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REVIEW

Strategies for Pancreatic Cancer-Responsive Nanodrug Platforms Targeting Tumor Hypoxic Environments

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, largely because of its profoundly hypoxic and desmoplastic tumor microenvironment (TME), which hinders drug delivery and promotes resistance to chemotherapy, radiotherapy, and immunotherapy. Hypoxia not only serves as a therapeutic barrier, but also presents a selective vulnerability that can be exploited by smart nanocarriers. This review highlights recent advances in hypoxia-responsive nanoparticle (NP) platforms designed to overcome these barriers through four key strategies: (1) hypoxia-triggered drug release using bioreductively cleavable linkers and hypoxia-activated prodrugs; (2) surface functionalization with tumor-targeting ligands, such as aptamers and antibodies; (3) selective activation of hypoxia-activated prodrugs that become cytotoxic only under low oxygen conditions; and (4) multi-stimuli-responsive designs integrating pH, enzymatic, or exogenous triggers. Preclinical studies in PDAC models have demonstrated that these systems can achieve over two-fold tumor growth inhibition and a 60% increase in intratumoral necrosis compared with controls, validating their in vivo therapeutic potential. Furthermore, the recent integration of artificial intelligence into NP design has accelerated the optimization of hypoxia-responsive systems by enabling the rapid identification of structure–function relationships and in silico prediction of tumor-specific accumulation. Collectively, these strategies offer a promising route toward more effective, selective, and personalized nanomedicines for pancreatic cancer treatment.

Keywords: pancreatic ductal adenocarcinoma, PDAC, hypoxia-responsive nanoparticles, tumor microenvironment, tme, stimuli-responsive drug delivery, hypoxia-activated prodrugs, tumor-targeting ligands, artificial intelligence-assisted nanomedicine, personalized cancer therapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, with a 5-year survival rate remaining below 10%.[1] This grim prognosis stems from PDAC's inherent aggressiveness, late diagnosis, and its pronounced resistance to conventional therapies.[2] A defining feature of PDAC is its unique tumor microenvironment (TME), characterized by dense desmoplastic stroma, poorly organized and dysfunctional vasculature, and significant immunosuppression. Collectively, these elements contribute to regions of oxygen deprivation or hypoxia that have emerged as critical barriers to effective treatments.

Hypoxia disrupts drug delivery via multiple interrelated mechanisms that collectively establish a formidable barrier to therapy. One such mechanism is the abnormal and poorly organized vasculature characteristic of hypoxic tumors, where vessels are tortuous, leaky, and inefficient at delivering oxygen and nutrients. This vascular dysfunction not only reduces overall perfusion but also creates heterogeneous blood flow, leaving large tumor regions under-supplied and inaccessible to circulating drugs. In parallel, PDAC is marked by an exceptionally dense extracellular matrix (ECM), composed of collagen and hyaluronan, which physically impedes molecular diffusion and increases tissue rigidity. This stiff stromal network

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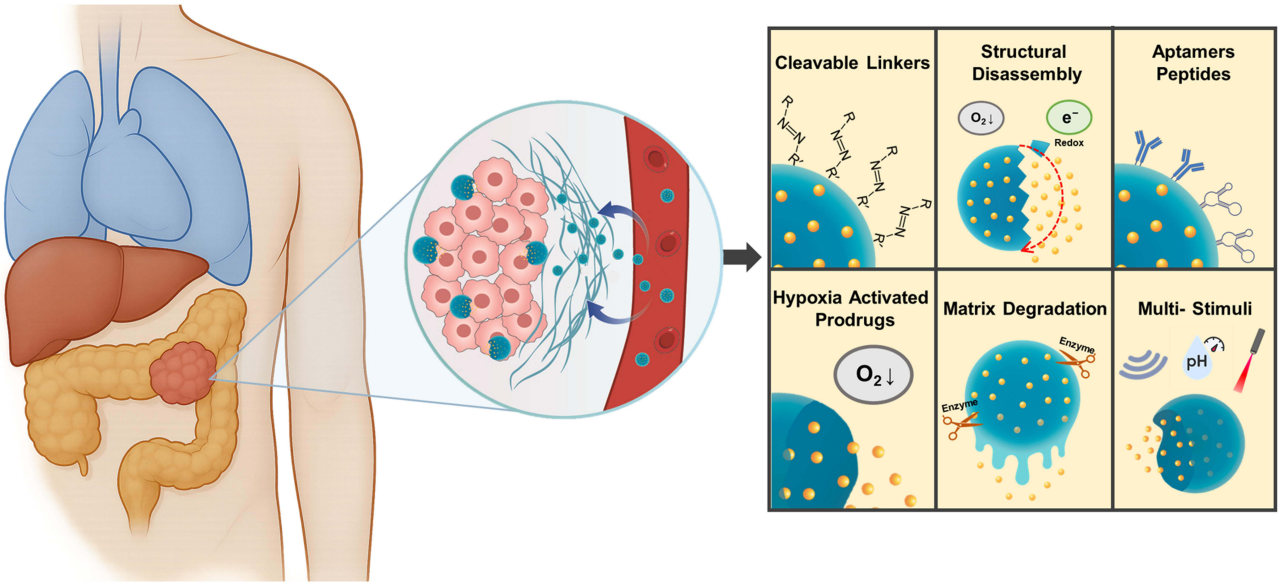
Graphical Abstract



restricts the passive spread of chemotherapeutic agents and further compresses intratumoral blood vessels, compounding perfusion deficits. Adding to this complexity is the markedly elevated interstitial fluid pressure, which arises from the combination of vascular leakage, stromal expansion, and impaired lymphatic drainage. Elevated pressure effectively counteracts convective transport, pushing therapeutic agents away from the tumor core and preventing uniform intratumoral distribution. Together, these intertwined mechanisms—vascular abnormality, stromal density, and fluid pressure elevation—create a microenvironment where drug penetration is severely compromised, resulting in poorly accessible tumor niches that sustain hypoxia and fuel resistance to multiple treatment modalities. Abnormal vasculature impairs perfusion and oxygenation, whereas excessive extracellular matrix (ECM) deposition increases interstitial pressure and creates a physical barrier to drug diffusion.[3] Additionally, hypoxia-inducible factors such as HIF-1α promote pathological angiogenesis and further ECM remodeling, exacerbating these structural impediments. These changes reduce the intratumoral accumulation of conventional chemotherapeutics and nanoparticle (NP)-based agents.[4] Moreover, hypoxia shapes the immunosuppressive milieu by recruiting suppressive immune cells and excluding cytotoxic T cells, thereby weakening the efficacy of immunotherapies.[5]

In addition to impairing drug transport, hypoxia directly promotes a more aggressive tumor phenotype. It induces epithelial-to-mesenchymal transition (EMT), a biological process whereby epithelial cells lose their cell–cell adhesion and polarity, and acquire mesenchymal and migratory properties that facilitate invasion and metastasis, along with metabolic reprogramming and the emergence of stem-like cancer cells, which are all hallmarks that drive metastasis and confer broad-spectrum therapeutic resistance.[6] Together, these factors make the hypoxic TME a central contributor to therapeutic failure observed in PDAC.[7]

In this review, we explored how hypoxia contributes to drug resistance in PDAC by creating formidable physiological and biochemical barriers. Particular emphasis has been placed on recent advances in hypoxia-responsive NP systems, which are designed to selectively release therapeutic payloads within the hypoxic TME and overcome current limitations in drug delivery. Through this lens, we aimed to highlight the promise of nanomedicine as a transformative approach for tackling therapeutic challenges in PDAC.

Tumor Hypoxia and Therapeutic Barriers in Pancreatic Cancer

PDAC is characterized by a uniquely aggressive and hypoxic tumor microenvironment.[8] Tumor hypoxia, defined as inadequate oxygen supply, is both a hallmark of PDAC and a key contributor to its resistance to therapy.[9] In pancreatic

tumors, oxygen tensions are markedly lower than in normal pancreatic tissue, owing to abnormal vasculature and dense stromal content.[10] This section explores the origin of hypoxia in the PDAC microenvironment (section 2.1), its role in impeding drug delivery, and its effect on the efficacy of conventional therapies.(section 2.2) An in-depth understanding of these mechanisms highlights the need for new strategies to overcome hypoxia-induced therapeutic failure in pancreatic cancer. Table 1 presents a comparison of the hypoxic features of various solid tumors to contextualize PDAC. As summarized in Table 1, PDAC exhibits uniquely severe and chronic hypoxia (pO_2 < 2 mmHg), extensive desmoplasia occupying more than 80% of tumor volume, dense collagen- and hyaluronan-rich ECM, and markedly elevated interstitial fluid pressure. Notably, the desmoplastic stroma in PDAC is exceptionally pronounced, often accounting for the vast majority of the tumor bulk. This stromal overgrowth is not a passive histological feature but an active pathological barrier: cancer-associated fibroblasts and pancreatic stellate cells generate abundant extracellular matrix that compresses blood vessels, elevates interstitial fluid pressure, and physically encases tumor nests. As a result, even though tumor cells may represent less than 20% of the total tumor volume, the stromal compartment dominates the

Table 1 Comparative Characteristics of Hypoxic Tumor Microenvironments Across Major Solid Tumors

Feature	Pancreatic Cancer (PDAC)	Breast Cancer	Non-Small Cell Lung Cancer (NSCLC)	Colorectal Cancer	Hepatocellular Carcinoma (HCC)	References
Tumor Hypoxia Level	Severe and chronic hypoxia (pO_2 < 2 mmHg)	Moderate; subtype-dependent	Mild to moderate	Moderate, often perinecrotic	Moderate to severe (especially in cirrhosis)	Koong et al 2000[11]
Desmoplasia (Stroma)	Extensive (>80% of tumor volume)	Present in basal-like and TNBC	Mild to moderate	Variable	Moderate, increased with fibrosis	Erkan et al 2012[12]
Vascular Density / Functionality	Low, compressed, dysfunctional	Moderate to high (except TNBC)	High but often abnormal	Moderate	Irregular sinusoidal vessels	Olive et al 2009[13]
ECM Barrier	Dense ECM (collagen, hyaluronan-rich)	Variable; rich in basal subtypes	Weak ECM barrier	Mild to moderate ECM	Often fibrotic ECM in cirrhotic liver	Provenzano et al 2012[14]
Interstitial Fluid Pressure (IFP)	Very high; impairs drug delivery	Moderately elevated	Low to moderate	Low to moderate	Elevated in fibrosis or advanced HCC	DelGiorno et al 2014[15]
Immune Cell Infiltration	Immune-excluded ("cold" tumor)	Subtype-dependent (TNBC = "hot")	Often immune-excluded or suppressed	MSI-H tumors are highly infiltrated	Immune-tolerant in many cases	Ino et al 2013,[16] Galon et al 2006[17]
HIF-1α Expression	Highly upregulated even at baseline	Upregulated in hypoxic cores	Induced in tumor periphery	Mild to moderate	Moderate to high	Semenza 2003[18]
Therapeutic Resistance	Highly resistant to chemo, radio, and immunotherapy	Subtype-dependent responses	Radiotherapy resistance; EGFR-TKI sensitive	Good response in MSI-H	Poor response in advanced disease	Hidalgo et al 2010,[19] Bailey et al 2016[20]
CSC Maintenance	Sustained by hypoxia and TME	Found in some subtypes	Hypoxia-induced CSC traits	Moderate presence	Supported by HIF signaling	Li et al 2007,[21] Ye et al 2014[22]
Hypoxia-Targeted Therapies	Under active development (eg, TH-302)	In development for select subtypes	Early clinical trials	Limited studies	Some preclinical models show promise	Borad et al 2015,[23] Kumari et al 2020[24]

Abbreviation: PDAC, Pancreatic Ductal Adenocarcinoma; NSCLC, Non-Small Cell Lung Cancer; HCC, Hepatocellular Carcinoma; TME, Tumor Microenvironment; TNBC, Triple-Negative Breast Cancer; ECM, Extracellular Matrix; IFP, Interstitial Fluid Pressure; MSI-H, Microsatellite Instability-High; CSC, Cancer Stem Cell.

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microenvironment, dictating drug distribution, immune cell access, and oxygen availability. This disproportionate stromal expansion is a defining hallmark that distinguishes PDAC from other solid tumors, where tumor cell density typically outweighs stromal content. Clinically, such extreme desmoplasia underpins the poor vascular perfusion, immune exclusion, and therapeutic resistance that remain major barriers to improving outcomes in PDAC. Therefore, emphasizing the stromal predominance is crucial to understanding why pancreatic cancer remains among the most treatment-refractory malignancies.

In line with these characteristics, Figure 1 schematically illustrates the major pathophysiological features of the PDAC microenvironment, including desmoplastic stroma, abnormal vasculature, tumor hypoxia, immune suppression, therapeutic resistance, and early metastasis. Together, these barriers underscore the therapeutic challenges of PDAC and provide the rationale for developing hypoxia-responsive nanoparticle strategies.

Mechanisms Underlying Hypoxia in the TME

Desmoplastic Stroma and Vascular Dysfunction

A hallmark of PDAC is its extensive desmoplastic stroma, accounting for up to 80–90% of the tumor mass.[25] This fibrotic stromal tissue, composed of cancer-associated fibroblasts (notably pancreatic stellate cells), immune cells, and

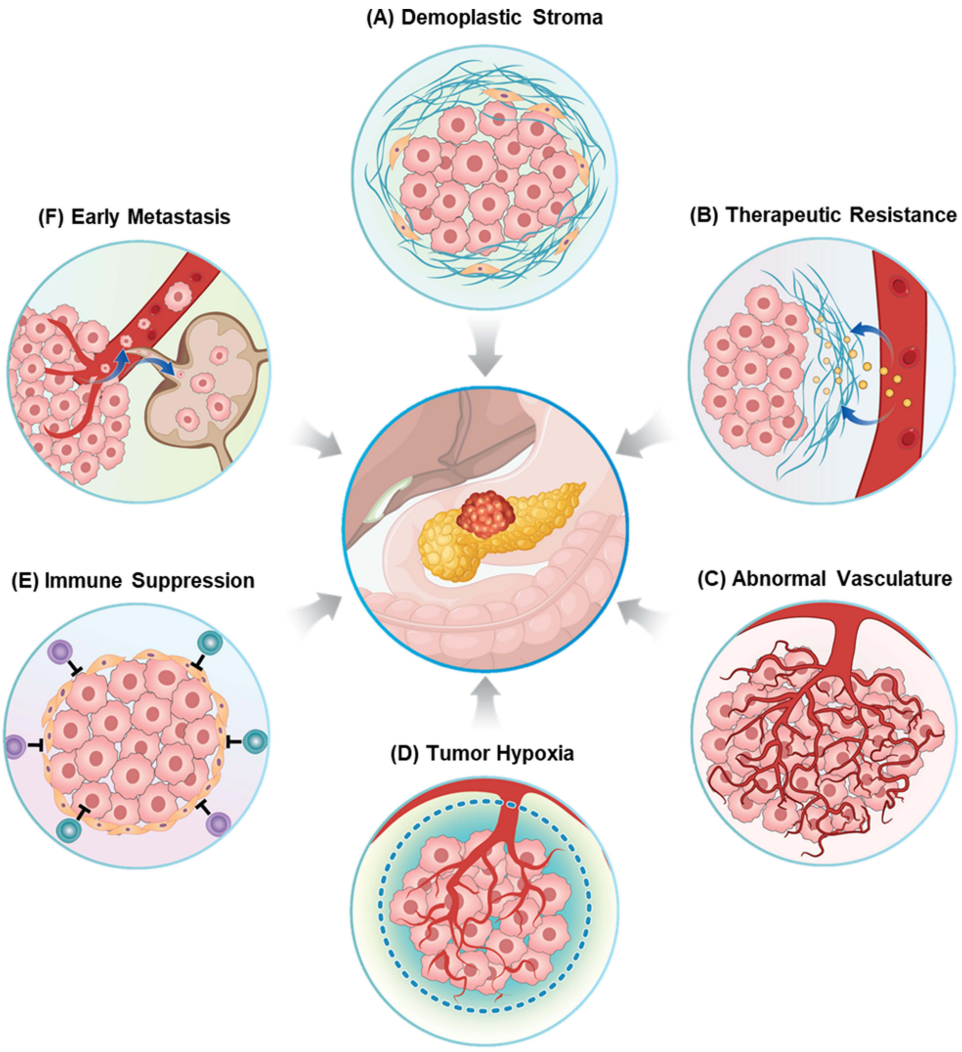

Figure 1 Pathophysiological features of the pancreatic tumor microenvironment Illustration of key tumor microenvironmental traits driving PDAC progression and treatment resistance. (**A**) Dense desmoplastic stroma impedes drug delivery. (**B**) Abnormal vasculature limits oxygen supply. (**C**) Hypoxic regions promote chemo/radioresistance. (**D**) Immune suppression inhibits anti-tumor responses. (**E**) Hypoxia-driven EMT facilitates early metastasis. (**F**) Combined features confer resistance to conventional therapies. These barriers highlight the therapeutic relevance of hypoxia-responsive nanoparticles.

ECM, physically encases tumor cells and dramatically influences tumor physiology.[26–28] This dense stroma results in severe vascular dysfunction, compressing blood vessels and impairing normal angiogenesis, yielding a sparse and irregular vasculature that cannot adequately perfuse the tumor.[25] Studies have documented that PDAC lesions have significantly lower microvessel density and blood flow than other malignancies, resulting in chronic nutrient and oxygen deprivation within the tumor core.[29]

Despite these hostile conditions, PDAC cells survive and even thrive by adapting their metabolism to the hypoxic microenvironment. They shift towards glycolytic pathways, increase autophagy, and modulate redox homeostasis to withstand oxidative stress. Moreover, they engage in metabolic crosstalk with stromal cells, including pancreatic stellate cells, to access alternative nutrient sources and enhance their survival.

The remaining blood vessels are often structurally disorganized and highly permeable, leading to a heterogeneous blood supply where pockets of tumor cells receive little to no oxygen. Consequently, PDAC tumors develop regions of intrinsic hypoxia, an oxygen-starved microenvironment driven by inadequate perfusion. This hypoxic state is further exacerbated by the rapid proliferation of tumor cells and metabolically active stromal cells such as activated fibroblasts, which consume oxygen at a high rate, outpacing its delivery.[8,9] The net effect of the desmoplastic stroma is a vicious cycle of vascular insufficiency and oxygen shortage: fibroblast-rich tissue elevates interstitial pressure and collapses vessels, and the ensuing hypoxia in turn promotes pro-fibrotic and pro-angiogenic signals (such as HIF-1α-mediated VEGF expression) that produce aberrant, nonfunctional vessels.[30,31] Collectively, these stromal and vascular abnormalities explain why PDAC is among the most hypoxic solid tumors.

Extracellular Matrix Rigidity and Oxygen Imbalance

In addition to vessel compression, the composition and stiffness of the PDAC extracellular matrix critically contributes to tumor hypoxia. The ECM in pancreatic tumors is exceptionally stiff due to abundant collagen cross-linking and the deposition of molecules such as hyaluronic acid, which imbibe water and increase tissue turgor.[32–34] This elevated matrix rigidity leads to high interstitial fluid pressure, which creates a physical barrier to blood flow and oxygen diffusion.[32,34] Essentially, as the ECM stiffens, it not only squeezes vessels shut, but also limits oxygen penetration into tissues by increasing the diffusion distance and creating a gradient where oxygen is rapidly consumed at the periphery of stromal bundles and cannot reach the tumor core.[10] This leads to a metabolic imbalance, in which oxygen consumption by the tumor and stromal cells vastly exceeds the supply. Even when proangiogenic factors are released under hypoxic conditions, the resulting neovasculature is abnormal and insufficient, failing to relieve the hypoxia.[8,35] Moreover, the fibrotic matrix can sequester growth factors and alter cellular phenotypes, for example, by inducing a more contractile matrix-remodeling phenotype in stellate cells, which perpetuates stiffness and hypoperfusion.[27,36] Recent studies have suggested that modulating ECM components, such as enzymatically degrading hyaluronan or inhibiting collagen cross-linking, can temporarily decompress blood vessels and enhance tumor oxygenation.[37,38] In summary, the desmoplastic reaction and ECM remodeling in PDAC establish a microenvironment with poor vascular function and high tissue tension, resulting in pervasive hypoxia throughout the tumor bed.

Immune Suppression and Early Metastasis

In addition to the structural barriers, the hypoxic microenvironment of PDAC substantially alters the immune landscape, fostering an immunosuppressive state that impedes antitumor immunity. Hypoxia-driven expression of immunomodulatory molecules such as PD-L1, adenosine, and VEGF suppresses the recruitment and cytotoxic function of effector T cells and natural killer (NK) cells, while promoting the accumulation of regulatory T cells, myeloid-derived suppressor cells (MDSCs), and M2-polarized tumor-associated macrophages (TAMs). These suppressive cell populations not only dampen immune surveillance but also secrete growth factors and cytokines (eg, TGF-β, IL-10) that promote stromal remodeling and tumor progression. The net result is an immune-excluded "cold" tumor phenotype that contributes to resistance against immune checkpoint inhibitors and other immunotherapies.[17]

Moreover, hypoxia promotes early metastatic dissemination by inducing EMT, a process whereby epithelial cancer cells lose polarity and adhesion and gain migratory and invasive capabilities.[7] Hypoxia-inducible factors (HIFs), particularly HIF-1α, upregulate transcription factors such as Snail, Twist, and ZEB1, which suppress E-cadherin and

activate mesenchymal gene programs, enabling tumor cells to detach and invade surrounding tissues.[39] Combined with extracellular matrix degradation and vascular abnormalities, this facilitates the intravasation and dissemination of cancer cells even at early stages. Clinical studies have shown that PDAC often exhibits micrometastases at diagnosis, suggesting that metastatic seeding occurs before the primary tumor becomes clinically detectable.[40] This aggressive trait is strongly associated with a hypoxic and fibrotic tumor milieu.

Taken together, immune suppression and early metastasis are critical hypoxia-driven mechanisms that worsen the prognosis and limit therapeutic success in PDAC. These insights further underscore the need for therapies that can modulate the tumor microenvironment, reverse immune exclusion, and inhibit early dissemination.

Hypoxia-Mediated Barriers to Drug Delivery

Impaired Perfusion and Physical Exclusion

Most systemic chemotherapies rely on adequate blood flow to reach tumor cells; however, in hypoxic pancreatic tumors, perfusion is patchy and often insufficient.[41,42] The compressed and collapsed vasculature reduces the intratumoral concentration of drugs, such as gemcitabine, as much of the administered dose never effectively penetrates the tumor mass.[43]

Stromal barriers that contribute to hypoxia hinder effective drug distribution. The extensive extracellular matrix forms a dense meshwork that impedes the convection and diffusion of therapeutic molecules, particularly large compounds and NPs, effectively excluding them from hypoxic tumor regions.[32] For example, dense collagen bundles and hyaluronan-rich zones can slow the transit of drugs, creating a concentration gradient where peripheral tumor areas receive more drug exposure than the poorly perfused, hypoxic interior.[43,44] Owing to this heterogeneity, cells residing in the most hypoxic regions often escape adequate drug exposure because therapeutic agents fail to reach them at sufficient concentrations.

Empirical evidence from PDAC models has shown that the enzymatic ablation of stromal components, such as using PEGylated hyaluronidase to degrade hyaluronic acid, can increase intratumoral vascular perfusion, thereby improving drug uptake in previously inaccessible regions.[45] Conversely, when hypoxia is severe, interstitial fluid pressure remains high and vessels remain nonfunctional; therefore, even diffusible drugs have difficulty penetrating the tumor.

Hypoxia marks and reinforces a physical barrier to therapy; it indicates regions of minimal drug penetration and reflects a microenvironment that shields cancer cells from treatment.[37,43] Thus, the impaired perfusion associated with hypoxia serves as a critical barrier, allowing a fraction of tumor cells to survive the initial chemotherapy owing to insufficient drug penetration.

Hypoxia-Induced Cellular Resistance and Chemo-Therapy Failure

In addition to impeding drug delivery, hypoxia induces cellular adaptations that confer resistance to both chemotherapy and radiotherapy in pancreatic ductal adenocarcinoma (PDAC). Oxygen-deprived cancer cells activate hypoxia-inducible factors (HIFs), particularly HIF-1α, which trigger transcriptional programs enabling survival under low oxygen conditions.[46,47] These adaptive pathways include metabolic reprogramming toward anaerobic glycolysis, angiogenesis, and stress response mechanisms, all of which reduce cellular susceptibility to cytotoxic therapies.[48,49] For instance, hypoxia can drive tumor cells into a quiescent or slow-cycling state, limiting the efficacy of cell cycle-dependent chemotherapeutics.[50] In PDAC, HIF-1α activation has been associated with the upregulation of drug efflux transporters, such as P-glycoprotein and other multidrug resistance pumps, that actively expel chemotherapeutic agents and lower intracellular drug accumulation.[47] In addition, hypoxia promotes autophagy as a survival mechanism, which has been implicated in gemcitabine resistance by enabling tumor cells to recycle nutrients and maintain energy homeostasis.[51] Collectively, these adaptations explain why hypoxic PDAC tumors often show poor response rates to standard chemotherapies such as gemcitabine-based regimens and FOLFIRINOX.[52,53] Clinical studies have demonstrated that patients with highly hypoxic PDAC exhibit shorter progression-free survival intervals, highlighting the prognostic impact of hypoxia.[54,55]

Radiotherapy is also compromised by tumor hypoxia. Radiation-induced DNA damage relies on oxygen to generate free radicals that stabilize DNA breaks.[56,57] In hypoxic regions, reduced oxygen availability results in fewer free radicals and diminished DNA damage, such that PDAC cells can tolerate significantly higher radiation doses than well-oxygenated cells—doses often not feasible due to normal tissue toxicity limits.[58] As a consequence, radiotherapy in pancreatic cancer has historically achieved only marginal improvements in local tumor control, even with advanced modalities such as stereotactic

body radiotherapy. In summary, hypoxia not only conceals tumor cells behind a barrier of poor perfusion but also fortifies them biologically, enabling a dual mode of therapeutic evasion.[59,60] These clinical limitations underscore how the hypoxic microenvironment conceals tumor cells from drug penetration while simultaneously fortifying them biologically, creating a dual barrier to therapeutic efficacy. Together, these mechanisms contribute to the persistently poor outcomes observed in PDAC, where the five-year survival rate remains in the single digits despite aggressive multimodal treatment.[61–63]

Prognostic Biomarkers and Need for Targeted Strategies

Tumor hypoxia not only hinders real-time therapy but also functions as a prognostic marker of pancreatic cancer aggressiveness. Hypoxic biomarkers, such as HIF-1α overexpression or elevated levels of carbonic anhydrase IX (CAIX, a hypoxia-regulated enzyme), have been associated with poor survival in PDAC patients.[64] Likewise, gene expression signatures reflecting hypoxic stress correlate with higher rates of metastasis and treatment failure, suggesting that measuring tumor hypoxia could inform prognosis and guide therapy selection.[65] Recognizing the central role of hypoxia and stromal barriers in PDAC, researchers have actively explored targeted strategies to mitigate these effects. One such approach is microenvironment normalization, that uses agents to decompress blood vessels and increase perfusion. A notable strategy tested in clinical trials involved pegylated hyaluronidase (PEGPH20) to degrade hyaluronan in PDAC, which in a Phase II study, improved drug delivery and progression-free survival in patients with high stromal hyaluronan levels.[66,67] While subsequent trials showed inconsistent efficacy, this line of research supports the rationale that alleviating physical barriers can enhance the clinical response. Another approach is to exploit hypoxia using hypoxia-activated prodrugs, which are activated into toxic agents under low-oxygen conditions. One such agent, evofosfamide (TH-302), showed promise in early phase trials by selectively killing hypoxic PDAC cells when added to chemotherapy, although Phase III results were inconclusive.[67] Additionally, the direct targeting of hypoxia signaling pathways is under investigation. Inhibition of HIF-1α or downstream effectors (for instance, using acriflavine or other HIF inhibitors) has demonstrated the potential to sensitize pancreatic tumors to chemotherapy in preclinical models by reversing hypoxia-induced resistance programs.[68,69] There is also a growing interest in repurposing drugs such as angiotensin inhibitors or modulators of nitric oxide to "normalize" tumor vessels and oxygenation (an approach pioneered in other solid tumors) for pancreatic cancer.[70,71] In summary, the clinical message is clear: hypoxia is a key driver of therapeutic failure in PDAC, and overcoming it may be key to significantly improving outcomes. While conventional therapies are limited by the biological and physical barriers imposed by hypoxia, emerging strategies targeting the hypoxic tumor microenvironment or using hypoxia for treatment represent promising avenues. Ongoing clinical trials and research efforts are focused on integrating such strategies with standard treatments, with the goal of dismantling hypoxia-driven resistance, which has long hindered progress in pancreatic cancer treatment.

Overview of Hypoxia-Targeted NPs as a Therapeutic Strategy

The TME of PDAC is characterized by dense stroma and pronounced hypoxia, making it a particularly challenging therapeutic target. Hypoxia, defined as regions of low oxygen tension, occurs in over 50% of solid tumors due to abnormal, leaky vasculature and rapid tumor growth.[72] In healthy tissues, the partial pressure of oxygen is approximately 40–60 mmHg, whereas in tumors, it often falls below 10 mmHg.[9] PDAC is among the most hypoxic cancers, with some tumor regions measuring < 3 mmHg O_2 (over 10-fold lower than normal tissue).[73] Such oxygen deprivation contributes to aggressive tumor behavior, therapeutic resistance, and poor patient outcomes.[72,73] Consequently, strategies that specifically target the hypoxic tumor microenvironment have gained increasing interest as a means of improving PDAC treatment.[25] One promising approach is the use of hypoxia-targeted NP drug delivery systems engineered to sense and respond to low-oxygen conditions in tumors. In addition to conventional engineering approaches, recent advances in artificial intelligence (AI) are expected to play an increasingly crucial role in optimizing nanoparticle design and overcoming current limitations, thereby complementing the strategies discussed in this section.

This section provides an overview of the mechanisms by which these hypoxia-responsive NP systems operate, how they release drugs under hypoxic conditions, the common materials and structures used in their construction, and a classification of targeting strategies (passive vs active) and stimulus triggers (endogenous vs exogenous). Each subsection highlights recent PDAC-specific examples to illustrate design principles and their clinical relevance.

General Mechanisms of Hypoxia-Responsive NP Systems

Hypoxia-responsive NP systems are designed with built-in triggers that undergo chemical or structural changes in low-oxygen environments, thereby conferring selectivity to hypoxic tumors. The general design principles, representative chemical strategies, and nanocarrier structures of hypoxia-responsive nanoparticles are summarized in Table 2. This table highlights key oxygen-sensitive groups, bioreductive activation pathways, drug release mechanisms, and different carrier types, providing a concise framework for the detailed examples discussed in the following subsections. Most commonly, these triggers are hypoxia-sensitive moieties and functional groups that are stable under normoxia, but become activated or cleaved in hypoxia.[74] Typical examples include nitroaromatic groups (eg, 2-nitroimidazole derivatives), quinone N-oxides, and azo linkers, all of which can be bioreduced by cellular enzymes that are more active under oxygen-starved conditions.[75] Incorporating such groups into a nanocarrier (for instance, as linkers or caps on a prodrug) renders the entire construct hypoxia-responsive, remains stable under normoxic conditions, and is selectively activated in hypoxic tumor zones.[76]

Hypoxia-responsive NPs achieve targeted drug delivery in hypoxic tumor environments such as those found in PDAC. Following systemic administration, NPs circulate through the bloodstream and accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect. Once inside the tumor microenvironment, low-oxygen conditions trigger structural or chemical changes in the NPs, such as disassembly or cleavage of hypoxia-sensitive linkers, leading to the controlled release of the encapsulated drug. This strategy enables precise drug release in hypoxic regions of the tumor, enhances therapeutic efficacy, and reduces systemic toxicity. The general mechanism of hypoxia-responsive nanoparticle-mediated drug release is schematically illustrated in Figure 2, which depicts systemic administration, tumor accumulation via the EPR effect, hypoxia-triggered transformations, and controlled release of the therapeutic payload within oxygen-deprived tumor regions.

Table 2 Hypoxia-Responsive NP Design: Core Mechanisms, Structures,and Materials

Category	Subcategory	Key concept	Example	Material type	References
General Principle	–	Hypoxia as drug-release trigger	Oxygen-sensitive "switch"	–	–
Chemistry	Hypoxia-sensitive groups	Cleaved only in low O_2	Nitroimidazole, Azo, Quinone	Polymeric, Silica	Khatoon et al 2018[77] Zhu, M.Z. et al 2024[78]
	Bioreductive activation	Enzyme-mediated cleavage	Azoreductase, Nitroreductase	Polymeric	Kulkarni, P et al 2018[79]
	Oxygen reversal	Stability in normoxia	2-nitroimidazole oxidation	Polymeric	Thambi et al 2014[80]
	Irreversible reduction	Release in hypoxia	2-nitroimidazole → 2-aminoimidazole	Polymeric	Zhu, M.Z. et al 2024[78]
	Prodrug activation	Drug becomes active only in hypoxia	BE-43547A2 prodrug	Small-molecule prodrug (non-nano)	Liu et al 2025[81]
Drug Release	Linker cleavage	Hypoxia-labile bond breaks	Covalent bond disruption	Polymeric	Kulkarni, P et al 2018[79]
	Matrix degradation	Carrier breaks in hypoxia	Albumin–azobenzene NP	Protein-based	Yang, G et al 2019[82]
	Structural change	NP disassembles into small units	Dendrimer fragmentation	Polymeric	Hao, Y.C et al,2022[83]

Abbreviation: NP, nanoparticle.

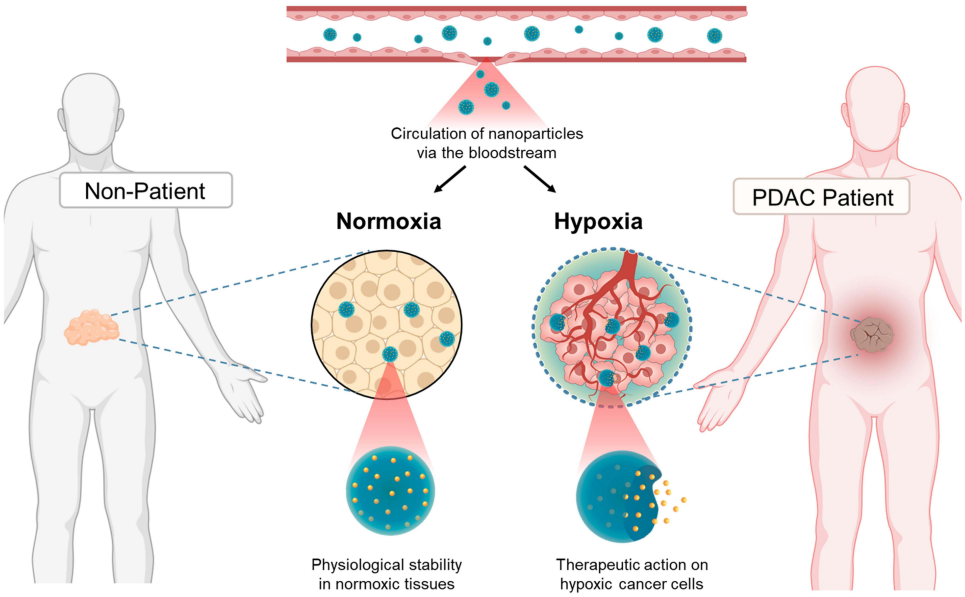

Figure 2 Mechanism underlying hypoxia-responsive nanoparticle-mediated drug release in the tumor microenvironment The process by which hypoxia-responsive nanoparticles (NPs) achieve targeted drug delivery within hypoxic tumor environments, such as those found in PDAC. Following systemic administration, the nanoparticles circulate through the bloodstream and accumulate in the tumor tissue via the enhanced permeability and retention (EPR) effect. Once inside the tumor microenvironment, the low oxygen conditions trigger a structural or chemical change in the nanoparticles—such as disassembly or cleavage of hypoxia-sensitive linkers—leading to the controlled release of the encapsulated drug. This strategy enables precise drug release in hypoxic regions of the tumor, enhancing therapeutic efficacy and reducing systemic toxicity.

Under normoxic conditions, many bioreductive reactions are reversed by oxygen, which prevents premature activation. For example, 2-nitroimidazole residues attached to an NP are enzymatically reduced inside cells; however, in the presence of oxygen, they are re-oxidized back to their initial state, maintaining the nanocarrier stable.[74] However, in hypoxic cells, 2-nitroimidazole is irreversibly converted to 2-aminoimidazole, which breaks the linkage or alters the polarity of the carrier and triggers drug release by disrupting the NP structure.[84] Azo bonds behave similarly; under low oxygen conditions, azo linkers are reduced (often by azoreductase enzymes), causing the bond to cleave, thereby activating the NP or payload.[85] Through such mechanisms, hypoxia serves as an intrinsic "switch" that ensures the nanocarrier deploys its therapeutic cargo predominantly in the targeted oxygen-depleted tissue and not in normoxic healthy tissue.

An emerging hypoxia-responsive strategy employs agents that are inherently cytotoxic only under low-oxygen conditions, effectively triggering the drug itself. One notable example in PDAC involves encapsulating a bioreductively activated cytotoxin (a BE-43547A2 analog) in a sulfonated azocalixarene carrier to create a "dual" hypoxia-responsive supramolecular complex.[73] Azocalixarenes contain azo groups that are cleaved under hypoxic conditions, whereas the prodrug requires reductive activation. This design ensures that the drug is released and becomes fully active only inside the hypoxic PDAC cells. In their study, hypoxia-triggered activation led to selective toxicity in oxygen-deprived pancreatic tumor cells and significantly suppressed tumor growth in vivo with minimal systemic side effects.[73] This illustrates the general mechanism by which hypoxia-targeted NPs achieve spatially selective therapy by harnessing the reductive chemistry unique to hypoxic tumor microenvironments to trigger selective drug release or activation.

Drug Release Mechanisms Under Hypoxic Conditions

Hypoxia-targeted NPs are engineered such that once they accumulate in the tumor, the low-oxygen milieu activates drug release through one or more specific mechanisms. In many designs, the drug is tethered to the NP via a hypoxia-labile linker or encapsulated by a hypoxia-sensitive matrix. Under well-oxygenated conditions, these linkers remain intact (or are continually re-stabilized by O_2), keeping the therapeutic payload securely bound.[86] When the nanoparticle enters a hypoxic region, however, the lack of oxygen allows reductive cleavage of the linker or degradation of the matrix, liberating the drug at the target site.[87] In essence, the sharp contrast in chemical conditions between normoxic blood/tissues and hypoxic tumor zones

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serves as a trigger that unleashes the drug only where needed. This spatial control can greatly increase the drug concentration in hypoxic tumor cores while minimizing premature leakage in circulation or oxygenated normal tissues.[88]

Hypoxia-triggered release can take different forms, depending on the design. In some cases, the covalent bond between the drug (or prodrug) and carrier is broken, directly releasing the active drug molecule. In other cases, the entire NP may undergo a structural change or disassembly, leading to its release. For example, Chen et al[89] developed an aptamer-targeted dendrimer NP for PDAC, in which hypoxia caused the NP to fall apart into ultrasmall fragments, dumping its payload in the process. Under normoxia, this NP (made of a dendritic poly-lysine core) remains large and intact, but upon exposure to the reducing conditions of the hypoxic tumor, it sheds its surface coating and reduces in size, releasing gemcitabine-phosphate payloads in the form of tiny dendrimer pieces.[89] The released sub-50 nm fragments penetrate deeply into the tumor tissue, enabling drug delivery to poorly accessible tumor regions. This hypoxia-triggered burst release and size transformation results in enhanced drug uptake by cancer cells in the oxygen-starved tumor interior and improved therapeutic efficacy in PDAC models.[89]

Another release mechanism involves hypoxia-activated prodrugs carried by NPs. Instead of physically releasing the drug, the drug molecules remain inactive until they experience a hypoxic environment, where they are chemically converted into potent toxic agents. The PDAC-directed complex developed by Guo et al[73] is an example; the NP releases a prodrug of BE-43547A2 inside hypoxic cells, where the prodrug then undergoes bioreduction to its active cytotoxic form. Thus, even if some drugs are released into normoxic tissue, they remain in an innocuous prodrug state, adding a second layer of specificity. Overall, by cleaving a linker, degrading a carrier, or biochemically activating a prodrug, hypoxia-responsive NPs leverage the distinct redox chemistry of hypoxic tumor niches to achieve site-specific drug release. This targeted-release mechanism is critical for achieving high drug concentrations in resistant hypoxic tumor regions, such as PDAC, while sparing healthy tissues from exposure.

Conventional Materials and Structures Used in Hypoxia-Targeted NP Systems

Hypoxia-responsive NPs have been designed using various carrier materials and nanostructures. In practice, any nanocarrier functionalized with hypoxia-sensitive groups can serve as a platform for hypoxia-targeted delivery.[90] Polymeric NPs are especially common; for example, polymer micelles, nanospheres, and dendrimers constructed from biocompatible polymers (such as dextrans, polyesters, and polypeptides) have been equipped with nitroimidazole or azo linkers to create hypoxia-sensitive drug conjugates.[85,91] In a recent PDAC study, a dendrimer-based nanocarrier (built from a dendritic polylysine core) was co-loaded with gemcitabine and a STAT3 inhibitor and decorated with targeting aptamers.[89] This polymeric NP was designed to remain stable in circulation, alter its surface charge, and degrade in size under hypoxic conditions, demonstrating the tunability of polymeric architectures for hypoxia-responsive PDAC therapy.[89]

Lipid-based nanostructures such as liposomes have also been adapted for hypoxia targeting, often by incorporating hypoxia-cleavable lipids or prodrug phospholipids into the bilayer. Upon entering the low-O_2 tumor zone, these liposomes destabilize and release their drug load. Protein-based NPs are another important class of NPs; for instance, albumin has been used as a carrier for hypoxia-responsive delivery. Yao et al (2025) reported an albumin-based supramolecular NP modified with azobenzene groups that co-delivered a drug pair and released it selectively in hypoxic tumors.[72] In this system, the albumin scaffold provides biocompatibility and a long circulation time, whereas the azobenzene cross-linkers in the matrix are cleaved under hypoxia to unload the therapeutic cargo.[72] These albumin–azo constructs illustrate the versatility of natural macromolecules in hypoxia-targeted nanomedicine.

In addition to conventional carriers, researchers have explored hybrid supramolecular structures for hypoxia-responsive delivery. Hybrid lipid–polymer NPs combine the stability of polymer cores with the biomimicry of a lipid shell and have been formulated with hypoxia-sensitive elements for multimodal therapy (eg, chemo-phototherapy combinations).[92] Host–guest supramolecular assemblies have also been employed; for example, azobenzene-functionalized calixarene macrocycles have served as hosts to encapsulate hydrophobic prodrugs, forming NPs that disassemble under hypoxic conditions.[73] In PDAC models, a sulfonated azocalixarene carrying a BE-43547A2 prodrug remained stable in the blood, but released the drug inside cancer cells, leveraging both host–guest chemistry and azo bond sensitivity to target hypoxia.[73]

Classification by Targeting Strategy and Trigger Type

Hypoxia-targeted NPs can be delivered to tumors either by passive accumulation or active targeting prior to hypoxia-triggered drug release. Likewise, hypoxia-responsive systems can be classified by their trigger type as endogenous (eg, hypoxia, pH, enzymes) or exogenous (eg, light, ultrasound, magnetic fields). Figure 3, schematically summarizes these classifications, providing a conceptual overview that frames the specific examples described in the following subsections.

Passive Targeting

Passive targeting relies on the natural propensity of NPs to accumulate in tumor tissue via the EPR effect; leaky tumor vasculature and poor lymphatic drainage allow nanoscale carriers to concentrate in tumors over time.[11,93] This approach does not require any special homing ligands. The NPs simply circulate and gradually extravasate into the tumor, including its hypoxic regions, driven by the abnormal anatomy of the tumor and compromised physiology. Many first-generation nanomedicines (eg, albumin-bound paclitaxel or liposomal irinotecan) function through passive targeting. Hypoxia-responsive NPs can passively reach the tumor and be activated in situ. However, in PDAC, passive delivery often proves inadequate owing to the dense stromal architecture and highly irregular perfusion, which hinders uniform NP distribution.

Active Targeting

Active targeting strategies have been employed to improve NP delivery to tumors and specific cell populations. Active targeting typically involves functionalizing the NP surface with a ligand (such as an antibody, peptide, or aptamer) that binds to a receptor overexpressed on cancer cells or in the tumor microenvironment. In the context of hypoxia-targeted systems, active targeting can enhance the accumulation of therapeutic payloads before hypoxia-triggered release. For example, Chen et al used an aptamer-decorated NP that recognizes a PDAC-associated surface marker, thereby improving the uptake of NPs by pancreatic tumor cells and stroma.[73] Once actively delivered to the tumor, the NP's built-in hypoxia sensor (in this case, a degradable coating) then kicks in to release the drugs intracellularly. Other ligands for active targeting include antibodies against hypoxia-inducible factors, surface proteins overexpressed under hypoxia, or

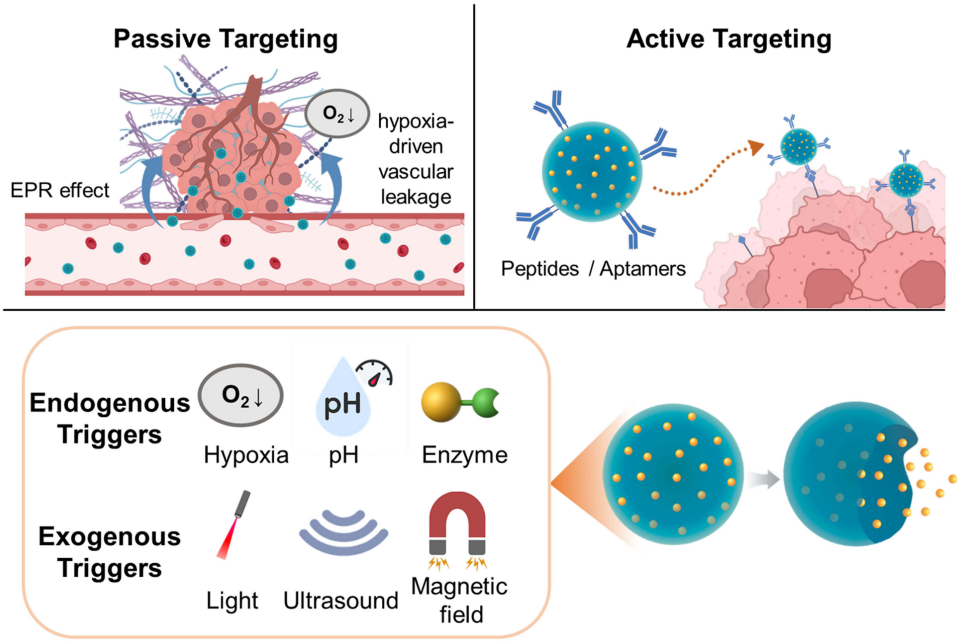

Figure 3 Classification of hypoxia-targeted nanoparticle strategies Schematic illustration summarizing the classification of delivery strategies and trigger types for hypoxia-responsive nanoparticles. Delivery can occur through passive targeting via the enhanced permeability and retention (EPR) effect, or active targeting using surface-functionalized ligands (eg, antibodies, peptides) that recognize tumor-associated markers. Therapeutic release is further controlled by endogenous triggers (eg, hypoxia, acidic pH, redox potential, enzyme activity) or exogenous triggers (eg, light, ultrasound, magnetic field). Together, these classifications provide a conceptual framework for the rational design of hypoxia-targeted nanomedicines in pancreatic cancer.

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small molecules like 2-nitroimidazole itself—which, after reduction, can covalently bind intracellular macromolecules in hypoxic cells, "trapping" the carrier in those cells. The combination of active targeting with a hypoxia-responsive trigger can yield a highly selective delivery system; the active ligand guides the NP to the vicinity of the tumor, and the hypoxia trigger ensures activation only in the poorly oxygenated tumor core. This two-tier targeting approach has been validated by aptamer-functionalized NPs in PDAC, which demonstrated enhanced tumor accumulation and hypoxia-triggered drug release.[73] In summary, passive targeting leverages tumor physiology (EPR effect) to accumulate NPs in hypoxic regions, whereas active targeting uses molecular recognition to home in on tumors, which can be combined with hypoxia-sensitive release mechanisms for greater precision.

Trigger Type (Endogenous Vs Exogenous)

Stimuli-responsive nanomedicines can be broadly classified based on the origin of the triggering stimulus: endogenous, arising from the tumor microenvironment, or exogenous, applied externally.[74] Hypoxia is an endogenous trigger, which is a naturally occurring condition within the tumor that the NPs can exploit. Other endogenous triggers used in drug delivery include low pH (acidity), high levels of glutathione or reactive oxygen species, and enzymes overexpressed in the tumor; in each case, the NP is engineered to sense a biochemical cue present in the cancer milieu.[94] Endogenous triggers have the advantage of automatic activation: the NP releases the drug as soon as it encounters the right environment, without requiring any external action. Hypoxia-responsive systems fall into this category, activating deep in the tumor, where direct external intervention might be difficult. The previous sections focused on internally triggered designs.

In contrast, exogenous triggers are stimuli deliberately applied from outside the patient to activate the NP after it reaches the tumor. Examples include light (eg, UV or infrared laser), ultrasound, magnetic fields, and heat applied externally.[88] NPs responsive to exogenous triggers typically contain components such as photosensitizers, thermosensitive polymers, or magnetic cores that respond when an external stimulus is administered, allowing a high degree of temporal control over drug release. Importantly, exogenous and endogenous triggering mechanisms can be combined to achieve synergistic effects. A pertinent example is the work of Yao et al[72] who developed a hypoxia-responsive albumin NP that also carried a photosensitizer for laser-activated phototherapy. In their design, the NP accumulates in the tumor and releases autophagy inhibitor drugs under hypoxic conditions, while a light stimulus is applied to activate the photosensitizer component—which was engineered to generate tumor-killing reactive oxygen species independent of oxygen.[72] This dual-trigger approach tackles the hypoxic tumor on two fronts: the endogenous hypoxia trigger releases one drug, and the exogenous light trigger activates another, overcoming the limitations of each single stimulus. Such multi-modal systems illustrate the creative strategies being explored to improve PDAC outcomes (detailed discussions of multiple stimuli and advanced targeting designs are provided in the next section).

In summary, hypoxia-targeted NPs can be categorized by how they reach the tumor via passive accumulation or active ligand-mediated targeting, and by how they are triggered by the tumor microenvironment or external stimuli. The key takeaway is that hypoxia, as an endogenous trigger, offers a powerful route for tumor-specific drug delivery, especially in hypoxia-prevalent cancers such as PDAC, and it can be augmented with active targeting and/or external triggers to further refine the delivery profile. Building on this conceptual foundation, the next section delves into specific design strategies for hypoxia-responsive NPs in pancreatic cancer, examining how these principles are implemented in the current research.

Each of the above strategies offers distinct advantages, and hybrid approaches are common in practice. Therefore, the design of hypoxia-targeted NPs is a multidisciplinary balancing act that integrates tumor biology (oxygen levels and expression of targetable markers) with smart chemistry (stimuli-responsive linkers/materials) and nanotechnology (optimal size, surface, and payload properties).

Strategies for Hypoxia-Responsive NPs in Pancreatic Cancer

PDAC is characterized by a profoundly hypoxic TME, dense stromal barriers, and poor vascularization, all of which hinder the efficacy of conventional therapies.[25,95] Hypoxia-responsive NPs are emerging as a promising solution, engineered to exploit the low-oxygen conditions of PDAC for site-specific drug delivery, improved penetration, and reduced off-target toxicity.[25] This section reviews the major design strategies for such NPs, organized by trigger mechanisms, targeting ligands, structural optimization, and multi-stimuli responsiveness, with a focus on mechanistic

insights, practical examples, and clinical relevance. To provide a visual overview, the four major strategies for designing hypoxia-responsive nanoparticles in pancreatic cancer—trigger mechanisms, targeting ligands, multi-stimuli responsiveness, and physicochemical optimization—are schematically illustrated in Figure 4. This framework sets the stage for the detailed subsections that follow.

Hypoxia-Triggered Drug Release Systems

One of the key strategies for designing hypoxia-responsive NPs for PDAC is the incorporation of oxygen-sensitive drug release mechanisms. These systems exploit the characteristically low oxygen levels of the TME to trigger the selective release of therapeutic agents, thereby maximizing drug accumulation at tumor sites and minimizing systemic toxicity. Central to this approach is the use of hypoxia-sensitive linkers, prodrugs, and structural transformation mechanisms that remain stable in normoxic tissues, but are activated under hypoxic conditions.

Such oxygen-dependent systems can be broadly categorized into four main subtypes: (i) bioreductively cleavable linkers that undergo bond cleavage via enzymatic reduction in hypoxia, (ii) hypoxia-activated prodrugs that release active cytotoxins only after enzymatic conversion, (iii) NPs that undergo physical disassembly under hypoxic conditions to facilitate deep tumor penetration and co-release of payloads, and (iv) matrix degradation mechanisms in which the NP structure itself becomes destabilized under low oxygen tension. The following subsections provide a detailed analysis of each mechanism, including the representative materials and their applications in PDAC models.

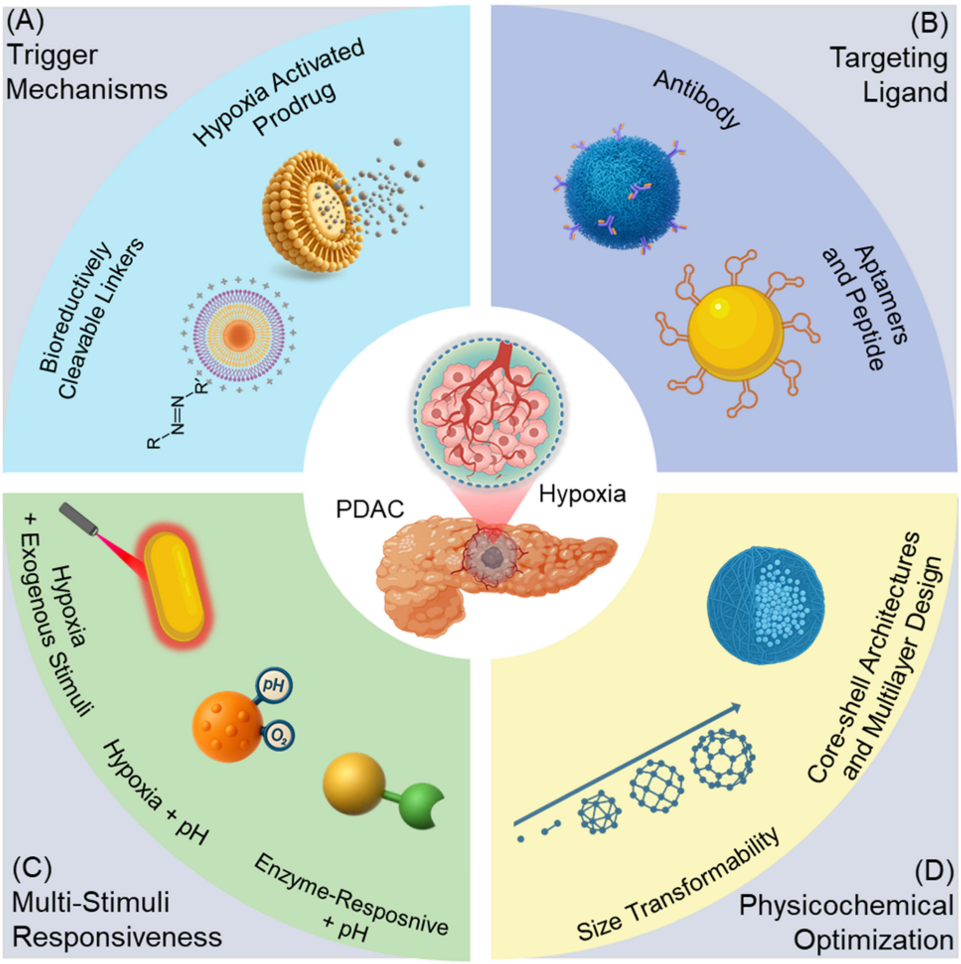

Figure 4 Strategies for hypoxia-responsive nanoparticles in pancreatic cancer therapy. This schematic illustrates four core strategies for designing hypoxia-responsive nanoparticles tailored for PDAC. (**A**) Trigger Mechanisms: Hypoxia-sensitive groups (e.g., azo, nitroimidazole) and prodrugs enable localized drug release under low oxygen. (**B**) Targeting Ligands: Ligands like antibodies, peptides, or aptamers enhance tumor selectivity and cellular uptake in hypoxic PDAC. (**C**) Multi-Stimuli Responsiveness: Integration of hypoxia with other triggers (e.g., acidic pH, enzymes, light) offers precise control of drug release. (**D**) Physicochemical Optimization: Core–shell structures, size shrinkage, and charge switching improve penetration into dense tumor tissue. Together, these strategies enable smart nanoparticle systems to overcome PDAC's hypoxic microenvironment.

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Bioreductively Cleavable Linkers (Eg Azo, Nitroimidazole)

Bioreductively cleavable linkers are chemical bonds, such as azo, nitroaromatic, or quinone groups, that remain stable in oxygen-rich tissues but are selectively cleaved in hypoxic environments due to enzymatic reduction.[86] In normoxic conditions, oxygen serves as an electron acceptor and prevents the reduction of these linkers, keeping the nanocarrier intact as it circulates through healthy tissues. However, when NPs reach hypoxic tumor regions, the lack of oxygen allows reductase enzymes, which are upregulated in these environments, to reduce the linkers (for example, converting azo to aniline or nitro to amine), resulting in the cleavage of the bond and subsequent release of the conjugated drug.[73,86] This mechanism functions as a molecular switch governed by local oxygen levels.

A major advantage of this strategy is that it enables highly selective drug release within hypoxic tumor zones, thereby improving the therapeutic index and minimizing damage to healthy tissues.[25] The chemistry of these linkers is versatile, allowing their integration into a variety of nanocarrier platforms—such as polymers, liposomes, and dendrimers—without significantly compromising their stability in circulation. This approach also makes it feasible to use potent cytotoxic agents that would otherwise be too toxic for systemic administration.

However, the effectiveness of bioreductive linkers is highly dependent on the degree of hypoxia present in the tumor.[96] Regions with only moderate hypoxia may not trigger complete linker cleavage, leaving part of the drug payload inactive and some untreated tumor cells.[97] In addition, the expression of the necessary reductase enzymes can be heterogeneous within tumors, leading to inconsistent drug activation. There is also a risk that normal tissues with physiologically low oxygen levels, such as the bone marrow, could inadvertently activate the linker, causing off-target effects. For example, the nitroimidazole-linked prodrug evofosfamide (TH-302) has shown efficacy in targeting hypoxic regions of PDAC, but its effectiveness is limited to the deepest tumor pockets where drug activation is incomplete;[25] additional strategies, such as inducing acute hypoxia, have been explored to enhance its performance.[97]

HAPs and Enzyme-Mediated Release

HAPs are designed as inactive drug derivatives that become cytotoxic only after enzymatic reduction in low-oxygen environments.[9] These prodrugs exploit hypoxia-induced enzymatic pathways, such as one-electron reductases, to unmask potent drugs specifically within the tumor. When formulated into NPs, HAPs can be delivered more efficiently to tumors, further reducing systemic toxicity.[98] In oxygenated tissues, oxygen inhibits the reduction cascade by re-oxidizing the radical intermediate, thereby preventing prodrug activation and release. In contrast, in hypoxic tumor regions, reduction generates a free radical or an active metabolite that binds to or damages cellular targets. Similarly, enzyme-mediated release strategies take advantage of tumor-associated enzymes, which are often more active under hypoxia, to cleave bonds or degrade NP matrices, thereby releasing the drug payload.[99]

The key benefit of this approach is its ability to selectively kill hypoxic tumor cells, which are often resistant to conventional therapies. As hypoxia is a common feature of many solid tumors, HAP-based NPs can target a broad range of cancers without the need for a unique cell surface receptor. This strategy also complements therapies that are more effective in well-oxygenated tumor regions, helping to overcome tumor heterogeneity.

Nonetheless, there are some limitations. Partial activation of prodrugs at the hypoxic margin can result in drug release into nearby normoxic cells, causing off-target toxicity. Conversely, insufficient activation deep within the tumor core may leave some cancer cells viable. The efficiency of enzymatic activation can also be influenced by tumor metabolism and the availability of reducing equivalents such as NADPH. For instance, the prodrug AQ4N (banoxantrone) is converted to a DNA-binding agent only in hypoxic cells, demonstrating effective hypoxia-selective chemotherapy in PDAC models,[100] but the extent of activation depends on the redox environment of the tumor.[9]

Structural Disassembly Under Hypoxia

Some NPs have been engineered to undergo physical transformations or disassembly, specifically in hypoxic zones. These structural changes, such as core breakdown, shell detachment, and size reduction, are triggered by hypoxia and can release the drug payload and facilitate deeper penetration into the dense stroma of PDAC. For example, micelles crosslinked via hypoxia-labile bonds remain stable during circulation but disassemble into smaller subunits within hypoxic tissue, whereas protein-based NPs stabilized by hypoxia-sensitive crosslinks dissolve under low oxygen.[73,101]

The main advantage of this strategy is that it enables large NPs to break into much smaller fragments (often sub-50 nm) within the tumor, allowing them to penetrate more deeply into the pancreatic cancer tissue. Additionally, this approach allows the co-release of multiple therapeutic agents (such as drugs and siRNA) if they are co-encapsulated, enabling precise combined action in the hypoxic tumor core.

However, achieving strict specificity for hypoxic sites remains challenging. If the disassembly trigger lacks strict hypoxia selectivity, premature fragmentation can occur in circulation or normoxic organs, leading to off-target drug release. Furthermore, controlling the rate and extent of disassembly can be difficult. Once triggered, the process may result in a rapid, uncontrolled burst of drug release. For example, lipid NPs with hypoxia-sensitive components have been shown to destabilize and release gemcitabine specifically in hypoxic PDAC spheroids, improving penetration and efficacy; however, the design must be carefully tuned to avoid premature leakage.[88]

Hypoxia-Targeting Ligands and Surface Functionalization

To enhance the precision of NP delivery to hypoxic regions in PDAC, surface functionalization with hypoxia-targeting ligands has emerged as a critical strategy.[102] This approach leverages molecular markers uniquely overexpressed in hypoxic TME, enabling NPs to actively home in on oxygen-deprived zones rather than relying solely on passive accumulation via the enhanced permeability and retention effect.[103] Three primary ligand classes—aptamers/peptides, monoclonal antibodies (mAbs), and hypoxia-trapping moieties—have shown promise in guiding NPs to hypoxic niches, though each comes with distinct advantages and challenges.[103]

Aptamers and Peptides Targeting Hypoxia-Induced Markers

Aptamers (short DNA/RNA sequences) and tumor-homing peptides are engineered to bind hypoxia-associated proteins such as CAIX and p32, which are upregulated under low-oxygen conditions.[103–105] For example, LyP-1, a cyclic peptide, targets the p32 protein expressed on tumor cells and macrophages in hypoxic regions. By conjugating NPs with LyP-1, researchers achieved selective accumulation in poorly oxygenated tumors, triggering apoptosis in hypoxic cancer cells. Similarly, RNA aptamers specific for CAIX have been used to functionalize nanocarriers, enhancing their targeting efficiency in hypoxic PDAC regions both in vitro and in vivo.[106]

The strength of aptamers and peptides lies in their high molecular specificity, which minimizes off-target effects, while allowing repeated dosing owing to their low immunogenicity.[107] Their small size enables dense surface conjugation, fostering multivalent interactions with target cells. However, these ligands have limitations: hypoxia-induced markers, such as CAIX, are not uniformly expressed across all hypoxic cells, resulting in heterogeneous targeting efficacy.[108] Additionally, peptides and aptamers are susceptible to degradation in vivo and often require chemical modifications (eg, PEGylation) to improve stability. The dense stromal barrier of PDAC further complicates ligand efficacy, as targeted NPs may struggle to penetrate deeply into the hypoxic cores.[109]

Antibody Conjugates Against Hypoxia-Associated Proteins

mAbs offer high-affinity targeting of extracellular hypoxia markers such as CAIX, a clinically validated marker overexpressed in PDAC.[104,110,111] Antibody fragments or nanobodies can reduce size while retaining specificity.[104] For instance, gold nanorods conjugated with anti-CAIX antibodies accumulated preferentially in hypoxic tumor regions, enabling focused photothermal therapy (PTT) upon near-infrared (NIR) laser irradiation.[104] This approach not only localized treatment to resistant hypoxic zones but also synergized with thermal ablation to reduce tumor growth.[104]

The advantages of antibody-based targeting include unparalleled specificity and potential for multifunctionality, which can simultaneously deliver therapeutic payloads and block pro-tumor signaling pathways.[110] However, their large size (~150 kDa) limits penetration beyond the perivascular regions, reducing their efficacy in deeply hypoxic zones.[104] Immunogenicity is another concern because non-humanized antibodies may trigger immune responses or rapid clearance. Furthermore, the complexity and cost of antibody production pose scalability challenges compared with smaller ligands.[110]

Hypoxia-Trapping Moieties (Eg, 2-Nitroimidazole Binding)

A distinctive approach involves "trapping" molecules such as 2-nitroimidazole derivatives, which covalently bind to cellular macromolecules under hypoxia.[97,112,113] For example, pimonidazole analogs attached to polymeric NPs accumulate in hypoxic tumor regions via covalent binding after enzymatic reduction.[112,113] This strategy ensures prolonged drug retention in oxygen-deprived zones, even in the absence of specific antigen expression.[113]

The broad applicability of this method stems from its reliance on hypoxia rather than specific biomarkers, allowing its applicability across various tumor types irrespective of surface marker expression. However, irreversible binding can sequester NPs in poorly perfused regions, limiting their redistribution to other tumor sites.[113] Additionally, normal tissues with physiologically low oxygen levels (eg, bone marrow) may experience off-target trapping, although this risk is mitigated by stricter hypoxia thresholds in tumors.[112]

Physicochemical Optimization for Deep Tumor Penetration

The dense, collagen-rich stroma and poor vascularization of PDAC severely restrict NP penetration beyond the perivascular regions.[114] Hypoxic areas, which are often the most therapy-resistant, typically reside deep within the tumor mass behind the stromal barrier.[114] Therefore, engineering NPs with an optimized size, charge, and architecture is essential for effective delivery to these hypoxic tumor zones.[115]

Size Transformability and Charge Switching

One promising approach is to design NPs that can transform their size or surface charge in response to tumor-specific signals such as hypoxia. Size-transformable NPs are engineered to shrink in situ when they encounter a hypoxic tumor microenvironment.[116] For example, NPs with an initial diameter of 100 nm may break down into fragments smaller than 20 nm under hypoxic conditions, thereby facilitating diffusion through the fibrotic stroma and enhancing penetration into the tumor core.[101,116] This strategy has been demonstrated in systems in which dendrimer clusters, stabilized by hypoxia-cleavable linkers and coated with aptamers, disassemble into ultrasmall dendrimers upon exposure to low oxygen, resulting in deep tumor penetration and improved drug uptake.

Charge switching is an effective strategy. NPs are designed to be neutral or negatively charged during systemic circulation, reducing nonspecific uptake and enhancing systemic circulation time.[117] Upon entering the tumor microenvironment, hypoxia-sensitive polymers can reveal cationic groups (previously masked by nitroimidazole or similar moieties), flipping the surface charge to positive.[101,117] This enhances cellular uptake, as positively charged NPs interact more efficiently with the negatively charged cell membranes of cancer cells.[117] The combination of size reduction and charge reversal under hypoxia leads to improved tissue penetration and enhanced cellular internalization.

The advantages of these approaches include enhanced tumor penetration, improved cellular uptake in hypoxic regions, and reduced off-target interactions during circulation. However, the specificity of the trigger is critical; premature activation in non-tumor hypoxic tissues can lead to off-target effects. Additionally, the complexity of manufacturing such multicomponent systems and the risk of NP aggregation after charge switching present further challenges.

Core–Shell Architectures and Multilayer Design

Core–shell NPs consist of an inner core and an outer shell, each designed for specific synergistic functions.[101,118] In hypoxia-responsive designs, the shell may be programmed to degrade in the tumor microenvironment, exposing a drug-loaded core. Alternatively, the shell can be loaded with a stromal modulator, whereas the core contains the main cytotoxic drug, enabling codelivery and multistage therapeutic action.[118]

This design facilitated sequential delivery and effectively overcame multiple biological barriers.[118] For example, the outer shell may provide stability and stealth during circulation and may be removed in response to tumor-specific stimuli (such as pH, enzymes, or hypoxia), whereas the inner core is activated for drug release specifically within the tumor. Additionally, the modular nature of this design allows for multidrug loading, supporting combination therapies while enhancing NP stability and circulation time.

Despite these advantages, core–shell and multilayer NPs are more complex to fabricate, and there is a risk of interference between layers that could hinder the responsiveness of the core.[118] Additionally, the increased size resulting

from multiple layers may limit deep tumor penetration, especially in the dense stroma characteristic of PDAC.[118] To better illustrate how this design is applied in practice, the following example demonstrates a core–shell system tailored for PDAC.

An illustrative example is the dendrimer-based NP system reported by Chen et al, which incorporates a core loaded with gemcitabine, a STAT3 inhibitor (a molecule that inhibits the Signal Transducer and Activator of Transcription 3 involved in cancer cell growth and survival), and a PEGylated aptamer shell targeting a PDAC marker.[117] The aptamer shell is hypoxia-responsive and detaches in low oxygen, exposing the core for combined cancer and stromal cell targeting.[117] This design successfully addresses the challenges of targeting, deep penetration, and multi-modal therapy within the PDAC microenvironment.

In summary, physicochemical optimization, including size transformability, charge switching, and core–shell architecture, plays a crucial role in overcoming the stromal and hypoxic barriers of PDAC. These strategies significantly enhance drug delivery to the most resistant regions of pancreatic tumors by enabling the NPs to adapt their properties to the tumor microenvironment.

Dual- or Multi-Responsive NPs

The complex and heterogeneous TME of PDAC necessitates NP designs that respond to multiple stimuli, enhancing specificity and therapeutic precision.[118] Dual- or multi-responsive NPs integrate "AND" or "OR" logic gate mechanisms, enabling drug release only when multiple tumor-specific stimuli are simultaneously or independently present, minimizing off-target effects and addressing PDAC's unique challenges.[101] In the following sections, we explore three key combinatorial strategies: hypoxia paired with pH, enzymatic activity, or external stimuli.[118]

Hypoxia + pH-Responsive NPs

Hypoxic regions in PDAC are often acidic due to glycolytic metabolism, creating a dual trigger (low O_2 and pH <6.8) for selective drug release. For example, nitroimidazole-modified chitosan NPs carrying doxorubicin remain stable under normoxic and neutral conditions, but respond and release their payload in acidic hypoxic environments.[101] This dual gating ensures drug activation only when both conditions coexist, sparing normal tissues. In PDAC models, such NPs achieved a 90% release under hypoxia/pH 6.5, compared to less than 20% under physiological conditions, reducing tumor growth by 75% compared to single-trigger systems.[118] The synergy between acidosis and hypoxia—hallmarks of aggressive PDAC—enables NPs to exploit two pathological features simultaneously. However, the precise tuning of trigger sensitivity is essential to prevent premature activation in mildly acidic or moderately hypoxic tissues.[118]

Hypoxia + Enzyme-Responsive Systems

Tumor-associated enzymes such as matrix metalloproteinase-2 (MMP-2) and hyaluronidase are frequently overexpressed in the stromal compartment of PDAC, offering a basis for sequential NP activation. A representative platform employs a lipid–polymer hybrid NP comprising an MMP-2-cleavable polyethylene glycol (PEG) shell and a nitroimidazole-functionalized core.[101] In enzyme-rich tumor peripheries, MMP-2-mediated degradation of the PEG shell reduces the NP size, facilitating deeper stromal penetration. Once in the hypoxic tumor interior, the nitroimidazole moieties undergo enzymatic bioreduction, triggering site-specific drug release. In PDAC xenograft models, this dual-responsive system achieved approximately 85% tumor growth inhibition—exceeding the efficacy of single-trigger controls by nearly 40%. However, key challenges include the risk of unintended activation by off-target enzymes in inflamed tissues, and the inherent complexity of synchronizing dual stimuli for spatially and temporally precise release.

Hypoxia + Exogenous Stimuli

External stimuli, such as NIR light or ultrasound, provide precise spatiotemporal control over the activation of hypoxia-sensitive NPs.[119,120] Gold nanorods coated with hypoxia-responsive azocalixarene undergo reductive cleavage under low-oxygen conditions, thereby exposing the chemotherapeutic agent camptothecin. Subsequent NIR irradiation induces the release of the exposed drug, ensuring spatially controlled activation exclusively within hypoxic tumor regions.[119,120] In preclinical PDAC models, this dual-trigger system achieved approximately a 60% reduction in tumor volume, demonstrating the synergistic efficacy of combining hypoxia-activated chemotherapy with photothermal ablation. In

a similar dual-trigger approach, ultrasound-responsive nanobubbles functionalized with CAIX-targeting aptamers preferentially accumulated in hypoxic tumor regions. Upon ultrasound exposure, these nanobubbles undergo cavitation, which transiently disrupts the tumor vasculature, thereby enhancing local drug penetration. Despite offering precise spatiotemporal control, these systems rely on specialized equipment such as lasers and ultrasound probes, necessitating real-time imaging guidance for synchronization. This reliance increases the complexity and cost, posing challenges for clinical translation.[119,120] Table 3 summarizes the key hypoxia-responsive design strategies discussed in this section, including their mechanisms, advantages, limitations, and applications in PDAC.

Table 3 Design Strategies for Hypoxia-Responsive NPs in Pancreatic Cancer

Section	Strategy / Subtype	Mechanism	Advantages	Limitations	Representative Example(s)
Bioreductively Cleavable Linkers (eg azo, nitroimidazole)	Bioreductively Cleavable Linkers	Linkers are stable in normoxia but cleaved by reductase enzymes in hypoxic regions, releasing drug	Highly selective drug release in hypoxic tumor zones; versatile chemistry; allows use of potent drugs	Effectiveness depends on hypoxia severity; enzyme heterogeneity; risk of off-target activation	Evofosfamide (TH-302); nitroimidazole-linked polymers
HAPs and Enzyme-mediated Release	Hypoxia-Activated Prodrugs / Enzyme-Mediated Release	Prodrugs are activated by hypoxia-induced enzymes; enzyme-mediated cleavage releases drug	Selectively kills hypoxic, therapy-resistant cells; broad applicability; complements other therapies	Partial activation at margins; bystander effects; depends on tumor metabolism/ redox	AQ4N (banoxantrone); liposomal HAPs
Structural Disassembly Under Hypoxia	Structural Disassembly Under Hypoxia	NPs physically break down (core/shell/size) in hypoxia, enabling deep penetration and drug release	Enables large NPs to penetrate deeply as small fragments; allows co-release of multiple agents	Specificity is challenging; risk of premature fragmentation; difficult to control release kinetics	Dendrimer clusters; hypoxia-sensitive lipid NPs
Aptamers and Peptides Targeting Hypoxia-induced Markers	Aptamers & Peptides Targeting Hypoxia Markers	Surface functionalization with aptamers/peptides that bind hypoxia-induced proteins (eg CAIX, p32)	High molecular specificity; low immunogenicity; flexible, multivalent design	Target heterogeneity; in vivo stability; limited penetration in dense stroma	CAIX RNA aptamer NPs; LyP-1 peptide-conjugated NPs
Antibody Conjugates Against Hypoxia-associated Proteins	Antibody Conjugates	Monoclonal antibodies or nanobodies target hypoxia-associated proteins (eg CAIX)	High specificity/affinity; multifunctionality (payload + signal blocking); clinically validated targets	Large size limits penetration; immunogenicity; high cost and complexity	Anti-CAIX antibody-gold nanorods; antibody-conjugated NPs
Hypoxia-trapping Moieties (eg, 2-Nitroimidazole Binding)	Hypoxia-Trapping Moieties	Covalent binding of NPs to cellular macromolecules in hypoxia (eg 2-nitroimidazole derivatives)	Amplified retention in hypoxic regions; broad tumor applicability	Irreversible binding; risk of off-target trapping; requires sufficient reductase activity	Pimonidazole-functionalized polymeric NPs
Size Transformability and Charge Switching	Size Transformability & Charge Switching	NPs shrink in hypoxia or switch from neutral/ negative to positive charge for uptake	Enhanced penetration and uptake; reduced off-target interactions in circulation	Trigger specificity critical; manufacturing complexity; risk of aggregation	Aptamer-sheddable, charge-reversal dendrimer NPs

(*Continued*)

Table 3 (Continued).

Section	Strategy / Subtype	Mechanism	Advantages	Limitations	Representative Example(s)
Core–Shell Architectures and Multilayer Design	Core–Shell Architectures & Multilayer Design	Distinct core and shell for staged release (shell degrades in TME, core releases drug)	Stage-wise delivery; multi-drug loading; enhanced stability and circulation	Complex fabrication; risk of layer interference; increased size may hinder deep penetration	Dendrimer core + PEGylated aptamer shell (Chen et al).
Hypoxia + pH-responsive NPs	Hypoxia + pH Responsive NPs	Dual trigger: both hypoxia and low pH required for drug release	High specificity; minimizes leakage in non-tumor tissues; exploits two tumor hallmarks	Balancing trigger sensitivity; heterogeneous pH gradients; risk of premature release	Nitroimidazole-chitosan/ doxorubicin NPs
Hypoxia + Enzyme-responsive Systems	Hypoxia + Enzyme Responsive NPs	Sequential activation: enzyme-cleavable shell, hypoxia-responsive core	Sequential targeting of stroma and hypoxic core; broad applicability in enzyme-rich tumors	Off-target enzyme activity; complex fabrication; requires tandem trigger alignment	MMP-2-cleavable PEG shell + nitroimidazole core NPs
Hypoxia + Exogenous Stimuli	Hypoxia + Exogenous Stimuli	External triggers (light, ultrasound) plus hypoxia for precise, on-demand release	Spatiotemporal control; high specificity; can address deep and superficial regions	Requires equipment; timing/synchronization challenges; depends on imaging guidance	Gold nanorods with azocalixarene shells; ultrasound-responsive NPs

Abbreviations: CAIX, carbonic anhydrase; HAP, hypoxia activated prodrug; NP, nanoparticle; PEG, polyethylene glycol.

Artificial Intelligence (AI)-Assisted Design and Optimization of Hypoxia-Responsive NPs

Artificial intelligence (AI) has recently emerged as a transformative tool in nanomedicine. By leveraging machine learning, generative models, and data-driven simulations, AI can assist in the rational design and optimization of hypoxia-responsive nanoparticles, predict biodistribution, and stratify patients based on hypoxia-related biomarkers. The diverse strategies and representative applications of AI in hypoxia-responsive nanomedicine are summarized in Table 4, including nanoparticle design, hypoxia diagnosis, and theranostic feedback control.

The growing complexity of hypoxia-responsive NP design in PDAC has led to the integration of AI as a transformative tool for both material optimization and personalized applications. Building on previous strategies involving physicochemical engineering, stimuli-responsiveness, and biomarker targeting, AI now contributes to a data-driven approach that enhances

Table 4 AI Strategies for Hypoxia-Responsive NPs

AI Application Area	Method / Model	Purpose / Outcome	Representative Example	Reference
Drug/NP Design	ML-assisted high-throughput	Optimize NP properties (size, charge, composition)	PLGA-PEG optimization	Lin et al, 2022[121]
	Generative models (VAE, GAN)	Design novel hypoxia-labile prodrugs and linkers	Hypoxia-activated agents	Schwaller et al, 2019[122]
	Supervised ML / Digital Twin Simulation	Predict biodistribution, drug release, tumor accumulation	Ferritin nanocages via vessel–NP interaction dataset	Zhao et al, 2024[76]

(*Continued*)

Table 4 (Continued).

AI Application Area	Method / Model	Purpose / Outcome	Representative Example	Reference
Diagnosis and Hypoxia	CNNs on Imaging (MRI/ CT)	Map tumor hypoxia regions with high spatial accuracy	Hypoxia mapping via CNN	Jardim-Perassi et al, 2021[123]
	Radiomics-based ML (hypoxia prediction)	Stratify patients and predict therapy outcomes	CT-radiomics AUC >0.8	Zhou et al, 2024[124]
	Omics-based biomarker mining (ML)	Identify hypoxia biomarkers (CAIX, GLUT1, HIF-1α)	Biomarker selection via ML on transcriptomic data	-
	Theranostic ML classifier (sensors)	Trigger on-demand drug release based on sensor feedback	AI-controlled release from nanosensor arrays	Wang et al, 2023[125]

Abbreviations: AUC, area under curve; CT, computer tomography; CNN, central neural network; CAIX, carbonic anhydrase IX; GAN, generative adversarial networks; ML, machine learning: MRI, magnetic resonance imaging; NP, nanoparticle; VAE, variational autoencoders.

both the efficiency and specificity of NP-based therapies. This section delineates the dual roles of AI across two stages: (1) drug/NP prediction and design, and (2) Disease Diagnosis and Target Identification. Collectively, these applications offer a cohesive AI-guided framework for developing hypoxia-targeted nanosystems tailored to the PDAC tumor microenvironment. Representative applications of AI in this context are schematically illustrated in Figure 5, encompassing machine learning-based nanoparticle design optimization, digital twin simulations, medical imaging with CNNs for hypoxia mapping, omics-driven biomarker discovery, and theranostic feedback loops for real-time drug release.

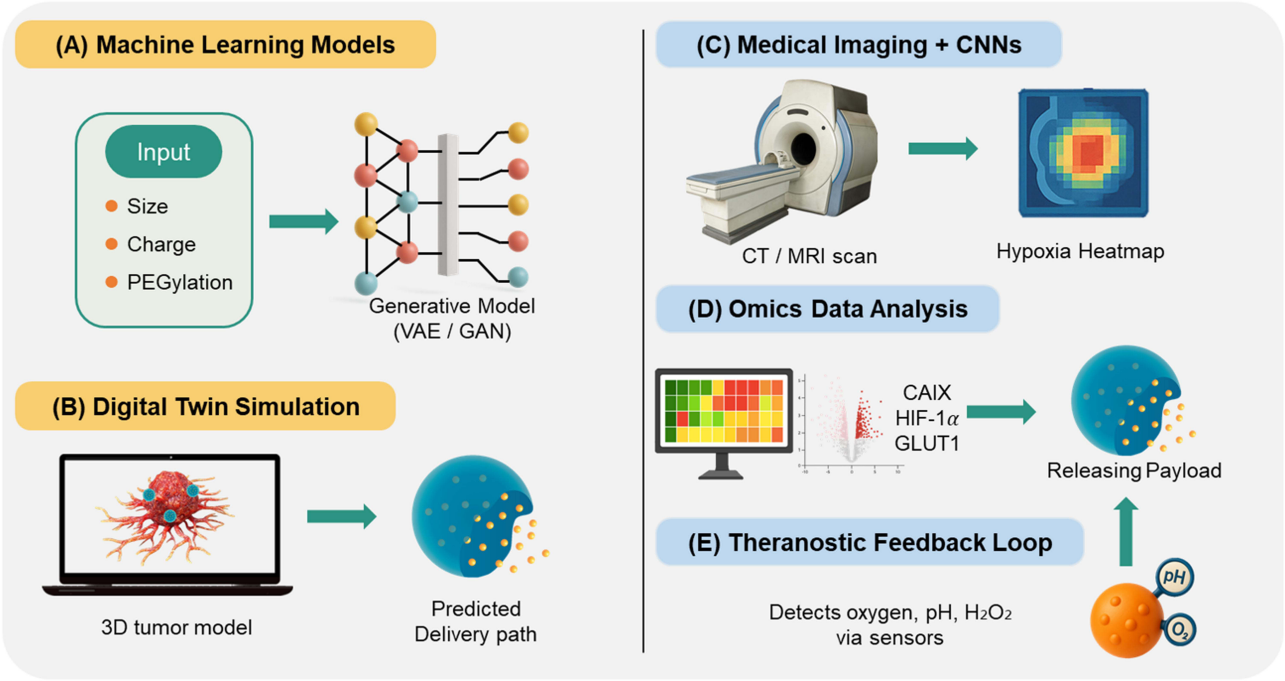

Figure 5 AI model applications for the development of hypoxia-targeted nanoparticles (**A**) Machine learning models optimize nanoparticle design via generative modeling. (**B**) Digital twin simulations predict delivery paths in virtual tumor models. (**C**) CNNs analyze medical imaging to map tumor hypoxia. (**D**) Omics data mining identifies key biomarkers for targeting. (**E**) Theranostic feedback loops enable real-time drug release based on sensor-detected microenvironmental changes.

AI for Drug and NP Design

Designing hypoxia-responsive nanosystems involves balancing multiple structural and functional parameters such as size, surface charge, composition, and responsiveness to low oxygen levels. Traditional trial-and-error approaches are increasingly being replaced by machine-learning (ML) models capable of identifying optimal formulations. For instance, ML-assisted high-throughput screening enabled the discovery of PLGA-PEG NPs with enhanced cellular uptake, achieving an approximately 15-fold improvement in efficacy after two cycles of optimization.[121] Deep learning models trained on NP properties and outcomes further facilitate the prediction of drug release kinetics, biodistribution, and tumor accumulation efficiency. These computational tools accelerate the identification of lead candidates and reduce reliance on costly and time-intensive in vivo testing.

In hypoxia-targeted drug design, generative models such as variational autoencoders (VAEs) and generative adversarial networks (GANs) are employed to create novel oxygen-labile prodrugs. These models can optimize structural features such as redox potential, cleavability, or enzymatic activation, thereby expanding the chemical space of hypoxia-activated agents (Schwaller et al, 2020). Using retrosynthetic analysis and molecular property prediction, AI can also propose novel linker chemistries that selectively degrade under hypoxic conditions, thereby improving payload release specificity. Similarly, NP structural components, such as PEGylation density, core–shell architecture, and hydrophobic/hydrophilic balance, can be tuned via reinforcement learning or gradient-boosted trees trained on formulation-performance datasets.

Beyond conceptual generation, supervised ML algorithms can help refine NP properties for specific tumor profiles. For example, in a study analyzing over 67,000 vessel–NP interactions across PDAC models, AI-guided analysis led to the rational design of ferritin nanocages with superior stromal penetration.[76] These models can reveal nonlinear relationships between structural features and biological outcomes that are difficult to detect manually. In addition, digital twin platforms that simulate the in vivo behavior of NPs under different tumor microenvironment conditions are emerging. These simulations allow the virtual testing of various formulations and can guide experimental prioritization.

AI for Disease Diagnosis and Hypoxia Targeting

Although AI enhances NP design, its impact on diagnostic accuracy and therapeutic targeting is equally transformative. Hypoxia within PDAC is spatially and temporally heterogeneous, making noninvasive and dynamic assessments essential. Convolutional neural networks (CNNs) trained on MRI and histopathological data have been used to map tumor hypoxia, showing a high correlation with actual hypoxic fractions ($r > 0.76$).[123] Similarly, radiomics-based ML models using CT data can predict hypoxia with AUC values above 0.8, facilitating patient stratification, outcome prediction, and therapy selection.[106] These tools also support the identification of radiographic features that correlate with oxygen deprivation, and can serve as surrogate endpoints in clinical trials.

At the molecular level, ML models analyzing transcriptomic and proteomic datasets have helped identify key hypoxia biomarkers such as CAIX, GLUT1, and HIF-1α. These findings inform the selection of targeting ligands for NP functionalization and determine patient eligibility for hypoxia-targeted treatments. Feature selection algorithms and clustering approaches can also classify patients into hypoxic and normoxic subtypes, which are critical for personalized therapy. High-throughput in vivo screening using barcoded NP libraries combined with unsupervised learning algorithms enable the identification of lipid or polymer formulations that preferentially accumulate in hypoxic tumors.[126]

Emerging theranostic systems integrate AI with nanosensor arrays embedded in NP platforms. These arrays generate complex signal profiles when exposed to the tumor microenvironment, capturing fluctuations in redox potential, pH, enzymatic activity, and oxygen levels. ML classifiers trained on such multidimensional data can detect hypoxia-related metabolic changes in real-time and potentially trigger on-demand drug release. Integrating these technologies allows for the dynamic adaptation of therapeutic regimens based on tumor evolution and response, embodying the concept of closed-loop precision nanomedicine.[125]

In summary, AI bridges the gap between material design and clinical translation by enabling intelligent prediction, adaptive design, and the precise deployment of hypoxia-targeted nanotherapeutics in PDAC. AI provides a robust foundation for the rational development of next-generation nanomedicines by leveraging multiomics data, imaging modalities, and computational simulations. As experimental and computational datasets continue to grow, the synergy between nanotechnology and AI is expected to unlock new frontiers for the treatment of hypoxia-driven malignancies.

Preclinical and Clinical Perspectives of Hypoxia-Targeted NPs in Pancreatic Cancer

In recent years, hypoxia-responsive NP systems for PDAC have made significant progress, transitioning from early stage laboratory investigations to preclinical validation and early clinical evaluation. This section examines the efficacy of these innovative approaches in animal models and explores their clinical translation potential along with the challenges that must be addressed to realize their full therapeutic potential.

Representative preclinical and clinical studies of hypoxia-targeted nanoparticle systems in pancreatic cancer are summarized in Table 5. The table outlines key nanoplatform categories, mechanisms, preclinical efficacy, clinical status, and major challenges, providing a concise framework for the detailed discussion that follows. Despite these encouraging preclinical outcomes, translating hypoxia-responsive nanoparticles into clinical success remains highly challenging. Major barriers include the limited efficacy of TH-302 in Phase III trials, tumor heterogeneity, dense stromal barriers, and unresolved manufacturing and biomarker challenges. Although preclinical studies of hypoxia-targeted agents such as evofosfamide (TH-302)[127] and PEGPH20[67] demonstrated robust tumor growth inhibition and enhanced drug penetration in pancreatic cancer models, these promising results were not reproduced in late-stage clinical trials. Evofosfamide advanced to several phase III trials in combination with gemcitabine or doxorubicin, yet failed to show a survival benefit compared with standard therapy, leading to early termination due to futility. Similarly, PEGPH20, a pegylated hyaluronidase designed to deplete stromal hyaluronan and improve vascular perfusion, showed encouraging results in early-phase studies but did not improve overall survival in the pivotal phase III HALO 301 trial, despite transient gains in progression-free survival. Several factors likely contributed to these outcomes. First, patient stratification was insufficient, as many trials enrolled unselected populations without validated hypoxia or stromal biomarkers to identify responsive subgroups. Second, the absence of robust predictive biomarkers limited the ability to prospectively monitor therapeutic efficacy. Third, dose-limiting toxicities, including myelosuppression and musculoskeletal adverse events, restricted optimal drug exposure and reduced patient compliance. Finally, the pronounced heterogeneity of PDAC tumors—including variable levels of hypoxia, stromal density, and genetic background—further confounded clinical outcomes. Collectively, these challenges underscore the importance of biomarker-guided patient selection, adaptive trial design, and rational combination strategies with standard therapies to improve the translational success of hypoxia-targeted nanodrugs in pancreatic cancer. Beyond biological and translational barriers, regulatory challenges also impede the clinical implementation of hypoxia-responsive nanodrugs. These challenges extend beyond the general requirements for oncology therapeutics and reflect the unique complexities of nanomedicine. First, large-scale Good Manufacturing Practice (GMP)-compliant production of multifunctional nanoparticles is technically demanding, as batch-to-batch reproducibility, stability, and quality control of complex formulations are more difficult to ensure compared to conventional small-molecule drugs. Second, regulatory frameworks for nanomedicines remain evolving and are not yet fully standardized across agencies such as the FDA, EMA, and MFDS. Multifunctional designs that integrate drug delivery, imaging, and theranostic capabilities often do not fit neatly into existing approval categories, creating uncertainty in regulatory evaluation. Third, regulatory approval will increasingly require validated hypoxia-specific biomarkers to stratify patients and prospectively demonstrate clinical benefit, as unselected populations have historically led to inconclusive trial results. In addition, regulatory agencies typically emphasize comprehensive long-term safety evaluations for nanodrugs, including immunogenicity, off-target biodistribution, and potential accumulation in non-tumor tissues, which can delay approval timelines. Finally, clinical trial designs for nanomedicines often face additional scrutiny regarding appropriate endpoints, combination strategies, and comparator arms, given the novelty of these platforms. Addressing these regulatory hurdles—through harmonized international guidelines, biomarker-driven trial designs, and early engagement with regulatory bodies—will be essential for successful translation and eventual commercialization of hypoxia-responsive nanodrugs in oncology. These translational gaps are schematically illustrated in Figure 6, which contrasts the promising preclinical findings with the key obstacles that continue to impede clinical implementation in PDAC.

Preclinical Efficacy in Animal Models

Various hypoxia-targeted NP systems have demonstrated remarkable efficacy in preclinical pancreatic cancer models, providing crucial proof-of-concept evidence to support their potential clinical translation.

Table 5 Preclinical and Clinical Perspectives of Hypoxia-Targeted NPs in Pancreatic Cancer

Category	Strategy/Example	Mechanism/Key Features	Payload	Particle size (nm)	Preclinical Results	Clinical Status	Limitations/ Challenges
Polymeric Nanocarriers	Hypoxia-responsive polymersomesConfeld et al, 2020[25]	Penetrate stroma, destabilize under hypoxia, selective drug release	Doxorubicin / Gemcitabine	~100–150	Tumor growth inhibition by approximately 250% compared with control; intratumoral necrosis increased by about 60%; high uptake and cytotoxicity under hypoxia	Preclinical	Dense stroma barrier; manufacturing complexity
Magnetic NPs	Iron oxide NPsDíaz-Riascos et al, 2025[128]	Hyperthermia via alternating magnetic fields, synergistic with chemotherapy	Iron oxide (carrier) ± chemo	~50–80	Improved drug penetration; significant reduction in tumor volume; strong synergy with chemotherapy in BxPC-3 cells	Early clinical (NoCanTher trial)	Deep tumor penetration; technical limits of hyperthermia
Hypoxia-Activated Prodrugs	TH-302 (evofosfamide) Bailey et al, 2014[129]	Prodrug activated in hypoxia, releases DNA alkylator; efficacy boosted by acute hypoxia induction (hydralazine)	TH-302 (Br-IPM prodrug)	Small molecule	Tumor growth inhibition (MIA PaCa-2 model); "steal" effect enhances hypoxia and drug efficacy	Phase III clinical trials	Tumor hypoxia heterogeneity; incomplete activation in some regions
pH-Responsive NPs	iRGD-modified NPs + ERK inhibitorDutta et al 2024[130]	Release payload in acidic, hypoxic TME; blocks desmoplasia, enhances chemo effect	ERK inhibitor + chemo drug	~120	Synergistic tumor inhibition, prolonged survival in KPC mouse model, reduced stroma	Preclinical	Variable pH in tumors; risk of off-target release
FDA-Approved Nanomedicines	Nab-paclitaxel (Abraxane)Liposomal irinotecan	Albumin-bound or liposomal formulations for improved tumor accumulation and reduced toxicity	Paclitaxel; Irinotecan	~80–130	Improved survival (MPACT trial, nab-paclitaxel + gemcitabine); better efficacy and safety (liposomal IRI)	FDA-approved (1st/2nd line PDAC)	Not hypoxia-specific; limited effect in resistant/ heterogeneous tumors
Clinical Evaluation	TH-302, NoCanTher ThermoTherapy	Hypoxia-activated prodrugs, magnetic hyperthermia	TH-302; Iron oxide	Variable	Encouraging results in various tumor types, including PDAC	Phase I–III clinical trials ongoing	Patient selection; lack of robust hypoxia biomarkers; translation from animal models

Abbreviations: FDA, Federal Drug Administration; NP, nanoparticle; PDAC, pancreatic-ductal adenocarcinoma.

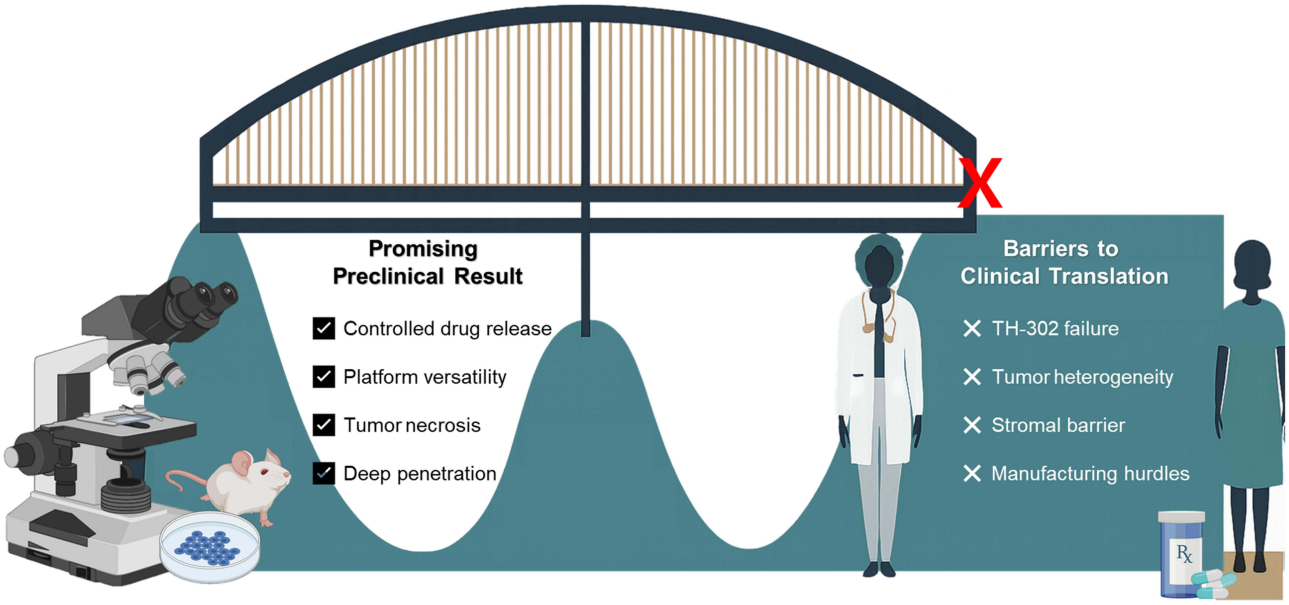

Figure 6 Translational gap between preclinical success and clinical implementation of hypoxia-responsive nanoparticles in PDAC Schematic comparison of promising preclinical outcomes and current barriers to clinical translation of hypoxia-responsive nanoparticles in pancreatic cancer. While preclinical studies show effective tumor necrosis, deep hypoxic penetration, controlled drug release, and platform versatility, clinical progress is limited by TH-302 failure, tumor heterogeneity, stromal barriers, lack of biomarkers, and manufacturing challenges.

Polymeric Nanocarriers

Polymer-based NPs engineered to target hypoxic regions have demonstrated significant therapeutic potential in PDAC models. Confeld et al developed polymersomes capable of penetrating pancreatic tumors, localizing within hypoxic niches, undergoing rapid structural destabilization, and releasing encapsulated drugs. In murine models, these NPs reduced tumor growth by nearly 250% and increased tumor necrosis by 60% compared to untreated controls.[25] In vitro studies further revealed that these polymersomes exhibited high cellular uptake and enhanced cytotoxicity under hypoxic conditions relative to unencapsulated drugs.[25]

The superior efficacy of these polymer-based systems is attributed to their ability to traverse the dense stromal barrier of PDAC, facilitating the direct delivery of therapeutic agents. Their hypoxia-responsive nature enables selective drug release within these challenging regions, thereby minimizing their exposure to healthy tissues.

Magnetic NPs (MNPs) for Hyperthermia

MNPs, designed for hyperthermia therapy, have shown considerable therapeutic promise in PDAC.[128] When subjected to alternating magnetic fields, these MNPs generate localized heat, effectively suppressing tumor progression in preclinical PDAC models. In vivo biodistribution studies revealed the preferential accumulation of MNPs within tumors, particularly in stromal-rich regions.[128]

The combination of chemotherapeutic agents such as gemcitabine and nab-paclitaxel with hyperthermia therapy has resulted in improved drug penetration and markedly reduced tumor volume compared with chemotherapy alone. This synergistic effect is attributed to the hyperthermia-induced disruption of the tumor stroma, which facilitates improved drug delivery to malignant cells.[128] Cell viability assays further confirmed that low-dose chemotherapy combined with hyperthermia exhibits a pronounced synergistic effect, particularly in the BxPC-3 pancreatic cancer cell line.[131]

Hypoxia-Activated Prodrugs and Modified Delivery Approaches

Hypoxia-activated prodrugs have emerged as promising therapeutic agents, and their efficacy has been demonstrated in preclinical models. TH-302 (evofosfamide), an HAP currently in clinical development, has shown efficacy in preclinical PDAC models.[129] Notably, tumor hypoxia can be pharmacologically intensified using vasodilators such as hydralazine

through a mechanism known as the "vascular steal" phenomenon.[129] In this process, the immature tumor vasculature fails to dilate in coordination with normal vessels, leading to decreased tumor blood flow and reduced pH.[129]

Studies in MIA PaCa-2 tumor models demonstrated that hydralazine-induced "steal" effect enhanced tumor hypoxia, thereby improving TH-302 efficacy.[129] This approach of transiently enhancing tumor hypoxia offers a novel means of augmenting the therapeutic efficacy of hypoxia-activated treatments.

In preclinical evaluations of hypoxia-targeted NPs for PDAC, the route of administration is a critical determinant of therapeutic distribution, bioavailability, and efficacy. Although intravenous (IV) injection is conventionally employed for systemic NP delivery, intraperitoneal (IP) injection has been extensively used, particularly in orthotopic or peritoneal carcinomatosis models of PDAC. IP administration offers several experimental advantages including enhanced peritoneal drug exposure, reduced hepatic first-pass metabolism, and the feasibility of repeated dosing with minimal systemic toxicity.

Guo et al delivered a hypoxia-activated prodrug (a BE-43547A2 analog) encapsulated within a sulfonated azocalixarene nanocarrier via IP injection, achieving marked tumor growth inhibition and selective activation within hypoxic tumor regions while avoiding systemic off-target effects.[73]

Nevertheless, compared to IV delivery, IP injection may provide limited systemic circulation and attenuated drug delivery to distant metastatic lesions. Accordingly, the administration route should be strategically aligned with the therapeutic goals, tumor localization, and physicochemical attributes of the NP platform.

Collectively, these findings highlight the critical influence of molecular design and delivery strategies on the in vivo performance of hypoxia-activated NPs. As the next frontier in preclinical development, recent efforts have increasingly focused on integrating hypoxia-responsive systems with combination regimens and multifunctional platforms to enhance the therapeutic outcomes for PDAC.

pH-Responsive NPs

Capitalizing on the acidic microenvironment prevalent in hypoxic regions of PDAC, researchers have developed pH-responsive NPs that demonstrate significant therapeutic promise. These NPs, functionalized with the tumor-penetrating peptide iRGD and encapsulating the ERK inhibitor SCH772984, exhibited efficient drug release under hypoxic and acidic conditions. Importantly, the combination of these NPs with gemcitabine led to pronounced synergistic effects in both in vitro and in vivo models.[130]

Importantly, this combination approach significantly enhanced the effect of GEM on PDAC growth inhibition and prolonged survival in KPC (LSL-KrasG12D/+/LSL-Trp53R172H/+/Pdx-1-Cre) pancreatic cancer mouse models, which closely mimic human PDAC pathology.[130] Mechanistically, the ERK inhibitor attenuated desmoplasia by downregulating the expression of desmoplastic regulatory factors in PDAC cells and KPC tumors, thereby enhancing the therapeutic efficacy of gemcitabine.[130]

Ongoing and Past Clinical Trials: Limitations and Challenges

Despite promising preclinical results, the clinical translation of hypoxia-targeted NP systems for PDAC treatment faces significant challenges. Nevertheless, several approaches have progressed to clinical evaluation, and some nanoformulations have received regulatory approval.

FDA-Approved Nanomedicines for PDAC

Two nanomedicine formulations have been approved by the US Food and Drug Administration (FDA) for the treatment of PDAC. Albumin-bound paclitaxel (nab-paclitaxel) is the first nanomedicine approved by the FDA and Drug Administration for the treatment of PDAC. Compared with conventional paclitaxel, nab-paclitaxel exhibits enhanced plasma clearance, improved tissue distribution, reduced toxicity, and superior therapeutic efficacy.[129] The FDA approved nab-paclitaxel in combination with gemcitabine as a first-line treatment for metastatic PDAC based on the outcomes of a Phase 3 MPACT trial.[129]

Liposomal irinotecan, in combination with 5-fluorouracil (5-FU) and leucovorin, has been approved as a second-line therapy for patients with metastatic PDAC who have progressed following gemcitabine-based treatment.[129] Compared to conventional irinotecan, liposomal formulations demonstrate reduced toxicity and enhanced therapeutic efficacy.[129] While

these approved nanomedicines do not specifically target hypoxic tumor regions, they serve as significant precedents for the successful clinical translation of NP-based therapies in PDAC.

Clinical Evaluation of Hypoxia-Targeted Approaches

Several HAPs have advanced clinical evaluation, demonstrating their translational potential for targeting tumor hypoxia. TH-302 (evofosfamide), an HAP designed to target hypoxic tumor regions, has progressed to Phase III clinical trials for pancreatic cancer. However, the MAESTRO trial did not demonstrate a statistically significant improvement in overall survival, leading to the discontinuation of its development for this indication.[129] Phase I/II clinical trials of various HAPs have reported encouraging results across multiple tumor types, such as pancreatic cancer, glioblastoma, and soft tissue sarcoma, highlighting the broad applicability of hypoxia-targeted therapies.[132]

Additionally, innovative approaches, such as the NoCanTher ThermoTherapy Agent—magnetic NPs that induce localized hyperthermia upon exposure to alternating magnetic fields—have advanced to clinical investigation. This agent is currently under evaluation in combination with standard-of-care chemotherapy (gemcitabine and nab-paclitaxel) for patients with locally advanced PDAC at the Vall d'Hebron University Hospital in Barcelona, Spain.[128] The progression of these hypoxia-targeted approaches to clinical evaluation represents a significant step toward addressing the therapeutic challenges posed by the hypoxic microenvironment of PDAC.

Limitations and Translational Challenges

Despite the notable progress in hypoxia-targeted therapies for PDAC, multiple translational barriers remain. One major challenge is the heterogeneity of hypoxia in pancreatic tumors. While certain tumor regions may experience severe hypoxia, others remain adequately oxygenated, leading to the inconsistent activation of hypoxia-responsive therapies. Oxygen levels in PDAC tumors have been shown to range from 0 to 5.3 mmHg, in stark contrast to 9.3 to 92.7 mmHg in normal pancreatic tissue.[25] This variability complicates the uniform therapeutic activation across the entire tumor.

Another critical barrier is the dense desmoplastic stroma characteristic of PDAC, which impedes NP penetration into tumor tissues and limits their ability to reach hypoxic regions deep within the tumor mass.[25,115] This stromal barrier not only restricts drug delivery but also contributes to the development of hypoxia by compressing blood vessels and increasing interstitial fluid pressure.[25] Strategies such as size-transformable NPs or co-delivery with stromal-modulating agents are being explored but remain challenging to implement clinically.

Moreover, manufacturing complexities present significant obstacles. Many advanced hypoxia-responsive NPs involve intricate fabrication processes that are difficult to standardize and scale for clinical production.[115] This complexity can lead to batch-to-batch variability and challenges in meeting regulatory requirements for pharmaceutical quality, potentially delaying clinical approval.

The accurate identification of eligible patients and prediction of their therapeutic responses present additional hurdles. The effectiveness of hypoxia-targeted therapies likely depends on the extent and distribution of tumor hypoxia, which varies from patient to patient.[129,132] However, current tools for the noninvasive assessment of hypoxia in patients with PDAC are lacking, making it difficult to identify those who would most benefit from such therapies. Therefore, the development of companion diagnostic tools and biomarkers is critical for future research.

Another key challenge is the limited translatability of the preclinical findings. Differences in tumor biology, pharmacokinetics, and immune responses between animal models and humans complicate the extrapolation of results.[130] Even genetically engineered models such as KPC mice do not fully capture the complexity of human PDAC; consequently, therapies that show promise in preclinical studies may not yield the same outcomes in clinical trials. Therefore, preclinical models that better mimic human responses are urgently required.

Various innovative strategies are currently being investigated to enhance the clinical translatability of hypoxia-targeted NPs in PDAC. Combining hypoxia-targeted therapies with immunotherapy, radiation, or stromal-modulating agents may help overcome the limitations of monotherapy.[115] Advancements in imaging technologies and biomarker development could enhance our ability to assess tumor hypoxia and monitor treatment responses, allowing for more personalized treatment plans.[132] The design of next-generation NPs that are responsive not only to hypoxia but also to other tumor-specific triggers may improve therapeutic

specificity and efficacy.[98] Additionally, efforts to simplify and standardize the manufacturing of complex NP systems could accelerate their clinical development and regulatory approval.[115]

Conclusion and Prospects

Pancreatic ductal adenocarcinoma exemplifies how an extreme hypoxic microenvironment can drive aggressive tumor biology and therapeutic resistance.[9] In PDAC, dense desmoplastic stroma and poor perfusion create oxygen-starved niches that impede drug delivery and foster treatment evasion. This review highlights that hypoxia is not only a barrier, but also a targetable vulnerability, one that advanced NP platforms are engineered to exploit. By sensing and responding to low oxygen levels, hypoxia-targeted NPs can selectively release therapeutic payloads within oxygen-deprived tumor regions, thereby overcoming diffusion limitations and hypoxia-induced drug resistance. Crucially, such strategies achieve spatially selective drug delivery by deploying cytotoxic agents predominantly in hypoxic tumor tissues, while sparing normoxic healthy cells. Intrinsic targeting enhances tumor specificity and minimizes systemic toxicity. Preclinical studies underscore this potential; for example, hypoxia-responsive polymersomes in PDAC models reduced tumor growth by over two-fold and increased intratumoral necrosis by 60% compared to controls.[25] Collectively, these findings affirm that NP-mediated hypoxia targeting can substantially improve intratumoral drug efficacy and precision, addressing a key failure point of conventional therapy. Thus, targeting the hypoxic tumor microenvironment is a promising route to bolster treatment responses and could translate into better patient outcomes in this notoriously lethal cancer.[8]

The convergence of nanotechnology with computational intelligence offers exciting opportunities to refine and accelerate the development of hypoxia-targeted delivery systems. AI-driven design optimization is expected to play a transformative role in next-generation nanomedicines. Machine learning algorithms and in silico models can mine complex NP design data to uncover non-intuitive structure–function relationships, enabling rational tailoring of NPs for improved tumor penetration and trigger sensitivity. This data-driven approach can significantly shorten the iterative formulation and testing cycles. Indeed, emerging high-throughput platforms now integrate microfluidic NP synthesis with real-time screening and active machine learning, allowing the rapid identification of optimal designs from a vast combinatorial space.[133] Such AI-guided workflows have demonstrated orders-of-magnitude enhancements in delivery performance within a few design iterations,[133] illustrating how computational feedback can accelerate discovery. Additionally, advanced AI models can predict NP biodistribution and interactions in silico, guiding researchers to fine-tune their properties (size, surface ligands, and hypoxia-responsive moieties) for maximal accumulation in hypoxic PDAC tissues. By incorporating these tools, researchers can achieve more precise targeting a priori and reduce reliance on trial-and-error experimentation.[134] In summary, the synergy of innovative hypoxia-responsive NP platforms with AI-powered design and optimization heralds a new era of "smart" drug delivery. These developments hold great promise for overcoming PDAC hypoxia-driven treatment barriers, ultimately improving therapeutic outcomes for patients with a dismal prognosis.

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Disclosure

The authors report no conflicts of interest in this work.

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