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TARGETING PANCREATIC CANCER CHEMORESISTANCE: FOCUS ON NOVEL DRUG THERAPIES AND NDDS PLATFORMS

G. Praveen Kumar[2], M. Rithika[2], C. Kalki[2], M. Dikshapriya[2], G. Kanimozhi[2], Pitta Sriramcharan[1*]

[1]Department of Pharmaceutics, P.S.V College of Pharmaceutical Science and Research, Krishnagiri, Tamilnadu-635108.

[2]B. Pharmacy Final year Students, [1]Department of Pharmaceutics, P.S.V College of Pharmaceutical Science and Research, Krishnagiri, Tamilnadu-635108.

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***Corresponding Author**

Pitta Sriramcharan

Department of Pharmaceutics, P.S.V College of Pharmaceutical Science and Research, Krishnagiri, Tamilnadu-635108.

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ABSTRACT

Pancreatic cancer is rapidly emerging as a global threat, with projections indicating it will become the second leading cause of cancer-related deaths by 2030. The main type of pancreatic cancer are pancreatic adenocarcinomas, which arise in the exocrine region of the pancreas and account for approximately 95% of all pancreatic tumors. The tumor develops without symptoms, which complicates early detection. It is marked by the overproduction of fibrotic stroma, referred to as desmoplasia, which facilitates tumor growth and metastasis through extracellular matrix remodeling and the release of tumor growth factors. For decades, substantial efforts have been directed toward creating more effective drug delivery systems for treating pancreatic cancer using nanotechnology, immunotherapy, drug conjugates, and combinations of these methods. None the less, even though these methods have shown promise in preclinical studies, there has been no significant clinical advancement, and the outlook for pancreatic cancer is deteriorating. This review offers insights into the challenges linked to delivering therapeutics for pancreatic cancer treatment. It discusses drug delivery strategies aimed at reducing the adverse effects of current chemotherapy options and enhancing the effectiveness of drug treatment.

KEYWORDS: Pancreatic cancer; desmoplasia; Hypoxia; nanotechnology; drug-conjugate; immunotherapy; pancreatic adenocarcinoma.

1.INTRODUCTION

Pancreatic cancer remains one of the most lethal yet treatable cancers. This factor ranks as the seventh most common reason for cancer-linked fatalities worldwide, with approximately 331,000 deaths each year.[1–6] In 2019, the US saw about 56,770 new pancreatic cancer cases and 45,750 deaths, whereas in 2021 there were 60,430 new cases and 48,220 fatalities.[1,4,7,8] In 2022, pancreatic cancer was the third leading cause of cancer-related deaths in the US, following colorectal and lung cancers, with an expected 59,143 new cases and 49,920 deaths.[9] It is anticipated that by 2030, it will be the second most prevalent cause of cancer-related deaths.[1,6,10–13] Pancreatic cancer, which has a dismal five-year survival rate of under 5% and a median survival time of about six months, is responsible for 8% of all cancer-related deaths.[1,14–16] Due to the fact that pancreatic cancer is a silent killer, it requires immediate treatment.

Previously, pancreatic cancer has been a silent killer that demands immediate attention. It is challenging to identify pancreatic cancer early as the disease progresses slowly and does not exhibit symptoms.[12] The link between the poor prognosis of pancreatic cancer and its excessive desmoplastic growth—also known as fibrotic stroma—and delayed diagnosis is evident, as treatment generally commences when the tumor has reached advanced stages.[11,12,14,17] The elevated mortality rate associated with pancreatic cancer can be attributed to multiple factors, such as a stringent tumor microenvironment, early metastasis to both adjacent and distant sites, a high rate of recurrence, and inadequate diagnostic techniques.[12, 18, 19] Based on the tumor's location, individuals may exhibit varying signs and symptoms of pancreatic cancer, including nausea, abdominal discomfort, jaundice, loss of appetite, weight reduction, steatorrhea, and back pain (Figure 1).[20, 21] Risk factors include age, obesity, diabetes, pancreatitis, alcohol consumption, genetics, a high-fat diet, and family history.[12,22–25] Black Americans have a higher pancreatic cancer risk and death rate compared to non-Hispanic white Americans. This may be due to genetic and socioeconomic disparities.[26,27]

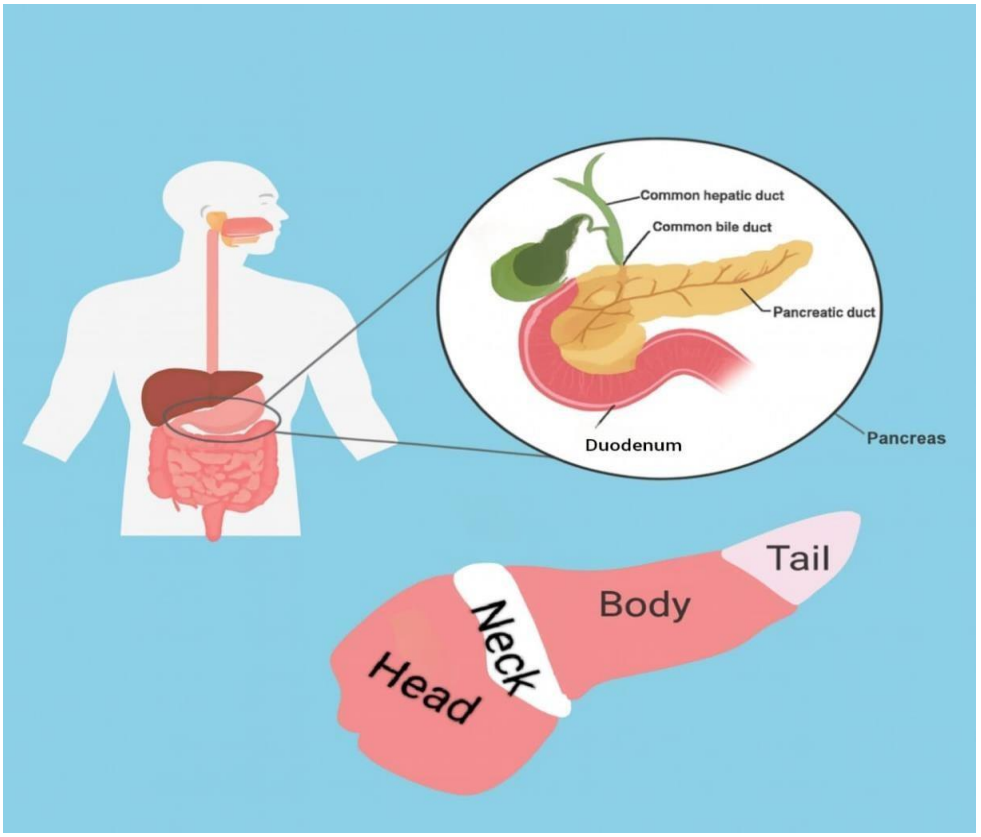

Figure 1: Schematic representation of the anatomy of the pancreas, highlighting the major anatomical regions and indicating the specific areas of the organ where pancreatic cancer may develop.

Pancreatic ductal adenocarcinomas, which occur in the exocrine portion of the pancreas, are responsible for over 95% of all pancreatic tumors and are the most common type of pancreatic cancer.[1,14,16,19] Neuroendocrine pancreatic cancer, which develops in the endocrine area, accounts for fewer than 5% of pancreatic cancer cases.[22,28] It is not as aggressive when compared to pancreatic adenocarcinoma. The dense tumor microenvironment (TME) of pancreatic adenocarcinoma fosters tumorigenesis and metastasis, inhibits chemotherapy penetration, and increases the incidence of both intrinsic and adaptive multidrug resistance.[5,11,18,29–31]

Nonetheless, even though there have been major advancements in cancer treatment that have raised the overall life expectancies of patients with various cancer types[1,18], survival rates for pancreatic cancer have not seen significant alterations over time. To enhance clinical outcomes for pancreatic cancer, it is crucial to detect the disease early and to use optimal therapeutic agents that have minimal or no side effects on non-target organs. For initial evaluations of individuals with doubts about them, computed tomography or magnetic

resonance imaging are generally recommended.[32, 33] Since endoscopic ultrasonography can detect small lesions, it is often used alongside other diagnostic techniques.[34] Fewer than 35% of patients who qualify for surgery have a five-year survival rate, and over 85% will experience a recurrence two years post-surgery.[11,16,18,34–36]

2. Cancer's peculiarities

Situated in the upper abdominal region, the pancreas can be found at the back of the stomach (see Figure 1).[41] It secretes hormones and digestive enzymes that regulate the body's metabolism and energy storage.[28] Pancreatic cancer can originate in any of the four sections: the head (which includes the uncinate process), neck, body, and tail.[20,21,41,42] Numerous studies indicate that the prognosis of pancreatic tumors is influenced by their anatomic location.[20, 24, 43, 44] A recent study by Lee and colleagues found that head tumors had better overall survival rates than body/tail pancreatic cancers. The head pancreatic tumor's early symptom onset was cited to explain the discovery.[24,43,44] Patients with head tumors frequently suffer from jaundice and its subsequent symptoms, while discomfort and weight loss are prevalent indicators of cancers in the body and tail. hyperbilirubinemia caused by a standard obstruction of the bile duct.[43]

Pancreatic cancer arises and advances as a result of numerous factors, with its pathophysiology shaped by different components of the cancer microenvironment.[45,46] Unlike other cancers, pancreatic adenocarcinoma is distinguished by a thick fibrotic stroma known as desmoplasia or desmo-plastic reaction (Figure 2), which releases tumour growth agents and modifies the extracellular matrix to facilitate tumour growth and spread.[7,11,47,48] Desmoplasia is caused by invasive immune cells and pancreatic stellate cells. It diminishes the efficacy of chemotherapy and worsens primary resistance to a variety of drugs.[48]

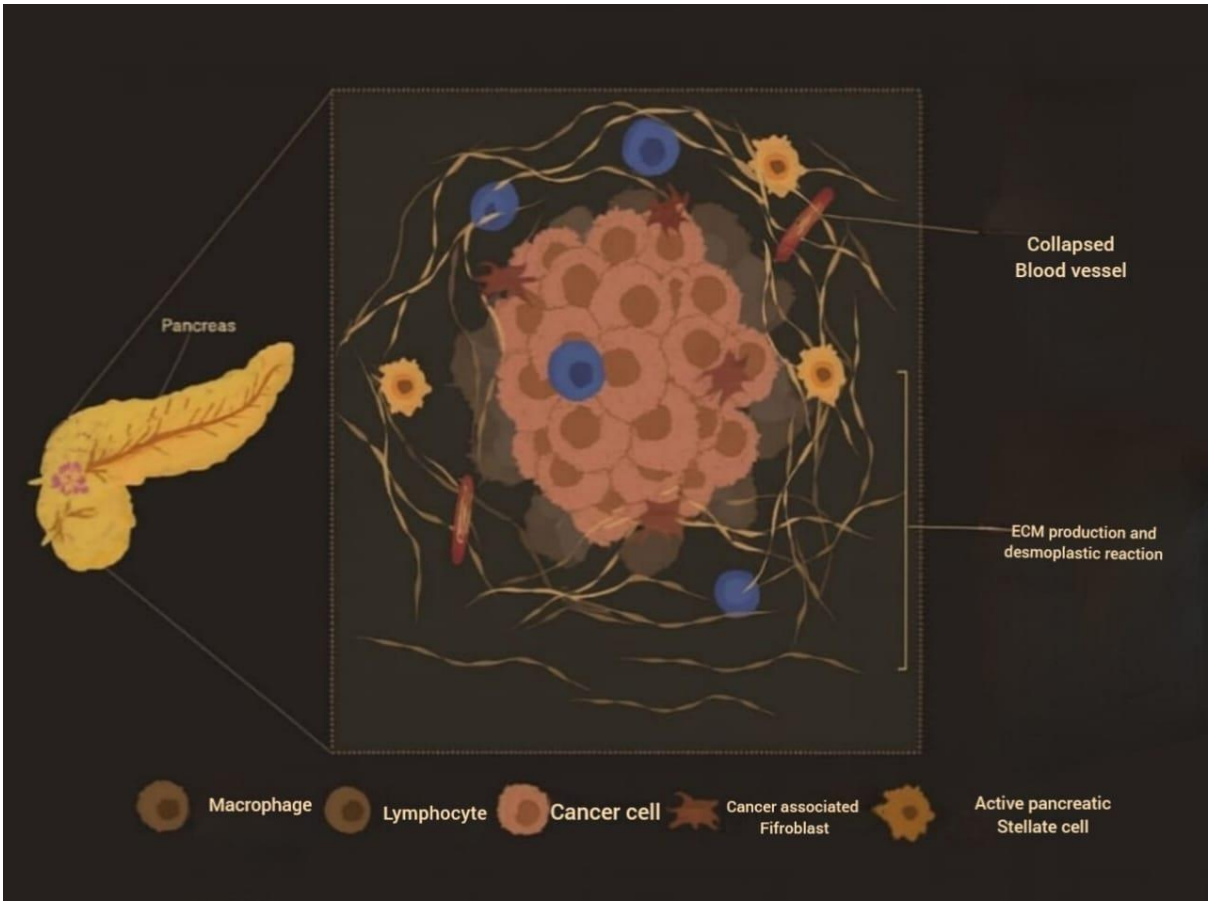

Figure 2: Illustration of the pancreatic tumor microenvironment, depicting abnormal vascular architecture and pronounced desmoplastic stroma characteristic of pancreatic cancer.

The stroma in pancreatic adenocarcinoma mainly consists of cancer-activated fibroblasts (CAFs) and pancreatic stellate cells (PSCs).[22,29,49,50] In healthy individuals, PSCs usually remain inactive; however, under pathological conditions, they can be stimulated by various factors such as cytokines, pancreatic parathyroid hormone-related protein, vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGFβ).[22,50] Among the extracellular matrix components secreted by CAFs, which are linked to the development of dense fibrosis in both orthotopic and metastatic tumors.[7,8,48,51–54], are collagen, laminin, fibronectin, alpha-smooth muscle actin, fibroblast activation protein, hyaluronic acid, cytokines, tumor growth factors, and extracellular proteases. The components of the extracellular matrix (ECM) produced by CAFs are believed to be significantly involved in the progression of pancreatic adenocarcinoma, thus making them appropriate targets for therapy.[46,55] As an illustration, a collagen surplus results in a greater rigidity of tumours. As a result, the interstitial pressure increases and blood vessels constrict.[22,54] This leads to

insufficient perfusion and diffusion in the centers of pancreatic tumors, heightening chemoresistance and complicating the uptake of cytotoxic drugs.[54,56] Prior studies have associated reduced stroma levels of collagen and hyaluronic acid with improved overall survival.[8,52,55] Moreover, the elevated levels of hyaluronic acid in the pancreatic tumor increase the interstitial fluid pressure, hindering the absorption and penetration of cytotoxic drugs.[36,50] Furthermore, a relationship exists between stroma deposition and the increased interstitial pressure associated with pancreatic tumours. This pressure intensifies treatment resistance by obstructing the intra-tumoral delivery of drugs.[57,58] Furthermore, studies show that the stroma of pancreatic adenocarcinoma contains a high concentration of proteolytic enzymes, including transforming growth factor, matrix metalloproteinases, and fibroblast activation protein, which facilitate stroma remodeling.[8,58,59] Pancreatic cancer is thought to be preceded by pancreatic intraepithelial neoplasia (PanIN), a precancerous lesion that accumulates genetic abnormalities over time and transforms into cancerous cells.[25,49,52] Mutations in Kirsten rat sarcoma (KRAS) occur in roughly 90% of human pancreatic cancer cells.[28,56] KRAS is crucial for cell signaling pathways, and its mutation impacts various aspects of cancer biology. It was said to be involved in the initiation and absorption of cytotoxic agents.[36,50] Furthermore, a relationship exists between stroma deposition and the increased interstitial pressure observed in pancreatic tumours. This pressure intensifies treatment resistance by obstructing the intra-tumoral delivery of drugs.[57,58] Furthermore, studies show that the stroma of pancreatic adenocarcinoma contains a high concentration of proteolytic enzymes, including transforming growth factor, matrix metalloproteinases, and fibroblast activation protein, which facilitate stroma remodeling.[8,58,59] Pancreatic cancer is thought to be preceded by pancreatic intraepithelial neoplasia (PanIN), a precancerous lesion that accumulates genetic abnormalities over time and transforms into cancerous cells.[25,49,52] [Kirsten rat sarcoma (KRAS) mutations occur in approximately 90% of human pancreatic cancer cells.[28,56] KRAS is crucial for cellular signaling pathways, and its mutation impacts cancer biology in various ways. Besides immune regulation, migration, metabolism, and apoptosis, it is said to play a role in the onset and progression of pancreatic cancer.[23,60] As an illustration, the oncogenic variant of KRAS boosts metabolic reprogramming, enabling pancreatic cancer cells to thrive in environments that lack oxygen and nutrients. Oxygen presence leads to increased glucose absorption, enhanced glycolysis, and lactate production.[47,61–63] Moreover, in pancreatic cancer, KRAS mutations correlate with a decreased presence of immune cells.[63] Moreover, KRAS has been considered a potential therapeutic target for specific cancers; however, efforts to target KRAS have proven

challenging, and it has been regarded as "undruggable" for a long time.[22,63] Despite the longstanding belief that KRAS is incurable in various cancers, new treatments such as KRAS inhibitors, MEK inhibitors, and PI3K inhibitors target KRAS or its downstream signaling pathways.[63] Sotorasib is an inhibitor that specifically targets KRAS. In 2021, the FDA approved the use of G12C mutations for treating advanced non-small-cell lung cancer.[64] Moreover, it is claimed that sotorasib has shown considerable anticancer effects in patients with KRAS p.G12C mutations and advanced pancreatic cancer who had undergone prior treatment.[65] Treatments that work for pancreatic cancer resulting from KRAS mutations are still in development.

3. Recent Advances in Pancreatic Cancer Targeted Therapy and Limitations

While more effective treatments are urgently needed, the early identification of pancreatic cancer is crucial for improving patient survival rates.[34] Chemotherapy has served as the foundation of treatment for most cancers, yet it has not significantly enhanced overall clinical outcomes for those with pancreatic adenocarcinoma.[109]

Possible treatment options include gemcitabine combined with nab-paclitaxel, capecitabine, 5-fluorouracil, and the poly-chemotherapy regimen FOLFIRINOX, which consists of folinic acid, fluorouracil, irinotecan, and oxaliplatin.[32] The FDA approved gemcitabine (GEM) for treating pancreatic cancer in 1977. It has been used since then both alone and in conjunction with other cytotoxic drugs such as 5-fluorouracil (5-FU), cisplatin, and docetaxel.[15,33] It is now recommended to use GEM-based treatment for patients with advanced pancreatic cancer.[15] Nevertheless, due to the genetic diversity of pancreatic adenocarcinoma and its extensive stroma, which hinders effective drug penetration and accumulation at tumor sites, this type of cancer is generally resistant to conventional chemotherapeutic agents. To boost the effectiveness of pancreatic cancer treatment, enhancing the targeted penetration and buildup of cytotoxic drugs is essential.[19,35,110]

Since chemotherapeutic drugs cannot tell the difference between cancerous and healthy cells, they carry the risk of unintended damage.[15,39,68,111] Additionally, a number of these cytotoxic drugs have low bioavailability due to factors such as physiological barriers, biological deterioration, and insufficient tumor penetration. As a result of these problems, the concentration of medication at the tumor site is low, which ultimately leads to therapy failure. Several targeting strategies, such as immunotherapy, nanotherapeutics, and various combination methods[38, 39], have been developed to address the drawbacks of chemotherapy.

Certain items are emphasized below.

3.1 Immunotherapy Methods for Pancreatic Cancer Treatment

Immunotherapy, which boosts the immune system to stop cancer from spreading, is gaining popularity.[112] Immunotherapy aims to target and alter the activation of stromal and immunosuppressive cells within the tumor microenvironment (TME), such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). It also seeks to affect the release of immune cells and cytokines at locations of cancer (Figure 3).[59,62,113,114] Immune checkpoint inhibitors, adoptive T cell therapy, targeted immunomodulators, vaccines, and combinations of these immunotherapeutic approaches are used to treat pancreatic cancer.[60] The suppression of immune checkpoints regulates the activation of T-cells and leads to the death of cancer cells by inhibiting the ligands for cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD1).[114–116]

CTLA-4 and CD28 vie for binding to the B7 (CD80) or B7-2 (CD86) ligands on the surface of activated T cells. This competition inhibits the immune system and reduces T cell activity while obstructing CD28's stimulatory signal.[116,117] In specific cancers like colorectal cancer, melanoma, and renal cell carcinoma, it has demonstrated remarkable efficacy in suppressing CTLA-4.[118] Ipilimumab is an entirely humanized antibody that acts as a CTLA-4 inhibitor, enhancing anticancer activity by preventing the interaction between CTLA-4 and B7-1/B7-2 to promote T cell activation. In 2011, the FDA approved ipilimumab for treating unresectable melanoma or advanced metastatic melanoma (stage III or IV). Due to the ineffectiveness of ipilimumab as a standalone treatment, it was recommended to use it alongside other immunotherapeutic and chemotherapeutic agents for pancreatic carcinoma. In a Phase 1b clinical trial, the ipilimumab-gemcitabine combination did not demonstrate superior anticancer effects compared to gemcitabine alone.[119] In another study conducted byWu et al., the anticancer effect of ipilimumab and GVAX vaccine was evaluated in metastaticpancreatic cancer using FOLFIRINOX as standard treatment.[120] The combination didnot demonstrate improved overall survival over chemotherapy and the treatment failurewas related to the tumor’s counterregulatory pathways, which prevented the induction ofpotent **anticancer effects in pancreatic cancer.[120]**

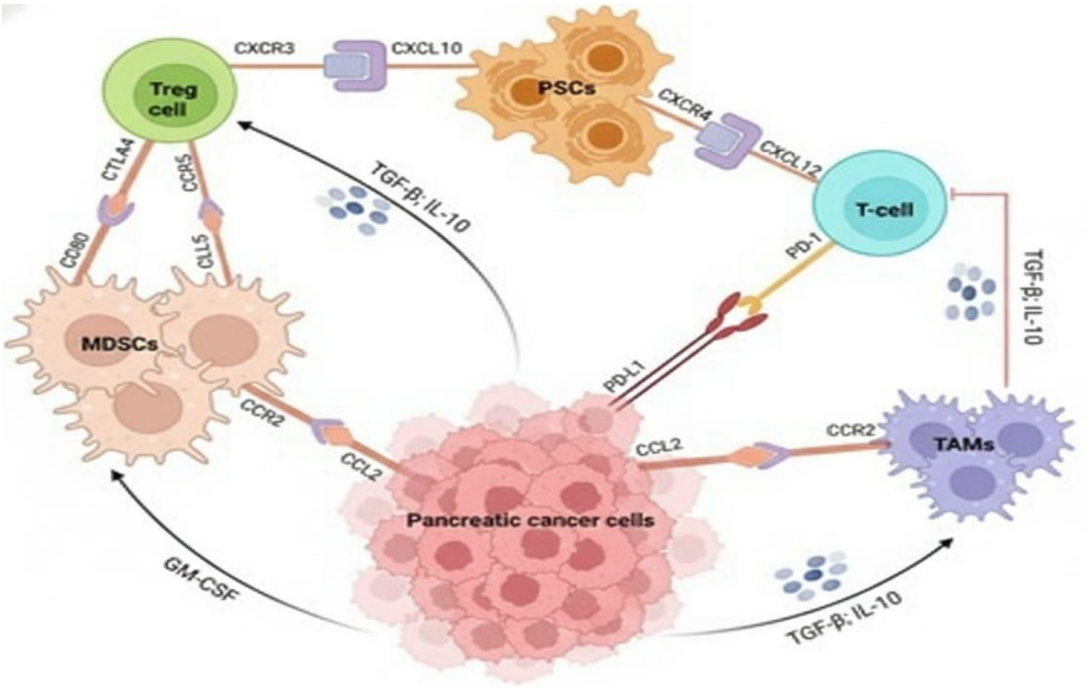

Figure 3: Schematic representation of the cross-interaction among different cell types within the pancreatic tumor microenvironment (TME). Immunosuppressive cytokines, including transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), promote the establishment of an immunosuppressive TME by recruiting and activating regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). Additionally, the interaction between programmed cell death ligand-1 (PD-L1) expressed on cancer cells and programmed cell death protein-1 (PD-1) on T cells induces T-cell apoptosis, leading to immune evasion. These immunosuppressive cells and their associated signaling pathways represent important targets for cancer immunotherapy.

3.2. Photodynamic Pancreatic Cancer Therapy

Photodynamic therapy (PDT) is emerging as a promising treatment option for pancreatic cancer. PDT offers an alternative to surgery and other invasive methods in cancer treatment. It requires photosensitising agents and specific light wavelengths to induce localized tissue necrosis.[68,129–133] Photosensitisers, typically administered orally or through intravenous injection, tend to accumulate in abnormal or cancerous cells. Macromolecular photosensitisers enhance PDT by ensuring preferential concentration in neoplastic tissues and reducing the rapid discharge of these tissues. When the photosensitiser is exposed to the designated light wavelength, reactive oxygen species (ROS), particularly singlet oxygen species, are generated by transferring excited electrons or absorbed photon energy to nearby

oxygen molecules.

PDT has been studied as a supplementary treatment for pancreatic cancer when combined with chemotherapy, radiation, immunotherapy, and surgical resection.[130] A variety of photosensitisers, such as sodium porfimer, photofrin, mesotetrahydroxyphenyl chlorin, and verteporfin[132,133], have been evaluated for their effectiveness in treating pancreatic cancer. PDT utilizing verteporfin has shown effective cytotoxicity in specific gemcitabine- resistant pancreatic cancer cells.[136] Lu et al. [132] documented the effectiveness of sodium porfimer and verteporfin across various pancreatic cell lines. It was discovered that, across various cell lines with differing sensitivities, both photosensitisers induced cell death in a dose-dependent manner. Nonetheless, verteporfin proved to be more effective at a significantly lesser amount than sodium porfimer. Huggett et al. showed that vertepofin is safe and effective for inducing tumor necrosis in locally advanced pancreatic cancer in their phase I/II study.[131] In addition, Xie et al. examined the potential anticancer effects of combining gemcitabine, a chemotherapeutic agent, with the PDT medication photosan.[130] Their results showed that PDT had a strong but short-lived anticancer effect. The findings indicate that combining chemotherapy with photodynamic treatment may enhance the anticancer efficacy.[130,136,137]

There are several factors that influence the effectiveness of PDT as a cancer treatment, including the selection of photosensitiser, the suitable dosage, and the depth of light penetration. The selective drug accumulation and cytotoxic response are influenced by the intracellular uptake, location, and vascular permeability of photosensitisers.[132] The stiff fibrotic stroma that surrounds pancreatic tumors restricts the effective delivery of photosensitizers, creates a reliance on tumor oxygenation, and leads to imprecise dosimetry, all of which have limited the clinical application of PDT in treating pancreatic cancer.[134,138,139] The review by Wang et al.[133] provides additional information on pancreatic cancer PDT, and readers are directed to it.

To improve the therapeutic use of PDT[135], delivery strategies that incorporate conjugated polymers and encapsulate photosensitizers within nanovehicles are under investigation. As an example, the conjugation of the PDT agent pheophorbide-a with nanoparticles enhanced both the drug's effectiveness and the overall efficacy of the delivery method.[137] Conjugate delivery systems and nanotechnology in PDT also offer enhanced selectivity and targeting as two additional benefits. By adding molecules that penetrate cells and aim at tumors, these delivery systems can be further functionalized, resulting in enhanced treatment accuracy. One

example of this is the pioneering drug delivery method developed by Hafiz et al. using a liquid metal nanoplatform (refer to Figure 4).

[139] This formulation is made up of eutectic gallium–indium nanoparticles that are linked to hyaluronic acid and a benzoporphyrin derivative, which function as a targeting ligand and photosensitiser, respectively. After activation, the technology exhibited remarkable cellular absorption and tumor targeting. Compared to the control group, near-infrared light significantly elevated intracellular ROS levels, leading to tumour regression and increased necrosis.

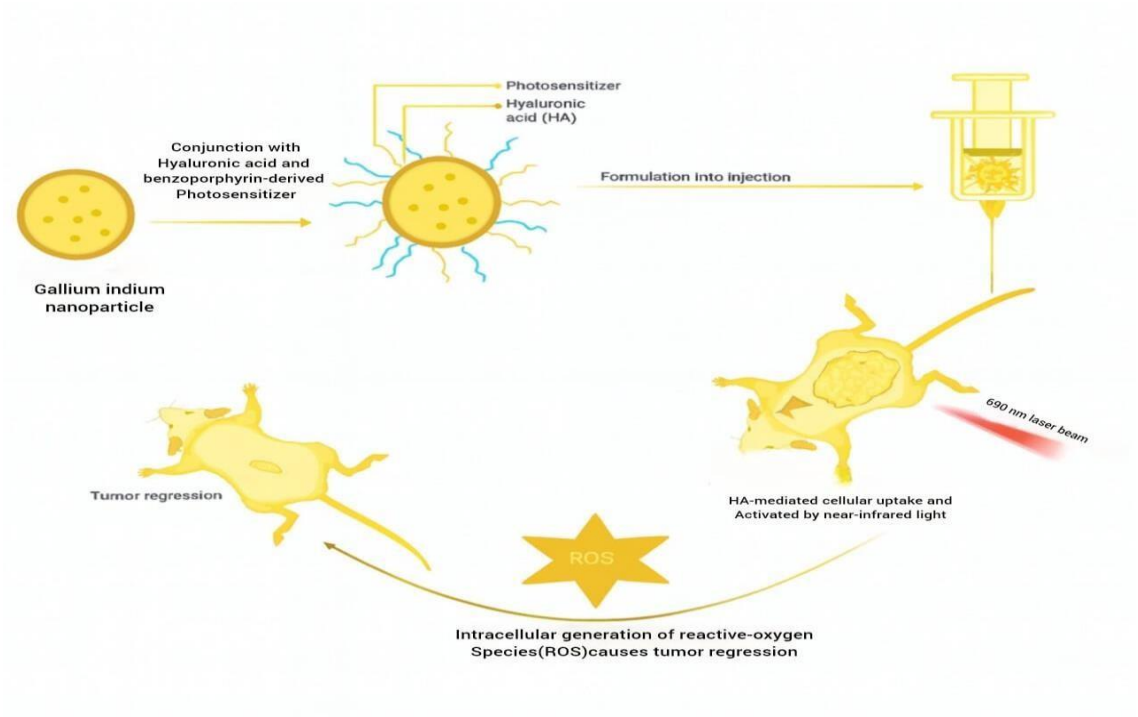

Figure 4: Schematic illustration of photodynamic therapy employing hyaluronic acid as a targeting ligand and gallium–indium nanoparticles functionalized with a benzoporphyrin-based photosensitizer for targeted cancer treatment.

It has been demonstrated that handling pancreatic cancer is rather difficult and that a multimodal approach is essential for achieving the best results. Therefore, additional research into the use of PDT as a supplementary therapy is necessary. For more information on photodynamic therapy, refer to the outstanding reviews by Meng et al.[135]

3.3 Treating Pancreatic Cancer with Nanotechnology

Nanotechnology integrates various scientific fields and is centered on developing materials and devices at the nanoscale.[140] Nanotechnology is one of the most widely used methods in

medicine for developing and discovering cancer-fighting drugs.[31,140] Nanotechnology has been extensively studied in cancer research to improve the delivery of anticancer drugs by utilizing the tumor's leaky vasculature, employing EPR-based passive and/or active targeting methods.[3,15,141] Recent studies emphasize the use of active targeting and/or a combination of passive and active targeting, as opposed to relying solely on passive targeting, for various applications aimed at enhancing the efficiency of drug delivery and minimizing off-target toxicity.[141,142] Moreover, vascular permeability can vary within a single cancer and between different types of tumors, with some tumors not exhibiting the effects of enhanced permeability.[36,69,75,142] There are multiple strategies that enable the aimed-at distribution of anticancer drugs, which can be used to actively target tumors.

Nanoparticulate drug delivery employs a diverse array of nanocarriers, including liposomes, polymeric nanoparticles, micelles, gold nanoparticles, and quantum dots (refer to Figure 5).[3,31,143] These nanocarriers are extensively utilized, and numerous nanoproducts have emerged as improvements over conventional chemotherapeutics. Nanocarriers can hold or be linked to therapeutic medications, resulting in the creation of nanoproducts.[36] Nanoparticle-based drug delivery systems are designed to minimize toxic effects and off-target exposure, improve the therapeutic agent's pharmacokinetic profile regarding solubility, half-life, and mean residence time, and ensure that cytotoxic agents reach the tumor site at concentrations greater than those of free drugs.[31, 144, 145] Nevertheless, there are several drawbacks to using nanovectors for drug delivery, such as elevated production costs, significant molecular size, nanotoxicity, accumulation in off-target tissues, burst release of the drug being carried, inadequate systemic circulation stability, and variations between different batches.[144] The burst or rapid release of large quantities of drugs carried by nanocarriers shortly after injection, before they arrive at the target site [141], is one of the main issues that impede the clinical translation of various nanoformulations. This event can lead to serious toxicity and unsuccessful treatment.[146,147]

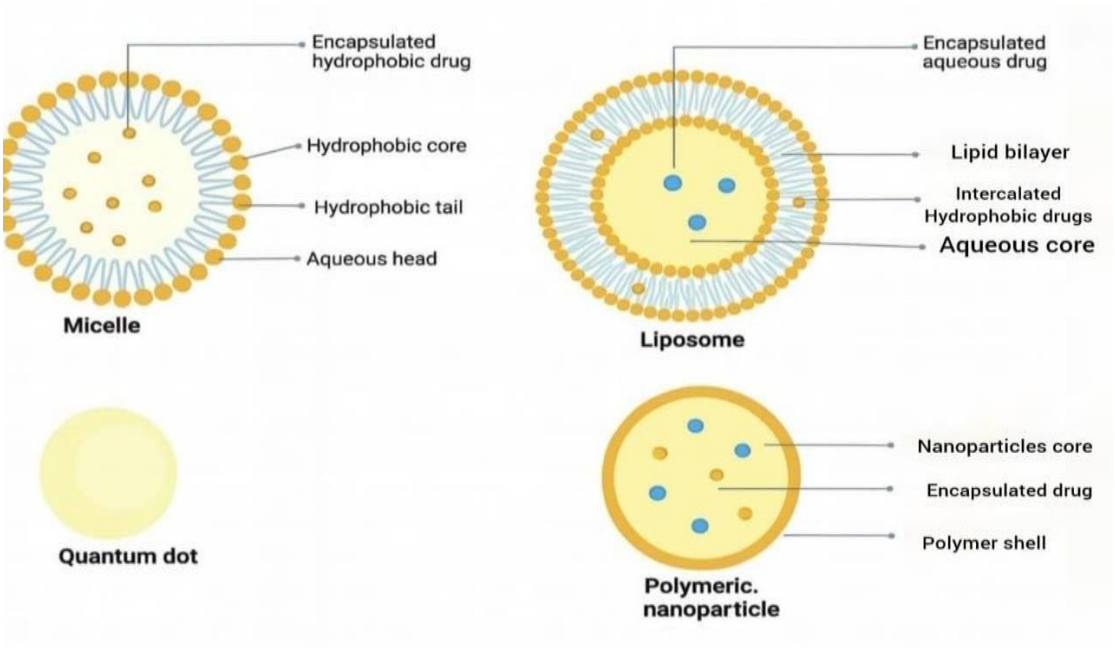

Figure 5: Schematic representation of nanoparticle-based drug delivery systems, illustrating the design, targeting mechanisms, and controlled release of therapeutic agents.

A key tactic for dealing with certain limitations of nanoparticulate drug delivery systems—like circulatory instability, short half-life, and rapid clearance—is the creation of stealth nanoparticles (PEGylated nanoparticles).[148] Polymers such as polyethylene glycol (PEG) and N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers are used to create a steric barrier by either covalently bonding or adsorbing them onto the surfaces of nanoparticles.[68,148–150] This approach enables prolonged circulation of nanoparticles by minimizing systemic clearance, which is achieved by lowering the uptake of the reticuloendothelial system. Additionally, it enhances the pharmacokinetic profile of the active medicinal ingredients, resulting in reduced toxicity and improved therapeutic efficacy.[150]

3.3.1. Albumin-Based Nanoparticles for Pancreatic Cancer Treatment

A protein nanomaterial obtained from various natural sources; albumin carries a diverse array of substances. Most of the protein in human plasma consists of albumin, which is often utilized to produce albumin-based nanoparticles.[151,152] Nanocarrier systems based on albumin nanoparticles have undergone thorough investigation in clinical trials for pancreatic cancer and are widely utilized in cancer therapy.[33,62,145] They demonstrate excellent tolerance, biocompatibility, biodegradability, and high safety standards. It has been shown that albumin nanocarriers enhance drug uptake and accumulation in tumors, prolong circulation time, and

improve the stability of various therapeutic payloads.[137,152–156] However, since albumin is a body-produced protein, the size and purity of its derived products can differ. Due to the organic solvents utilized in manufacturing processes, they exhibit increased vulnerability to denaturation and unwanted reactions. Furthermore, due to albumin's interactions with various endogenous substances within the body, its presence in systemic circulation could potentially increase the risk of immunogenicity and instability.[152,157] Bovine serum albumin (BSA) is often used in place of human serum albumin. BSA is low-cost, has minimal immunogenicity, and has structural similarities to human serum albumin.[152,158] Other publications provide thorough assessments of albumin and its uses as a nanocarrier.[151,159,160]

Abraxane®, the first nanoparticle based on albumin, was launched in 2013.[156,161] Abraxane®, also known as nanoparticle albumin-bound paclitaxel or nab-paclitaxel, is an albumin-stabilized form of paclitaxel that is approved as a first-line treatment for metastatic pancreatic cancer in combination with gemcitabine. The nanoformulation demonstrated improved overall survival and an exceptional safety profile when compared to the conventional delivery of chemotherapeutic medication.[158] In addition, a phase III clinical trial conducted by Goldstein et al. in 2015 demonstrated that gemcitabine plus nab-paclitaxel was more effective than gemcitabine alone. The combination group had an overall survival of 8.7 months, while the gemcitabine group had 6.6 months, resulting in a median difference of 2.1 months.[161] To enhance therapeutic efficacy and minimize side effects, various albumin-based formulations have been investigated for bioimaging applications in pancreatic cancer treatment.[137,152,155,156,158] In vitro and in vivo studies have demonstrated that albumin nanoparticles co-loaded with curcumin and paclitaxel exhibit enhanced anticancer activity and a controlled-release effect.[153] Considered a nanocarrier, albumin is adaptable, effective at loading a variety of drugs, and functional.[162] Another novel delivery method under consideration for pancreatic cancer treatment is the enzyme-sensitive, albumin-based gemcitabine therapy.[163] An albumin nanocarrier was used to bind gemcitabine via a linker that can be cleaved by cathepsin B. The formulation was created by complexing the albumin nanocarrier with IR780. The near- infrared dye IR780 is used for cancer imaging and phototherapy. Due to its associated toxicity, it is not recommended to use IR780 directly for cancer treatment.[164] Compared to free IR780, the albumin-based formulation resulted in a longer retention of IR780, significantly increasing gemcitabine concentrations in tumor tissue while minimizing side effects.[163] Also, Yu et al. created a versatile nanoparticle based on albumin that aims to deliver gemcitabine and the photodynamic agent pheophorbide to

patients with lymph metastases from pancreatic cancer.[137] Due to its short half-life, gemcitabine has a low concentration in cancer tissue, which ultimately results in therapy failure. In addition, pheophorbide's hydrophobic characteristics reduce its photodynamic impact when it is provided freely. The formulation based on albumin exacerbated the deficiencies in pheophorbide and gemcitabine. The trial's findings showed that the administration method effectively halted the growth of both primary and metastatic tumors and offered good imaging-guided medication distribution.[137] Despite extensive investigation into albumin's function in therapeutic advancement, only a small number of albumin-based treatments have progressed to the clinical phase.

3.3.2. Liposomal Nanoformulations for the Management of Pancreatic Cancer

Liposomes are another popular nanocarrier for delivering anticancer drugs.[36] Over 60% of all authorized nanoproducts are liposomes, which have demonstrated notable success compared to other nanoparticles.[165–167] Liposomes, which consist of phospholipids, are vesicles with a hydrophilic core and two layers. Liposomes serve as a suitable therapeutic carrier for payloads that are either hydrophilic or hydrophobic.[143] Their outstanding biocompatibility and biodegradability, combined with their small size and low toxicity profiles, make them promising candidates.[165,167,168] Liposomal drug delivery systems have been reported for site-specific administration and are suitable for surface functionalization in active targeting due to their enhanced permeability and retention effect, which leads to their accumulation in tumor tissues.[169]

A number of formulations based on liposomes have been evaluated for their efficacy in addressing pancreatic cancer. Using a pancreatic cancer xenograft model, Ranjan and colleagues demonstrated the anticancer properties of a liposomal form of curcumin that they developed. Curcumin, a naturally occurring anticancer agent, has its effectiveness reduced due to its hydrophobic nature and low systemic bioavailability. According to the research, liposomal curcumin exhibits a significantly stronger anticancer effect than free curcumin.[170]

To improve the penetration of paclitaxel micelles in pancreatic cancer, Zinger and colleagues developed collagozome, a nanoliposomal formulation of collagenase.[171] Collagen overexpression causes the stroma to thicken considerably and become rigid. Collagozomes are equipped with collagenase enzymes that degrade collagen and reduce fibrotic tissue in cases of pancreatic cancer. The liposomal formulation demonstrated a sustained release rate and protected collagenase from premature degradation in the plasma.[171] The overall

effectiveness was attributed to the liposomal collagozome's ability to alter the tumors' extracellular matrix, and further investigation of this method has been proposed. The liposomal delivery technique has also progressed with the development of LPGem-siMcl-1, a formulation that uses liposomes as a nanocarrier to deliver gemcitabine and Mcl-1 siRNA together.) Mcl-1 siRNA is a small interfering RNA (siRNA) molecule that was specifically designed to target and quiet the myeloid cell leukemia-1 (Mcl-1) gene, enhancing apoptosis and perhaps delaying the growth of cancer cells. A protein called Mcl-1 inhibits apoptosis, which is essential for controlling this kind of cell death in many cell types, including cancer cells. According to reports, the liposomal method effectively delivered the two active medications into the pancreatic tumor, shielding them from early degradation and boosting their anti-tumor effectiveness.[172] Nonetheless, considering the average particle size of the liposomal formulation (188.7 nm) and the established relationship between therapeutic efficacy and particle size, further examination is required to ascertain the mechanism underlying the observed activity in the pancreatic adenocarcinoma model. Ji et al. created MMP-2-responsive liposomes that were modified with β-cyclodextrin (β- CD) and contained the antifibrotic drug pirfenidone as well as the chemotherapeutic agent gemcitabine.[167] Gemcitabine was encapsulated in the liposomes, while pirfenidone was incorporated into the β-CD. Using a peptide that can be cleaved by MMP-2, β-CDs were attached to the liposome. To aim at tumor cells, RGD (ArgGly-Asp) peptides were incorporated into the liposome. After being exposed to MMP-2 in the tumor microenvironment, pirfenidone was released from the formulation. This led to a reduction of dense fibrotic tissue and improved the absorption and accumulation of the gemcitabine-loaded liposomal product compared to free gemcitabine.

Liposomes are used in various drug delivery applications, and ongoing research aims to develop liposomes suited for these purposes. Methods for liposomal drug delivery with multiple functions seek to create numerous functionalities. If they are programmed to respond to specific stimuli, such as changes in pH, temperature, or enzyme activity, the encapsulated medication can be released at the target site of action. Additionally, they can be modified by focusing on ligands such as proteins, aptamers, peptides, and monoclonal antibodies. The goal is to lessen the damaging impact of anticancer drugs on healthy cells while enhancing their targeted delivery to tumor cells. These liposomes, which serve multiple functions, have demonstrated preclinical success.[168,175] Even though preclinical results show that these nanoformulations have better pharmacokinetic profiles and therapeutic efficacy compared to

the active medication, they have not been clinically translated.[168] In that location A variety of liposomal formulations are presently undergoing preclinical and clinical testing, and it is expected that additional innovative liposomal formulations with improved efficacy will soon be introduced.[165,166,168]

3.3.3 Using Polymeric Nanoparticles to Treat Pancreatic Adenocarcinoma.

Polymeric polymers, commonly used as drug delivery vehicles, can encapsulate and conjugate immunotherapeutic and chemotherapeutic agents. Due to their extraordinary biocompatibility, they can be customized for targeted drug delivery.[176] When cytotoxic drugs are conjugated or encapsulated in polymeric nanoparticles, they are delivered more effectively, have a longer half-life, and accumulate to a greater extent at the tumor site. A range of polymeric nanocarriers, such as polymeric micelles, dendrimers, nanogels, and polymeric nanoparticles, have been investigated for the treatment of pancreatic cancer. Polymeric nanoparticles are made up of various polymers, including poly- (lactic-co-glycolic acid) (PLGA), polyglycolic acid (PGA), polyamidoamine (PAMAM), and polylactic acid.[36,143,177,178]

The surface of PEGylated PLGA nanoparticles containing paclitaxel was modified by Wu et al. using the tumor- specific mucin-1 antibody (TAB004).[179] Mucin-1 is overexpressed in over 80% of pancreatic adenocarcinomas, and this is associated with a poorer prognosis and an increase in metastases. PEG-PLGA serves as a suitable nanocarrier with a high loading efficiency, while PEGylation offers prolonged circulation and reduced systemic clearance. The limited internalization and accumulation of cells observed during an infection were linked to the interaction between the conjugated antibody and the antigen produced by cancer cells, as demonstrated in vitro research.[179] Moreover, Sun et al. employed a redox-responsive gemcitabine polymer with a small particle size (15.40 nm) for the co-loading of paclitaxel and the immunomodulating drug NLG919.[180] The generated micelles exhibited robust anticancer effects in the pancreatic (PANC02) xenograft model. The connection between micelle size and improved anti-tumor efficacy supports the hypothesis that the thick stroma in pancreatic cancer hinders the absorption of nanoproducts with larger particle sizes. The research demonstrated the benefits of administering chemotherapeutic and immunotherapeutic drugs together.[180]

To enhance the efficacy of nanodrugs, recent studies have focused on using smart

nanocarriers that allow for surface functionalization to improve selectivity in targeted drug delivery.[181] These nanocarriers can take in and discharge drugs at targeted locations based on physiological or environmental signals. Even though scientists have tried hard to depict nanotechnology as the solution for the deficiencies of chemotherapeutics, a considerable gap remains between pre-clinical findings and clinical trial results.[36,145] Only a limited number of nanoparticle delivery methods, despite their seeming promise, have been used in clinical environments for the treatment of pancreatic cancer. Three new nanoparticle systems are currently in clinical trials for the treatment of pancreatic cancer (see Table 1). Imx-110 is distinctive due to its nanoscale and water solubility. It consists of nanoparticles that encapsulate the anticancer agent anthracycline and doxorubicin, a drug with low water solubility. Curcumin has demonstrated anticancer properties in various cancer types, such as pancreatic cancer, by targeting multiple signaling proteins, including nuclear factor Kappa B (NF-kB) and signal transducer and activator of transcription 3 (STAT3).[182,183] These proteins are involved in the initiation of cancer as well as in its resistance to chemoradiation and targeted therapies.[182] Utilizing Imx-110 nanoparticles for doxorubicin delivery could enhance the drug's capacity to infiltrate tumors. Using Imx-110 nanoparticles to transport doxorubicin could enhance the drug's capacity to infiltrate tumours. Moreover, co-delivery with curcumin may bypass the multidrug resistance pathways of tumor cells and prove effective against chemoresistant tumor cells by inhibiting the activity of NF-kB and STAT3. Comprising inert inorganic hafnium oxide (HfO2) crystals, NBTXR3 is a 50 nm nanoparticle that has shown clinical efficacy in treating hepatocellular carcinoma and advanced solid tumors with lung or liver metastases.[184] Upon the delivery of radiation after the intratumoral injection of NBTXR3, NBTXR3 becomes activated at the target site, leading to an enhanced absorption of ionising radiation aimed at destroying cancer cells.[184] NBTXR3 is inert, which means it only emits electrons when exposed to radiation. This feature makes radiation more effective than standard radiotherapy. Finally, AGuIX-NP is a nanoparticle based on polysiloxane with a hydrodynamic diameter of 4 ± 2 nm that serves as a paramagnetic contrast enhancer for theranostic applications and contains gadolinium.[185] Following intravenous administration, AGuIX-NP can build up passively in the tumour microenvironments due to the EPR effect. Its diminutive dimensions enable rapid renal clearance as well as thorough tumour penetration.

Table 1: Nanoparticle delivery systems in clinical trials for the treatment of pancreatic cancer.

Anticancer Agent	Molecular Target	Phase	Sponsor	ClinicalTrials.gov Identifier
Curcumin and doxorubicin (Imx-110)	Stat3/NF-kB/poly-tyrosine kinase /topoisomerase II	1/2a	Immix Biopharma Australia Pty Ltd.	NCT03382340
Inorganic hafnium oxide (NBTXR3)	Radiation	1	M.D. Anderson Cancer Center	NCT04484909
AGuIX-NP (Theranostic agent)	EPR effect	1/2	Dana-Farber Cancer Institute	NCT04789486

4. Drug-Conjugate Delivery Systems in Pancreatic Cancer Treatment

Due to their smaller size and ability to accurately target tumors, drug conjugates are being utilized more frequently to enhance the effectiveness of medicine delivery for desmoplastic pancreatic adenocarcinoma.[186] Monoclonal antibodies and peptides can be employed to target tumor-specific elements or receptors that are overexpressed on cancer cell surfaces, which may help surmount the challenges of treating pancreatic cancer. Systems based on drug conjugates, including polymer-drug conjugates, antibody-drug conjugates, and peptide-drug conjugates (refer to Figure 6), have demonstrated advantages in cancer treatment and seem to hold promise for treating pancreatic adenocarcinoma in comparison to conventional nanoparticulate drug delivery systems.[187,188] Using suitable linkers to covalently bond drug molecules to macromolecules, drug conjugates utilize the "pro-drug" method.[189] With the “pro-drug” strategy, the molecule’s physicochemical and pharmacokinetic properties are modified and its bioactivity concealed so that it remains inactive while circulating until it arrives at the target areas. In comparison to nanoparticle drug delivery systems, drug conjugates offer greater adaptability, reduced risk to off-target chemotherapeutic agents, and easier manufacturing processes.[189,190]

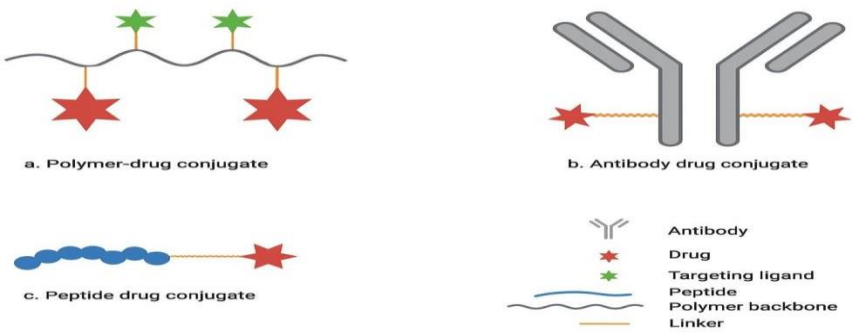

Figure 6. Schematic overview of the different types of drug conjugates employed in cancer therapy, highlighting their structural components and therapeutic mechanisms.

4.1. Polymer drug conjugates for the treatment of pancreatic cancer

A variety of diseases are the target of ongoing clinical investigations into numerous polymer-drug conjugates, which are often called polymeric prodrugs and have drawn considerable interest.[191] Cytotoxic agents and hydrophilic polymers are typically linked covalently, either directly or via suitable stimuli-responsive linkers (Figure 6a), including the peptide linkers PLGLAG (Pro-Leu-Gly-leu-Ala-Gly) and GFLG (glycylphenylalanyl- leucine-glycine).[192,193] Polymer-drug conjugates release harmful compounds when exposed to stimuli such as relatively lower pH or enzymes near the tumor site, causing the substrate linkers that attach the drugs to the polymer backbone to break.[193] Polymer-drug conjugates, when subjected to stimuli such as a relatively lower pH or enzymes near the tumor site, experience the breaking of substrate linkers that attach the drugs to the polymer backbone, resulting in the release of harmful compounds.[193] As a result, polymer-drug conjugates mitigate the risk of premature or off-target drug release and unintended toxicity to healthy cells—two significant concerns associated with nanoparticulate delivery systems.[191,193] Polymer-drug conjugates provide improved water solubility, prolonged drug circulation, and enhanced drug accumulation in the tumor microenvironment via the EPR effect. Compared to the traditional polymeric nanoparticulate method, which involves encasing the therapeutic medication within polymeric nanocarriers, the polymeric-drug conjugate approach offers a greater loading capacity and more controlled drug release.[193] Polyethylene glycol-betulinic acid (PEG-BA), a distinctive and simple polymer-drug combination, was developed by Mosiane et al.[194] Due to its poor solubility, short half- life, and high molecular weight, which limit cellular uptake, betulinic acid—a potent anti-cancer compound derived from medicinal plants—is not recommended for direct use. PEG-BA exhibited greater antioxidant and anticancer effects than free betulinic acid.[194] It has been shown that the conjugation of betulinic acid with polyethylene glycol yields a molecule that possesses improved pharmacological activity and pharmacokinetic characteristics. Wang et al. created a combination of polyamidoamine dendrimer and camptothecin for the treatment of pancreatic cancer. Wang et al. devised a combination of polyamidoamine dendrimer and camptothecin as a treatment for pancreatic cancer.[133] In this research, camptothecin was attached to the dendrimer with a thioketal linker that reacts to reactive oxygen species (ROS) after surface modification with glutathione. Gamma (γ)-glutamyl transpeptidase (GGT), which is abundantly present on the surface of pancreatic cancer cells, triggered the transformation of glutathione into amines via a charge-reversal mechanism, resulting in a positive charge on the dendrimer-camptothecin conjugate by facilitating γ-glutamyl transfer reactions that yield

primary amines. At neutral pH, glutathione carries a negative charge. With the transition to a positive charge, the substance can deeply infiltrate the tumor. By taking on a positive charge, the chemical can penetrate deeper into the tumor via caveolae- mediated endocytosis and transcytosis. Reports indicate that the optimal method for transporting nanoparticles to tumors involves using a neutral or slightly negative surface charge during intravenous injection, and then switching to a positive charge once the particles arrive at the tumor site (68). When camptothecin was cleaved by intracellular ROS, it became liberated. The thioketal linker, which is responsive to ROS, was utilized because cancer cells produce significant amounts of ROS as a result of hypoxia. In orthotopic pancreatic cancer cell xenografts, the dendrimer–camptothecin combination demonstrated a powerful anticancer effect, achieving a tumor inhibition rate of 92.8%. This was significantly higher than that of the control dendrimer lacking the ROS- sensitive linker (68.3%) and gemcitabine, the first-line FDA-approved treatment (62.2%). The significant cellular absorption and accumulation of this conjugate in desmoplastic tumors may be attributed to its reduced size (18.3 nm) and the mechanisms of caveolae-mediated endocytosis and transcytosis.[178] Almawash et al. also investigated the anti-cancer efficacy of docetaxel and cyclopamine polymeric conjugates in both primary and metastatic pancreatic cancer.[195] Cyclopamine, a steroidal alkaloid, blocks the hedgehog (Hh) pathway. The development and dissemination of pancreatic tumors is largely driven by the Hh pathway. In contrast, docetaxel, which attaches to β-tubulin and leads to mitotic arrest, is a microtubule stabilizer that causes cancer cell death.[38,50,195] The drug conjugates were created through a covalent bond between each drug and methoxy poly (ethylene glycol)-block- poly (2-methyl-2-carboxyl-propylene carbonate) using carbodiimide chemistry. The conjugates had average particle sizes of 73.11 nm for cyclopamine and 66.28 nm for docetaxel. The two polymeric conjugates demonstrated significant intra-tumoral accumulation and inhibition of tumor progression when used together. Moreover, in contrast to the free drugs that cause severe side effects like hypersensitivity and peripheral neuropathies, the conjugates were tolerated well. Despite the fact that a number of preclinical studies have demonstrated promising results concerning the efficacy of polymer-drug conjugates for treating pancreatic cancer, their clinical use remains limited.

4.2. Antibody-Drug Conjugates for Pancreatic Cancer Treatment

In the US, over 30 monoclonal antibodies have received approval for use, and they have been effectively developed to address various types of cancer.[196] Antibody–drug conjugates (ADCs) deliver toxic drugs by utilizing antibodies that attach to specific antigens on tumor

cell surfaces that are either not found or only minimally found on healthy cells. This contributes to the active targeting of cancer by enhancing selectivity for tumor cells.[197,198] Besides using complete antibodies, smaller antibody fragments such as fragment antigen binding (Fab), single-chain fragment variable (scFv), and single-domain antibodies are also employed for drug administration. Compared to full-length antibodies, the smaller pieces are easier to produce and can penetrate tissues more successfully.[196,199,200] ADCs are produced by combining antibodies with cytotoxic drugs using a suitable linker[197,198] (Figure 6b). ADCs lower off-target toxicity and enhance the cellular uptake of anticancer therapies.[198,199,201] Nagaoka et al. investigated the anti-tumor effects of a novel ADC, SNS-622-emtansine, in pancreatic adenocarcinoma cases. The antibody SNS-622 is directed against aspartate-β-hydroxylase (ASPH), a type II transmembrane protein that is produced in excess amounts in pancreatic adenocarcinomas. ASPH overexpression accelerates the development, migration, invasion, and metastasis of pancreatic cancer. The ADC demonstrated selectivity for ASPH by preventing lung metastasis and the development of the primary tumor.[201] An additional investigation looked into the tumor-suppressive impact of an antibody–drug pairing on pancreatic cancer cell lines centers on monomethyl auristatin F, or glypican-1.[202] The majority of primary pancreatic adenocarcinomas contain extra glypican-1, which is linked to a poor prognosis and recognized as a promoter of cancer proliferation. The formulation greatly reduced tumor development and led to the internalization of glypican-1-positive pancreatic cancer cells.[202] Moreover, Huang et al. developed a new ADC known as ICAM1- antibody, which is connected to mertansine via a succinimidyl 4-(N-maleimidomethyl) cyclohexane-1- carboxylate (SMCC) linker.[203]In the case of pancreatic cancer, a poor prognosis is associated with the overexpression of the transmembrane glycoprotein ICAM1. In preclinical studies, the targeted ADC demonstrated substantial accumulation in tumor tissues and induced tumor regression.[203] Although many preclinical studies have investigated the promise of antibody-drug conjugates for pancreatic adenocarcinomas, none have received approval for use againstNo observable anti-cancer effects have been seen in clinical contexts for this kind of malignancy. About twelve ADC cancer treatments for solid tumors and hematologic cancers have been approved by the FDA.[204] Only approximately five antibody-drug conjugates are currently being examined in clinical trials for the treatment of pancreatic cancer (refer to Table 2). Because of their large molecular dimensions, desmoplasia significantly restricts the ability of antibody–drug conjugates to infiltrate pancreatic tumor cells; this may explain why these conjugates are not effective in treating pancreatic adenocarcinoma.[58] In addition, the expression of antigens in

pancreatic adenocarcinoma is heterogeneous; this variability may occur over time within a single patient or among different patients. Treatment failure may be influenced by this diversity.[200,205] For the development of ADCs aimed at treating pancreatic cancer, it is recommended to use smaller antibody fragments like single-chain fragment variable and single-domain antibodies.[36,205] Drago et al. and Marei et al. [206,207] conducted recent studies that offer thorough insights into antibody-drug conjugates and their impact on cancer therapy.

Table 2: Antibody–drug conjugates in clinical trials for the treatment of pancreatic cancer.

Anticancer Agent	Molecular Target	Phase	Sponsor	ClinicalTrials.gov Identifier
Monomethyl auristatin E (TORL-2-307-ADC)	Claudin 18.2	1	TORL Biotherapeutics, LLC	NCT05156866
Anthracycline PNU- 159682 (SOT102)	Claudin 18.2	1/2	SOTIO Biotech	NCT05156866
Auristatin moiety (A166)	* HER2	1/2	Klus Pharma Inc	NCT03602079
Monomethyl auristatin E (XB002)	Tissue factor	1	Exelixis	NCT04925284
Duocarmycin analog (vobramitamab duocarmazine)	B7-homolog 3	1	MacroGenics	NCT05293496

* HER2: Humanepidermal growth factor receptor 2

4.3. Peptide-Drug Conjugates for Pancreatic Cancer Therapy

Peptide–drug conjugates can be found in other publications.[188–190,208] To summarize, peptide–drug conjugates represent a type of drug delivery system that utilizes an appropriate linker to covalently attach active pharmaceutical agents to a peptide sequence (see Figure 6c). Peptide-drug conjugates possess properties of biocompatibility, biodegradability, and lack of immunogenicity.[188,190] Like other drug conjugates, this delivery method can ensure precise targeting and alter the pharmacokinetic properties of drugs. Peptide-drug conjugates represent a new approach to delivering treatment for various cancers, such as pancreatic adenocarcinoma.[188,209] Peptide-drug conjugates are smaller than nanoparticulate drug delivery systems and antibody-drug conjugates, allowing them to penetrate the refractory tumor microenvironment of pancreatic cancer and micrometastatic tumors more easily.[45,189] The average IgG antibody consists of roughly 1000 amino acids (150 kDa), whereas a peptide used for cancer targeting comprises 5 to 25 amino acids (2–5 kDa).[189] Peptide–drug conjugates are primarily composed of two types of peptides: targeting peptides and cell-penetrating peptides.[210,211]

Comprising fewer than thirty amino acids, cell-penetrating peptides (CPPs) include transportan, octaarginine (R8), and HIV transactivator of transcription (TAT) peptides. Their successful internalisation into cells has resulted in improved cellular drug uptake across various cancer types.[210] Cell-penetrating peptides are capable of transporting conjugated payloads such as proteins, nucleic acids, nanoparticles, and small molecule drugs.[212] However, due to their low cell selectivity and non-specific cellular absorption, CPPs are not used as frequently as targeting peptides.[210,213,214] Due to their specificity for cancers, negatively charged cell-penetrating peptides are utilized more frequently than cationic ones.[209,212]

Cell-targeting peptides are a type of peptide that can specifically target and enter cells or tissues.[211] Cell-targeting peptides, which are smaller and made up of three to fourteen amino acids, are a type of penetrating peptide. When used in peptide–drug conjugates, the targeting peptides iRGD (cyclic CRGDKGPDC), iNGR (CRNGRGPDC), somatostatin, and CKAAKN demonstrate remarkable specificity and selectivity for specific overexpressed ECM components, integrin receptors, EGFR, and amino-peptidase N receptor.[7,30,181,190] Due to the overexpression of integrin receptors in tumor cells, RGD (arginine glycine-aspartic acid) is the most commonly used tumor-homing peptide motif in therapeutic conjugates for various cancers.[209] Integrins govern the development of tumors and their invasion of blood or lymphatic vessels.[215–217] Eight distinct varieties of integrin receptors exist: αvβ1, αvβ3, αββ5, αββ6, αββ8, α5β1, α8β1 und αIIbβ3. These encompass αββ3, αββ5, α5β1, and αββ6, all of which play a role in the initiation and advancement of cancer.[188,216] Nevertheless, conventional RGD has a limited range of applications in drug delivery methods because it cannot penetrate extravascular tumor tissue.[38]

The potential of a disulfide-based cyclic iRGD that enhances RGD to boost the penetration and cellular uptake of different medications across various cancer types has garnered significant interest.[8,38,217,218] The attachment of the peptide to β5 integrins results in the cleavage and release of the c-terminal sequence. This sequence interacts with the neuropilin-1 receptor to enable therapeutic medicine delivery by initiating endocytic transcytosis and trans-tissue transport.[38,94,218] The iRGD peptide enhances the infiltration of anti-cancer medications into blood vessels associated with tumour development, making iRGD-mediated targeting a promising approach for pancreatic adenocarcinoma. It aims to increase the permeability of these blood vessels so that medications can more readily home in on and

arrive at the tumor.[217,219] Moreover, research has indicated that iRGD peptides that attach to integrin receptors can reduce the expression of ECM glycoproteins such as fibrinogen and fibronectin, thereby decreasing cell adhesion and tumor proliferation. It has been shown that polymeric and liposomal iRGD conjugates are effective against various cancers, including breast and prostate cancer. It has been shown to have greater penetration and accumulation of anticancer drugs compared to the naked form of nanoparticles.[188,220]

Another commonly used tumor-homing peptide in peptide–drug conjugates is somatostatin. Somatostatin identifies and attaches to the somatostatin receptor (SSTRI-5). Along with its antisecretory and antiproliferative properties, somatostatin regulates the uptake and internalization of payloads in cells through its interaction with receptors. Many neuroendocrine tumors, such as those affecting the pancreas, breast, lung, and ovary, possess somatostatin receptors.[221] Cyclic peptides derived from somatostatin and connected to three different drugs— camptothecin, azatoxin, and combretastatin-4A—were created by Ragozin et al.[221] The drug conjugates demonstrated significant anti-tumor effects and selective accumulation in tumors within the evaluated pancreatic cancer cell lines.[221] Ragozin et al. synthesized cyclic peptides derived from somatostatin, which were conjugated with three different drugs: camptothecin, combretastatin-4A, and azatoxin.[221] All drug conjugates demonstrated significant anti-tumor effects and selective accumulation in tumors within the evaluated pancreatic cancer cell lines.[221] Additional tumor-homing peptides comprise angiopep-2, gonadotropin-releasing hormones, and epidermal growth factor protein.[15,30,212] Peptide-drug conjugates have not yet become common in cancer treatment.neu. The FDA-approved peptide-drug conjugate LutatheraTM (177lu-dotatate) is used to treat neuroendocrine tumors. Melfluten, another peptide-drug combination approved for treating refractory multiple myeloma, was recently delisted after failing phase III clinical trials.[214] In a recent phase I clinical trial, Dean and colleagues found that for 93% of patients with metastatic pancreatic cancer, the combination of gemcitabine/nab- paclitaxel with CEND-1 (iRGD) yielded a response rate of 59% and a median overall survival of 13.2 months.[222] Von Hoff et al., in a phase III clinical trial, found that the median overall survival for the gemcitabine/nab- paclitaxel group was 8.5 months.[23,223] Dámus et al.[30] additionally documented the development of effective Ser-Lys-Ala-Ala-Lys-Asn (SKAAKN) peptide-daunomycin conjugates aimed at selective targeting in PANC-1 pancreatic cancer. Cathepsin B might cleave the GFLG peptide, which connects the tumor-homing peptide SKAAKN to daunomycin. The peptide–drug conjugates showed significant inhibition of tumour growth

and no toxicity in the PANC-1 xenograft model compared to the free antibiotic daunomycin.[30] Peptide-drug conjugates should be considered as a potential treatment for pancreatic cancer.

5. Delivery Strategy in Multiple Stages

A multistage drug delivery system is characterised by the sequential release of medications at different stages of the illness and in response to stimuli.[224] This approach aims to enhance therapeutic outcomes and minimize the adverse effects associated with traditional drug delivery methods, including toxicity to non-targeted areas, rapid clearance from the body, and inadequate drug concentration at the intended site. In order to allow for the site- specific targeting of cytotoxic drugs, a stimuli-responsive system is anticipated to disintegrate into particles that differ in size, shape, or surface charge.[224,225] 1. In terms of functionalities and preparation technique, this differs from the system of functionalised single nanoparticles. Usually, a multistage drug delivery system consists of a carrier with cytotoxic substances that are either affixed to or housed within other carriers intended to convey these agents to a designated target.[226, 227]

The design of this delivery system necessitates a primary particle that serves as a carrier for secondary nanoparticles containing anticancer drugs.[228,229] After the injection, factors like alterations in pH or particular enzymes present in the tumour microenvironment lead to the disintegration of the primary nanoparticles, resulting in secondary nanoparticles that hold one or more anticancer drugs (see Figure 7). Utilizing the EPR effect, it may be possible to develop the first nanoscale product made up of liposomes, mesoporous silicon particles, nanoparticles, and other nanocarriers that preferentially aggregate in solid tumors. If targeted, the smaller secondary construct can penetrate deeper into the cancer and be internalised through receptor-mediated endocytosis.[226,230] Wong et al.[230] developed multistage quantum dot nanoparticles that initially measured 100 nm. After being injected, it enters the tumor microenvironment where matrix metalloproteinases induce a 10 nm reduction in size. Their findings indicated that the approach enhanced penetration through the tumor's interstitial space.[230]

Liang et al. demonstrated, in a similar vein, the effectiveness of multistage drug delivery devices for treating HER2-overexpressing breast cancer.[231] The work resulted in the creation of a unique nanovehicle with a lipid envelope, core-shell structure, and cascaded aptamers designed to reduce toxicity and enable stepwise drug release. Epigallocatechin gallate, a

naturally occurring anticancer agent, was incorporated into the nanovehicle and linked to an ATP (adenosine-5′-triphosphate) aptamer to form a ternary complex. An aminofunctionalized lipid matrix provided protection for this molecule. Liang et al.[231] have also demonstrated the effectiveness of multistage drug delivery devices in HER2-overexpressing breast cancer. This endeavor yielded a new nanovehicle with a lipid envelope, core shell architecture, and cascaded aptamers designed to minimize toxicity and enable stepwise drug release. A ternary complex was formed by incorporating the naturally occurring anticancer drug epigallocatechin gallate into the nanovehicle and linking it to an ATP (adenosine-5′-triphosphate) aptamer. This molecule was shielded by a lipid matrix with amino functionalization.

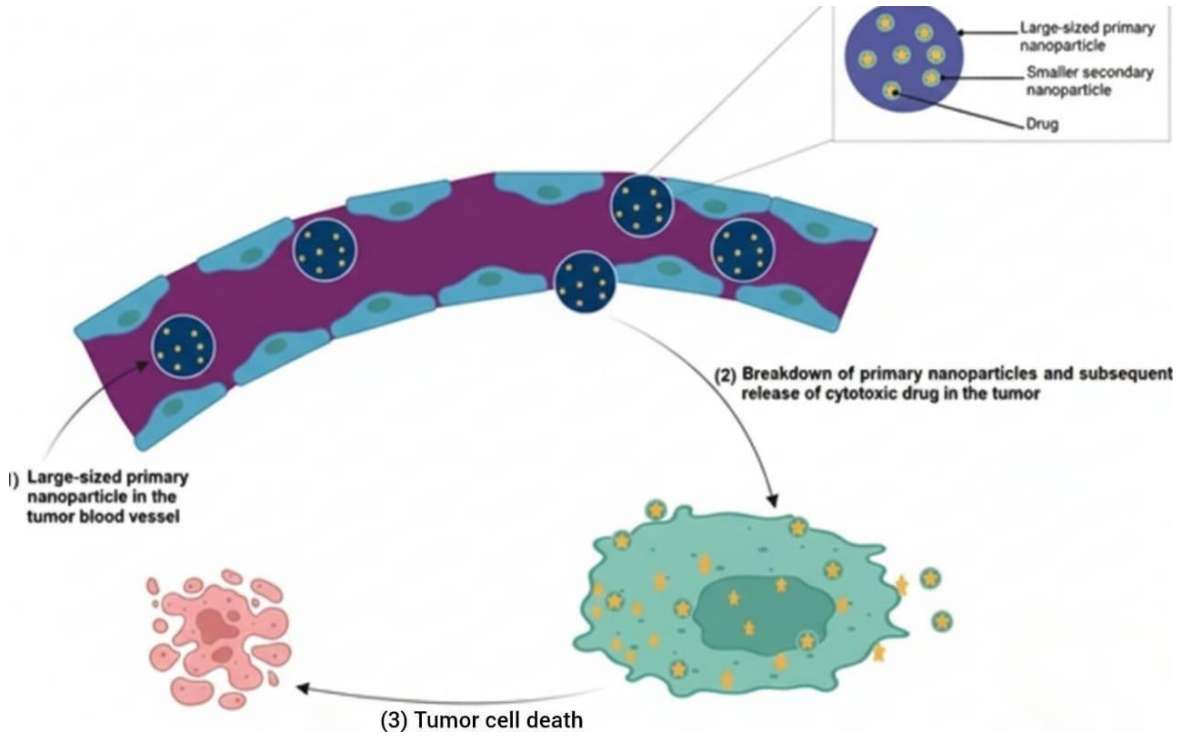

Figure 7: Illustration of a multistage drug delivery strategy in which primary nanoparticles transport secondary, payload-loaded nanoparticles to the tumor microenvironment via the enhanced permeability and retention (EPR) effect. Exposure to acidic pH or tumor-associated enzymes triggers the degradation of the primary nanoparticles, releasing the secondary nanoparticles and enabling localized delivery of cytotoxic agents within the tumor.

Although the multistage delivery approach has been utilized for over four decades, its effectiveness in treating pancreatic cancer remains uncertain.[224] Considering the unique characteristics of this cancer type, including its thick stroma that complicates drug delivery, a

multistage design could provide a greater array of options and significant potential for drug administration. Research has demonstrated that decreasing the size of nanoparticles enhances their ability to target cancer cells, but this may lead to their swift removal from circulation following intravenous injection. It is essential to strike a balance so that drug delivery systems are of the appropriate size— not so small that they are rapidly eliminated from circulation, and not so large that they hinder cancer cell absorption. Furthermore, a multistage design approach can modify the physicochemical characteristics of nanoparticles, including their shape and surface charge, all of which impact the overall effectiveness of the delivery systems.[232] To guarantee the advancement of ideal medication delivery systems, it is vital to further explore the potential of multistage design applications in cancer research.[224,233] The research conducted by[234] resulted in the creation of multifunctional, size-switchable nanoparticles that improved deep tissue penetration, optimized intracellular release, and exhibited a considerable anticancer effect in models of stroma-rich pancreatic and breast cancer. In a comparable manner, Li et al. developed a size-switchable, ultra-pH-sensitive nanoformulation that showed improved therapeutic efficacy and tumor penetration.[5,235]

6. CONCLUSION

The shortcomings of traditional chemotherapeutic applications can finally be addressed with nanodelivery systems. Sadly, pancreatic tumors remain resistant to these "promising products," and overall patient survival rates have not seen significant improvement. Even though these treatments have demonstrated some encouraging preclinical outcomes, there have not yet been any significant advancements in pancreatic cancer treatment. Desmoplasia plays a major role in the unfavorable prognosis of pancreatic cancer by hindering the infiltration and buildup of anticancer drugs. Alongside the heterogeneity of tumor cells, the presence of mutations in tumor suppressor genes and micro-sized metastatic tumors—known to resist large molecules—are further contributors to insufficient therapeutic outcomes. Consequently, the low penetration and storage levels of nanoproducts in tumors have restricted their usefulness, irrespective of targeting strategies. The significant physiological and anatomical differences between humans and study animals are responsible for the considerable gap between preclinical and clinical trial results, which is worth mentioning. While preclinical studies provide important information about the potential effectiveness and safety of new treatments or drugs, their reliability can be questionable. This complicates the direct application of their findings to human patients. Moreover, human studies are inherently complex, whereas animal models tend to be uniform. The main goal is to enhance deep penetration and internalization

for optimal drug delivery in pancreatic cancer. These aims can be achieved by devising delivery strategies that ensure penetration, intracellular absorption, and a considerable accumulation of cytotoxic drugs at tumor sites. Based on our understanding of the characteristics of pancreatic cancer and the design of drug delivery systems, targeting proteolytic enzymes that are overexpressed in the pancreatic tumor microenvironment with drug-conjugates—such as peptide–drug conjugates and multi-stage drug delivery systems—may enhance drug internalization, accumulation, and overall antitumor activity due to the small particle size of these delivery systems.Even though multistage drug delivery methods are often used in nanotechnology, more research is needed to completely grasp this approach in relation to small-sized drug conjugates. Moreover, the use of experimental models like genetically modified mouse models that accurately represent the unique characteristics of pancreatic adenocarcinoma should be employed during the preclinical phase to reduce discrepancies between preclinical and clinical findings and aid in clinical translation.

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