Review Article

Nanoscale Drug Delivery Platforms for Pancreatic Ductal Adenocarcinoma Treatment

Fatemeh Barati[1], Mohammad Javad Hadi[1], Maryam Khosravi[1], Elaham Afjeh-Dana[2*]

[1] Department of Medical Nanotechnology, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences. Tehran, Iran

[2] Radiation Biology Research Center, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) exhibits profound therapeutic resistance driven by a dense desmoplastic tumor microenvironment (TME). Orchestrated by cancer-associated fibroblasts (CAFs), this fibrotic matrix elevates interstitial fluid pressure and physically abolishes the extravasation of conventional chemotherapeutics. Nanomedicine offers a paradigm-shifting approach to dismantle these biophysical barriers. This review critically evaluates recent advancements in nanoscale delivery systems engineered specifically for PDAC. Moving beyond the ineffective enhanced permeability and retention (EPR) effect, we examine intelligent nanoplatforms capable of localized stroma remodeling, active receptor-mediated targeting, and stimuli-responsive payload release triggered by TME hallmarks. We also explore biomimetic carriers, such as exosomes and albumin-based platforms, that exploit PDAC metabolic scavenging pathways while evading immune clearance. Finally, we address critical translational bottlenecks bridging preclinical success and clinical reality, prioritizing manufacturing scale-up, murine-to-human predictive disparities, and the delicate clinical balance between matrix remodeling and metastatic risk.

Keywords: Pancreatic ductal adenocarcinoma; Nanomedicine; Tumor microenvironment; Targeted drug delivery; Desmoplasia; Biomimetic nanocarriers; Stimuli-responsive nanoparticles.

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**Corresponding Author:*
Elham Afjeh-Dana, Ph.D
Radiation Biology Research Center, Iran University of Medical Sciences, Tehran, Iran
Email: elham_dana@yahoo.com
Elham_dana@sbmu.ac.ir
Tel: + 98 21 86704580
Fax: + 98 21 88607966
Address: Hemmat Highway,Tehran, Iran

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) represents more than 90% of all pancreatic malignancies and continues to be a formidable global health crisis. Despite decades of intensive oncological research, clinical outcomes remain universally poor. The 5-year relative survival rate is currently around 13%, with most patients diagnosed with unresectable or metastatic disease (1-3). Standard first-line systemic therapies, including modified FOLFIRINOX or gemcitabine plus nab-paclitaxel, offer only modest improvements in median overall survival. This deep therapeutic recalcitrance is not only due to aggressive intracellular mutations but is overwhelmingly dictated by the localized, highly restrictive biophysics of the PDAC tumor microenvironment (TME) (3).

The severe desmoplasia is the defining pathophysiological hallmark of PDAC (4). The tumor mass is largely made up of a dense, fibrotic extracellular matrix (ECM) orchestrated by hyperactive cancer-associated fibroblasts (CAFs), not neoplastic cells (2). This CAF-driven stroma is heavily fortified with crosslinked collagen networks and highly hydrophilic hyaluronic acid (HA), and acts as a pressurized mechanical sieve. The resulting elevation in interstitial fluid pressure actively collapses the local microvasculature, causing profound hypoxia and effectively reversing the normal convective pressure gradients needed for drug extravasation. Therefore, conventional small molecule therapeutics are sterically and convectively excluded from reaching the tumor core. Figure 1 shows the schematic of the PDAC microenvironment and the cellular interplay.

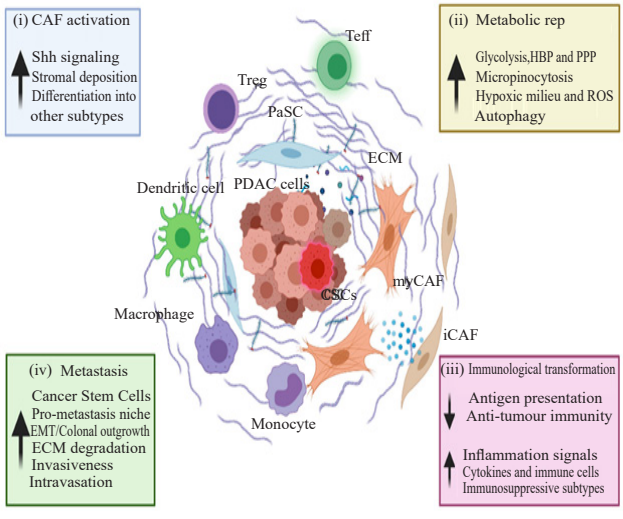


Figure 1. PDAC microenvironment and the cellular interplay. The major interplay in PDAC includes (i) CAF activation, which leads to creating a desmoplastic stroma, (ii) metabolic reprogramming, (iii) immunological transformation, and (iv) metastasis-initiating events in early stages of tumor development (5).

Historically, clinical efforts to beat this desmoplastic barrier have involved starting systemic enzymatic degradation of the matrix. But these efforts did not perform well in human trials. The Phase III HALO-109-301 clinical trial, which employed pegvorhyaluronidase alfa (PEGPH20) to systemically degrade HA, was prematurely terminated due to its failure to improve overall survival and its unexpected promotion of tumor dissemination (6). This clinical failure cemented an important paradigm shift: the stroma cannot be indiscriminately destroyed because it also physically restrains metastasis (4). Instead, it has to be intelligently and transiently navigated.

Nanomedicine has emerged as the most promising strategy to perform this nuanced intervention. Through nanoscale engineering of carriers (typically 10-200 nm), researchers can fine-tune the pharmacokinetic profile, surface functionalization, and controlled release mechanics of encapsulated payloads. However, the traditional reliance on passive accumulation through the enhanced permeability and retention (EPR) effect is made obsolete by the hypovascular nature of PDAC. Modern nanoscale intervention requires dynamic, stimuli-responsive architectures and active-targeting ligands capable of forcibly traversing the ECM and delivering sequential, multimodal cytotoxicity without aggravating systemic toxicity.

This review comprehensively synthesizes the latest generation of nanoscale delivery platforms engineered specifically for PDAC. We review the evolution from simple passive carriers to more sophisticated, stimuli-responsive, and biomimetic nanomedicines that can affect the local stroma, target receptors, and exploit the aberrant metabolic scavenging of pancreatic cancer cells. Furthermore, we assess the important translational bottlenecks that still bridge the gap between profound preclinical success and human clinical reality.

1.1. Literature Search Strategy

We searched PubMed and Elsevier databases for relevant literature on nanoscale drug delivery platforms for PDAC and also used Google Scholar as a search engine. The search queries were based on Boolean combinations of the primary keywords “PDAC”, “pancreatic ductal adenocarcinoma”, “pancreatic tumor”, “nanomedicine”, and “nanocarriers”.

This narrative review is limited to peer-reviewed original research, clinical trial data, and mechanistic studies that explicitly discuss biophysical barriers in the PDAC microenvironment and corresponding engineered nanoparticle interventions. We prioritized recent publications to accurately reflect the current preclinical and translational landscape of PDAC nanomedicine.

2. The Biological Barriers of PDAC: Mechanisms of Therapeutic Failure

The profound failure of conventional chemotherapeutics in PDAC is not simply a product of intrinsic cellular resistance. Instead, it results from an organized, multi-tiered defense system. The defining pathophysiological characteristic of PDAC is its dense desmoplastic stroma, which often constitutes most of the total tumor volume. The neoplastic epithelium is embedded in a highly fibrotic stroma, a key mediator of disease progression. This tumor stroma consists mainly of three components: the extracellular matrix (ECM), chaotic vasculature, and heterogeneous populations of cancer-associated fibroblasts (CAFs). The ECM is mainly made up of dense collagen and high concentrations of hyaluronic acid (HA). This matrix acts as a strong physical barrier that prevents the effective delivery of systemically administered drugs to the cancer cells (7, 8).

Aggressive accumulation of these ECM components significantly increases tissue stiffness and interstitial fluid pressure. This has the effect of physically compressing and collapsing the local capillary network, thus greatly restricting blood flow and preventing deep tissue perfusion of therapeutic agents (8). The structural collapse of the tumor vasculature directly leads to a severe, chronic hypoxia in the PDAC microenvironment. Hypoxia is an important obstacle to overcoming pancreatic cancer and a major promoter of tumor progression and therapeutic resistance. This hypoxic environment triggers downstream signaling pathways that inhibit apoptosis, regulate cellular metabolism, and promote the survival of highly aggressive cancer cell phenotypes (9).

Even if chemotherapeutic agents reach the dense stroma, they face a second layer of molecular defense at the cell membrane. For example, gemcitabine is a hydrophilic nucleoside analog; hence, it cannot passively diffuse across the lipid bilayer of the plasma membrane. To enter the cancer cell, it requires specific transport proteins, mainly the human equilibrative nucleoside transporter 1 (hENT1). The lack or downregulation of hENT1 in PDAC tumors limits drug uptake, leading to high resistance to therapy (10). Furthermore, acquired resistance also counteracts internalized drugs by upregulating ATP-binding cassette (ABC) transporters. Specific multidrug resistance proteins, including MDR1 (P-glycoprotein) and MRP1, act as energy-dependent molecular pumps that actively pump chemotherapeutics out of the intracellular. This ongoing drug efflux largely reduces intracellular drug levels and decreases therapeutic sensitivity (11).

3. Nanoscale Strategies for Overcoming the TME

To address the complex biophysical and molecular barriers of the pancreatic tumor microenvironment, nanomedicine transforms the therapeutic system from passive diffusion to engineered, active navigation. Conventional chemotherapeutics in free form are subject to rapid clearance, enzymatic degradation, and the mechanical forces of the desmoplastic stroma, which is impenetrable. Encapsulation of these payloads within nanoscale architectures allows researchers to precisely calibrate the physicochemical properties of the delivery carrier (e.g., size, surface charge, structural stability) to dictate its pharmacokinetic fate. More importantly, these nanoplatforms act as versatile scaffolds that can be functionalized with targeting ligands or engineered to respond dynamically to the unique pathophysiological triggers of the TME. The following subsections describe how these nanoscale strategies are being used to remodel the dense stroma, selectively target cancer cell receptors, and deliver drugs in a synchronized, stimuli-responsive manner.

3.1. Stroma Remodeling and Penetration

The dense pancreatic ECM applies physical and mechanical restrictions, which represent the most important biophysical challenge in PDAC therapy. Cancer-associated fibroblasts (CAFs) are the primary stromal cells that synthesize and remodel the extracellular matrix within the tumor microenvironment and continuously drive the formation and maintenance of this desmoplastic stroma. CAFs overproduce structural components, forming a highly reinforced ECM with crosslinked collagen networks and high concentrations of the highly hydrophilic HA, thereby generating a dense, high-pressure physical barrier that restricts macromolecular transport and cellular infiltration. Excessive accumulation of these matrix components severely increases interstitial fluid pressure, actively reversing the normal convective pressure gradients required for drug extravasation from the vasculature, and highly restricting the spatial diffusion of nanoscale therapeutics. Moreover, CAFs engage in constant reciprocal signaling with tumor cells to maintain this fibrotic state and create and sustain localized immunosuppression. Therefore, engineering a nanocarrier with extended circulation time is not sufficient; achieving therapeutically relevant drug concentrations at the tumor core requires specialized interventions that alter the CAF-driven stromal matrix to reduce interstitial fluid pressure, restore vascular perfusion, and improve macromolecular diffusion. In the past, the approach to solving this problem has been through non-targeted enzymatic degradation. Previous strategies for total ECM destruction, such as using PEGPH20 to degrade HA, have caused serious side effects, including

muscle spasms (12). Furthermore, this non-specific degradation paradoxically promoted tumor progression by removing physical barriers to metastatic dissemination and producing tumor-promoting low-molecular-weight HA fragments. Therefore, recent nanoscale strategies have moved to intelligent, highly specific stromal remodeling. An alternative to degrading existing HA is to inhibit its production at the source. Researchers engineered a biomimetic nanocarrier (13) with a calcium phosphate core encapsulated by a liposome shell to deliver siRNA targeting glutamine-fructose-6-phosphate amidotransferase 1 (GFAT1), a key enzyme in the hexosamine biosynthesis pathway. This platform achieved effective suppression of HA synthesis by silencing GFAT1, decompression of tumor vasculature, and significant improvement of the penetration and antitumor efficacy of co-administered chemotherapeutics without affecting HA levels in healthy tissues. Another strategy for stroma remodeling is the employment of a hypoxia-responsive, CD44-targeted micellar platform loaded with gemcitabine monophosphate and silibinin (14).

In a hypoxic microenvironment, the micelles become unstable, releasing silibinin to inhibit STAT3 signaling, which reduces extracellular matrix stiffness and modulates the CAF-driven immunosuppressive environment, allowing the polyarginine segments of the nanocarrier to facilitate deep-tissue diffusion and localized accumulation of the chemotherapeutic payload. Besides pharmacological remodeling, nanoplatforms can be designed to dynamically alter their physical properties to penetrate the dense stroma. A cascade-responsive delivery system was designed with a hyaluronic acid shell that provides a negative surface charge and large size for prolonged systemic circulation (15). When the nanoparticle reaches the tumor, the shell encounters overexpressed hyaluronidase, which degrades the shell, reduces the nanoparticle size to allow further tissue penetration, and exposes a positively charged core that facilitates cellular uptake.

3.2. Receptor-Mediated Active Targeting

While passive accumulation through the EPR effect is significantly affected by the hypovascular and dense characteristics of PDAC stroma, active targeting strategies use overexpressed surface antigens to trigger strong receptor-mediated endocytosis. This strategy implies the accurate functionalization of the nanocarrier surfaces with high-affinity ligands to ensure that the payload is efficiently internalized by the target cell after navigating the extracellular matrix and not trapped in the interstitial space (Figure 2).

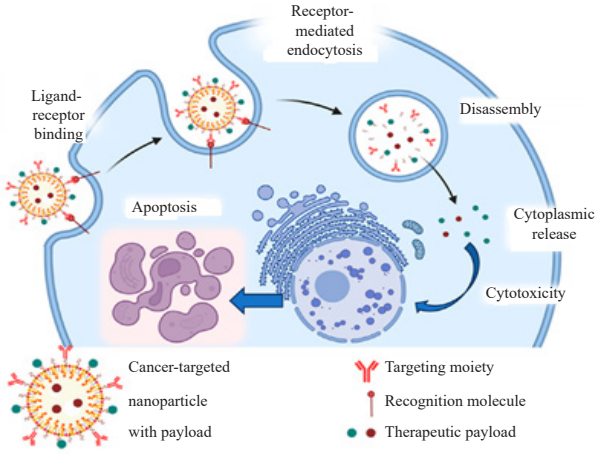


Figure 2. Simplified schematic representation of uptake of tumor-targeted nanoparticles by cancer cells (16).

Claudin-4 (CLDN4) is an integral membrane protein of epithelial tight junctions, and its aberrant spatial exposure during tumorigenesis renders it a highly selective molecular target. In physiological conditions, CLDN4 is sequestered in the apical tight junction complex and is sterically inaccessible to systemic circulation. However, the pathophysiological disruption of cellular polarity and tight junction integrity in pancreatic malignancies translocates CLDN4 to the accessible cell surface. Using this differential accessibility, liposomal carriers were functionalized with CPE17 (17), a 17-amino-acid peptide fragment derived from Clostridium perfringens enterotoxin that specifically binds to the extracellular loop of CLDN4 without inducing the cytotoxicity associated with the full-length toxin. This dual-targeting modality, combining passive EPR extravasation with active CPE17-CLDN4 receptor-mediated endocytosis, increased intratumoral doxorubicin accumulation threefold compared with non-targeted formulations. This increased internalization led to extensive apoptosis, which considerably decreased primary tumor weight and extended lifespan in murine models without increasing off-target systemic toxicity.

Ideally, the therapeutic effect should target not only the neoplastic epithelium but also different cell populations in the TME, particularly cancer-associated fibroblasts and pancreatic stellate cells (PSCs). Pancreatic cancer cells and the surrounding stromal fibroblasts are characterized by a heavy overexpression of the CD44 transmembrane glycoprotein. Hollow mesoporous silica nanoparticles targeted this pathway using HA as a high-affinity targeting ligand, exploiting the common overexpression of CD44 and its role as an enzymatic gatekeeper (18). The HA coating is specifically degraded by enzymes after binding to CD44-positive cells in the hyaluronidase-rich tumor milieu, resulting in the controlled, localized release of encapsulated

gemcitabine and vincristine at the receptor interface. Similarly, to target multiple cellular compartments at the same time, highly stable 5 nm gold nanoparticles were functionalized with monoclonal antibody cetuximab (C225) for active targeting of epidermal growth factor receptor (EGFR) (19). The high level of EGFR overexpression on the primary pancreatic cancer cells (PCCs) and activated PSCs that drive desmoplasia enabled the dual-compartment targeting strategy to deliver payloads precisely across the heterogeneous tumor landscape. Furthermore, conjugation with a 1000 Da polyethylene glycol (PEG) chain improved the pharmacokinetic profile by reducing rapid reticuloendothelial clearance, resulting in a nanoconjugate that achieved antitumor efficacy similar to free combination therapy while maintaining a markedly improved safety profile in healthy ductal epithelium. In one study, a liposomal nanodrug delivery system was fabricated for PDAC cells using paclitaxel and the somatostatin analog 5-pentacarbonyl-octreotide via receptor-mediated active targeting by SSTR2 binding. The authors applied the nanodrug system in PDAC cell lines with different SSTR2 expression levels and in mouse xenograft models. The results show that cellular uptake using targeted nanodrugs was increased. Also, the cytotoxicity of this system was higher than that of the untargeted system. Figure 3 represents the liposomal nanodrug system that was used in this research (20).

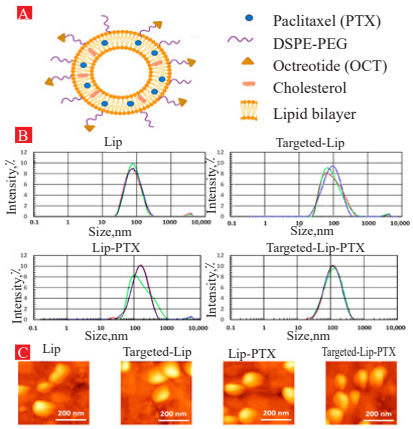


Figure 3. The structure, size distribution, and atomic force microscopy (AFM) images of the formulation. (A) The structure of the targeted liposomal delivery system containing paclitaxel. (B) The size distribution of empty liposomes (Lip), targeted liposomes without drugs (Targeted-Lip), non-targeted liposomes containing paclitaxel (Lip-PTX), and targeted liposomes containing paclitaxel (Targeted-Lip-PTX). (C) Representative AFM images of liposomal formulations (20).

3.3. Stimuli-Responsive and Synergistic Release

The pancreatic tumor microenvironment exhibits a highly abnormal physiological milieu, characterized by profound extracellular acidity, severe hypoxia, and elevated intracellular reactive oxygen species (ROS) concentrations. Rather than viewing these pathophysiological anomalies solely as therapeutic barriers, advanced stimuli-responsive nanoplatforms exploit these specific biochemical signatures as localized triggers to execute precise spatiotemporal drug release and synchronize multimodal synergistic therapies. The aberrant metabolism of PDAC is driven by the Warburg effect, a metabolic shift where cancer cells rely on aerobic glycolysis to rapidly generate the energy and biological building blocks required for tumor growth (21, 22), and compounded by hypoperfusion, which establishes a distinctly acidic extracellular space. To capitalize on this, pH-sensitive platforms have been engineered to undergo charge-reversal upon entering the TME. For instance, a peptide dendrimer nanoparticle constructed with a tris(2-aminoethyl)amine core and terminal arginine residues was sterically masked with 2,3-dimethylmaleic anhydride (DMA) to maintain a neutral surface charge during systemic circulation (23). Upon exposure to the acidic tumor interstitium, the pH-labile amide bonds hydrolyze, cleaving the DMA masking and exposing a highly dense, cationic arginine surface. This dramatic conformational and electrostatic shift drives strong electrostatic interactions with the anionic tumor cell membrane, significantly permeabilizing the lipid bilayer and enhancing intracellular accumulation of co-administered chemotherapeutics such as doxorubicin and gemcitabine. After internalization, endogenous intracellular triggers, such as ROS, can break down the nanocarrier.

A cascade-responsive polymeric platform was developed using a polyethyleneimine core linked to a photosensitizer via a ROS-sensitive thioketal bond (15). After the cells take up the material, light stimulation of the photosensitizer at the target site amplifies intracellular ROS, which specifically cleaves the thioketal linkages. This localized chemical degradation breaks the polymer backbone, rapidly releasing encapsulated gemcitabine and KRAS-targeting siRNA into the cytoplasm while simultaneously promoting photodynamic toxicity.

In addition to endogenous triggers, nanoplatforms can be combined with exogenous physical stimuli, such as near-infrared (NIR) irradiation, to facilitate complex combination regimens. In a study, researchers designed a highly sophisticated multilayer liposomal platform for the sequential delivery of the aggressive FOLFIRINOX regimen together with localized photothermal therapy (24). This system used a dual-liposome core-shell structure separated by a layer of gold nanoparticles, taking advantage

of the different thermal phase-transition temperatures of the lipid layers. The localized surface plasmon resonance of the gold nanoparticles under 808 nm NIR irradiation raised the temperature above 57°C. This hyperthermic state not only caused direct thermal ablation but also exceeded the phase transition threshold of the inner liposome, resulting in a controlled, sequential release of the encapsulated chemotherapeutics to achieve true synergistic cytotoxicity. In addition, smart platforms may use one TME anomaly to catalytically enhance another, thereby hijacking resistance mechanisms to create self-sustaining therapeutic cascades. One group engineered a biomimetic nanoliposome that contains an iron-polydopamine core and evofosfamide, a hypoxia-activated prodrug (25). The core iron catalyzes a Fenton-like reaction (26, 27) for the generation of highly toxic hydroxyl radicals in the TME with high concentrations of hydrogen peroxide. The liposomal shell actively converts these radicals into lipid peroxidation products, leading to catastrophic ferroptotic cell death. Importantly, ferroptosis consumes most of the cell's oxygen, worsening the already severe local hypoxia. This synthetic ultra-hypoxic niche serves as a secondary trigger to quickly and aggressively activate the evofosfamide prodrug, turning the hypoxic barrier into a catalytic engine for synergistic tumor eradication.

3.4. Modulating Intracellular Signaling and Overcoming Drug Efflux

In addition to structural barriers, pancreatic cancer cells rely on abnormal intracellular signaling pathways to escape apoptosis and pump out chemotherapeutics. Increasingly, researchers are designing nanocarriers to deliver pathway-specific inhibitors directly into the cytoplasm. For instance, the Akt protein kinase is constitutively active in PDAC, and actively inhibits cell death. To directly intercept this, researchers engineered elastin-like recombinamers to self-assemble into nanoparticles that carry an Akt-blocking peptide (28). These protein carriers use a cathepsin D-sensitive sequence to ensure specific lysosomal escape and effectively block the Akt survival pathway with reduced systemic toxicity. In addition, the fibroblast growth factor receptor 1 (FGFR1) is frequently overexpressed in PDAC. Co-delivery of gemcitabine and paclitaxel using amphiphilic triblock polymer nanocarriers conjugated with an FGFR1-targeting peptide (29). The combination of two drugs loading with the glutathione-responsive intracellular release showed significant synergistic cytotoxicity with single-drug formulations.

Other platforms target resistance by blocking signaling pathways that drive metastasis and angiogenesis. Palmitoyl carnitine-anchored nanoliposomes were used to deliver gemcitabine elaidate, a lipophilic derivative that bypasses the restrictive hENT1 transporter (30). In addition to providing a cationic charge for vascular targeting, the palmitoyl carnitine surface also directly inhibited protein kinase C (PKC), significantly reducing tumor cell migration. In addition, beta-cyclodextrin nanosponges presenting ICOS-Fc, a recombinant protein that is a strong metastasis inhibitor and immunomodulator, can be used to combat immune evasion and metastasis. This porous structure encapsulated a gemcitabine-oleic acid complex, leading to transporter-independent cellular entry and multi-targeted tumor suppression (31).

3.5. Formulations for Hydrophobic and Unstable Payloads

Many promising anticancer drugs, from FDA-approved drugs to natural polyphenols, are dropped in PDAC trials because they are too hydrophobic, require toxic solvents, or are cleared from the body too quickly. Nanoscale encapsulation rescues the required pharmacokinetics. Niclosamide is an anthelmintic drug with strong anticancer activity, but its use is greatly limited by its poor solubility. Researchers encapsulated niclosamide into flash-nanoprecipitated polyanhydride nanoparticles, avoiding toxic solvents, and increased intraperitoneal retention by 300-fold, synergistically halving the dose of co-administered gemcitabine (32). Free gemcitabine in combination with similar polyanhydride platforms has been used successfully to rescue the bioavailability of curcumin, increasing its plasma concentration exponentially and resulting in complete tumor regression (33). Similarly, liposomal formulations of lecithin and cholesterol were formulated to stabilize 4-farnesyloxycoumarin (4-FLC), which suppressed metastasis-associated matrix metalloproteinases and induced strong apoptosis without systemic clearance issues (34).

To overcome the inherent instability of conventional aggregate micelles in the bloodstream, researchers developed unimolecular micelle nanoparticles (UMNp) composed of a single highly branched polycaprolactone-polyethylene glycol chain (Pathan & Jayakannan, 2025). Pathan & Jayakannan (2025) showed that UMNps remained highly stable upon severe dilution, unlike conventional micelles that disassemble below their critical micelle concentration, which dramatically improved tumor accumulation and the DNA-damaging efficacy of doxorubicin. Prodrug modifications are needed for highly hydrophilic drugs resistant to micellar loading, such as gemcitabine. Conjugating gemcitabine with vitamin E succinate yields a lipophilic compound that can be efficiently loaded at high capacity into Pluronic F127 polymeric micelles, creating a highly stable, controlled-release reservoir that far surpasses free drug performance in cellular internalization (35). Finally, natural compounds such as resveratrol have been

protected from fast degradation by conjugating them to gold nanoparticles directly through polyvinylpyrrolidone linkers, reducing their IC50 significantly and inducing cell cycle arrest through the mitochondrial apoptosis pathway (36).

3.6. Radiosensitization and Magnetic Hyperthermia

The combination of nanocarriers with external physical stimuli allows extreme cytotoxicity on a very localized level, exploiting the physical properties of the incorporated metals. The high atomic numbers of metal nanoparticles, particularly gold, make them excellent radiosensitizers. Spherical gold nanoparticles coated with either hyaluronic acid or bombesin peptides targeting CD44 and GRPR receptors, respectively, accumulated and localized the radiation damage from 6-megavolt X-rays, resulting in greater than 20% reduction in cancer cell viability compared to radiation therapy alone (37).

Magnetic iron oxide nanoparticles have the property of alternating magnetic field (AMF) hyperthermia. A magnetic nanoparticle system was prepared in a layer-by-layer manner with polyelectrolyte layers to load gemcitabine (38) (Figure 4). Using an AMF-induced lethal hyperthermia, which inhibited proliferation, and the simultaneous application of X-ray radiotherapy produced a massive synergistic effect, increasing cell death 13-fold. Additionally, magnetic carriers can be loaded with genetic payloads to reverse resistance before thermal ablation. Disulfide-bonded iron oxide nanoparticles conjugated to gemcitabine and a miRNA34a mimic successfully sensitized PANC-1 cells resistant to gemcitabine (39). The generated hyperthermia after AMF application induced severe cell cycle arrest and reactive oxygen species generation, resulting in catastrophic cell death

Another approach uses external physical triggers such as ultrasound, which allows penetration into deep tissues. Using sonoporation, Amine-terminated generation 3 poly(amidoamine) (PAMAM) dendrimer nanogels containing gold nanoparticles and toyocamycin were used to drive the nanogel deeper into the tumor mass (40). The subsequent degradation of the nanogel in the acidic TME not only released the drug to induce immunogenic cell death but also drove a crucial polarization of tumor-associated macrophages from a protumorigenic M2 state to an antitumorigenic M1 phenotype. Table 1 shows the review on Nanoparticle Platforms that Synthesized for Pancreatic Ductal Adenocarcinoma treatment.

4. Emerging Biomimetic and Biological Carriers

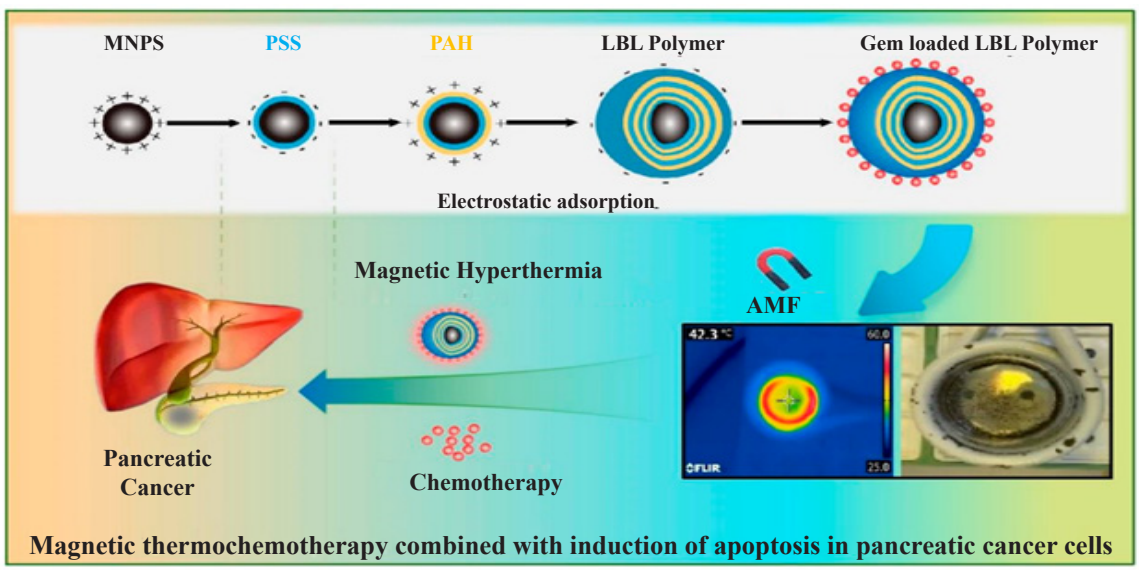


Figure 4. Schematic of layer-by-layer nanoparticle preparation combined with thermal chemoradiotherapy for efficient synergistic treatment of pancreatic cancer (38).

A major challenge for synthetic nanocarriers in clinical translation is rapid immune clearance and off-target accumulation, despite their extensive tunability. When given intravenously, synthetic nanoparticles are rapidly covered with serum proteins (opsonization), and are quickly recognized and sequestered by the mononuclear phagocyte system (MPS). Thus, resident tissue macrophages, mainly in the liver and spleen, clear most of these foreign

vehicles from systemic circulation, greatly limiting the fraction of the injected dose that ultimately reaches the tumor. To overcome the limitations of the MPS, the field is gradually moving to biomimetic and naturally derived carriers, especially exosomes and protein-based platforms, which have an innate tumor-homing ability and better biocompatibility (41, 42).

4.1. Exosome and Vesicle-Based Delivery

Exosomes are naturally occurring nanoscale extracellular vesicles that play a key role in cell-to-cell communication. Their unique advantage is that they do not suffer from MPS evasion and have native integration with target cell membranes, as they are made of endogenous cellular membranes (42). The exosomes obtained from bone marrow mesenchymal stem cells can naturally target pancreatic tumor tissue, avoiding the need for conventional membrane transporters such as hENT1, and directly enter target cells through endocytosis. This platform, loaded with a gemcitabine prodrug, siRNA, and indocyanine green, demonstrated a pH-dependent release profile triggered by the slightly acidic tumor microenvironment, delivering a combination of chemotherapy, immunotherapy, and phototherapy (43). Researchers fused human pancreatic cancer cell line-derived exosomes directly with synthetic liposomes to create hybrid carriers to further enhance targeting specificity. A homing property of the parent cancer cells was exploited by a dasatinib-loaded liposome–exosome hybrid, resulting in a significantly improved uptake over fully synthetic alternatives (44). Plant-derived vesicles are also emerging as promising alternatives to mammalian exosomes due to their high scalability and low immunogenicity. To get around the complicated manufacturing bottlenecks of mammalian cell culture, we used carrot-derived exosomes to encapsulate the herbal medicine icariin, leveraging the natural antioxidant properties of the vesicles to induce apoptosis and ferroptosis in an orthotopic mouse model of PDAC (45).

4.2. Protein and Albumin-Based Nanocarriers

Protein-based delivery systems leverage the specific metabolic needs of pancreatic cancer cells, especially those derived from human serum albumin (HSA) or bovine serum albumin (BSA). Constitutive activation of mutant KRAS is one of the most common oncogenic drivers of PDAC. KRAS-driven PDAC tumors increase macropinocytosis, a process in which they non-selectively scavenge extracellular proteins, especially albumin, from the surrounding stroma to support their rapid, uncontrolled proliferation (46, 47). And those tumors have low levels of the recycling receptor FcRn, which results in the scavenged albumin being trapped within the tumor mass (48). Researchers took advantage of this phenomenon by designing an albumin-based nanoparticle to deliver the prodrug β-lapachone. Once trapped and internalized within the tumor's aberrant metabolic landscape, the prodrug was activated locally by the overexpressed enzyme NQO1, generating lethal reactive oxygen species while dramatically lowering systemic hemolytic toxicity. Albumin carriers might also directly interfere with the cellular machinery underlying chemoresistance. Nanoparticles of HSA loaded with gemcitabine were used against gemcitabine-resistant PDAC cells that overexpress the efflux transporters MDR1 and MRP1 (49). The intracellular degradation of the scavenged albumin consumes significant amounts of ATP, and thus the nanocarrier effectively depleted the cellular energy reserves needed by the ATP-dependent ABC transporters, leading to the shutdown of drug efflux and resensitization of the resistant cells to gemcitabine. These protein cores can also be further modified on the surface; e.g., modification of BSA nanoparticles with a cationic polyallylamine hydrochloride shell enabled targeted delivery of α-solanine via strong Gp60-mediated transcytosis and deeper penetration into dense pancreatic tumor mass (50, 51).

5. Translational Challenges and Future Perspectives

Table 1. Nanoparticle Platforms Synthesized for Pancreatic Ductal Adenocarcinoma

Nanoparticle Platform	Therapeutic Payload	Biological Barrier Addressed	Targeting Strategy / Stimuli	Experimental Model	Key Biological Outcome	Reference
Lipid-Based Nanocarriers						
Biomimetic CaP liposomes	GFAT1-targeting siRNA & Chemotherapy	Dense ECM / Hyaluronic Acid Synthesis	CXCR4 targeting, macrophage membrane	In vivo xenograft	Suppressed HA synthesis, decompressed vasculature, and enhanced deep penetration.	(13)
DSPE-PEG liposomes	Doxorubicin	Non-specific targeting / Epithelial junctions	Claudin-4 (CLDN4) receptor targeting	In vivo murine model	3-fold higher tumor accumulation; extended murine lifespan to 42 days.	(17)
Multilayer liposomes w/ Gold NPs	FOLFIRINOX regimen	Chemoresistance / Thermal barriers	Near-infrared (NIR) photothermal	In vitro / In vivo	Achieved 70.45% synergistic therapeutic efficacy via sequential NIR release.	(24)

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Nanoparticle Platform	Therapeutic Payload	Biological Barrier Addressed	Targeting Strategy / Stimuli	Experimental Model	Key Biological Outcome	Reference
Lipid-Based Nanocarriers						
Nanoliposomes w/ Fe-PDA core	Evofosfamide	Severe Hypoxia / ROS depletion	Hypoxia-activated, ROS-generating	In vivo xenograft	Exacerbated hypoxia to trigger synergistic ferroptosis and chemotherapy.	(25)
Palmitoyl carnitine liposomes	Gemcitabine elaidate	hENT1-dependence / Angiogenesis	Cationic vascular targeting, PKC inhibition	In vitro / In vivo	Bypassed hENT1; caused a 46% reduction in tumor cell migration.	(30)
Lecithin-cholesterol liposomes	4-Farnesyloxycoumarin	Metastasis / MMP overexpression	Passive (EPR), PEGylated stealth	In vitro PDAC cells	Induced apoptosis and suppressed metastasis-associated MMP-2/9.	(34)
Polymer-Based Nanocarriers						
Polyethyleneimine (PEI) / HA shell	Gemcitabine & KRAS siRNA	Dense Stroma / Endosomal entrapment	CD44 targeting, HAase/ROS-responsive	In vivo xenograft	Enabled bidirectional size/charge tuning for penetration and endosomal escape.	(15)
Triblock copolymer micelles	p-GEM & Silibinin	Dense ECM / STAT3 signaling	CD44 targeting, Hypoxia-responsive	In vivo xenograft	Softened ECM via STAT3 inhibition without destroying structural stroma constraints.	(14)
Peptide dendrimers (TAEA core)	Doxorubicin & Gemcitabine	Acidic TME / Poor membrane permeability	pH-responsive charge reversal	In vitro / In vivo xenograft	Enhanced membrane permeability; increased co-administered drug entry.	(23)
Amphiphilic triblock polymers	Gemcitabine & Paclitaxel	FGFR1 survival signaling	FGFR1 targeting, GSH-responsive	In vitro / In vivo xenograft	Lowered IC50 via synergistic intracellular dual-drug release.	(29)
Flash-nanoprecipitated polyanhydrides	Niclosamide	Drug insolubility / Rapid clearance	Passive (intraperitoneal retention)	In vivo intraperitoneal model	Increased drug accumulation; reduced required gemcitabine dose by half.	(32)
PAMAM dendrimer nanogels	Toyocamycin & Gold NPs	Immunosuppressive TME	pH-swelling, GSH-responsive, sonoporation	In vivo xenograft	Induced immunogenic cell death and M2-to-M1 macrophage polarization.	(40)
Elastin-like recombinamers	Akt-in peptide	Akt survival pathway signaling	Cathepsin D-sensitive lysosomal release	In vitro PDAC cells	Specifically blocked the Akt survival pathway with minimal systemic toxicity.	(28)
Beta-cyclodextrin nanosponges	Gemcitabine-oleic acid	Transporter dependence / Immune evasion	ICOS-Fc metastasis inhibitor targeting	In vivo xenograft	Executed multi-targeted tumor suppression via transporter-independent entry.	(31)
Pluronic F127 polymeric micelles	Gemcitabine-vitamin E succinate	Hydrophilic encapsulation limits	Passive (EPR)	In vitro PDAC cells	Overcame encapsulation limits; produced strong growth inhibition.	(35)
Unimolecular micelles (UMNp)	Doxorubicin & IR-780	Micellar instability under dilution	Passive (EPR), highly dilution-stable	In vivo xenograft	Superior tumor accumulation; >90% reduction in tumor volume.	(52)
Polyanhydride nanoparticles	Curcumin	Extreme hydrophobicity / Poor bioavailability	Passive (EPR)	In vivo xenograft	300-fold plasma increase; complete tumor regression with gemcitabine.	(33)

Table 1. Nanoparticle Platforms Synthesized for Pancreatic Ductal Adenocarcinoma

Nanoparticle Platform	Therapeutic Payload	Biological Barrier Addressed	Targeting Strategy / Stimuli	Experimental Model	Key Biological Outcome	Reference
Metal & Inorganic Nanocarriers						
Hollow mesoporous silica NPs	Gemcitabine & Vincristine	Fibrotic CAF signaling	CD44 targeting, HAase-responsive	In vitro / In vivo	Degraded specifically in TME for controlled, gradual dual-drug release.	(18)
Functionalized gold NPs	Gemcitabine	Dual compartments (Cancer + Stellate cells)	EGFR targeting (Cetuximab)	In vitro co-culture / In vivo	Concurrent targeting of cancer and stellate cells with lower healthy cell toxicity.	(19)
Layer-by-layer magnetic NPs	Gemcitabine	Radio/chemo-resistance	Alternating magnetic field (AMF)	In vitro / In vivo	13-fold increase in cell death with concurrent X-ray radiotherapy and hyperthermia.	(38)
Magnetic iron oxide NPs	Gemcitabine & miRNA34a	Acquired gemcitabine resistance	GSH-responsive, AMF hyperthermia	In vitro Gem-resistant PANC-1 cells	Sensitized resistant cells and forced severe cell cycle arrest.	(39)
Dual gold NPs (HAOA & BBN)	Radiosensitizers (No drug)	Radioresistance	CD44 and GRPR receptor targeting	In vitro PDAC cells (X-ray)	Increased X-ray absorption; reduced viability up to 26% more than radiation alone.	(37)
Gold NPs with PVP linker	Resveratrol	Drug instability / Rapid degradation	Passive (EPR)	In vitro PDAC cells	3-fold increase in apoptosis and cell cycle arrest in G1 phase.	(36)
Biological & Biomimetic Carriers						
Human serum albumin (HSA) NPs	Gemcitabine	MDR1/MRP1 efflux pumps	Intracellular ATP depletion	In vitro Gem-resistant cells	Shut down MDR1/MRP1 efflux pumps; resensitized resistant cells.	(49)
MSC-derived exosomes	DOGEM, siRNA, ICG	Macrophage clearance / hENT1 dependence	pH-responsive, inherent tumor homing	In vivo xenograft	Bypassed hENT1; facilitated lysosomal escape and deep tissue penetration.	(43)
Core-shell albumin NPs	Pro-β-lapachone	Altered metabolism (Macropinocytosis)	NQO1 enzyme activation	In vivo xenograft	Generated lethal ROS leading to programmed necrosis; expanded therapeutic window.	(48)
Bovine serum albumin (BSA) NPs	α-Solanine	Deep tumor penetration	Cationic surface, Gp60 transcytosis	In vitro / In vivo	Improved cellular internalization; inhibited cell migration and invasion.	(50)
Liposome-exosome hybrid	Dasatinib	Off-target accumulation	Inherent tumor homing	In vitro Panc0403 / HuP-T3 cells	Significantly enhanced specific uptake by parent cancer cells.	(44)
Carrot-derived exosomes	Icariin	Production scalability / Immunogenicity	Passive, inherent antioxidant	In vivo orthotopic mouse model	Significant tumor reduction in orthotopic models; high scalability.	(45)

Despite the strong preclinical efficacy of the nanoplatforms discussed in this review, translating these highly engineered systems from murine models to human clinical realities is fraught with challenges. Overcoming this translational gap requires overcoming significant biological and manufacturing bottlenecks (53).

5.1. The Gap between Murine Models and Human Pathology

Standard two-dimensional cell cultures and traditional murine xenograft models do not faithfully recapitulate the dense desmoplasia, extreme hypoxia, and highly immunosuppressive microenvironment of human PDAC. As a result, nanocarriers that work well in mice (good penetration and efficacy) often fail in humans (54). To

fill this gap, the field is increasingly moving towards the use of patient-derived organoids (PDOs) (55). PDOs are 3D in vitro models that are directly grown from patient biopsies and have successfully maintained the specific morphologic architecture, histologic complexity, and genetic heterogeneity of the parental tumor (56, 57). Incorporating PDOs into preclinical screening pipelines enables researchers to perform highly accurate, patient-specific drug sensitivity assays, significantly enhancing the predictive validity of nanomedicine efficacy before in vivo translation

5.2. Manufacturing and Scalability Bottlenecks

Stimuli-responsive and multi-layered nanoplatforms provide incredible spatial and temporal precision, but they face massive hurdles in large-scale GMP production (54). The clinical translation of nanomedicine is often delayed or stopped by the failure to maintain batch-to-batch physicochemical consistency (uniform size, charge distribution, drug-loading efficiency) during scale-up from small laboratory synthesis to industrial production (58). Moreover, as delivery systems incorporate more functional components (e.g., surface targeting ligands, magnetic cores, or sequential release layers), the regulatory approval process becomes exponentially more complex, demanding rigorous, independent validation of the safety and pharmacokinetic profile of each individual component. The future of nanomedicine development must emphasize simplifying these architectures and aggressively balancing biological functionality with industrial manufacturability.

5.3. Managing Stroma Remodeling vs. Metastasis

Stroma remodeling requires a delicate clinical balance: the extracellular matrix must be disrupted enough to restore perfusion and allow nanocarrier penetration, but not so much that it removes the physical barriers restraining tumor metastasis. The Phase III HALO-109-301 clinical trial failure starkly demonstrated the danger of brute-force matrix degradation. Systemic administration of pegvorhyaluronidase alfa (PEGPH20), an enzyme designed to completely strip away stromal hyaluronic acid, in combination with standard chemotherapy failed to improve overall survival in patients with metastatic PDAC and was subsequently terminated (6). Paradoxically, total, non-specific stromal degradation removes protective constraints on metastatic spread, highlighting the absolute need for intelligent, localized, and transient remodeling strategies (such as localized HA-synthesis inhibition) discussed in this review, rather than systemic stroma ablation.

6. CONCLUSION

Pancreatic cancer is a highly challenging disease, driven by an impenetrable and immunosuppressive tumor microenvironment. As this review highlights, the future of PDAC therapy depends heavily on the advanced nanoscale delivery of existing therapeutic agents. Next-generation nanomedicines can break down PDAC's biophysical barriers by evolving from passive accumulation to intelligent stroma remodeling, active receptor targeting, and biomimetic immune evasion. Ultimately, translating these sophisticated nanoscale platforms into viable clinical realities will require overcoming current manufacturing bottlenecks and embracing patient-derived predictive models.

7. CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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