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Overcoming the Tumor Microenvironmental Barriers of Pancreatic Ductal Adenocarcinomas for Achieving Better Treatment Outcomes

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive disease with the lowest survival rate among all solid tumors. The lethality of PDAC arises from late detection and propensity of the tumor to metastasize and develop resistance against chemo and radiation therapy. A highly complex tumor microenvironment composed of dense stroma, immune cells, fibroblast, and disorganized blood vessels, is the main obstacle to current PDAC therapy. Despite the tremendous success of immune checkpoint inhibitors (ICIs) in cancers, PDAC remains one of the poorest responders of ICIs therapy. The immunologically “cold” phenotype of PDAC is attributed to the low mutational burden, high infiltration of myeloid-derived suppressor cells and T-regs, contributing to a significant immunotherapy resistance mechanism. Thus, the development of innovative strategies for turning immunologically “cold” tumor into “hot” ones is an unmet need to improve the outcome of PDAC ICIs therapies. Other smart strategies, such as nanomedicines, sonic Hedgehog inhibitor, or smoothened inhibitor, are discussed to enhance chemotherapeutic agents’ efficiency by disrupting the PDAC stroma. This review highlights the current challenges and various preclinical and clinical strategies to overcome current PDAC therapy difficulties, thus significantly advancing PDAC research knowledge.

Graphical Abstract

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Conflict of Interest:
The authors declare that there are no conflicts of interest.

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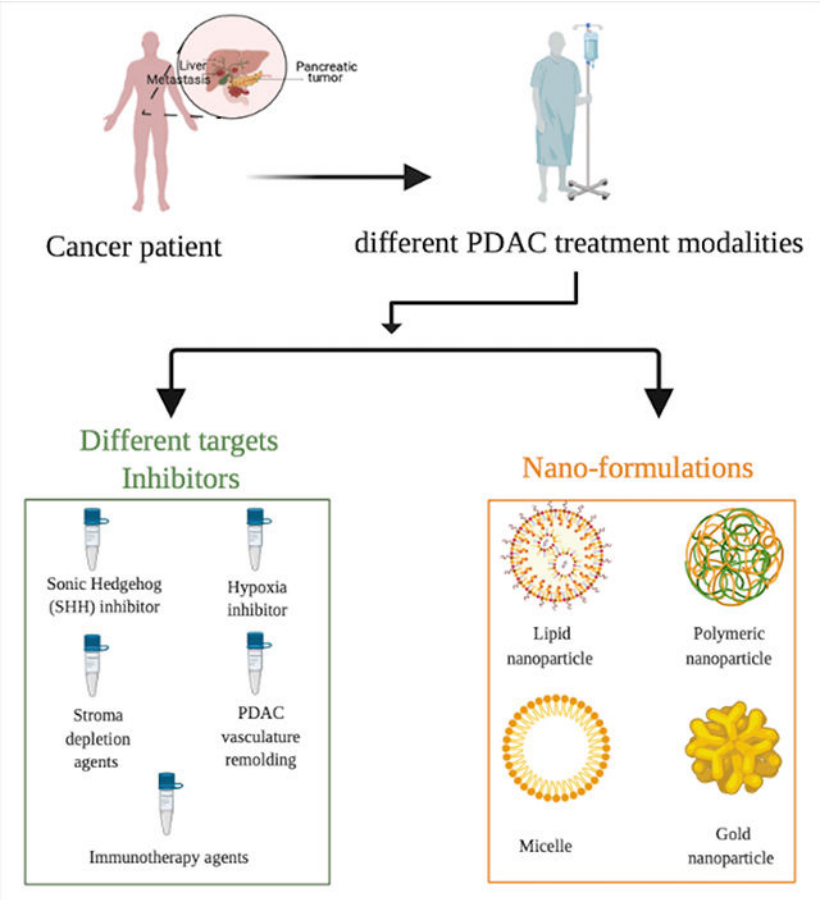

The current work highlights the challenges that play a crucial role in minimizing the therapy efficiencies of pancreatic ductal adenocarcinomas. The potential strategies that can mitigate the challenges in therapy and diagnosis such as utilizing novel targets and nanomedicines are discussed. Together, these methods have potential to improve the overall treatment efficacy and survival rates of patients with pancreatic ductal adenocarcinoma.

Keywords

Pancreatic cancer; Tumor microenvironments; Nanomedicine; Stroma; Immune checkpoints inhibitors

1. Introduction

In 2020, pancreatic cancer (PC) was the fourth leading cause of cancer-related death in the US. The 5-year survival rate of pancreatic cancer is the lowest among other solid cancers, 7% [1]. Within PCs, 90% accounts for pancreatic ductal adenocarcinoma (PDAC) [2]. Many risk factors are associated with PDAC, such as smoking, family history, and genetic diseases. In PDAC, poor prognosis is the main challenge due to the tumor's propensity to metastasize and develop resistance against chemo and radiation therapy [3]. One of the main challenges is dense stroma produced by the mucin-producing gland [4]. Stroma is one of the major

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tumor microenvironment components that draw attention to researchers due to its role in patients' poor prognosis [5]. Thus, the presence of stromal components in PDAC elevates the interstitial fluid pressure (IFP), leading to vasoconstriction that in turn impedes the chemotherapeutic delivery efficiency [6,7]. In recent years, researchers have begun to focus on finding new ways to better understanding PDAC's genetics and biology to improve therapeutic outcomes. Biologically, desmoplastic reaction (DR) is one of the hallmarks of PDAC that contributes to PDAC's poor prognosis. The dense desmoplasia plays a major role in distorting the normal architecture of pancreatic tissue and blood perfusion; thus, drug penetration decreases, and resistance increases [8]. Tumor hypoxia or low oxygen levels and hypovascular environment is another obstacle that reduces drug delivery efficiency to the tumor site [9]. The vasculature within the PDAC tumor microenvironment (TME) is obscured or obstructed by the tumor-associated fibroblast or pericytes [10]. Therefore, cells that grow within these harsh conditions are resistant to most chemotherapeutic agents and radiotherapy [11]. Within TME, the absence of immune surveillance and inflammatory cells supports aggressiveness and tumorigenesis of PDAC [12]. The signs of genetic alteration in PDAC have been studied extensively; Kristen rat sarcoma viral oncogene homolog (KRAS) mutation and CDKN2A alteration are found to be one of the early events in low-grade pancreatic intraepithelial neoplasia (Figure 1A) [13,14]. On the other hand, alteration of P53 and loss of Smad4 was found to be one of the late events that occur in intraepithelial neoplasia grade 3 (Figure 1A) [13].

Several approaches, including immunotherapy, have been studied in patients with pancreatic cancers; nevertheless, most of them have not shown any clinically meaningful outcome noted in other malignancies [15]. Moreover, the complexity of PDAC tumor stroma composition attenuates most PDAC therapies due to poor drug penetration through the stroma barrier. Thus, new immunotherapy approaches need to be established to trigger a potent immune response against tumors. Also, nanoparticles approach is another way to overcome different PDAC barriers through its ability to accumulate in the tumor site [16,17]. Nanomedicine such as liposome and polymeric nanoparticles can overcome additional biological obstacles via protecting encapsulated payloads from degradation in blood circulation, and lowering their accumulation in non-target organs and tissues, thus minimizing the toxicity to normal cells and tissues. Nanoparticles can be designed to improve the delivery efficiency to target tissues, which lowers the needed therapeutic dose. Moreover, nanomedicines can minimize immunogenicity and prolong circulation time [18]. Therefore, nanoparticles provide a viable solution to improve current PDAC therapy's efficiency. So far, *in vitro* and *in vivo* data of nanoparticles that have been tested on PDAC tumors showed promising results. In this review, the current PDAC challenges will be covered. The different ways that clinicians and researchers currently use varying approaches to overcome these challenges and improve the overall disease response will be discussed.

2. Current PDAC therapy

One of the most critical challenges of the PDAC treatment is the tumor microenvironment characterized by constantly changing morphology and genetics that contribute to its aggressiveness [19]. The PDAC tumor microenvironment is also characterized by desmoplasia (dense stromal cells) that adds to the resistance to conventional therapies.

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However, significant improvements have been made in the treatment strategies of the PDAC, which include monotherapy such as gemcitabine, multidrug regimen like the FOLFIRINOX, and combination therapies (gemcitabine plus adjuvant/neoadjuvant therapies/immune checkpoint inhibitors) (Table 1,2). The following are some of the novel therapeutic strategies for PDAC that have been developed based on the stage of cancer and the resistance mechanisms involved at that stage of the disease.

Most of the reasonably successful treatments applied so far for PDAC include a combination of chemotherapy, immunotherapy, and radiotherapy. Currently, most clinical trials consist of these combinations (Table 1, 2).

2.1. First-line therapy:

The main PDAC treatment is surgical resection followed by chemotherapy, radiotherapy, and targeted therapy [20]. In resectable tumors, gemcitabine has so far been the most successful and preferred the first-line drug because of its lower toxicity and reasonable response rate [21]. This drug is used as a single therapy and in combination with other drugs such as 5-fluorouracil (5-FU) [22,23]. Using gemcitabine alone for six months after tumor resection has increased the 5-year overall survival (OS) to 20.7% compared to the observation arm (OS 10.4%) [21]. Other clinical trials had shown no major difference in OS and quality of life after using 5-FU/ leucovorin (23.6 months) or gemcitabine (23 months) in resectable PDAC patients [24]. Moreover, a recent clinical trial (phase III NCT03610100) has designed a modified version of gemcitabine (Acelarin) to overcome the current resistance to gemcitabine and enhance its efficiency via delivering a high intracellular level of dFdCTP (gemcitabine active agent). Due to the pancreatic relapse after 6 months of gemcitabine treatment, a combination regimen should be considered as adjuvant therapy [24]. Neoptoloms et al. have investigated the efficiency of another combination of resectable PDAC using gemcitabine and capecitabine. The team found that this regimen increased OS to 28 months compared to 25.5 months using gemcitabine alone. Interestingly, the adverse effects of using gemcitabine and capecitabine were tolerable [24].

For locally advanced pancreatic cancer, treatment is solely based on combination therapy. One of the more explored combinations with some success in the metastatic PDAC is the FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) [25]. Clinical trial PRODIGE 4/ACCORD 11 has shown that FLOFIRINOX increased the OS rate up to 11.1 months compared to 6.8 months of using gemcitabine alone. FLOFIRINOX showed some adverse effects such as thrombocytopenia, neutropenia, febrile neutropenia, diarrhea, and alopecia.; however, the patients' quality of life was better than gemcitabine alone [26]. In this regard, several retrospective studies have suggested reducing the initial chemotherapy doses of FLOFIRINOX, which could reduce side effects and maintain the regimen efficiency [27]. A phase II trial has shown that using a modified FOLFIRINOX regimen enhanced treatment efficacy and reduced toxicity [28]. Also, PEFG (cisplatin, epirubicin, fluorouracil, and gemcitabine) was one of the first combinations taken to the clinical trials that showed fewer adverse effects and higher therapeutic efficacy [29]. Another combination studied used gemcitabine with the EGFR inhibitor (erlotinib) approved by the FDA for PDAC [30]. Gemcitabine also has been paired with Abraxane, capecitabine alone, and gemcitabine/

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docetaxel/capecitabine (GTX) to give a good response and better survival rates in PDAC patients [31]. Gemcitabine with Abraxane was a successful combination [32] tried in phase III trials and was approved by the FDA, although it showed severe adverse reactions (such as neutropenia, leukopenia, neuropathy, febrile neutropenia, or fatigue). The reason for approval was because of the advantages that outweighed the side effects of treatment.

Other combination therapies that have shown promise in clinical trial results are listed (Table 1 and 2). Several different combinations are put to the test for PDAC constantly so that we could increase the success rate of therapy and make personalized medicine achievable. The main criteria taken into account in choosing the appropriate combination therapy are efficacy/survival, adverse effects, and patient compliance [33].

2.2. Second-line therapy:

Second-line therapy is mainly depending on the chosen first-line therapy. Thus, healthcare providers should take clinical trials into account for selecting the appropriate regimen that does not impact patients' quality of life and has minimal side effects. For instance, for patients who received FOLFIRINOX as first-line therapy, a gemcitabine-based regimen should be considered. For patients who failed to respond to FOLFIRINOX, gem-based therapy (gem-nap) played a significant role in improving OS (8.8 months) [34] with manageable side effects. On the other hand, if gem-based therapy is used as first-line therapy, 5-FU can be used either as a single agent or with other agents such as oxaliplatin as the second-line therapy.

2.3. Current ongoing clinical trials for PDAC therapy:

Currently, there are many new pathways and targets for PDAC therapy that are being explored, such as the Hedgehog pathway, KRAS pathways, JAK/STAT pathways, hyaluronidase/hyaluronic acid, angiogenesis, tyrosine kinase inhibitors, and growth factor receptors. Most of these trials are in phase I and phase II and are initially evaluated for their safety and toxicity profiles [35]. CYL-02 is a non-viral gene therapy that is used to sensitize the chemotherapy of PDAC (NCT01274455). Patients with locally advanced PDAC remained free of metastasis after receiving CYL-02. CA 19–9 cancer biomarkers in locally advanced PDAC patients significantly reduced after receiving gene therapy combined with gemcitabine. [36]. Another clinical trial (NCT03450018) combined SLC-0111 (CAIX inhibitor) with gemcitabine for treating metastatic PDAC. SLC-0111 was found to play a role in increasing intratumor acidosis and slowing tumor growth [37]. Some other clinical trials are listed in Tables 1 and 2.

3. Challenges of PDAC treatment

PDAC prognosis is the poorest among all solid tumors. Even though there are new advancements in finding the initial sign of PDAC, inadequate response to current therapies is still prevalent [38]. One of the hypotheses that have emerged in the last few years is that the PDAC microenvironment is responsible for increasing both carcinogenesis and drug resistance [39]. The tumor microenvironment of PDAC is enriched by the stromal barrier, which is composed of fibroblast, immune cells, blood vessels, neural cells, and cellular

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proteins such as growth factors and cytokines (Figure 1B) [40]. Because of the stromal barrier, most combination therapies failed to increase the survival rate significantly[41]. the overall survival (OS) achieved in resectable tumors aged from 25.5 months using gemcitabine alone or 28 months when combined with capecitabine [24]. While in locally advanced PDAC tumor, the OS ranged from 6.8 using gemcitabine alone or 11.1 months after using FOLFIRINOX (fluorouracil (5-FU), irinotecan, and oxaliplatin) [26]. The following factors are believed to play a role in attenuating current therapeutic efficiency, as discussed below.

3.1. Tumor microenvironments (TME)

One of the main challenges in PDAC therapy is heterogeneous TME [42]. The genetically engineered mouse model (GEMM) of pancreatic cancer has enabled researchers to mimic human pancreatic cancers in many asp,ects such as resistance to gemcitabine, which opens new avenues for understanding pancreatic cancer microenvironments [43–45]. It has been discovered that PDAC has a stroma enriched TME, which keeps changing its composition, especially during progression from preneoplastic pancreatic intraepithelial neoplasms (PanINs) to invasive pancreatic cancer. Pancreatic intraepithelial neoplasms is a PDAC precursor lesion that is classified into a low grade (PanIN-1 and PanIN 2) and high grade (PanIn-3) [46]. The progression from PanIN low grade to PanIN high grade is associated with alteration in cancer-associated genes such as KRAS, P53, CDKN2A, and SMAD4 (figure 1, A) [46]. Stroma, a component of TME, has a major role in increased proliferation, metastasis, immune escape, and drug resistance [40]. Desmoplastic reaction (DR) is one of the PDAC hallmarks that contributes to PDAC's poor prognosis. The dense desmoplasia plays a major role in distorting the normal architecture of pancreatic tissue and creating a mechanical barrier around the PDAC tumor, that limits tumor vascularization. Thus, drug penetration into tumor site is diminished [47]. Olive, K. et al. have reported that accumulation of active gemcitabine metabolites (2',2-difluorodeox-cytidine triphosphate (dFdCTP) was high in poor stromal cancer in subcutaneous and orthotopic mice model while it was barely detectable in high dense stroma cancer such as PDAC [48]. One of the pathways that enhances PDAC desmoplastic reaction is sonic hedgehog (SHH) signaling. Importantly, DR consists of multiple components such as fibroblasts, pancreatic stellate cells, and extracellular matrix (collagen I, collagen II, and fibronectin) that all react together, and worsen the clinical outcomes of PDAC patients [49]. The major two components of DR are pancreatic stellate cells (PSCs) and fibroblasts. It has been found that PSCs are involved in secreting many cytokines such as IL6, CLL2, CLL5, and CLL8 [50,51]that are contributing to proliferation, migration, and producing extracellular matrix (ECM) protein [52]. Several studies showed PSCs' role in reorganizing the collagen fibers to parallel alignments that enhance cancer cells' migration and invasion [53]. Cross talk between the pancreatic cell and PSCs is a trigger for PDAC cells to grow and migrate via releasing some growth factors such as insulin-like growth factor, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) and cytokines [54]. Several pathways are believed to play a significant role in the PSCs process, such as transforming growth factor-beta (TGF-β), hepatocyte growth factor (HGF), fibroblast growth factor, and epidermal growth factor (EGF). Lohr et al. found that the co-culture of TGF-β expressing Panc-1 is more proliferative and induces more collagen I and fibronectin [52]. Armstrong et

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al. have shown that PSCs incubated with TGF-β enhanced [^{3}H] thymidine uptake, induce collagen production, promote the malignancy of PDAC tumor, and increase cancer resistance toward chemo and radiation therapies [55,56]. It has been found that fibroblasts play a role in producing secreted protein acidic and rich in cysteine (SPARC) that enhances cell migration and proliferation and worse prognosis in PDAC patients [3,57]. The activated factors of pancreatic cells promote activation of stromal cells, which consequently affect other epithelial tumor components of pancreatic cancer [3]. Therefore, PSCs, fibroblast, and epithelial cells play a significant role in controlling ECM through the proteolytic enzyme of metalloproteinase (MMPs) which expresses in pancreatic cancer cells. It has been found that several enzymes of MMPs such as (MMP-1, MMp-2, and MMp-9) overexpressed when coming in contact with specific ECM proteins [58,59]. ECM is one of the major factors that enhance tumor aggressiveness and invasiveness. Further understanding of PSCs' activated pathway- PDAC cross-talk is needed to develop PSCs targeted therapy [60,61].

3.2. Cancer Stem Cells (CSCs) in PDAC

It is well known that TME is characterized by its heterogenicity, and its pathological and physiological effects on tumor therapy are not well understood. Epithelial to mesenchymal effect (EMT) is a stem cell characteristic that is believed to have a significant role in promoting tumor heterogenicity and cell metastasis [62]. Within TME, there is a subpopulation of the cells called cancer stem cells (CSCs) that are capable of self-renewal [63], and that can justify why many tumors regenerate after being mostly eradicated during chemotherapeutic treatment [64]. CSCs were firstly found in the hematopoietic system; however, researchers found CSCs to be presented in solid tumors such as breast [65], colon [66], brain [67], and pancreatic cancer [64]. Breast CSCs were characterized by $CD44^{high}/CD24^{low}$ antigenic phenotypes that promote tumor initiation compared to other carcinomas with $CD44^{low}/CD24^{high}$ [65]. However, in the xenograft animal model of pancreatic cancer, it has been identified that a subpopulation of cells has CSC properties and has $CD44^{+}$, $CD24^{+}$, and ESA^{+}. In this study, the authors found that $CD44^{+}$, $CD24^{+}$, and ESA^{+} pancreatic cells have a high potential to form a tumor when injected as low as 100 cells per mouse compared with $CD44^{-}$, $CD24^{-}$, and ESA^{-} [64].

CD44 is a non-kinase, transmembrane glycoprotein (P-glycoprotein) expressed on several cells and tissues such as embryonic stem cells and bone marrow. It has been found that CD44 is overexpressed in various tumor cells, and it is known as a biomarker of CSCs [68]. Furthermore, CD44 has a significant role in cancer stemness and promoting cancer tumorigenicity [69]. Hyaluronic acid binds to CD44; thus, many drug delivery researchers have reported the efficiency of using hyaluronic acid as CD44 binding ligand to improve the efficiency of PDAC first-line therapy [70–72].

In addition, hepatocyte growth factor receptor (c-Met), present in both normal and tumor cells, is essential for embryonic development and tissue repair [73]. c-Met is a unique receptor with only one ligand that can bind to it, namely, HGF [73]. Upon HGF binding to c-Met, a series of downstream signaling pathway events are mediated, leading to enhancement of normal cell growth, cell motility, and protection of normal cells from apoptosis [74]. In cancer cells, c-Met functions differently than normal cells due to c-Met being overexpressed

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or mutated, which ultimately enhances pancreatic carcinoma [75]. It has been found that exposing cells to chemotherapeutic agents such as gemcitabine enhanced EMT, increase c-Met phosphorylation that promotes expression of CSCs biomarkers such as CD44 and CD24 [76]. Interestingly enough, CD44 plays a role in regulating the HGF/c-Met signaling pathway, which maintains CSCs function. Overexpression of c-Met in pancreatic cancer is a sign of poor prognosis, which elevates EMT phenotype. Li et al. have studied the role of c-Met in forming tumor spheres. They found that c-Met^{+} cell lines could form spheres while c-Met^{-} cell lines could not.

Moreover, treating pancreatic xenografts in NOD-SCID mice with a combination of c-Met inhibitor (XL184) and gemcitabine showed significant tumor growth regression even after 32 days of therapy cessation [77]. Also, Alex et al. successfully designed an antibody-drug conjugate (TR1801-ADC) that enhanced the tumor inhibition (*in vitro* and *in vivo*) in Met overexpressed pancreatic cancer and worked in synergy with gemcitabine [78]. CSCs are one of the leading players of PDAC distal metastasis. Hermann et al. showed that PDAC distal metastasis is correlated with the presence of CD133^{+} of pancreatic CSCs and CXCR4^{+} expression. [79].

Based on the findings mentioned above, PDAC has a subpopulation of cells (CSCs) which plays a crucial role in developing metastasis and fortifying chemotherapeutic resistance. Moreover, c-Met is another PDAC biomarker that enhances the CSCs subpopulation's tumorigenicity. Together, these studies suggest that CSCs biomarkers (CD44^{+} and CD133^{+} cells) and c-Met^{+} cells can be used as a new target for therapy to minimize tumor growth and enhance the tumor response to current treatment.

3.3. Hypoxia

Hypoxia is an essential feature of PDAC tumor microenvironment, which plays a major role in activating several molecular and signaling pathways contributing to PDAC aggressiveness [80]. Chang Q *et al.* performed a study to measure the oxygen levels within pancreatic cancer. In this experiment, which was conducted on seven patients, they found a dramatic reduction of oxygen in pancreatic tumors than normal tissue [81]. The ability of cancer cells to survive in the hypoxic condition is attributed to the activation of hypoxia-inducible factor (HIF) pathways. HIF can activate several genes such as STIM1, PKM2, MiR21, and MTA2 [82] that help cancer cells controlling metabolism, survival, pH, migration, as well as some angiogenic growth factors [83–85]. In PDAC, many studies have shown that pancreatic cancer cells induce the angiogenesis process via secreting vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [86,87].

Furthermore, HIF mediates several pathways, such as c-Met and Hedgehog pathways, that enhance cancer invasiveness and drug resistance [3,88]. Moreover, hypoxia is known to activate the notch signaling pathway, which plays a role in cancer cell proliferation and differentiation [89]. Yoshiharu et al. found almost 21 of 34 examined specimens (62%) showed moderate to high expression of at least one notch in pancreatic cancer as well as in PanIN lesions. [90]. Notch signaling pathway is an early sign of PDAC that acts as a mediator to activate EGF receptors and PDAC precursors [90]. Furthermore, notch pathway activates transforming growth factor-alpha (TGF-α), which functions as an activator of

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acinar-to-ductal metaplasia [91]. All these factors mediate cancer invasiveness, drug resistance and increase the challenge of reaching drugs to TME of pancreatic cancer. Therefore, new novel targeted therapies or delivery systems that could target hypoxic regions or inhibit notch signaling pathways are needed to improve the overall therapeutic efficiency.

3.4. Inflammation and Immune cells

One of the major characteristics of TME is an absence of immune surveillance and the presence of inflammatory cells that support aggressiveness and tumorigenesis of PDAC [12]. Inflammatory and immune cells are crucial components of TME that play a pivotal role in PDAC aggressiveness. Within TME, at the early stage, many immune cells such as anti-tumor Th1, $CD4^+$, $CD8^{+,}$ and natural killers (NKs) are recruited to eliminate the cancer cells. However, the tumor cells start to develop an escape mechanism via recruiting monocyte and neutrophil, acquiring the anti-inflammatory phenotype (M2 and N2, respectively). Furthermore, tumor cells recruit or polarize T regulatory cells (Treg), shift anti-tumor Th1 to Th2, and recruit myeloid-derived suppressive cells (MDSCs). All these events result in the deactivation of $CD4^+$, $CD8^+$, NKs and increase the tumor progression [92,93].

3.5. Role of RAS in PDAC

The Ras family belongs to a small GTPase composed of HRAS, NRAS, and KRAS [94]. KRAS ($KRAS^{G12D}$ and $KRAS^{G12V}$), CDKN2A, TP53, and SMAD4 are the most common genetic mutations found in pancreatic cancer. However, until now, none of them are druggable. The absence of specific inhibitors for all of these genes limits the therapeutic options for PDAC patients [95]. Recent studies found that almost 95% of the patients have a mutational activation of oncogenic KRAS at codon 12 [96] that is crucial in activating and maintaining PDAC. Moreover, KRAS mutation is a sign of poor prognosis in resectable and advanced PDAC patients [97]. Normally, KRAS proteins have a crucial role in cell survival, differentiation, and proliferation [98]. However, the mutated KRAS compromises oncogenic KRAS's normal function; thus, the pancreatic cells' growth becomes uncontrollable. In genetically engineered mice models, functional studies have found that KRAS switching off led to dramatic tumor regression [99,100]. Therefore, extensive preclinical and clinical ongoing studies explore KRAS to design an effective targeted therapy.

In OA02.02 phase 1 clinical trials, it has been found that AMG510 can inactivate KRAS by irreversibly occupying His95 groove near the cysteine pocket of $KRAS^{G12C}$. Interestingly, AMG510 is potent against $KRAS^{G12C}$ mutation of non-small-cell lung cancer tumor while it is not active against wild type [101]. Moreover, AMG510 showed good anti-tumor activity either alone or with PD-1 checkpoint inhibitors. The adverse effects of AMG510 were tolerable such as nausea and vomiting [101]. However, the use of AMG510 is limited in PDAC due to $KRAS^{G12C}$ mutation that accounts for only 2% in PDAC[102]. This study will stimulate researchers to develop new drugs that can inactivate $KRAS^{G12D}$ and $KRAS^{G12V}$ that is accounting for 80% of PDAC. Due to the undruggable nature of $KRAS^{G12D}$ and $KRAS^{G12V}$, targeting the KRAS downstream (MEK-ERK and/or PI3K) is the putative way to manage the KRAS related cancers. Inhibition of a single downstream pathway (RAF,

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MEK1/2, ERK1/2, and PI3K) of RAS did not show significant clinical effect, and drug resistance may be induced via several compensatory activations mechanisms such as PI3K, which activates several pathways such as Akt and mTOR [103].

Several inhibitors of RAS downstream pathway are clinically tested, as shown in Figure 2. The role of KRAS in enhancing TME is not well understood. Mills, L et al. have demonstrated the role of KRAS in TME. KRAS activates SHH expression, which further induces GLI family zinc finger 1 (transcriptional factor) in fibroblasts. The binding of GLI1 to IL-6 promotor regulates the activation of cancer STAT3. In this study, loss of GLI family zinc finger 1 impaired the carcinogenic of KRAS in PDAC animal model [104]. Thus, targeting the cross-talk between cancer cells and TME components is a viable way for promoting PDAC tumor regression.

4. Strategies to overcome PDAC barriers

4.1. Stroma-Targeting Therapy in PDAC

PDAC tumor is characterized by one of the densest stroma among several tumors types that arise from pancreatic stellate cells (PSCs). Activation of PSCs leads to the formation of an extracellular matrix that enhances the strength and resistance of PDAC cells to chemotherapeutic and radiation therapy [105,106]. Currently, several agents are being tested in preclinical and clinical studies to enhance delivering of cytotoxic drugs to PDAC microenvironments (Figure 2).

4.1.1. Utilizing hyaluronidase enzyme—A variety of methods to enhance the effectiveness of chemical therapeutic agents have been developed to address the physical and biological obstacles to successful PDAC therapies and reverse the effects of stroma on tumor growth. One of these strategies is to use Hyaluronic acid (HA) or hyaluronan, which is one of the major components of PDAC stroma. HA interacts with cellular receptors to ensure tumor cell survival and to activate downstream signaling pathways relevant to tumor progression [107,108]. Accumulating evidence found an abundance of hyaluronan (HA) in PDAC tumors, which significantly enhances tumor proliferation. A high level of HA is a sign of poor prognosis compared to those who have a low level of expression [109]. Therefore, one of the strategies in enhancing PDAC drug delivery is depleting HA using hyaluronidase [110]. In HALO202 clinical trial that recruited 279 patients, PEGylated hyaluronidase (PEHPH20) combined with gem-nap in one arm and gem-nap alone on the other arm. In this study, it has been found that patients who had a high level of HA responded much better than low HA with overall response rate (ORR) (45% vs. 31%) and OS (11.5 vs. 8.5 months), respectively [111]. Despite the promising results in phases 1 and 2, the phase 3 clinical study (HALO109–301) failed to achieve the primary endpoint of OS, and further development of PEHPH20 was halted. The authors concluded that targeting desmoplasia alone is not sufficient; other factors such as tumor stroma, epithelial to mesenchymal transition, low tumor mutational burden should be considered to enhance the overall PDAC response [112].

4.1.2. Sonic Hedgehog (SHH) signaling—One of the pathways that participate in improving PDAC desmoplastic reaction is Sonic Hedgehog (SHH) signaling. The Hedgehog

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pathway is abnormally activated in PDAC [113]. It is evident that Hedgehog signaling pathway stimulates pancreatic stellate cells (PSCs) through direct effects on non-pancreatic tissues and controls stromal deposition [114]. A variety of strategies are being considered to inhibit the Hedgehog pathway, which is the pro-inflammatory stage of PDAC, in order to remove tumor-stroma [115]. The Hedgehog Signal Pathway is blocked by cyclopamine as a natural steroid alkaloid [116]. It reduced the fibronectin content of a PDAC xenograft mouse model and increased tumor vascularization. Cyclopamine improves tumor growth inhibits by 63.3% in combination with nanomaterials loaded with paclitaxel [117]. One research on induced pluripotent stem cells demonstrated that IPI-926, a small molecule that inhibited the Hedgehog pathway, gave favorable effects of inducing blood vessel density and drug concentration in pancreatic ductal adenocarcinoma (PDAC) [118]. In phase, I clinical trial of IPI-926, patients who were previously affected by PDAC did not have any significant side effects [118]. Sadly, despite the promising findings in phase I trials, phase II clinical trials of IPI-926 showed no major benefits to prevent PDAC in pancreatic cancer patients [119]. In similar conditions, in patients with metastatic PDAC relative to gemcitabine alone, Vismodegib, another Hedgehog inhibiter in conjunction with gemcitabine, improved median total survival and progression-free survival significantly [120]. Although multiple therapies that target the Hedgehog pathway showed positive effects in preclinical models, few improved survival rates and their use was followed by side effects and toxicity [121]. Overall, Using SSH signaling inhibitors is an effective way to deplete the stromal barrier and enhance gemcitabine delivery [122,123]. Feig et al. have combined smoothened inhibitor (IPI-926) with gemcitabine which majorly reduced tumor stroma, promoted micro-vessel density, and significantly increase intra-tumor gemcitabine active metabolite (dFdCTP); as a result, the overall survival increased [40]. Olive et al. have found that using Hedgehog inhibitors allows the chemotherapeutic agent to be delivered to the tumor site [48].

4.1.3. Targeting Inflammation and Immune cells in TME—PDAC stroma is enriched in many inflammatory cells, such as mast cells, which are considered the cornerstone of angiogenesis, tumor growth, and lymph node involvement [124]. Therefore, inhibition of mast cell activity is one of the current strategies to limit tumor progression. Ibrutinib, a small molecule that permanently inhibits Bruton's tyrosine kinase (BTK) protein, is used to decrease fibrosis and inhibit mast cell cytokines release (IL-8, TNFα, and MPC-1) within PDAC TME. Ibrutinib has shown a reduction in tumor fibrosis in a mouse model and improve the mouse response to standard therapy [124,125].

4.1.4. Targeting Hypoxia in TME—Many methods have been utilized by targeting hypoxia, including prodrugs that are activated in hypoxic conditions, drugs that target HIF-1α active cells, and nanoparticles with active hypoxia targeting, which are being developed [126,127]. Evofosfamide (TH-302), a cytotoxic prodrug, comprises a mustard derivative converted in hypoxic conditions to an active metabolite [128]. Clinically, Evofosfamide has been indicated to minimize radiotherapy resistance in PDAC. However, another clinical trial for NSCLC using Evofosfamide with tarloxotinib (a hypoxia-activated tyrosine kinase inhibitor) was terminated early because the patients did not meet the minimum response rate to this combination [128,129]. Another anticancer agent that was identified years ago is POP33. POP33 is a prodrug with the potential to elevate caspase-3

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activity and induce apoptosis in HIF-1–active/hypoxic cells [130]. This drug, which is a fusion protein, consists of a cleaved caspase pro-enzyme and a transduction HIF-1α dependent stabilization domain to deliver the drug into cells [130]. Although POP33 exhibited a promise in an animal model of PDAC, it has yet to make its way for human application. While no direct HIF protein inhibitors have reached the clinical studies for PDAC, treatment strategies that target heat shock protein (HSP) 90 have led to HIF degradation [131,132].

4.1.5. Remodeling Tumor Vasculature—The thick fibrotic stroma covering the blood vessels and the proliferation of cancer-associated fibroblasts (CAFs) destroy intratumoral blood vessels, creating a hypoxic microenvironment, which supports pancreatic adenocarcinoma metastasis and the development of chemoresistance [133,134]. Remodeling PDAC vessels improves drug delivery and exposes living cells to better environments which improves drug effectiveness and its disposition in the body. Many agents with varying aims have been employed to target the tumor microenvironment [135]. In 2015, a Phase II study tested the effectiveness of the new medication, FOLFIRINOX, in conjunction with lisinopril in patients with locally advanced pancreatic cancer. The approach was found to have a high proportion of patients achieving R0 resection [136]. It is also noteworthy thatthe lack of the Angiotensin II Type II receptor (AT2R) in pancreatic fibroblasts contributes to tumor cell proliferation [137]. In the future, Ang II signaling pathway will need to be analyzed in more depth before its use in the clinic.

4.2. Other Important strategies

One of the target protein that facilitates PDAC stromal depletion is secreted protein acidic rich in cysteine (SPARC). Abraxane (albumin conjugated paclitaxel) has been hypothesized for its ability to deplete stroma and accumulate in overexpressed SPARC pancreatic TME. There are contradictory results in this regard. One clinical trial has shown that combining gemcitabine with nab-paclitaxel increased the overall survival of high expressed SPARC patients (17.8 months) compared to those who had low SPARC expression (8.1 months) [138,139]. However, stromal depletion was not seen in a preclinical study of the patient-derived xenograft mice model. The author observed that gemcitabine activity was impaired due to activation of reactive oxygen species (ROS). The interesting observation was after using gemcitabine combined with nab-paclitaxel [140]. Thus, the exact role of SPARC is unknown and in-depth investigations are needed to reveal the particular role of this biomarker and its prognostic impact after treating it with nab-paclitaxel or other targeted therapy.

Another target is cancer stem cells (CSC) which have a significant role in tumor proliferation and metastasis [141]. One of the signaling pathways that promote CSC growth is STAT3. It is well documented that STAT3 is activated in PDAC tumor and functions as a tumor promotor. Therefore, inhibition of STAT3 would enhance PDAC response to chemotherapeutic agents and promote tumor inhibition [142].

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5. Immunotherapy as a promising approach for PDAC therapy

Since FDA approval of different immunotherapeutic agents such as ipilimumab (2011) and nivolumab (2014), immunotherapy became a candidate therapy for multiple tumors such as melanoma, renal cancer, lung cancer, and others [143]. Using immunotherapies have shown a drastic improvement in OS and enhance the therapeutic response of many solid tumors such as (melanoma and renal cancer). Hence, immune checkpoints in designing a treatment regimen for PDAC is a promising avenue [144]. The most widely used immune checkpoint inhibitors are against the programmed cell-death-1 (PD-1), and the cytotoxic T lymphocyte antigen-4 (CTLA-4) receptors and programmed cell-death ligand-1 (PD-L1) [145].

5.1. Reasons for checkpoint inhibitors failure in PDAC

Immune checkpoints refer to immunogenic regulatory mechanisms pertaining to T-cell immune response. Immune checkpoint blockades (ICB) such as PD-1, PD-L1, and CTLA-4 have shown promising results and varied responses in solid tumors [146]. Cancer immunotherapy has a variable patient outcome that is dependent on the leukocyte population in the tumor microenvironment [147]. Not every patient of either the same or different tumor subtype will elicit a similar anti-tumor immune response to ICB. For highly resectable tumors, chemotherapy may be surpassed by immunotherapy owing to fewer side effects and irreversible tumor regression. However, clinical trials with ICB for PDAC have been disappointing [148].

A major reason for the failure of immunotherapy in PDAC is the dense tumor microenvironment (TME) that is the limiting factor for a number of PDAC chemotherapies. PDAC TME consists of a dense fibrous stroma consisting of tumor cells, immune cells, growth factors for tumor metastasis, extracellular matrix, fibroblasts making it highly complex and heterogenous [3]. Tumor-infiltrating lymphocytes are present at a lower population in the PDAC TME, driving factors for effective clinical response to ICB.

Single-agent clinical trials for employing ICB for PDAC have not shown promising results. Single-agent anti-CTLA-4 (Ipilimumab) dosed intravenously at 3mg/kg/dose (4 doses/course, every 3 weeks, for maximum 2 courses) was practically ineffective for the treatment of advanced pancreatic cancer [149]. Monotherapy with PD-1/PD-L1 ICB durvalumab showed partial response in 2 out of 29 patients who received the intervention and had evaluable data [150]. In essence, single-agent immunotherapies for PDAC have not garnered an effective patient outcome.

Antigenicity and immunogenicity are two major factors responsible for the failure of ICB in PDAC [151]. Reduced antigenicity in PDAC refers to tumor cells' inability to produce and present tumor-associated antigens to the effector cells of the immune system. This, in turn, negatively affects T-cells' ability to mount an immune attack in response to antigen producing cells [152]. Immunogenicity, which is the ability to induce an immune response in cancer, is dependent on multiple factors like composition of the stroma, infiltration of CD8+ and CD4+ T-cells, B cells, antigen presentation [152].

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PDAC tumor can be classified into subtypes based on RNA expression analysis, and it reveals prominent immune cell signatures specific to the PDAC subtype. Since each subtype has a different signature that characterizes the tumor microenvironment components, they will show different outcomes in response to ICB therapies. Tumors are classified into inflamed (hot) and non-inflamed (cold) based on T-cell infiltration [153]. Most of the preclinical and clinical studies have concluded that only patients who have T-cell inflamed tumors would have a high chance of responding to ICB. However, non-inflamed tumors respond poorly to monotherapy of ICB due to low level of tumor infiltrating lymphocytes (TIL) and PDL-1[153]. Therefore, combining ICB with other agents is a valid strategy to (i) enhance tumor immunogenicity, (ii) recruit more TIL to the tumor site, and (iii) minimize tumor microenvironments immunosuppression [154,155]. PDAC is the lowest mutational tumor among other solid tumors, where the average of mutation is 1 mutation per megabase (Mb) compared to 11 mutations per Mb in melanoma [156]. Thus, immune system recognition of neoantigen is solely based on neoantigen quality, where it can be recognized if it is high-quality neoantigen such as microbial-like sequence [157,158].

5.2. Possible approaches to improve tumor immunogenicity

Various reports have shown the ineffectiveness of monotherapies for PDAC. Hence, it is worthwhile to explore the effect of combinations of ICB or chemotherapy and ICB to tackle PDAC. Patients with poor prognosis and rapidly advancing cases of metastatic PDAC were dosed with a combination of Durvalumab and Tremelimumab. No patients responded well to Durvalumab monotherapy, a response rate of 3.1% was seen in patients receiving combination therapy, although with adverse toxicity in 22% of the cohort of patients [159].

Gemcitabine, frontline chemotherapy for PDAC, has been tested in combination with ICB to disengage PD-1/PD-L1 interaction. Attempts have been made to deliver gemcitabine and anti-PD-L1 in a controlled manner to the tumor [160]. Daniel et al. found that prolonged exposure of PDAC cancer to gemcitabine promotes the expression of several immune markers such as MHC class 1, PD-L1, and PD-L2. The authors also found that gemcitabine plays a role in increasing the secretion of several cytokines and TGFβ [160].

The activity of gemcitabine and anti-PD-1 was tested in vivo on transgenic mice; the current combination failed to inhibit the tumor growth unless the mice had genetic ablation of TGFβ. In TGFβ deficient mice, gemcitabine and anti-PD-1 activity in inhibiting tumor regression were improved by enhancing CTL infiltration into the TME [160]. These observations suggest that gemcitabine primes the PDAC tumor for enhanced antigen presentation, making anti-PD-1 therapy more effective in eliciting a robust CD8+ T-cell response and reducing tumor load [161]. Other drugs such as Cisplatin, albumin-bound paclitaxel, nivolumab are currently under clinical trials to expand on the promising outcomes of the combination of ICB with chemotherapy. So far, it is likely that moving ahead, immunotherapy for PDAC shall shift clinical focus from monotherapy to combination therapy.

Radio and chemotherapy, which have immunogenic cell death effects, have actively reduced tumor burden and enhanced T-cell infiltration to tumor microenvironments.

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Chemotherapeutic agents that induce immunogenic cell death are platinum-based drugs and taxanes combined with ICB to improve the immune system against cancer cells [162,163].

CCL2-CCR2 leads to recruiting Tumor-associated macrophages (TAM) that play as immunosuppressive within tumor microenvironments [164]. Many clinical trials tried to modulate the immune system to recognize and fight cancer cells. One of the clinical trials is using chemokines receptor 2 antagonist (PF-04136309), which inhibits the binding of chemokines ligand 2 to its receptor CCR2, resulting in inhibition. Immunosuppressive TAM [165].

Another way of inducing immune cells against cancer cells is via using the vaccine. GVAX is one of the vaccines composed of two human pancreatic cells engineered to secret immune cytokines (Granulocyte-Macrophage Colony Stimulating Factor (GM- CSF)) [166]. GVAX efficiency was evaluated as adjuvant therapy in resected PDAC and as a treatment regimen combined with ipilimumab in metastasis PDAC. In clinical trials phase I/II, GVAX was found to induce mesothelin-specific CD8+ T cells in the tumor section and improved the overall survival rate in PDAC patients. Thus, using GVAX, which functions as a trigger for dendritic cells that phagocytes released GM-CSF and migrate to lymph node to activate T cells, is a promising way to enhance tumor immunogenicity in PDAC patients [167,168].

All these methods have been either well established or are being rapidly developed to treat this severe disease. These have a lot of prospects to be explored and challenges to be overcome.

5.3. Other promising targets and strategies

Many teams have used groundbreaking bioinformatics, biochemistry, and cell biology approaches to identify specific mKRAS protein sequences that can be recognized by T cells. These teams have uncovered a set of molecular receptors that enable T cells to be home to mKRAS-expressing cancer cells. On the basis of these findings, Vonderheide RH and his group is undertaking two different clinical trials of new technologies designed to trigger mKRAS immune activity in patients with resected pancreatic cancer. The team is planning to use the most effective T - cell receptor identified and to perform a clinical trial of optimized T -cell therapy for the treatment of metastatic pancreatic cancer [169]. Furthermore, there many other targets and promising strategies are still under development for better therapeutic outcomes as shown in Table 3

6. Advances in nanoparticle diagnosis and treatment

The currently available treatment models have limited clinical response, and continuous efforts are being made to increase the treatment efficacy. Nanomedicine and gene therapy have been found to give promising preclinical outcomes in treating aggressive pancreatic tumors, a few of which also went into the clinical trial. Due to the complex tumor stroma composition in PDAC, many drugs failed to penetrate the stroma barrier that negatively impacted their efficiency. Nanomedicines and gene therapy have potential use in enhancing PDAC diagnosis and treatment [18]. Moreover, the exact mechanism of how the nanoparticles accumulate at the PDAC tumor site is unknown. Most of nanoparticles relay

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on leaky vasculature (EPR effect) to be accumulated in the tumor sites, however, hypovasculature of PDAC tumor compromises the EPR effect and attenuates the nano-medicines delivery [170]. Therefore, using targeted nanoparticles provide a viable solution to improve the diagnostic test's sensitivity and help treat PDAC as shown in Figure 3. Preclinically, several nanoparticles have been synthesized to enhance PDAC therapy.

Biodegradable nanoparticles characterize by its ability to escape the immune system and improve *in vivo* circulatory time. [171]. Albumin NPs have been used widely to deliver the cytotoxic gemcitabine to PDAC. Albumin NPs enhance the absorption of the drug in the circulatory system and be renewable and economical [172]. Many studies have revealed that gem-albumin nanoparticles enhanced the tumor regression activity compared to free gem [173–175].

Liposomal formulation characterizes by its biocompatibility, longer circulation time, and most importantly, the potential of surface modulation by ligands for active targeting. Recently, NAPOLI-1 trial showed the role of using irinotecan liposomal formulation combined with 5-FU/folinic acid as second-line therapy for patients who received gem-based therapy as first line therapy. NAPOLI-1 trial confirmed that receiving irinotecan liposomal formulation in combined with 5-FU/folinic acid improved OS (6.1 months) compared to 5-FU/folinic acid OS (4.2 months) [176].

Polymeric nanoparticles have several advantages: size uniformity, good release kinetics, malleability for customization, pH responding properties, and hydrophilic shell; all these properties make it a perfect PDAC delivery system that can deliver different cytotoxic drugs, DNA, proteins, and siRNA [177]. For example, using paclitaxel in its free form does not show significant activity against PDAC, but when administered via poly-lactic-co-glycolic acid (PLGA) nanoparticles, it penetrates the tumor and inhibits protein synthesis. The PDAC tumor uptake of paclitaxel PLGA nanoparticles was 5 folds higher than conventional therapy [178]. Furthermore, Couvreur et al. as shown in Figure 4. have enhanced Gem's stability and efficiency via using self-assembled nanoparticles composed of gemcitabine and the natural lipid squalene (Gem-SQ) [179]. In mice bearing Panc-1 orthotopic model, Gem-SQ inhibited the tumor regression and enhanced the mice survivability compared to free [180,181].

Gene therapy is a promising way to enhance the overall PDAC therapy, but its delivery challenges limit its usage. For example, the main siRNA challenge is their stability issue within the biological systems; therefore, many researchers are trying to overcome this issue using drug delivery systems [182]. Khvalevsky et al. have used a biodegradable polymer matrix loaded with anti-$KRAS^{G12D}$ siRNA. siG12D loader improved siRNA stability, overcame renal clearance, and, most importantly, knockdown $KRAS^{G12D}$ expression, which improved overall tumor inhibition in the xenograft animal model [183]. Zhao et al. have constructed a hybrid lipid polymer nanoparticle to co-deliver siRNA (si-HIF1α) and gemcitabine (Gem) to target the HIF1α in PDAC cells. They have successfully shown a synergistic killing effect with siRNA and Gem combination therapy *in vitro* and *in vivo* and can inhibit tumor metastasis in the orthotopic tumor model [184]. Frederico P. et al. have designed pegylated polymeric nanoparticles conjugated with calcium phosphate to deliver

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VEGF siRNA. In this work, hybrid nanoparticles enhanced the serum stability and gene silencing efficiency [185].

The hypoxic TME in PDAC produces more HIFs, which are responsible for the activation of genes that control invasion, angiogenesis, chemoresistance, and proliferation [40]. The polymeric lipids coated NPs that loaded with GEM and siRNA, which was complexed to positively charged polylysine residues on the NPs surface, significantly inhibited the growth of subcutaneous PANC-1 tumor xenografts. Thus, it indicated a synergistic effect between HIF-1alpha inhibition and the chemotherapy (Gem). Not only that the combination treatment significantly shrunk the tumor size in an orthotopic PDAC model in comparison with un-encapsulated siRNA and GEM, or with NPs loaded with GEM only, but also, no peritoneal metastases were observed in the combination treatment group as shown in Figure 5. Also, because PDAC TME becomes resistant to chemo and radiotherapy, Wason et al. used nanoparticles to deliver drugs using cerium oxide nanoparticles (CONPs) to regulate production of ROS that might sensitize PDAC cells to radiotherapy (RT) [186,187]. CONPs-based pretreatment limited tumor growth in an orthotopic model nude mice, leading towards significant shrinkage in tumor weight and volume as compared to radiotherapy alone. Several nanomedicine-based strategies have been designed and tested for the treatment of PDAC. There is a need for more smart strategies to overcome these barriers and maximize treatment accumulation in the pancreatic tumor site [188].

7. Conclusion and Future Direction

PDAC is an extraordinarily high malignancy cancer entity, particularly characterized by poor prognosis and constantly increasing patient numbers. The aggressive biology and the fact that most patients participate in advanced or disseminated disorder stages make the development of new PDAC therapeutic approaches one of the superordinate modern oncological science tasks. Research over the last 20 years led to a systematic multi-step model of PDAC growth and progress. While this has certainly changed our understanding of PDAC as a disease, so far, neither of these findings could be successfully converted into a medical breakthrough. It is becoming increasingly obvious that the clinical effectiveness of single-agent treatments tends to lag below acceptable estimates, and smart combinations seem to be required instead. In addition, PDAC anti-CSC therapies of the next generation should be produced to attack active stroma cells and target cells such as Wnt-cell components, PSC, MSC, and/or TAMs that are extremely penetrable by small molecules, nanoparticles, or oligonucleotides and perhaps immunotherapy.

Furthermore, nanomedicines' ability to aggregate and target tumors could be leveraged to enhance early tumor identification, significantly improve survival, and increase the extent of surgical resection. Novel compounds and nanoparticles are continuing to be developed in non-viral vector technology [189]. And a combination of gene therapy with these, along with conventional drug therapy would also prove to be beneficial.

Despite substantial advances in cancer research over the last era, PDAC seems to have very poor survival rates. The present failure to diagnose early-stage prevents the use of effective treatments. Additionally, drug resistance growth is a key factor for recognizing current

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therapy failure in both the tumor and metastatic tissues. Hence, the improvement in survival of PDAC patients will occur not only through the identification of early serum markers but also through therapeutic approaches directed towards reducing pancreatic CSCs and decreasing drug resistance. Importantly, genetic analyses have strengthened our mechanistic and translational understanding of pancreatic cancer. Genetic principles and techniques are eventually applied to clinical practice, especially for precision medicine initiatives. However,, Epigenomics is evolving rapidly as a promising scientific and computational model for advancing the comprehension of this disease. More significantly, recent studies have identified possible actionable mechanisms supporting the assumption that prospective pancreatic cancer trials will include rigorous epigenomic therapy research. Therefore, epigenomics aims to produce a large amount of new biological as well as scientific relevant information.

In this respect, all the above strategies, and especially modern techniques, represent attractive strategies for both biologically inspired utilizing PDAC TME and immunotherapy strategies that might be the future for finding a new cure to manage PDAC disease.

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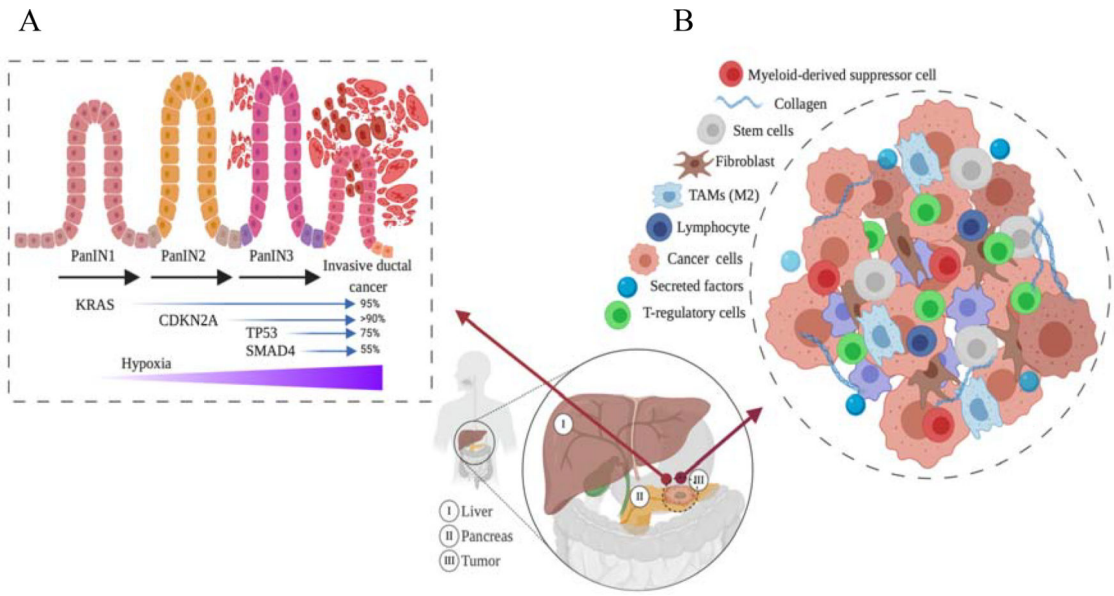

Figure 1:

Pancreatic ductal adenocarcinoma (PDAC) stages and tumor microenvironments (TME). (A) different stages of PDAC, and the expression of oncogenes at each stage is shown. (B) The complexity of TME components that attenuate cytotoxic drug penetration is shown.

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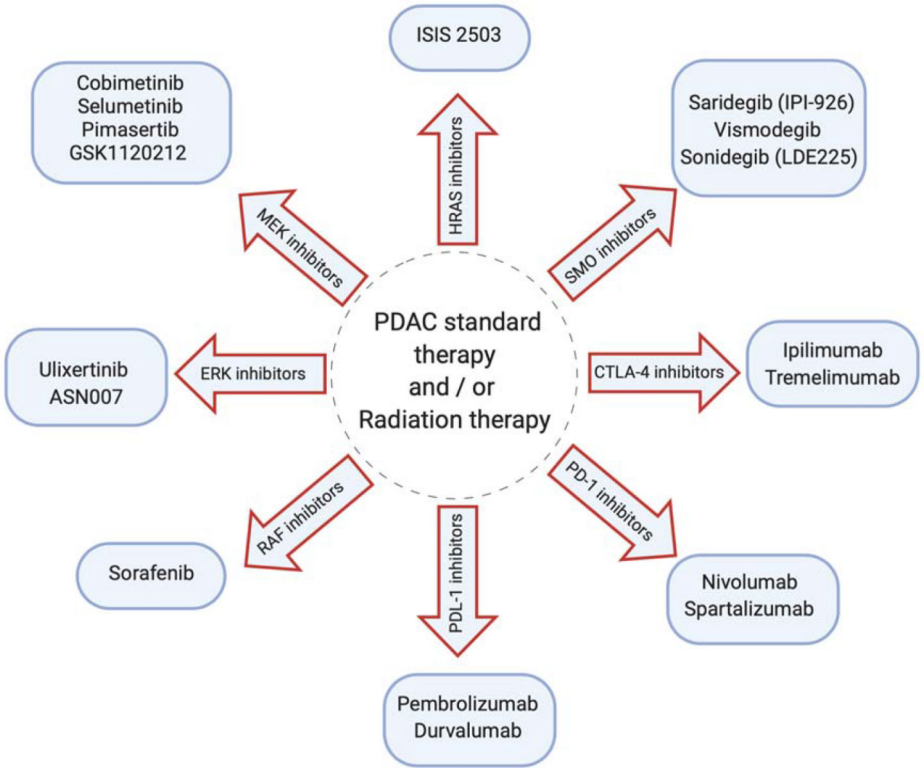

Figure 2:

Various classes of drugs that are being explored in the clinical trials in combination with PDAC standard therapy and/or radiation therapy to enhance the efficiency and the overall PDAC response are shown.

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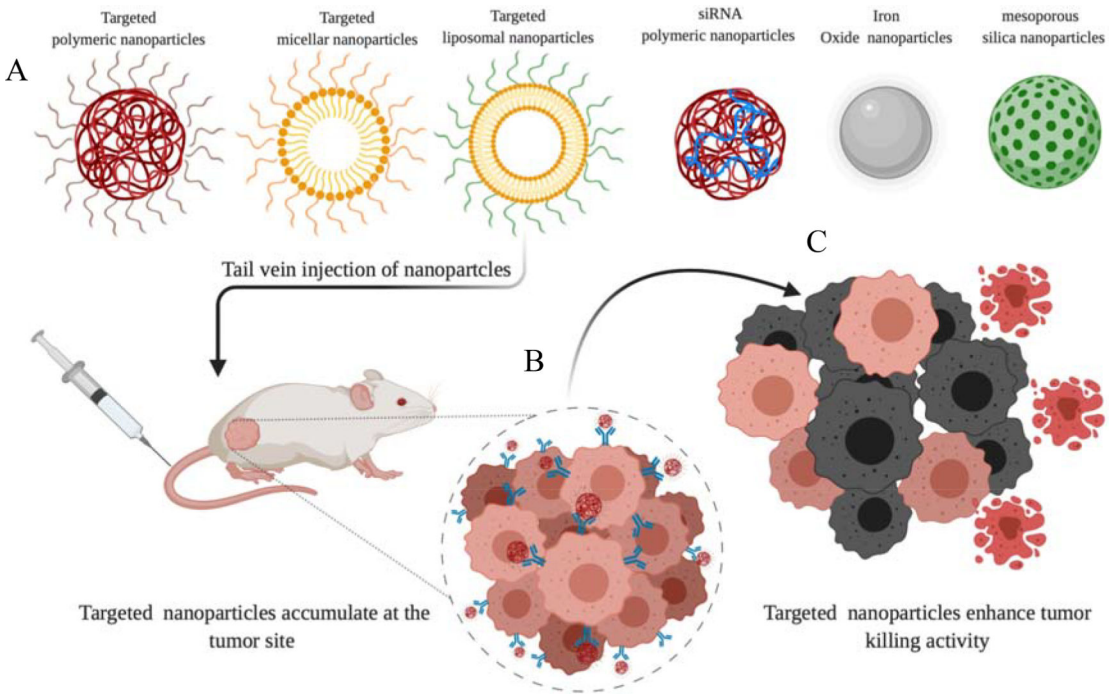

Figure 3:

Various types of nanoparticles for PDAC therapy. (A) surface decorated nanoparticles to actively enhance the tumor selectivity is shown. (B) Specific nanoparticles that actively target tumor cells via receptor recognition are shown. (C) The uptake of nanoparticles via the endocytosis process results in cancer cell eradication. (Modified from Brachi et al. “Nanomedicine for imaging and therapy of pancreatic adenocarcinoma.” Frontiers in bioengineering and biotechnology 7 (2019)

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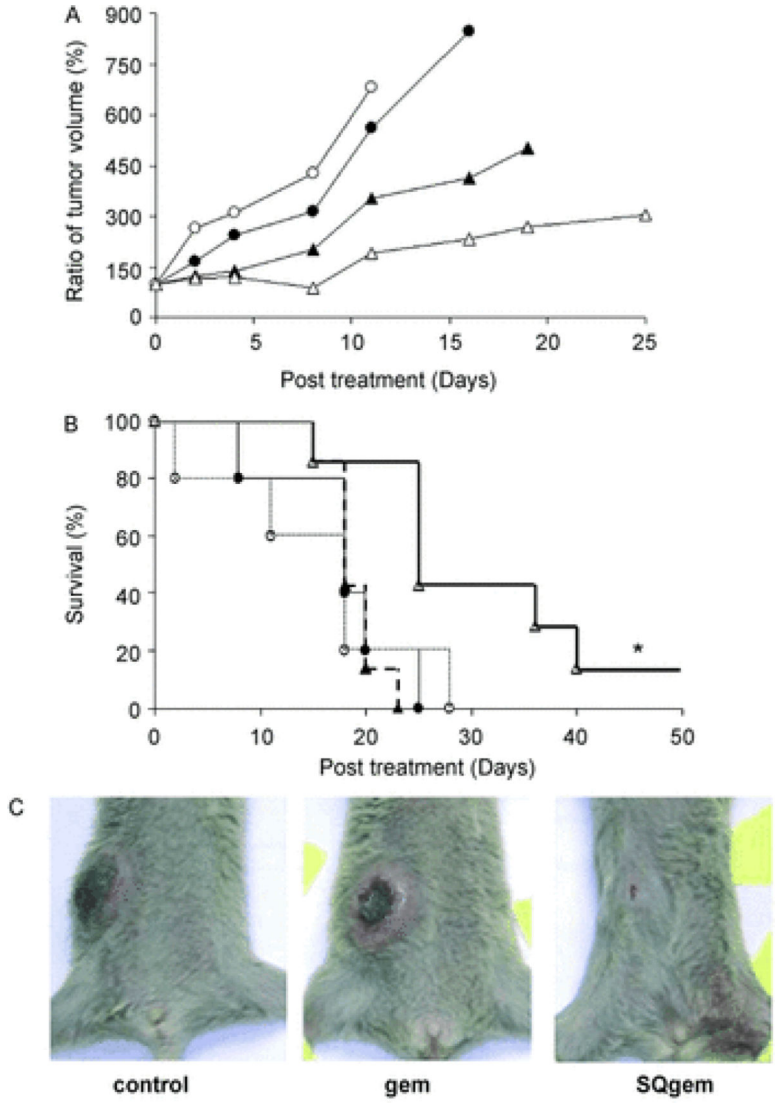

Figure 4. Anticancer activity of SQgem in nanoparticles platform and gem (5 mg/kg equivalent doses) following intravenous treatment (on 0, 4, 8, and 13 days) of mice bearing P388 subcutaneous tumors.

A) Tumor progression: Control (black spheres), saline (white spheres), gem (black diamonds), SQgem nano assemblies (white diamonds). B) Survival curve of mice: Control (solid line), saline (dotted line), gem (dashed line), SQgem nano assemblies (heavy solid line). * indicates $P<0.05$, as assessed by Kaplan–Meier test. C) Photograph showing the difference in tumor growth in mice following the completion of indicated treatment. Reproduced from [179]

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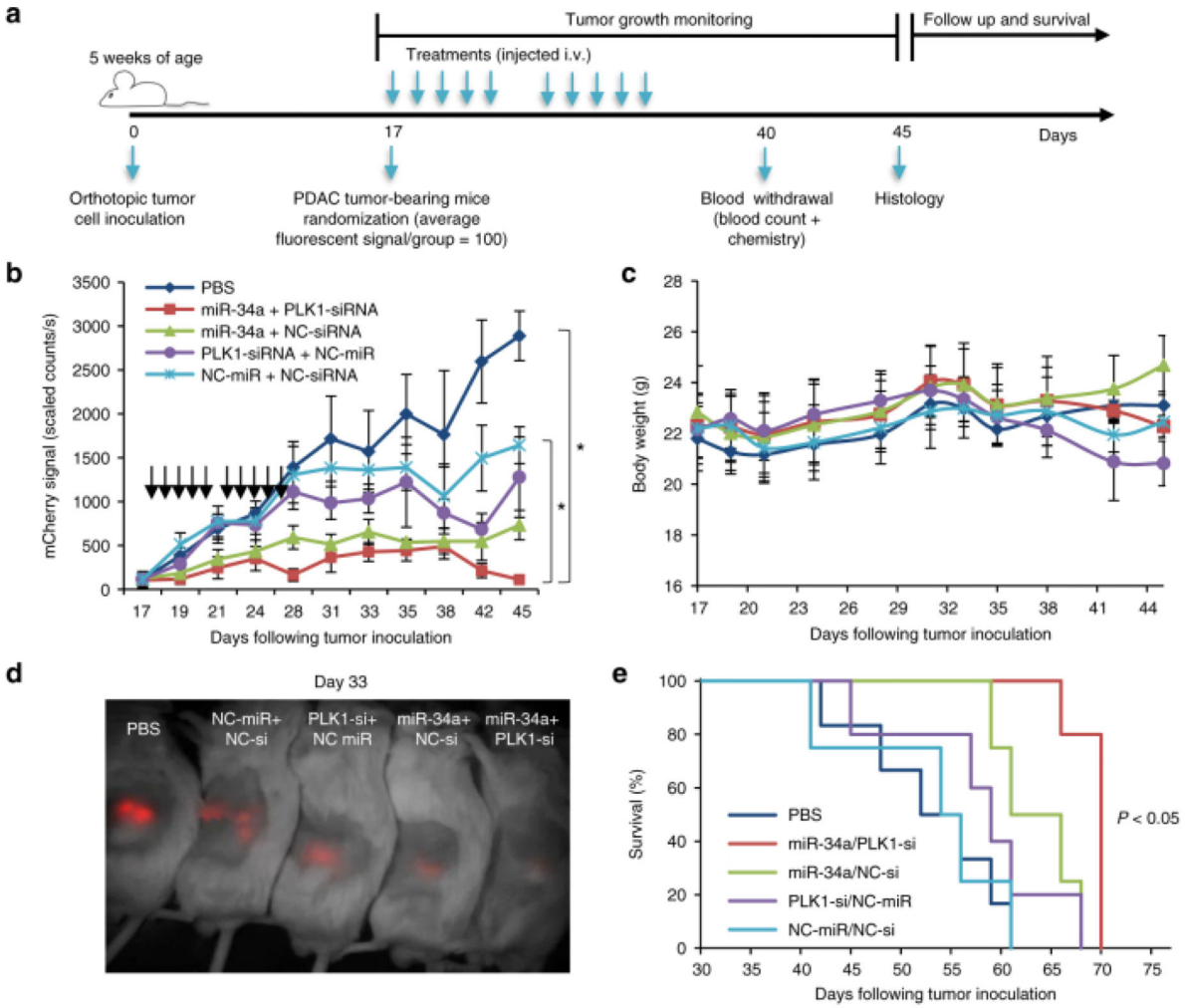

Figure 5. In vivo antitumor effect of miRNA–siRNA combination.

A study design for testing miRNA–siRNA combination efficacy in the orthotopic PDAC model. b Tumor growth curves from twice a week fluorescent measurement of tumor-bearing mice treated with APA complexed with miR-34a/PLK1-siRNA, miR-34a/NC-siRNA, PLK1-siRNA/NC-miR, NC-miR/NC-siRNA or PBS (treatments are marked with arrows). (n = 6, 7). Data represent mean ± SEM. One-way ANOVA. c In vivo toxicity via mouse body weight evaluation. Data represent mean ± SEM. d An image of a representative mouse from each treatment group 33 days post tumor inoculation showing the difference in tumor fluorescent signal. e Kaplan–Meier survival graph. Log-Rank test, $P < 0.05$ for the combination miR-34a/PLK1-siRNA compared to all other treatment groups. Reproduced from [188].

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Table 1:

Clinical trials of Drug delivery in PDAC (Gemcitabine based therapies)

Study Title	Phase	NCT number
Gene Therapy of Pancreatic Ductal Adenocarcinoma	Phase 1	NCT01274455
Study to Investigate the Preliminary Efficacy and Safety of INNO-206 in Advanced Pancreatic Cancer	Phase 2	NCT01580397
Study of siG12D LODER in Combination with Chemotherapy in Patients with Locally Advanced Pancreatic Cancer	Phase 2	NCT01676259
Atu027 Plus Gemcitabine in Advanced or Metastatic Pancreatic Cancer (Atu027-I-02)	Phase 1/2	NCT01808638
Study of Gemcitabine, Abraxane® Plus Placebo Versus Gemcitabine, Abraxane® Plus 1 or 2 Truncated Courses of Demcizumab in Subjects with 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma	Phase 2	NCT02289898
Modified FOLFIRINOX for Gemcitabine Refractory Pancreatic Cancer: A Phase II Multicenter Trial	Phase 2	NCT02440958
Phase Ib/II Study of MEDI4736 Evaluated in Different Combinations in Metastatic Pancreatic Ductal Carcinoma	Phase 1/2	NCT02583477
A Study of Abemaciclib (LY2835219) Alone or in Combination with Other Agents in Participants with Previously Treated Pancreatic Ductal Adenocarcinoma	Phase 2	NCT02981342
A Study of SLC-0111 and Gemcitabine for Metastatic Pancreatic Ductal Cancer in Subjects Positive for CAIX	Phase 1/2	NCT03450018
Scheduling Nab-paclitaxel With Gemcitabine	Phase 2	NCT03529175
Nab-Paclitaxel + Cisplatin + Gemcitabine in Untreated Metastatic Pancreatic Adenocarcinoma	Phase 2	NCT03915444
Retrospective Analysis of 2nd-line Nab-Paclitaxel + gemcitabine After 1st-line FOLFIRINOX in Pancreatic Cancer	N/A	NCT04133155

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Table 2:

Clinical trials of Drug delivery in PDAC (Immunotherapy for PDAC)

Study Title	Phase	NCT number
A Study of Epacadostat in Combination with Pembrolizumab and Chemotherapy in Subjects with Advanced or Metastatic Solid Tumors (ECHO-207/KEYNOTE-723)	Phase 1/2	NCT03085914
Paclitaxel Protein Bound Plus Cisplatin Plus Gemcitabine and Paricalcitol for Pancreatic Adenocarcinoma (NABPLAGEMD)	Phase 2	NCT03415854
Second-line Study of PEGPH20 and Pembro for HA High Metastatic PDAC	Phase 2	NCT03634332
Study of Pembrolizumab With or Without Defactinib Following Chemotherapy as a Neoadjuvant and Adjuvant Treatment for Resectable Pancreatic Ductal Adenocarcinoma	Phase 2	NCT03727880
Trial of Neoadjuvant and Adjuvant Nivolumab and BMS-813160 With or Without GVAX for Locally Advanced Pancreatic Ductal Adenocarcinomas.	Phase 1/2	NCT03767582
A Multiple Ascending Dose Study of MEDI7247 in Advanced or Metastatic Solid Tumors	Phase 1	NCT03811652
Nivolumab in Combination with Chemotherapy Before Surgery in Treating Patients with Borderline Resectable Pancreatic Cancer	Phase 1/2	NCT03970252
Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined with Nivolumab and Ipilimumab for Patients with Resected MMR-p Colorectal and Pancreatic Cancer	Phase 1	NCT04117087
Mutant KRAS G12V-specific TCR Transduced T Cell Therapy for Advanced Pancreatic Cancer	Phase 1/2	NCT04146298
A Multi-Cancer, Multi-State, Platform Study of Durvalumab (MEDI4736) and Oleclumab (MEDI9447) in Pancreatic Adenocarcinoma, Non-Small Cell Lung Cancer and Squamous Cell Carcinoma of the Head and Neck to Correlate Clinical, Molecular and Immunologic Parameters with DNA Methylation	Phase 2	NCT04262388

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Table 3.

Potential Targets in Pancreatic Cancer.

Molecular targets	Molecular pathways	Reference
a. Transmembrane Receptor Proteins and downstream signaling cascade	The receptor tyrosine kinases (RTKs): Ras/MAPK, PI3K/AKT, PLCγ/PKC, and JAK/STATs.	[190,191]
	The phosphoinositide 3 kinases/AKT/ mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway	[191]
	EGFR: detected in up to 90% of PDAC	[192]
	FGF/FGFR: The fibroblast growth factor (FGF)/FGFR pathway plays a key role in PDAC development and progression.	[193]
	IGF/IGFR: high expression of Insulin-like Growth Factor-1 (IGF-1) and IGF1R	[192]
	TRK: TRK gene fusions	[194,195]
	Vascular endothelial growth factor (VEGF)/vegfr): Angiogenesis pathway	[192]
b. Other pathways	WNT/β-CATENIN:	[196,197]
	NOTCH:	[197]
	ROUNDABOUT (ROBO) RECEPTORS/ SLIT GLYCOPROTEIN LIGANDS (SLIT):	[198,199]
	TRANSFORMING GROWTH FACTOR BETA (TGF-β):	[192,197]
	HEDGEHOG (Hh):	[35,200,201]
	NEUREGULIN-1 (NRG1):	[202]
c. Tumor-Suppressor Genes	TP53:	[197]
	SMAD4 (DPC4):	[203]
	BRCA:	[204–206]
	MMR DEFICIENCY	[145]
	EMT	[193,197,207]
	Extracellular Matrix (ECM)	[208,209]
	Cancer Stem Cells	[210]