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Review

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Therapeutic targets in the pancreatic adenocarcinoma microenvironment: past challenges and opportunities for the future

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer-related mortality, with cytotoxic chemotherapy still the mainstay of treatment. Beyond effective therapeutic agents alone, successful drug delivery is paramount. In PDAC, the tumor microenvironment represents a physical barrier that limits *in vivo* drug delivery and efficacy. In this review, we highlight therapeutic targets in the tumor microenvironment, focusing on past challenges and opportunities for the future. Targets discussed include the Hedgehog pathway, angiogenesis, hyaluronic acid, cancer-associated fibroblasts and associated cytokines, among others. Despite the obstacles in successfully recapitulating promising lab results to practice-changing clinical results, many important lessons have been learned to improve clinical trial design within a highly engaged and motivated scientific community. These collaborative efforts and the collective optimism will continue to propel the momentum forward to overcome these barriers and ultimately improve patient outcomes.

Keywords: Pancreatic cancer, PDAC, tumor microenvironment, pancreatic stroma

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) represents a leading cause of cancer-related mortality, with a 5-

year survival rate of 9%[1]. Cytotoxic chemotherapy remains the mainstay of treatment for patients with unresectable locally advanced and metastatic PDAC, with PARP inhibitors recently approved for the subgroup of patients with germline *BRCA* mutations[2,3]. Despite the advent of improved genomic sequencing and the recognition of specific molecular subtypes, direct therapeutic implications are still being investigated[4-8].

Beyond effective therapeutic agents alone, successful drug delivery is paramount and in PDAC, the tumor microenvironment embodies a physical barrier that limits *in vivo* drug delivery and efficacy. The PDAC tumor microenvironment consists of a complex arrangement of extracellular matrix (ECM), vasculature, fibroblasts, stellate cells, and immune cells[6,9,10]. Pancreatic stellate cells (PSCs), which make up about half of the stroma, are activated by a number of mechanisms, including chronic inflammation, hypoxia-inducible factor 1-alpha (HIF1α), and molecular signaling pathways[11]. Once activated, PSCs drive desmoplasia by producing significant quantities of the ECM, such as collagen, hyaluronic acid (HA), fibronectin, and matrix metalloproteases. This desmoplastic reaction represents a cardinal feature in PDAC [Figure 1][12,13].

This dense ECM lends itself to high interstitial fluid pressure (IFP), hindering perfusion and preventing the successful delivery of chemotherapy through the stroma[14,15]. Stroma-specific subtypes have been described, with a "normal" subtype demonstrating high expression of PSC markers compared to the "activated" subtype consisting of macrophages and proinflammatory cytokines[6,9]. These subtypes play a role in the regulation of tissue tension and stiffness. Despite the hostile environment of the ECM, PDAC tumors seem to thrive within. Physical forces within this microenvironment, including hydrostatic pressure and tissue tension, appear to direct epithelial cell signaling and promote tumor progression[16]. Stress from the expanding tumor also leads to direct expression of vascular endothelial growth factor (VEGF) A and promotes hypoxia by physically compressing surrounding vasculature[17]. This hypoxic milieu promotes the epithelial to mesenchymal transition and further contributes to a favorable setting for PDAC growth.

While PSCs and cancer-associated fibroblasts (CAFs) were terms that were traditionally used interchangeably, recent studies have shown that CAFs actually comprise a heterogeneous population. CAFs not only play a role in the production of ECM proteins and soluble factors, but are also active in facilitating interaction with immune cells. Inflammatory CAFs (iCAFs) play an important role in immune regulation, and may contribute to the immunotherapeutic resistance seen in early trials. One such mechanism involves increased NF-κB signaling from iCAFs leading to the subsequent blockade of cytotoxic T cell infiltration[18]. Another mechanism involves IL-6 secretion from iCAFs, representing the production of another immunosuppressive cytokine within the tumor microenvironment[19]. There are also mesenchymal stem cell CAFs, acting through the CSF-1 receptor pathway to increase the accumulation of tumor-associated macrophages, which can also block T cell intratumoral infiltration[20,21]. Additionally, single cell RNA sequencing has delineated another distinct CAF subtype, antigen-presenting CAFs, characterizing yet another mechanism of influence within the immune environment of PDAC[22].

KRAS mutations have been identified in > 90% of patients with PDAC[4]. The most common $KRAS^{G12D}$ mutation has been demonstrated to up-regulate inflammatory pathways and stimulate stromal activation[23]. Genetically engineered mouse (GEM) models designed with various driver mutations resulted in differing amounts of stromal desmoplasia, highlighting the impact not only on tumor cell proliferation but also on the tumor microenvironment[24]. Furthermore, molecular profiling has elucidated stroma-specific subtypes, which have prognostic implications and are correlated with distinct immune infiltrates and biomarkers[6,9,25].

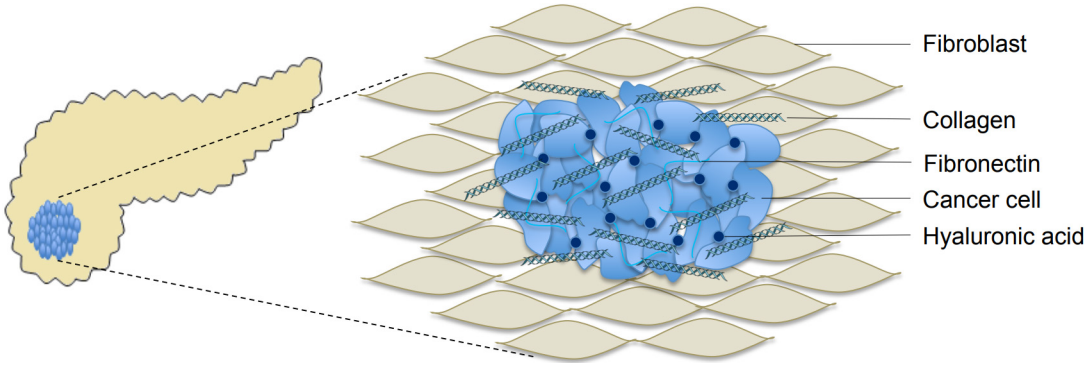

Figure 1. Schematic figure of the desmoplastic stromal reaction in PDAC involving fibroblasts, collagen, hyaluronic acid and extracellular matrix proteins (courtesy of Drs. A. Hosein, R. Brekken, and A. Maitra). PDAC: Pancreatic ductal adenocarcinoma.

In addition to the tumor microenvironment surrounding the PDAC primary, metastatic sites such as the liver also have their own microenvironment to create a pro-metastatic niche often with resultant chemo- and immunotherapeutic resistance[26]. This pro-metastatic niche is defined by the presence of increased myeloid cells and matrix proteins, with involvement of hepatocytes, tissue inhibitor matrix metalloproteinase 1, and tumor-derived exosomes[27-29]. Preclinical modeling has demonstrated that the presence of a liver metastasis triggers a systemic immune response mediated independently from programmed cell death protein 1 (PD-1)[30]. This provides additional mechanistic rationale for the challenges with immunotherapeutic resistance, particularly in the presence of liver metastases.

With an increased understanding of the biology of the tumor microenvironment, therapeutic agents targeting specific features and pathways of the stroma have been developed [Figure 2]. While immunotherapeutics are one of several exciting and upcoming strategies, an in-depth focus is beyond the scope of this manuscript. Here we review therapeutic targets in the tumor microenvironment focused on advanced PDAC, highlighting past challenges and opportunities for the future. Over the last several decades, there have been a plethora of clinical trials that failed to meet their primary endpoints; however, many important lessons have been learned to improve clinical trial design within a highly engaged and collaborative scientific community. The collective optimism and momentum remain high to overcome these barriers to ultimately improve patient outcomes.

BREAKING DOWN THE BENCH TO BEDSIDE ADAGE

The traditional bench to bedside model has proven successful in other malignancies, where promising results in the lab can be translated into practice-changing clinical trials that prolong survival and improve quality of life. Over the last several decades, we have learned that PDAC does not fall neatly into this mold where the dynamic *in vivo* tumor microenvironment interacts differently than expected based on preclinical models. One such example involves the hedgehog (Hh) pathway, which is involved in the pathogenesis of PDAC[31-34]. The overexpression of Shh has been reported in more than 70% of primary tumors[33,35]. Within stromal cells, paracrine Hh signaling is reversed, leading to angiogenesis and contributing to the tumor microenvironment[36-38]. In an effort to overcome chemoresistance, Olive *et al.*[39] administered gemcitabine with the Hh pathway inhibitor saridegib (IPI-926) to mice. They observed a subsequent increase in intratumoral gemcitabine concentration and stable disease. With this convincing preclinical evidence and scientific rationale for combination with chemotherapy, early phase clinical trials in patients with PDAC were launched.

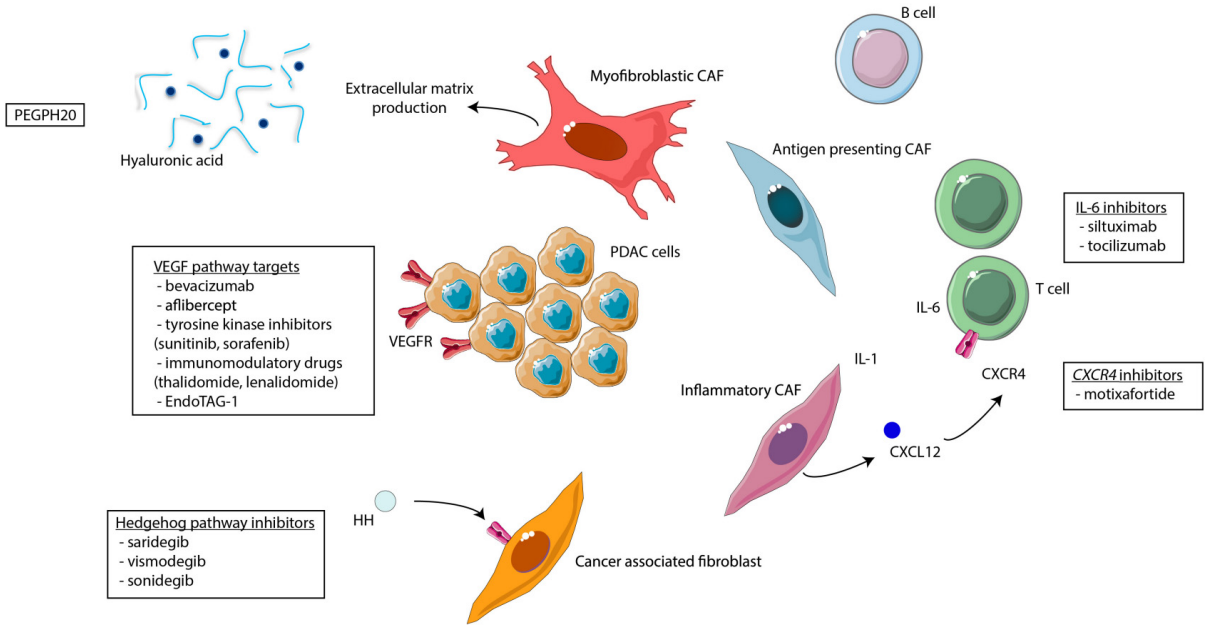

Figure 2. Schematic figure of select PDAC tumor microenvironment targets and therapeutic agents. HH: Hedgehog; CAF: cancer-associated fibroblast; PDAC: pancreatic ductal adenocarcinoma.

Saridegib was combined with gemcitabine in a phase Ib trial, demonstrating safety and tolerability[40,41]. However, the phase II portion of this combination was stopped after an interim analysis demonstrated a shorter median overall survival (OS) for the saridegib/gemcitabine arm compared to the placebo/gemcitabine arm. Saridegib was also studied with FOLFIRINOX in a phase I trial with a 67% objective response rate (ORR) in 15 patients, but this study was stopped early with the release of the interim phase II results of the saridegib and gemcitabine study[42].

In one pilot study, Kim *et al.*[43] enrolled 25 patients, 75% with elevated Shh expression at baseline biopsy, who received gemcitabine with vismodegib. Median progression-free survival (PFS) and OS measured 2.8 and 5.3 months, respectively. Correlative studies comparing the pre- and post-treatment PDAC cancer stem cells showed no significant difference with vismodegib treatment. In a separate study, Catenacci *et al.*[44] investigated the combination of vismodegib with gemcitabine in a phase Ib/randomized phase II trial of unselected patients (n = 106 in phase II arm) with advanced PDAC. There was no difference in PFS or OS, and associated preclinical models did not demonstrate an improvement in drug delivery or efficacy with vismodegib. Vismodegib has also been studied in combination with gemcitabine and nab-paclitaxel where interim results were published in abstract form (59 patients of the planned sample size of 80), with median PFS of 5.5 months[45]. Final results have not yet been published.

A third Shh inhibitor sonidegib was investigated in combination with gemcitabine in a phase I study, with no clear clinical benefit and a median PFS similar to the current standard of care[46]. A second phase I trial of sonidegib, this time in combination with gemcitabine and nab-paclitaxel, has also been reported in abstract form demonstrating tolerability[47]. Given the disappointing results from combination Shh inhibitor and standard of care chemotherapy, the use of Shh inhibitors has not advanced to phase III trials or become incorporated into routine clinical care.

Rather than simply moving onto the next target, understanding the mechanisms underlying this unsuccessful recapitulation from encouraging lab results to clinical trials was critical. Rhim *et al.*[48] conducted experiments to genetically delete sonic Hh, resulting in decreased stromal desmoplasia. Paradoxically, this hastened tumor growth and metastasis, with increased mortality. One potential contributor to this paradoxical effect was the observation of increased vascularity and blood vessel density surrounding these undifferentiated tumors. Another important observation was that tumors with either genetically deleted Shh or post saridegib treatment were smaller in size but exhibited a more aggressive, undifferentiated histology. This may correlate with the clinical cachexia seen in patients with PDAC treated with a sonic Hh inhibitor. These observations highlight the value of appreciating the underlying complexity of the tumor stroma and provide insights into potential combinations that can be explored in the future. For example, rather than a one-size-fits-all approach, anti-angiogenesis targets could be considered as an adjunct for the subgroup of well-vascularized and poorly differentiated tumors.

In another study evaluating the discordant clinical results of Shh inhibitors, Lee *et al.*[34] reported that Hh pathway inhibition hastened growth, specifically impacting the epithelial and stromal element equilibrium. While stromal desmoplasia was suppressed, pancreatic intraepithelial neoplasia epithelium proliferated. By contrast, Hh pathway activation led to stromal hyperplasia and decreased epithelial growth, suggesting another therapeutic mechanism to be explored. A separate experiment examined the impact of unintended depletion of αSMA myofibroblasts by Shh inhibitors during stromal depletion, resulting in increased epithelial to mesenchymal transition and tumor proliferation[49]. Preclinical models demonstrated an immunosuppressive effect in the myofibroblast-depleted setting with anti-CTLA4 agents effectively decreasing tumor burden, thus representing yet another potential avenue for further study.

DOES THE ANSWER LIE IN THE SEQUENCE?

The bench to bedside model was also applied in studying angiogenesis targets in PDAC. VEGF expression was found to be associated with microvessel density (MVD), and high VEGF expression correlated with early recurrence post-resection[50,51]. Using mouse models injected with PDAC cells, Baker *et al.*[52] demonstrated that chemotherapy with VEGF blockade resulted in tumor shrinkage with decreased MVD. Other preclinical studies similarly supported the clinical exploration of anti-angiogenesis agents in PDAC[41,53-55].

Initial trials focused on concurrent combination therapy with an anti-angiogenic agent with cytotoxic chemotherapy. In a phase II trial published by Kindler *et al.*[56], 52 patients with advanced PDAC were treated with upfront bevacizumab and gemcitabine. Median survival measured 8.8 months, with 21% of partial responses and 46% with stable disease[56]. Additional phase II trials investigated the combination of bevacizumab with other agents, including docetaxel, erlotinib, gemcitabine with cisplatin, and gemcitabine with capecitabine[57-60].

In the phase III setting, the CALGB 80303 trial randomized patients with untreated metastatic PDAC to gemcitabine/bevacizumab *vs*. gemcitabine/placebo, with a similar median OS of 5.8 and 5.9 months between the two arms, respectively[61]. Bevacizumab in combination with erlotinib, a tyrosine kinase inhibitor that targets HER1/EGFR, was the next anti-angiogenic combination to be reported in a phase III clinical trial, with a similar OS between the two arms. There was a statistically significant improvement in PFS, with a hazard ratio of 0.73, but this has not changed practice[62]. Another EGFR inhibitor, cetuximab, was combined with bevacizumab with or without gemcitabine in a phase II trial[63]. This study was terminated early for futility, suggesting that dual VEGF and EGFR blockade was not an effective mechanism in PDAC.

Aflibercept, a recombinant fusion protein that "traps" VEGF, was studied in combination with gemcitabine in a phase III trial that was also stopped early for lack of efficacy[64]. Other VEGF-inhibiting tyrosine kinase inhibitors have been studied in combination with chemotherapy. With potentially promising results in the early phase setting, the phase III trial with axitinib and gemcitabine did not meet its primary endpoint and the trial was stopped early[65-67]. Sorafenib represented a similar trajectory, with variable results in the early phase setting when combined with chemotherapy[68-71]. The phase III BAYPAN trial comparing sorafenib with gemcitabine *vs.* placebo with gemcitabine also did not meet its primary endpoint of PFS, with no significant difference in median OS, either[72]. Additional tyrosine kinase inhibitors, including cabozantinib, sunitinib, vandetanib, and vatalanib, have been investigated in early phase trials with disappointing results[73-77].

In addition to drugs with a primary VEGF target, immunomodulatory drugs, including lenalidomide, thalidomide, and pomalidomide, which also act as VEGF inhibitors, have also been studied in PDAC. Thalidomide was combined with capecitabine in a phase II trial of 31 patients with advanced PDAC, with a median PFS measuring 2.7 months and OS of 6.1 months[78]. Pomalidomide was studied in a phase I setting with gemcitabine, and found to be well-tolerated[79]. Lenalidomide, a more potent immunomodulatory drug, was shown to decrease *ERK* expression and enhance gemcitabine activity[80]. Lenalidomide was subsequently studied in a phase II trial in combination with gemcitabine[81]. Low response rates, and a limited 6-month OS of 37% have halted continued development in the setting of PDAC.

EndoTAG-1, cationic liposomes formulated with paclitaxel, is a novel antiangiogenic agent that is still being investigated[82]. A phase II study of EndoTAG-1 with gemcitabine in chemotherapy-naïve patients demonstrated good tolerability[83]. EndoTAG-1 is now being studied in a prospective phase III setting with gemcitabine in patients with advanced PDAC after FOLFIRINOX failure (NCT03126435), and we await readout of these results[84].

Among the largely negative trials involving anti-angiogenesis agents, Reni *et al.*[85] explored a different approach using maintenance single agent sunitinib among patients who demonstrated disease stability after 6 months of cytotoxic chemotherapy. In this phase II study, 22% of patients remained progression-free at 6 months, with 2-year overall survival of 23% and stable disease of 52%. While sunitinib and other anti-angiogenic agents were not effective alone or concurrently with systemic therapy as discussed earlier, this suggests that targeting the VEGFR pathway may be successful after optimal cytoreduction with traditional chemotherapy agents. Rethinking traditional paradigms of treatment in PDAC, such as sequencing an anti-angiogenic strategy after chemotherapy in this case, may unveil novel opportunities for treatment.

LEARNING FROM TRADITIONAL APPROACHES IN THE IMMUNOTHERAPY ERA

Targeting and depleting HA represents another example of extensive bench to bedside work. An ECM dense with HA forms a physical barrier that precludes successful diffusion of small molecules from the surrounding vasculature to the tumor itself, thus inhibiting successful drug delivery of therapeutic agents[14,86]. Using GEM models of PDAC, Provenzano *et al.*[14] demonstrated that degradation of hyaluronan with PEGPH20, a pegylated human recombinant PH20 hyaluronidase, leads to a significant decrease in IFP, thus removing this physical barrier. *In vitro* studies using gemcitabine with PEGPH20 demonstrated that PEGPH20 successfully altered the tumor microenvironment, with a subsequent reduction in tumor size. In a separate study, Jacobetz *et al.*[87] also showed that the administration of PEGPH20 resulted in the re-expansion of vasculature and increased intratumoral concentrations of gemcitabine and doxorubicin.

With this substantial preclinical evidence of efficacy in modifying the tumor microenvironment and enhancing drug delivery, early phase combination trials of PEGPH20 with FOLFIRINOX or gemcitabine-based chemotherapy were undertaken[88-90]. In the SWOG S1313 phase Ib/II clinical trial, PEGPH20 was administered with modified (m)FOLFIRINOX among patients with unselected HA levels, and compared to mFOLFIRINOX alone[90]. In a preplanned interim safety analysis, there was a significant increase of thromboembolic events in the PEGPH20/mFOLFIRINOX arm, necessitating an amendment to incorporate enoxaparin prophylaxis. One year later, in a preplanned interim analysis, the hazard ratio for OS was significantly increased at 2.07, with a median OS of 7.7 months (PEGPH20/mFOLFIRINOX arm) *vs.* 14.4 months in the mFOLFIRINOX arm, resulting in early study closure. Potential explanations for these unexpected results include increased gastrointestinal toxicity and thromboembolic events in the combination arm, leading to dose delays and reduced drug exposure. The impact of FOLFIRINOX or granulocyte colony-stimulating growth factor on the tumor microenvironment is also unclear and may contribute to the difference in survival.

By contrast, the HALO-202 study compared the combination of PEGPH20 with gemcitabine and nab-paclitaxel to gemcitabine and nab-paclitaxel in a randomized phase II trial among patients with unselected HA status[89]. PFS was longer in the combination arm among all patients, and in the subgroup of patients with HA-high tumors. Given that this study achieved its primary endpoints, the prospective phase III HALO-301 trial was launched. Patients with HA-high PDAC were randomized to gemcitabine and nab-paclitaxel with or without PEGPH20, coupled with enoxaparin prophylaxis[91]. OS was similar between the two groups, measuring 11.2 months in the PEGPH20 arm compared to 11.5 months in the placebo/chemotherapy arm. PFS was also similar (median of 7.1 months in both arms), as was the objective response rate (47% *vs.* 36% in the PEGPH20/chemotherapy and placebo/chemotherapy arms, respectively). Despite the compelling pathophysiological preclinical data and biologic rationale, these disappointing negative phase III clinical trial results highlight the inherent complexity of the tumor microenvironment and stromal remodeling.

Prior to the readout of the negative phase III trial with PEGPH20, combinations with immunotherapeutic agents were also being explored. In the MORPHEUS phase Ib/II trial (NCT03193190), patients with advanced PDAC received second-line PEGPH20 with atezolizumab[92]. Response rates measured 6% and median OS was 7.1 months, compared to 6.8 months in the control arm. While this combination did not benefit all trial participants, the response rate of 6% still warranted correlative analyses for potential predictive biomarkers to identify responders and to inform future immunotherapeutic combinations. Furthermore, depletion of HA may still prove effective as an adjunct to cellular based treatments, such as chimeric antigen receptor (CAR) T-cell therapy.

CANCER-ASSOCIATED FIBROBLASTS AS THE NEXT FRONTIER?

iCAFs contribute to inhibiting the immune response in PDAC, with increased NF-κB signaling[18]. This leads to increased *CXCL12* expression, which blocks cytotoxic T cell infiltration. *CXCR4* is also involved in this pathway, and preclinical data demonstrated that *CXCR4-CXCL12* inhibition enhanced PD-L1 inhibitor sensitivity[93,94]. The recently published phase IIa COMBAT trial investigated motixafortide (BL-8040), a *CXCR4* antagonist, in combination with pembrolizumab, 5-fluorouracil, and nanoliposomal irinotecan[95]. While median OS measured 3.3 months, the cohort with motixafortide, pembrolizumab, and chemotherapy demonstrated an ORR of 32% and median duration of response of 7.8 months. Given the limited efficacy of immune checkpoint blockade with or without chemotherapy in patients with biomarker-unselected PDAC, the addition of a *CXCR4* inhibitor may improve the efficacy of immunotherapeutic strategies[96,97]. Another combination therapy with motixafortide, this time with cemiplimab, gemcitabine, and nab-paclitaxel, is

currently being investigated (NCT04543071; Table 1)[98]. *NOX4* has also been identified as another important factor in the immune regulation by CAFs, and preclinical studies demonstrated that *NOX4* inhibition with setanaxib helped to mediate immunotherapy resistance[99]. This pathway may be yet another avenue to overcome immunotherapeutic resistance.

IL-6, also secreted by iCAFs, is actively being studied in enhancing the efficacy of PD-L1 blockade in PDAC. Il-6 subsequently activates STAT3 signaling and plays a role in PDAC pathogenesis[19,27,100]. Nab-paclitaxel, part of the chemotherapy backbone in the approved armamentarium against advanced PDAC, has been shown to disrupt the stroma by decreasing IL-6 expression[101,102]. Furthermore, Il-6 inhibition, when administered in combination with PD-L1 blockade, improved survival outcomes in GEM models, and demonstrated increased T cell infiltration[103]. Siltuximab, a monoclonal antibody targeting IL-6, has been shown to be well-tolerated in an early phase clinical trial of patients with advanced solid tumors[104]. With the preclinical mechanistic rationale of combination IL-6 inhibition with immunotherapy, siltuximab is now being investigated with spartalizumab in a phase Ib/II trial (NCT04191421)[105]. Tocilizumab, another IL-6 inhibitor, is also being studied with gemcitabine and nab-paclitaxel chemotherapy in a phase II setting (NCT02767557)[106]. Results from these trials are pending, and correlative studies may help to further elucidate the role of IL-6 inhibition in PDAC.

Another member of the IL-6 cytokine family, leukemia inhibitory factor (LIF), is produced by PSCs and stimulated by *KRAS* mutations[107,108]. LIF serves as a critical paracrine factor in STAT3 activation in pancreatic cancer cells. Circulating LIF levels have been shown to correlate with responses to chemotherapy, suggesting its role as a potential biomarker[109]. In a preclinical $KRAS^{G12D}$ pancreatic mouse model, LIF-neutralizing antibodies combined with gemcitabine appeared to be synergistic and successfully inhibited tumor growth[108]. This represents yet another potential therapeutic target to be further investigated.

Another important signaling pathway identified in iCAFs includes Janus Kinase (JAK)-STAT and IL-1 mediated signaling[110]. In murine models, ruxolitinib, an oral JAK1 and JAK2 inhibitor, decreased tumor cell proliferation[111]. Despite potentially favorable early phase results, ruxolitinib combined with capecitabine did not result in an OS benefit and phase III trials were stopped early for futility[112,113]. IL-1 receptor blockade using anakinra, in combination with FOLFIRINOX, was investigated in a phase I trial, with preliminary results presented in abstract form demonstrating safety and tolerability (NCT02021422)[114].

Platelet-derived growth factor (PDGFR)-α has been identified as a prominent cell surface marker, with *Saa3* overexpression, particularly in iCAFs[115]. While other tyrosine kinase inhibitors discussed previously were primarily studied for their anti-angiogenic properties, masitinib is a tyrosine kinase inhibitor targeting PDGFRα/β, c-Kit, and Lyn with preclinical evidence demonstrating improved sensitivity to gemcitabine when administered together[116]. While early phase trial results appeared promising, median OS with masitinib and gemcitabine measured 7.7 months *vs.* 7.1 months compared to a placebo and gemcitabine arm in a phase III trial[117,118]. Olaratumab, a monoclonal antibody that binds to PDGFRα, is also being investigated in a phase Ib/II trial with gemcitabine and nab-paclitaxel in patients with untreated metastatic PDAC (NCT03086369)[119].

While many of these clinical trials stemmed from initial favorable findings in the lab, one of the key differences in these recent trials has been the incorporation of correlative studies and treatment-related biopsies to better comprehend *in vivo* effects. While we eagerly await the clinical trial results investigating these novel strategies, equally important will be the correlative findings that may provide further insights.

Table 1. Selected clinical trials that are ongoing with PDAC tumor microenvironment targets

Experimental agent	Trial ID	Experimental regimen	Trial design	Primary endpoint	Estimated completion date
Motixafortide (CXCR4 antagonist)	NCT04543071[98]	Motixafortide, cemiplimab, gemcitabine, nab-paclitaxel	Phase II non-randomized	ORR	July 2025
Olaptesed pegol (CXCL12 antagonist)	NCT03168139[164]	Olaptesed +/- pembrolizumab	Phase I/II non-randomized	Pharmacodynamics and safety (adverse events)	March 2020 (not yet reported)
Tocilizumab (IL-6 inhibitor)	NCT02767557[106]	Tocilizumab, gemcitabine, nab-paclitaxel	Phase II randomized	OS at 6 months	January 2021
Siltuximab (IL-6 inhibitor)	NCT04191421[105]	Siltuximab, spartalizumab	Phase Ib/II non-randomized	Recommended phase II dose	December 2022
L-DOS47 (CEACAM6 inhibitor)	NCT04203641[165]	L-DOS47, doxorubicin	Phase Ib/II non-randomized	ORR and adverse events	October 2021
Defactinib (focal adhesion kinase inhibitor)	NCT02546531[166-168]	Defactinib, pembrolizumab, gemcitabine	Phase I non-randomized	Maximum tolerated dose	Expansion cohort ongoing
Olaratumab (PDGFRα inhibitor)	NCT03086369[119]	Olaratumab, gemcitabine, nab-paclitaxel	Phase Ib/II non-randomized	Number of patients with DLTs (phase Ib), OS (phase II)	January 2022
Canakinumab (IL-1β inhibitor)	NCT04581343[169]	Canakinumab, spartalizumab, gemcitabine, nab-paclitaxel	Phase Ib non-randomized	Recommend phase II/III dose	March 2021
Paracalcitol (vitamin D analogue)	NCT03331562[160,161]	Paracalcitol, pembrolizumab	Phase II randomized	Percentage of patients with radiographic progression at 6 months	July 2020 (results not yet reported)

PDAC: Pancreatic ductal adenocarcinoma; OS: overall survival.

WHAT ABOUT MYELOID SUPPRESSION IN THE TUMOR MICROENVIRONMENT?

Mesenchymal stem cell CAFs have also been identified, with increased expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) leading to downstream epithelial-mesenchymal transition and subsequent oncogenesis[120]. Inhibition of GM-CSF, particularly via CSF-1 receptor (CSF-1R) blockade, depletes the accumulation of tumor-associated macrophages (TAMs)[20,21]. TAMs have been demonstrated to block T cell intratumoral infiltration and can limit PD-1 blockade, thus contributing to immune checkpoint inhibitor resistance[121-123]. Cabiralizumab, a monoclonal antibody targeting CSF-1R, has been studied in combination with nivolumab[124,125]. In a phase II study, cabiralizumab is being investigated with nivolumab and various chemotherapy combinations (gemcitabine/nab-paclitaxel, 5-FU/oxaliplatin/leucovorin, or investigator's choice). The preliminary safety cohort has been completed, but efficacy results are being awaited (NCT03336216)[126,127]. Another anti-CSF1R monoclonal antibody, AMG 820, was recently reported with pembrolizumab in an early phase study among patients with various tumor types, including 31 patients with PDAC[128]. There were no partial responses, and median time to progression measured 2.1 months. This did not meet the predefined threshold for efficacy, so this combination is not being further investigated.

In addition to TAMs, inflammatory monocytes facilitate PDAC development and immunosuppression within the tumor microenvironment, with the *CCR2* axis playing a pivotal role[129,130]. An oral *CCR2* antagonist (PF-04136309) was administered in combination with gemcitabine and nab-paclitaxel in patients with previously untreated metastatic PDAC in a phase Ib trial[131]. While there was an ORR of 23.8%, there was also a incidence rate of 24% for pulmonary toxicity, thus raising a significant safety concern. In another

early phase trial, Linehan *et al.*[132] reported using a different CCR antagonist, CCX872, this time in combination with FOLFIRINOX. Overall survival at 18 months measured 29%, with correlative studies demonstrating reduction of circulating and inflammatory monocytes, and myeloid-derived suppressor cells. In the borderline resectable/locally advanced setting, the combination of the oral *CCR2* inhibitor with FOLFIRINOX in a phase Ib trial showed a 49% rate of response with no increased pulmonary toxicity[133]. While *CCR2* antagonists have been combined with chemotherapy in an attempt to overcome chemoresistance, there is also preclinical rationale for exploring the combination with immune checkpoint inhibitors[134]. Further investigation of these combination approaches is merited.

OTHER STROMAL TARGETS

Connective tissue growth factor (CTGF) is implicated in promoting fibrosis in PDAC cells[135]. Pamrevlumab, a monoclonal antibody targeting CTGF, in combination with gemcitabine and nab-paclitaxel as neoadjuvant therapy demonstrated a remarkable decrease of 20.6% in size of target lesions in a phase I/II trial[136]. Based on these exciting results, the phase III trial using this combination is now being explored (NCT03941093)[137]. Further exploration in the advanced setting may also be warranted given these promising findings.

Matrix metalloproteinases (MMPs) have also been explored as a therapeutic target within the PDAC tumor microenvironment. MMPs are proteolytic enzymes that facilitate ECM degradation, with increased MMPs leading to ECM degradation and allowing for increased tumor invasion and metastasis[138]. BAY 12-9566, an oral MMP inhibitor, was compared to gemcitabine in a phase III trial, but this was terminated after an interim analysis identified shorter median OS in the BAY 12-9566 arm compared to the control arm[139]. Marimastat, another oral MMP inhibitor, demonstrated encouraging results in the phase II setting[140]. When marimastat was combined with gemcitabine in a randomized phase III trial, there was no significant difference in OS when compared to gemcitabine alone[141]. A recent phase I trial of andecaliximab, a monoclonal antibody that inhibits MMP-9, in combination with gemcitabine and nab-paclitaxel in patients with advanced PDAC demonstrated tolerability and an overall response rate of 44.4%[142]. However, further development of andecaliximab was stopped after a phase III study among patients with gastric and gastroesophageal junction cancer was negative[143].

Heparin sulfate proteoglycans supply growth factors and cytokines to the tumor microenvironment[144]. Administration of low molecular weight heparin has demonstrated anti-angiogenic, antiproliferative, and immune modulatory effects, but the bleeding risk is significant and must be considered prior to clinical use[145,146]. A rationally engineered heparin sulfate with decreased anticoagulant effects, necuparanib, has been designed with early phase results supporting further investigation[147]. O'Reilly *et al.*[148] reported the results of the phase II trial of gemcitabine/nab-paclitaxel with or without necuparanib. Median OS measured 10.71 months in the necuparanib arm, compared to 9.99 months in the placebo arm, and the study was terminated early for futility.

Preclinical studies showed that the Bruton tyrosine kinase (BTK) and PI3Kγ interact to promote M2 polarization, resulting in increased suppression of the immune system within the tumor microenvironment and promoted PDAC growth[149]. The administration of ibrutinib, an oral BTK inhibitor, demonstrated efficacy in mouse models, leading to the phase III RESOLVE trial evaluating ibrutinib in combination with gemcitabine and nab-paclitaxel in patients with untreated advanced PDAC[150,151]. There was no difference in OS or PFS with the addition of ibrutinib.

While targeting of the renin-angiotensin-aldosterone system (RAAS) has traditionally been used in the treatment of hypertension and cardiac disorders, angiotensin II has also been reported to stimulate stromal cells, including fibroblasts, with subsequent cancer cell proliferation[152]. Losartan and lisinopril, inhibitors of the RAAS pathway, have been shown to decrease collagen and hyaluronan in preclinical models[153,154]. In a phase II trial of 49 patients with locally advanced PDAC treated with neoadjuvant FOLFIRINOX, losartan and chemoradiation, there was an impressive R0 resection rate of 61%[155]. In a retrospective study where RNA-Seq was used for resected pancreatic primaries, chronic use of RAAS inhibitors was associated with longer survival in patients without metastatic disease[156]. Taken together, further study of adjunct RAAS inhibition as a stromal target is warranted in larger prospective studies and should also be explored in the metastatic setting.

Other avenues being explored with significant interest include high-dose vitamin D and all-trans retinoic acid (ATRA). Preclinical studies demonstrated that the vitamin D receptor expression occurs in PDAC stroma. Administration of calcipotriol, a vitamin D receptor ligand, subsequently decreased inflammatory cytokines and growth factors[157]. Calcipotriol has also been shown to decrease T cell effector function, thus providing justification that combination vitamin D analogue with immune checkpoint blockade may be synergistic. Results from a pilot study of 24 patients receiving paracalcitol, nivolumab, nab-paclitaxel, gemcitabine, and cisplatin demonstrated an ORR of 83%, with a median PFS of 8.17 months and median OS of 15.3 months. This study is now being expanded further (NCT02754726)[158,159]. Another phase II trial is investigating the role of a vitamin D analogue with a PD-1 inhibitor as maintenance treatment for patients who have achieved maximal response with chemotherapy (NCT03331562)[160,161]. ATRA, a vitamin A derivative, was administered with gemcitabine in GEM models, with decreased tumor size[162]. An early phase trial consisting of 28 patients who received ATRA, gemcitabine, and nab-paclitaxel demonstrated tolerability. Preliminary median OS measured 11.7 months, and this regimen will be further investigated in a planned phase IIb trial (NCT04241276)[163]. Selected ongoing clinical trials focused on tumor microenvironment targets are highlighted in Table 1.

CONCLUSIONS AND FUTURE DIRECTIONS

Over the last several decades, many lessons have been learned both in trial design and understanding of the tumor microenvironment. The majority of clinical trials now include an interim analysis for futility to allow for an early signal to be detected and to avoid unnecessary exposure and toxicity to a futile treatment. In addition, the incorporation of treatment-related biopsies can provide key correlative insights and contribute to biomarker identification to inform future studies. With the advent of novel technologies and advanced sequencing techniques, there is growing understanding of the make-up and complex interplay between stromal factors. Furthermore, an increased recognition of the role of the tumor environment in both chemo and immunotherapeutic resistance will help to improve drug design and delivery. Taken together, we are optimistic that these ongoing collaborative efforts will improve the quality of life and oncologic care for patients with PDAC.

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Authors' contributions

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