs Nanomed. Nanobiotechnol. 16 (4), e1983.

Agwa, M.M., Elmotasem, H., Elsayed, H., Abdelsattar, A.S., Omer, A.M., Gebreel, D.T., Mohy-Eldin, M.S., Fouda, M.M.G., 2023. Carbohydrate ligands-directed active tumor targeting of combinatorial chemotherapy/phototherapy-based nanomedicine: a review. Int. J. Biol. Macromol. 239, 124294.

Akbarzadeh, A., Rezaei-Sadabady, R., Davaran, S., Joo, S.W., Zarghami, N., Hanifehpour, Y., Samiei, M., Kouhi, M., Nejati-Koshki, K., 2013. Liposome: classification, preparation, and applications. Nanoscale Res. Lett. 8 (1), 102.

Alavi, M., Karimi, N., Safaei, M., 2017. Application of various types of liposomes in drug delivery systems. Adv. Pharm. Bull. 7 (1), 3–9.

Anand, U., Dey, A., Chandel, A.K.S., Sanyal, R., Mishra, A., Pandey, D.K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A., Dhanjal, J.K., Dewanjee, S., Vallamkondu, J., Pérez de la Lastra, J.M., 2023. Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. Genes Dis. 10 (4), 1367–1401.

Bang, C., Park, M.G., Cho, I.K., Lee, D.-E., Kim, G.L., Jang, E.H., Shim, M.K., Yoon, H.Y., Lee, S., Kim, J.-H., 2023. Liposomes targeting the cancer cell-exposed receptor, claudin-4, for pancreatic cancer chemotherapy. Biomater. Res. 27 (1), 53.

Cheetham, A.G., Keith, D., Zhang, P., Lin, R., Su, H., Cui, H., 2016. Targeting Tumors with Small Molecule Peptides. Curr. Cancer Drug Targets 16 (6), 489–508.

Deng, L., Ke, X., He, Z., Yang, D., Gong, H., Zhang, Y., Jing, X., Yao, J., Chen, J., 2012. A MSLN-targeted multifunctional nanoimmunoliposome for MRI and targeting therapy in pancreatic cancer. Int. J. Nanomedicine 7 (null), 5053–5065.

Di, J., Xie, F., Xu, Y., 2020. When liposomes met antibodies: drug delivery and beyond. Adv. Drug Deliv. Rev. 154-155, 151–162.

du Toit-Thompson, T., Leck, L., Gillson, J., Pavlakis, N., Gill, A.J., Samra, J.S., Mittal, A., Sahni, S., 2025. Overcoming therapy resistance in pancreatic cancer: challenges and emerging strategies. Adv. Drug Deliv. Rev. 224, 115647.

Golombek, S.K., May, J.N., Theek, B., Appold, L., Drude, N., Kiessling, F., Lammers, T., 2018. Tumor targeting via EPR: strategies to enhance patient responses. Adv. Drug Deliv. Rev. 130, 17–38.

Gregoriadis, G., 2016. Liposomes in drug delivery: how it all happened. Pharmaceutics 8 (2).

Guimarães, D., Cavaco-Paulo, A., Nogueira, E., 2021. Design of liposomes as drug delivery system for therapeutic applications. Int. J. Pharm. 601, 120571.

Hu, Z.I., O'Reilly, E.M., 2024. Therapeutic developments in pancreatic cancer. Nat. Rev. Gastroenterol. Hepatol. 21 (1), 7–24.

Jiang, Z., Guan, J., Qian, J., Zhan, C., 2019. Peptide ligand-mediated targeted drug delivery of nanomedicines. Biomater. Sci. 7 (2), 461–471.

Khan, A.A., Allemailem, K.S., Almatroodi, S.A., Almatroudi, A., Rahmani, A.H., 2020. Recent strategies towards the surface modification of liposomes: an innovative approach for different clinical applications. 3 Biotech 10 (4), 163.

Kim, M., Lee, J.S., Kim, W., Lee, J.H., Jun, B.-H., Kim, K.-S., Kim, D.-E., 2022. Aptamer-conjugated nano-liposome for immunogenic chemotherapy with reversal of immunosuppression. J. Control. Release 348, 893–910.

Large, D.E., Abdelmessih, R.G., Fink, E.A., Auguste, D.T., 2021. Liposome composition in drug delivery design, synthesis, characterization, and clinical application. Adv. Drug Deliv. Rev. 176, 113851.

Lin, H.-J., Liang, T.-L., Chang, Y.-Y., Liu, D.-Z., Fan, J.-Y., Roffler, S.R., Lin, S.-Y., 2022. Development of irinotecan liposome armed with dual-target anti-epidermal growth factor receptor and anti-fibroblast activation protein-specific antibody for pancreatic cancer treatment. Pharmaceutics 14 (6), 1202.

Liu, Q., Liao, Q., Zhao, Y., 2017. Chemotherapy and tumor microenvironment of pancreatic cancer. Cancer Cell Int. 17 (1), 68.

Liu, X., Jiang, J., Meng, H., 2019. Transcytosis - an effective targeting strategy that is complementary to "EPR effect" for pancreatic cancer nano drug delivery. Theranostics 9 (26), 8018–8025.

Liu, P., Chen, G., Zhang, J., 2022. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules 27 (4).

Moosavian, S.A., Sahebkar, A., 2019. Aptamer-functionalized liposomes for targeted cancer therapy. Cancer Lett. 448, 144–154.

Moosavian, S.A., Kesharwani, P., Singh, V., Sahebkar, A., 2023. 6 - Aptamer-Functionalized Liposomes for Targeted Cancer Therapy. Aptamers Engineered

Nanocarriers for Cancer Therapy. P. Kesharwani. Woodhead Publishing, pp. 141–172.
Nabyla Paixão, P., José Raimundo, C., 2018. Pancreatic cancer: treatment approaches and trends. J. Cancer Metastasis Treat. 4, 30.
Olajubutu, O., Ogundipe, O.D., Adebayo, A., Adesina, S.K., 2023. Drug delivery strategies for the treatment of pancreatic cancer. Pharmaceutics 15 (5), 1318.
Park, J.Y., Cho, Y.L., Chae, J.R., Moon, S.H., Cho, W.G., Choi, Y.J., Lee, S.J., Kang, W.J., 2018. Gemcitabine-incorporated G-quadruplex aptamer for targeted drug delivery into pancreas cancer. Mol. Ther. Nucleic Acids 12, 543–553.
Paul, S., Konig, M.F., Pardoll, D.M., Bettegowda, C., Papadopoulos, N., Wright, K.M., Gabelli, S.B., Ho, M., van Elsas, A., Zhou, S., 2024. Cancer therapy with antibodies. Nat. Rev. Cancer 24 (6), 399–426.
Raza, F., Evans, L., Motallebi, M., Zafar, H., Pereira-Silva, M., Saleem, K., Peixoto, D., Rahdar, A., Sharifi, E., Veiga, F., Hoskins, C., Paiva-Santos, A.C., 2023. Liposome-based diagnostic and therapeutic applications for pancreatic cancer. Acta Biomater. 157, 1–23.
Reiss, K.A., Soares, K.C., Torphy, R.J., Gyawali, B., 2025. Treatment innovations in pancreatic cancer: putting patient priorities first. Am. Soc. Clin. Oncol. Educ. Book 45 (3), e473204.
Riaz, M.K., Riaz, M.A., Zhang, X., Lin, C., Wong, K.H., Chen, X., Zhang, G., Lu, A., Yang, Z., 2018. Surface functionalization and targeting strategies of liposomes in solid tumor therapy: a review. Int. J. Mol. Sci. 19 (1), 195.
Saung, M.T., Zheng, L., 2017. Current standards of chemotherapy for pancreatic cancer. Clin. Ther. 39 (11), 2125–2134.
Sawant, R.R., Torchilin, V.P., 2012. Challenges in development of targeted liposomal therapeutics. AAPS J. 14 (2), 303–315.
Sercombe, L., Veerati, T., Moheimani, F., Wu, S.Y., Sood, A.K., Hua, S., 2015. Advances and challenges of liposome assisted drug delivery. Front. Pharmacol. 6, 2015.
Sorbara, M., Cordelier, P., Bery, N., 2022. Antibody-based approaches to target pancreatic tumours. Antibodies 11 (3), 47.
Swami, R., Vij, S., Sharma, S., 2024. Unlocking the power of sugar: carbohydrate ligands as key players in nanotherapeutic-assisted targeted cancer therapy. Nanomedicine 19 (5), 431–453.
Taghipour, Y.D., Zarebkohan, A., Salehi, R., Rahimi, F., Torchilin, V.P., Hamblin, M.R., Seifalian, A., 2022. An update on dual targeting strategy for cancer treatment. J. Control. Release 349, 67–96.
Tarannum, M., Vivero-Escoto, J.L., 2022. Nanoparticle-based therapeutic strategies targeting major clinical challenges in pancreatic cancer treatment. Adv. Drug Deliv. Rev. 187, 114357.
Victoir, B., Croix, C., Gouilleux, F., Prié, G., 2024. Targeted therapeutic strategies for the treatment of cancer. Cancers (Basel) 16 (2).
Wang, J., Gong, J., Wei, Z., 2021. Strategies for liposome drug delivery systems to improve tumor treatment efficacy. AAPS PharmSciTech 23 (1), 27.
Wang, S., Chen, Y., Guo, J., Huang, Q., 2023. Liposomes for tumor targeted therapy: a review. Int. J. Mol. Sci. 24 (3).
Wu, J., 2021. The enhanced permeability and retention (EPR) effect: the significance of the concept and methods to enhance its application. J. Pers. Med. 11 (8), 771.
Yan, S., Na, J., Liu, X., Wu, P., 2024. Different targeting ligands-mediated drug delivery systems for tumor therapy. Pharmaceutics 16 (2).
Yang, F., Jin, C., Jiang, Y., Li, J., Di, Y., Ni, Q., Fu, D., 2011. Liposome based delivery systems in pancreatic cancer treatment: from bench to bedside. Cancer Treat. Rev. 37 (8), 633–642.
Yang, W., Hu, Q., Xu, Y., Liu, H., Zhong, L., 2018. Antibody fragment-conjugated gemcitabine and paclitaxel-based liposome for effective therapeutic efficacy in pancreatic cancer. Mater. Sci. Eng. C 89, 328–335.
Zhang, M., Gao, S., Yang, D., Fang, Y., Lin, X., Jin, X., Liu, Y., Liu, X., Su, K., Shi, K., 2021. Influencing factors and strategies of enhancing nanoparticles into tumors in vivo. Acta Pharm. Sin. B 11 (8), 2265–2285.
Zhou, X., Zheng, Z., Yang, J., Chen, Y., Li, M., Silli, E.K., Tang, J., Ma, Y., Ma, G., Zong, Y., Yu, L., Guo, R., Hou, G., Tan, C., Wang, Y., 2024. Development of cationic pH-sensitive liposomes with Gemcitabine loading and Fucoidan-coating against pancreatic cancer cells. J. Drug Delivery Sci. Technol. 100, 106035.