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Special Section on Drug Delivery Technologies—Minireview

Combination Therapies and Drug Delivery Platforms in Combating Pancreatic Cancer

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC), the fourth leading cause of cancer-related death in the United States, is highly aggressive and resistant to both chemo- and radiotherapy. It remains one of the most difficult-to-treat cancers, not only due to its unique pathobiological features such as stroma-rich desmoplastic tumors surrounded by hypovascular and hypoperfused vessels limiting the transport of therapeutic agents, but also due to problematic early detection, which renders most treatment options largely ineffective, resulting in extensive metastasis. To elevate therapeutic effectiveness of treatments and overt their toxicity, significant enthusiasm was generated to exploit new strategies for combating PDAC. Combination therapy targeting different barriers to mitigate delivery issues and reduce tumor recurrence and metastasis has demonstrated optimal outcomes in patients' survival and quality of life, providing possible approaches to overcome therapeutic challenges. This paper aims to provide an overview of currently explored multimodal therapies using either conventional therapy or nanomedicines along with rationale, up-to-date progress, as well as the key challenges that must be overcome. Understanding the future directions of the field may assist in the successful development of novel treatment strategies for enhancing therapeutic efficacy in PDAC.

Introduction

Pancreatic cancer (PC) remains a treatment-refractory malignancy with a median survival of 5 to 6 months (Rahib et al., 2014). PCs are split into two main groups: endocrine and exocrine tumors. Pancreatic ductal adenocarcinoma (PDAC) is an exocrine tumor, representing over 90% of all pancreatic malignancies (Pelosi et al., 2017). Although PDAC accounts for only about 2% of all cancer cases, it is the fourth leading cause of death due to cancer in the United States. It is estimated that ~45,750 deaths from this disease will be reported in 2019 (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf). PDAC is associated with a very poor prognosis, in which mortality closely parallels incidence. The 5-year survival rate has only improved marginally over the past decades and remains as low as 6%, which is perhaps due to the fact that the majority of PDAC cases are diagnosed at late stages with widespread metastases (Hall et al., 2018). Although the evolution of PDAC starts from its earliest non-malignant precursor lesions, most patients with PDAC are asymptomatic until the disease develops to an advanced stage. The retroperitoneal position of the pancreas and the absence of sensitive and noninvasive biomarkers represent additional hurdles to the imaging, screening, and early detection of PDAC (Kaur et al., 2012). Although surgical resection is considered as the only potentially curative treatment of PDAC, less than 20% of patients are suitable candidates for this procedure since the disease is far too advanced when diagnosed and thus inoperable (Adamska et al., 2017). PDAC remains one of the most difficult-to-treat cancers, owing to its aggressive nature, complex tumor microenvironment, and intrinsic resistance to chemotherapeutics, which renders most treatment options mostly ineffective. Since the 1990s, single-agent gemcitabine, a nucleoside analog of deoxycytidine that blocks DNA replication and several forms of DNA repair, has been the standard of care for patients with advanced PDAC. For the subsequent years, many therapies were investigated to improve chemotherapeutic strategies for PDAC but the rate of successful clinical trials was relatively low (Hall et al., 2018). To date, only two systemic therapies have

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ABBREVIATIONS: 5-FU, 5-fluorouracil; ECM, extracellular matrix; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; GEM, gemcitabine; HHI, Hedgehog inhibitor; mFOLFIRINOX, modified folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; nab-PTX, nanoparticle albumin-bound paclitaxel; OS, overall survival; PAMAM, polyamidoamine; PC, pancreatic cancer; PCSC, pancreatic cancer stem cell; PDAC, pancreatic ductal adenocarcinoma; PEGPH20, (polyethylene glycol, PEG) PEGylated version of Halozyme's proprietary recombinant human hyaluronidase enzyme, rHuPH20; PFS, progression-free survival; RR, response rate.

demonstrated the improved outcomes of the treatment compared with gemcitabine alone, at the expense of increased adverse effects (Conroy et al., 2011). Thus, new more effective and less toxic therapeutic strategies targeting both cancer cells and the tumor microenvironment are urgently needed to combat PDAC. In this context, nanotechnology-based drug delivery platforms can offer the possibilities to achieve efficient tumor targeting, lower drug-related toxicities, and improve clinical outcome (Meng and Nel, 2018). Overall, this review aims to provide a synopsis of currently explored multimodal therapies using either conventional therapy or nanomedicines to treat PDAC, and discusses new challenges, presented along with further considerations, and the crucial roles of interdisciplinary approaches.

Pathophysiology, Diagnosis, and Staging of PDAC

PDAC follows a pathway of progression from normal ductal epithelium to duct lesions and invasive ductal adenocarcinoma. It takes approximately 17 years for PDAC to progress from a tumor-initiating cell to the development of metastatic disease (Yachida et al., 2010). This process is characterized by multiple genetic alterations that trigger the tumor progression cascade, such as activation of oncogenes, of which mutationally activated *KRAS* plays the utmost vital role in tumor initiation and maintenance during the whole PDAC progression through regulation of cell division, differentiation, and apoptosis (Korc, 2010; Eser et al., 2014). On the other hand, the frequent inactivation of tumor suppressor genes, including *p16INK4A*/*CDKN2A*, *TP53*, and *DPC4*/*SMAD4*, also contribute to the deregulation of cell cycle and biologic aggressiveness of PDAC (Zhang et al., 2016a). The *CDKN2A* gene encodes two different proteins, p16 and p14ARF, which are both cell-cycle regulators. Loss or promoter methylation of the CDKN2A gene markedly promotes cell proliferation and tumor progression. *TP53*, a cellular stress sensor, is mutated in about 70% of human PDAC (Morton et al., 2010). Its inactivation leads to uncontrolled cell growth and increased cell survival, and in combination with activated KRAS has been shown to drive the genomic instability and tumor metastatic capacity (Bardeesy et al., 2006). The loss or loss of function of the DPC4/*SMAD4* tumor suppression gene is another common genetic alteration that results in disruption of the TGF-β pathway, occurs relatively late in pancreatic carcinogenesis, and was found to be associated with poor prognosis in PDAC patients. In addition to the driver mutations in these four genes, high-frequency alterations in wingless-related integration site signaling, chromatin remodeling, Hedgehog signaling, DNA repair, and cell cycle processes were also observed (Witkiewicz et al., 2015). By histologic studies and clinical observations, it is postulated that before the final formation of invasive cancer, there is a stepwise progression of precursor lesions such as intraductal papillary mucinous neoplasms, mucinous cystic neoplasms (Hruban et al., 2004), and pancreatic intraepithelial neoplasia, a most common and well-defined precursor to PDAC (Yonezawa et al., 2008). The progression of pancreatic intraepithelial neoplasia lesions follows a pathway from no dysplasia to moderate dysplasia, to high-grade dysplasia (carcinoma in situ), and to invasive carcinoma, accompanied by increased frequency of multiple genetic alterations (Koorstra et al., 2008; Muniraj et al., 2013; Distler et al., 2014; Kamisawa et al., 2016). Among different types of cancers, PC is recognized as the utmost devastating and difficult-to-treat cancer. There are a number of key features that make it a particularly challenging disease. PC is characterized by significant genomic heterogeneity: recent extensive genetic studies showed an average of 63 genetic aberrations across 12 functional pathways in the majority of PCs (Jones et al., 2008; Cancer Genome Atlas Research Network, 2017). Importantly, the pathway components that may be altered in a specific tumor vary widely, which makes developing tailored therapies targeting specific genes quite challenging. Tumor stroma is another defining hallmark of PDAC, which is considered to be one of the most stroma-rich cancers. Dense fibrotic stroma occupies the majority of the tumor mass and consists of extracellular matrix (ECM) components and non-neoplastic cells including fibroblastic, vascular, and immune cells. The excessive deposition of ECM generates high interstitial fluid pressures that compress blood vessels and cause hypoperfusion, hypovascularity, and hypoxia. This desmoplastic hypovascular tumor microenvironment is now recognized as promoting tumor growth, facilitating its invasive and metastatic potential and immunosuppression, and impairing the delivery of chemotherapeutics (Kaur et al., 2013; Xie and Xie, 2015).

Early and accurate diagnosis of PDAC is crucial for oncologists to determine effective and timely treatment options for patients. Currently, there are no validated early detection strategies for PDAC, even for high-risk patients. PDAC detection and staging is usually based on a combination of imaging techniques (e.g., computed tomography, transabdominal ultrasound, and magnetic resonance imaging), tumor markers (e.g., carbohydrate antigen 19-9, carcinoembryonic antigen, and osteopontin), and clinical presentations (e.g., progressive weight loss, anorexia, and abdominal pain), as well as the gold standard diagnostic tool: biopsy. Staging assessment is based on the extent of invasion into the pancreas and surrounding tissue, presence or absence of spread to lymph nodes, and presence or absence of metastasis. The tumor/node/metastasis staging system serves as a clinically useful tool in prognosis, surveillance, and treatment planning as well as risk stratification in clinical trials for patients with PDAC (Zhang et al., 2016a).

Therapeutic Strategies

Surgical resection with chemotherapy (usually adjuvant) remains the preferable and only potentially curative approach in PDAC clinical management. Sadly, due to the aggressive nature of the disease, late prognosis, and early metastasis, patients suffering from locally advanced or metastatic PDAC at presentation are usually no longer candidates for surgical removal of the tumor (Manji et al., 2017). As a result, the primary goal of clinical management for these patients is to control the disease and improve the quality of life. Gemcitabine (GEM) has been accepted as the standard first-line therapy for patients having advanced PDAC. There is no alternative monotherapeutic regimen proven to be more beneficial compared with GEM in terms of progression-free survival (PFS) and overall survival (OS) (Conroy et al., 2016). However, due to the drawbacks of GEM (instability in plasma leading to extremely short half-life, inefficient cell uptake, and complex intracellular metabolism), and the fast growth of intrinsic and acquired chemo-resistance during treatment, there is an urgent need for new and disruptive strategies for PDAC

(Spadi et al., 2016; Cloyd et al., 2017). Combination therapy is emerging at this point with superior cost-to-efficacy value and overall outcomes.

Combination Therapies

Combination therapy has become the major means to combat cancer thanks to its primary advantages of increased efficacy without, or with minimal, addictive toxicities at equal or reduced administrating doses, which in most cases is recommended for patients if available. Ideal combination therapy should address the following aspects: 1) maximization of therapeutic efficacy of each single drug of the combination; 2) minimization of intrinsic and acquired crossresistance of drugs possibly occurring in the treatment; and 3) diminishing overlapping adverse effects for better tolerability. Drug combinations with distinct molecular mechanisms of action exhibit various remarkable improvements in treatment outcomes, ultimately leading to more promising patient compliance. Regarding PDAC, as previously mentioned, GEM is the only approved first-line monotherapy in PDAC; however, unfortunately it still delivers unsatisfactory therapeutic outcomes in prolonging PFS and OS of patients with locally advanced and metastatic PDAC (Hidalgo et al., 2015). As a result, most of the combination regimens tested have centered on GEM. Multiple combination therapies composed of GEM and different cytotoxic and biologic agents have undergone clinical evaluation for patients with various stages of PDAC. The gold standards for evaluating the efficacy of these treatments are PFS and OS (Table 1).

Generally, GEM-based combination therapies include previously approved or well-known chemotherapeutic regimens currently being used for PDAC (Teague et al., 2015), such as capecitabine, oxaliplatin, irinotecan, paclitaxel, and molecular targeting agents like erlotinib (an epidermal growth factor inhibitor) (Chiorean and Coveler, 2015; Seicean et al., 2015), sunitinib (a vascular endothelial growth factor receptor inhibitor), pimasertib (a mitogen-activated protein kinase inhibitor), bevacizumab (a vascular endothelial growth factor), vismodegib (a heat shock protein inhibitor), etc. Among the GEM-based molecular targeting combination therapies tested in clinical trials, the only one that received Food and Drug Administration approval is the erlotinib + GEM combination, with

TABLE 1
Selected Gemcitabine-based combination therapies evaluated in clinical trials

Treatment	Target	RR	PFS	OS	Reference
		%	*mo*	*mo*	
GEM-based combination therapy					
Capecitabine	DNA	19.1 vs. 12.4	5.3 vs. 3.8	7.1 vs. 6.2	Cunningham et al., 2009
		7.3 vs. 5.9	—	8.4 vs. 7.2	Herrmann et al., 2007
Cisplatin	DNA	26.4 vs. 9.2	5.0 vs. 2.0	7.5 vs. 5.0	Colucci et al., 2002
		11.5 vs. 9.0	5.3 vs. 3.1	7.5 vs. 6.0	Heinemann et al., 2006
		12.9 vs. 10.1	3.8 vs. 3.9	7.2 vs. 8.3	Colucci et al., 2010
Oxaliplatin	DNA	26.8 vs. 17.3	5.8 vs. 3.7	9.0 vs. 7.1	Louvet et al., 2005
		9.0 vs. 6.0	2.7 vs. 2.6	5.7 vs. 4.9	Poplin et al., 2009
Irinotecan	Top I	15.0 vs. 10.0	2.8 vs. 2.9	6.4 vs. 6.5	Stathopoulos et al., 2006
		16.1 vs. 4.4	3.5 vs. 3.0	6.3 vs. 6.6	Rocha Lima et al., 2004
Pemetrexed	Folate metabolism	14.8 vs. 7.1	3.9 vs. 3.3	6.2 vs. 6.3	Oettle et al., 2005
Erlotinib	EGFR	8.6 vs. 8.0	3.8 vs. 3.6	6.2 vs. 5.9	Moore et al., 2007
Cetuximab	EGFR	12.0 vs. 14.0	3.4 vs. 3.0	6.3 vs. 5.9	Philip et al., 2010
Nimotuzumab	EGFR	8.6 vs. 8.6	5.1 vs. 3.4	8.6 vs. 6.0	Schultheis et al., 2017
Bevacizumab	VEGF	13.0 vs. 10.0	3.8 vs. 2.9	5.8 vs. 5.9	Kindler et al., 2010
Ablifercept	VEGF	—	3.7 vs. 3.7	6.5 vs. 7.8	Rougier et al., 2013
Sunitinib	VEGFR and PDGFR	7.1 vs. 6.1	2.9 vs. 3.3	7.6 vs. 9.2	Bergmann et al., 2015
Axitinib	VEGFR 1-3, c-KIT, and PDGFR	5.0 vs. 2.0	4.4 vs. 4.4	8.5 vs. 8.3	Kindler et al., 2011
		4.9 vs. 1.6	4.4 vs. 4.4	5.1 vs. 5.4	Ioka et al., 2015
Sorafenib	VEGFR, PDGFR, and Raf	23.0 vs. 19.0	5.7 vs. 3.8	9.2 vs. 8.0	Gonçalves et al., 2012
Vismodegib	SMO	8.0 vs. 13.0	4.0 vs. 2.5	6.9 vs. 6.1	Catenacci et al., 2015
		0	3.7 vs. 2.4	6.3 vs. 5.4	Catennaci 2012
		21.7	2.8	5.3	Kim et al., 2014
Trametinib	MEK	22.0 vs. 18.0	3.7 vs. 3.5	8.4 vs. 6.7	Infante et al., 2014
Pimasertib	MEK	9.1 vs. 9.1	3.7 vs. 2.8	7.3 vs. 8.3	Van Cutsem et al., 2018
Rigosertib	PLK1 and PI3K	19.0 vs. 13.0	3.4 vs. 3.4	6.1 vs. 6.4	O'Neil et al., 2015
Tipifarnib	Farnesyltransferase	6.0% vs. 8.0	3.7 vs. 3.6	6.4 vs. 6.1	Van Cutsem et al., 2004
Ganitumab	IGF-1R	16.0 vs. 10.0	3.7 vs. 3.6	7.1 vs. 7.2	Fuchs et al., 2015
Evofosfamide	DNA (hypoxia activated)	26.0 vs. 12.0	5.6 vs. 3.6	9.2 vs. 6.9	Borad et al., 2015
		20.0 vs. 16.0	5.5 vs. 3.7	8.7 vs. 7.6	Cutsem et al., 2016
GEM + Erlotinib–based combination therapy					
Oxaliplatin	DNA	45.0	4.8	8.4	Cascinu et al., 2014
		21.0	5.2	10.5	Yun et al., 2014
Bevacizumab	VEGF	13.5 vs. 8.6	4.6 vs. 3.6	7.1 vs. 6.0	Katopodis et al., 2014
Cixutumumab	IGF-1R	—	3.6 vs. 3.6	7.0 vs. 6.7	Van Cutsem et al., 2009
GEM + Cisplatin–based combination therapy					
Sorafenib	VEGFR, PDGFR, and Raf	3.4 vs. 3.6	4.3 vs. 4.5	7.5 vs. 8.3	Philip et al., 2014

c-KIT, mast/stem cell growth factor receptor; EGFR, epidermal growth factor receptor; IGF-1R, insulin-like growth factor 1 receptor; MEK, mitogen-activated protein kinase; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; PLK1, polo-like kinase 1; Raf, family of three serine/threonine-specific protein kinases; SMO, smoothened [a class frizzled (class F) G protein-coupled receptor]; Top I, topoisomerase I; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; —, no data available.

improved PFS and OS (although the improvement in OS was merely 2 weeks) (Wang et al., 2015). Combining platinum-based agents with GEM is not as efficient as combining them with 5-fluorouracil (5-FU), since no improvement in primary measures of the trials was demonstrated. As a result, platinum-based agents are mostly used in combination with 5-FU. Despite encouraging outcomes of other GEM-based combination therapies in early phase studies including response rate (RR), adverse effects, and tolerability, most phase III trials have failed to improve the survival benefits and quality of life, with PFS and OS still limited to 5–9 months for locally advanced or metastatic PDAC (Aprile et al., 2017). No statistically significant progress was achieved throughout the clinical trials compared with GEM monotherapy, whereas some results were even inferior to GEM monotherapy. For instance, rigosertib, a small-molecule RAS mimetic and inhibitor of the phosphoinositide 3-kinase and polo-like kinase 1 pathways, showed promising synergistic activity with GEM in preclinical patient-derived xenograft models of PDAC. However, the combination of rigosertib and GEM did not improve the treatment outcome in patients with metastatic pancreatic cancer in a phase II/III trial (NCT01360853). Median OS was 6.1 months for the rigosertib + GEM combination versus 6.4 months for GEM alone (O'Neil et al., 2015). It was suggested that the lack of clinical activity for rigosertib in KRAS mutant PDAC patients could be linked to the inherent heterogeneity of the disease.

Rapid growth of resistance to GEM-based regimens and frequent relapse vastly accelerate the development of non-GEM–based combination therapies as alternatives for PDAC patients who are refractory to GEM-containing regimens. It has been proven that there is low crossresistance between GEM and 5-FU despite the fact that they are both nucleoside analogs. Alternatively, GEM-based therapies can also be given to patients previously treated with fluoropyrimidine-based therapies. Among these therapies, the most impressive and successful one is a multidrug regimen consisting of folinic acid, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX). Before that, extensive partial combinations of FOLFIRINOX were tested in the clinic, catalyzing the emergence of FOLFIRINOX. The three most representative regimens are the following combinations: 1) 5-FU, folinic acid, and oxaliplatin; 2) 5-FU, folinic acid, and irinotecan; and 3) capecitabine, an oral prodrug of 5-FU, and oxaliplatin (Vaccaro et al., 2011). The superiority of FOLFIRINOX over GEM was recognized in all efficacy parameters, including OS (11.1 vs. 6.8 months), PFS (6.4 vs. 3.3 months), and 1-year survival rate (48.4% vs. 20.6%). Unfortunately, FOLFIRINOX treatment–related side effects also are severe, including fatigue, bone marrow suppression with 45.7% grade 3 or 4 neutropenia, 12.7% diarrhea, and 9.0% sensory neuropathy, which leads to the termination of treatment in one-third of patients due to poor tolerability issues. On the other hand, the quality-of-life measures strongly support FOLFIRINOX for patients at the late stage with definitively less decrease in the health status (Khushman et al., 2015; Rombouts et al., 2016). Consequently, FOLFIRINOX is reserved as a preferred first-line therapy for patients with locally advanced or metastatic PDAC when they have good performance status. In some cases, it is also recommended (Jutric and Melstrom, 2017) for disease down-staging or can be considered as a neoadjuvant regimen for patients with borderline resectable tumors (Paniccia et al., 2014; Hackert et al., 2016; Godhi et al., 2017). In the hope of being beneficial for those unqualified patients, regimens with dose reduction of chemotherapeutics, referred to as modified FOLFIRINOX (mFOLFIRINOX) (Marsh Rde et al., 2015), are widely implemented in the clinic and have demonstrated comparable results (PFS and OS of 6.1 and 10.2 months, respectively) with manageable adverse effects. The recent PRODIGE 24/CCTG PA.6 multicenter randomized phase III clinical trial (NCT01526135) also assessed the benefit of mFOLFIRINOX compared with GEM monotherapy in an adjuvant setting for patients with resected PDAC. Based on reported data, median disease-free survival was 21.6 months for mFOLFIRINOX and 12.8 months for GEM. However, grade 3/4 toxicities were reported in 75.5% of patients receiving mFOLFIRINOX compared with 51.5% of patients receiving GEM (Lee and Park, 2016; Conroy et al., 2018). To further extend the potential of this promising regimen, some innovative combinations with FOLFIRINOX as a chemotherapeutic platform are underway in early phase clinical trials (Chiorean et al., 2016), including molecular targeting therapy (IPI-926 and NCT01383538) (Ko et al., 2016a), immunoradiation therapy (nivolumab with stereotactic body radiation and NCT03563248), redox metabolism therapy (CPI-613, NCT03699319, and NCT01835041), vaccination therapy (ipilimumab and NCT01896869) and tumor-associated macrophage targeting therapy (PF-04136309 and NCT01413022).

Despite success, conventional combination therapies in the treatment of PDAC confer a small advantage over single agent therapy and the survival times of PDAC patients remain unsatisfactory. Chemotherapy regimens are inevitably facing challenges such as poor bioavailability and intrinsic toxicity, compromising their efficacy and further utilization. As such, new strategies that will allow better delivery of chemotherapeutic agents to the tumor while decreasing systemic toxicity are urgently needed. To this end, one promising option is the implementation of nanothechnology-based therapeutic approaches in PDAC. Indeed, the unique characteristics of nanocarriers such as their nanoscale sizes, high surface-to-volume ratios, high loading capacity, and favorable drug release profiles make them suitable for delivering chemotherapeutic drugs to the target tumor tissue (Au et al., 2016; Shi et al., 2017). The physicochemical characteristics of nanocarriers can be readily adjusted to facilitate the delivery of a variety of therapeutic agents including small molecular drugs, biomacromolecules, and inorganic nanoparticles. These nanomedicines can be surface functionalized to present targeting ligands to a receptor of interest in order to home them at the desired site. Combining drugs in one delivery carrier is another advantageous strategy for controlling the pharmacokinetics and co-delivery of the desired drug ratio in vivo, and a variety of nanoscale carriers have been investigated in terms of their ability to deliver multiple drugs (Hu et al., 2016; Zhang et al., 2016b). Several nanomedicines have been approved for clinical use in cancer treatment, including PDAC, and many others in clinical development have demonstrated great promise.

Nanomedicines in PDAC Treatment Protocols

Currently, two nanotechnology-based therapeutics, nanoparticle albumin-bound paclitaxel [nab-paclitaxel (nab-PTX) or abraxane] and liposomal formulation of irinotecan (onivyde) have been approved for PDAC treatment in combination with other chemotherapeutic agents (Zhang et al., 2016b; Shi et al., 2017).

Taxanes are useful components in the systemic treatment of many cancers; however, unfortunately, it had exhibited very few noticeable benefits as single or combination therapies in PDAC until the emergence of nab-PTX. The encapsulation of paclitaxel into the human serum albumin–based drug delivery system allows for enhanced delivery of paclitaxel to the tumor, consequently leading to increased bioavailability and alleviated toxicity to normal tissue compared with cremophor-based paclitaxel formulation (Kim, 2017). In the combination regimen with GEM, it demonstrated significant improvements in most of the clinical outcome parameters (RR: 23% vs. 7%; PFS: 5.5 months vs. 3.7 months; OS: 8.5 and 6.7 months) compared with GEM alone. The number of patients with serious adverse events was similar in the two treatment groups (Von Hoff et al., 2013). These results have led to the approval of nab-PTX by the Food and Drug Administration as a first-line combination therapy with GEM for patients with locally advanced and metastatic PDAC. Targeting tumor stromal cells and modulation of the tumor microenvironment by nab-PTX have been proposed as contributing factors underlying the therapeutic activity of nab-PTX in this combination (Fig. 1). A clinical study that evaluated the effects of pretreatment with the nab-PTX and GEM combination in patients with operable PDAC showed that improved outcomes of this treatment were in good correlation with reduced tumor stiffness as determined by endoscopic ultrasound elastography (Alvarez et al., 2013). Moreover, in marked contrast with tumors exposed preoperatively to conventional chemoradiation, studied for comparison, less abundant collagen matrix and decreased number of tumor-associated fibroblasts around tumor glands were detected in the resected tumor tissues from patients treated with nab-PTX and GEM (Alvarez et al., 2013). Although the number of patients in this study was small, the reported data support the hypothesis that the therapeutic benefits of nab-PTX can be associated with stromal distortion. In addition, active transport mechanisms mediated by albumin cellular receptors may be responsible for the increased intratumoral concentrations of paclitaxel. Other possible mechanisms, like inactivation of GEM catabolizing enzymes, are still under investigation. Since the regulatory approval of the nab-PTX/GEM regimen in 2013, this combination has been intensely evaluated in multiple clinical trials in conjunction with a variety of other drugs targeting cancer stem-like cells, tumor microenvironment, kinase and signaling pathways, and immunotherapy (Tables 2 and 3).

Liposomal formulation of irinotecan is another nanomedicine that was approved for use in a combination regimen with 5-FU and folinic acid as a second-line therapy for patients with metastatic PDAC who progressed after gemcitabine-based chemotherapy (Ko, 2016; Kipps et al., 2017; Wang-Gillam et al., 2017). Based on the results of a pivotal NAPOLI-1 trial, the combination treatment of liposomal irinotecan with 5-FU and folinic acid demonstrated enhanced RR (16% vs. 1%), prolonged PFS (2.3 months vs. 1.4 months, demonstrated as time to treatment failure), and OS (6.1 months vs. 4.2 months) compared with the 5-FU/folinic acid regimen with a manageable safety profile (Wang-Gillam et al., 2016). No significant OS advantage was observed between patients assigned to liposomal irinotecan monotherapy and those allocated to the 5-FU/folinic acid regimen. Quality-of-life measures did not differ substantially from baseline in any treatment group. The observed excellent performance of liposomal irinotecan led to initiation of clinical studies evaluating the safety, tolerability, and preliminary efficacy of this nanomedicine in combination with other anticancer therapies (Chen et al., 2015; Wang-Gillam et al., 2016; Glassman et al., 2018). For example, the combination of liposomal irinotecan, 5-FU/folinic acid, and oxaliplatin, which mimics the FOLFORINOX regimen (Rahman et al., 2017), is currently being explored for patients with advanced PDAC who have not received prior

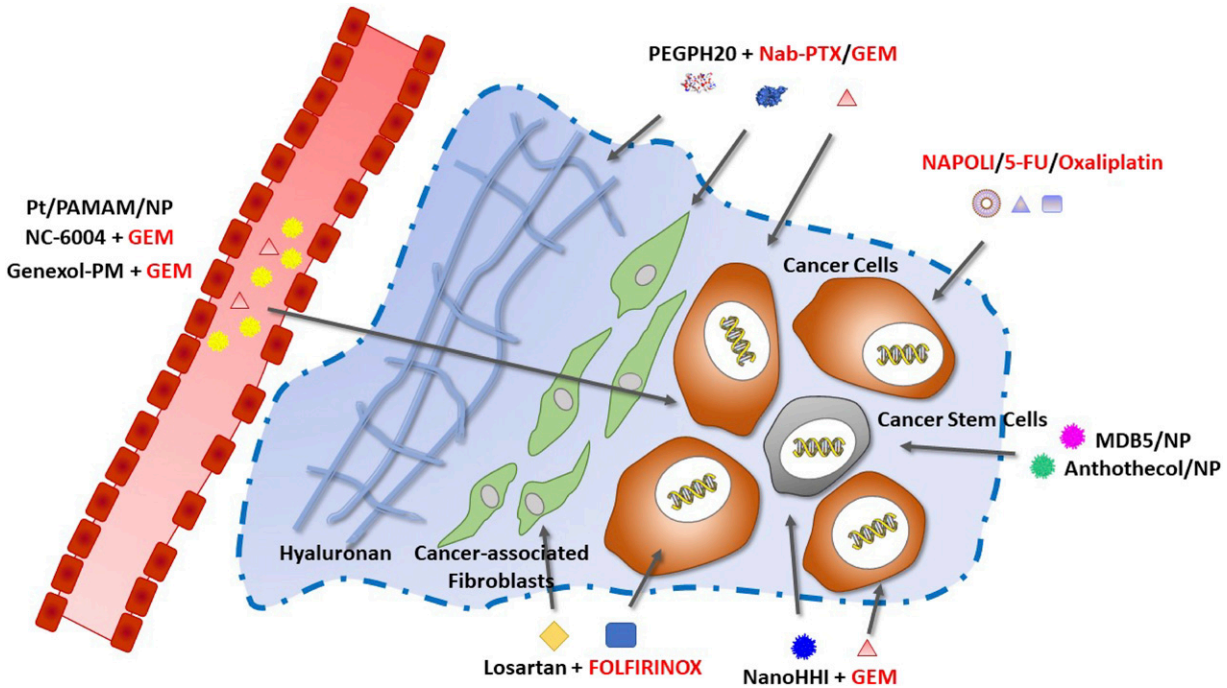

Fig. 1. Targets and therapeutic approaches including conventional and nanotechnology-based drugs that have been approved by the Food and Drug Administration (red) or in pre-clinical or clinical evaluation (black) for PDAC treatment.

TABLE 2
Nab-PTX/GEM–based combination therapy in clinical trials (completed)

Regimen	Target	RR	PFS	OS	Reference
		%	*mo*	*mo*	
PCSC targeting					
Vantictumab	WNT	53.0	7.2	—	Messersmith et al., 2016
Ipafricept	WNT	29.0	3.9	—	Weekes et al., 2016
Tarextumab	Notch 2/3	19.1 vs. 31.8	3.7 vs. 5.5	6.4 vs. 7.9	O'Reilly et al., 2017
Vismodegib	SMO	43.0	5.5	10	Jesus-Acosta et al., 2014
Sonidegib	SMO	39.0	—	—	Lee et al., 2017
VERSUS-4718	FAK	—	—	—	
Kinase or signaling pathway targeting					
LCL161	Apoptosis proteins	—	—	—	
Istiratumab	IGF-1R/ErbB3	—	—	—	Ko et al., 2016b
Erlotinib	EGFR	46	5.3	9.3	Leichman et al., 2012
Aptorsen	HSP27 (NF-κB)	18.0 vs. 18.0	2.7 vs. 3.8	5.3 vs. 6.9	Ko et al., 2017
Momelotinib	JAK	28	—	—	Ng et al., 2019
Itacitinib	JAK	24	—	—	Beatty et al., 2018
Other targets					
PEGPH20	HA	45.0 vs. 31.0	11.5 vs. 8.5	—	Hingorani et al., 2018
Evofosfamide	DNA (hypoxia-activated)	53.0	—	—	Borad et al., 2016

ErbB3, receptor tyrosine-protein kinase (also known as human epidermal growth factor receptor 3); EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; HA, hyaluronic acid; HSP27, heat shock protein 27 (also known as heat shock protein beta-1); IGF-1R, insulin-like growth factor 1 receptor; JAK, Janus kinase; NF-κB, nuclear factor kappa B; Notch 2/3, neurogenic locus notch homolog protein 2/3; SMO, smoothened; WNT, wingless-related integration site; —, no data available.

chemotherapy or as a preoperative regimen in resectable pancreatic cancer (NCT03528785, NCT02551991, NCT03487016, and NCT03483038). Other liposomal irinotecan plus 5-FU/folinic acid–based therapies under investigation include combinations with BAX2398 (NCT02697058), eryaspase (NCT03665441), cabiralizumab + nivolumab (NCT03336216), bermekimab (NCT03207724), and rucaparib (NCT03337087).

Similar to conventional chemotherapy, treatment regimens involving nanomedicines only modestly improve the overall survival of patients. As our understanding of the complex tumor microenvironment and molecular landscape of PDAC continues to improve, substantial effort is being undertaken in the development of targeted multiagent therapeutic strategies and drug delivery systems that might improve the effectiveness of PDAC treatment. The novel approaches employing combination therapies that are discussed in following section may provide a means of overcoming pathophysiological barriers in patients with PDAC, thus reducing therapeutic resistance.

Targeting Desmoplastic Stromal Barriers

The resistance of human PDAC to systemic therapies is unusual compared with other solid carcinomas, and the observed lack of survival benefit might at least partly evolve from the predominant desmoplastic stroma reaction and the pronounced hypovascularity that impede efficient drug delivery to the tumor cells. Thus, normalization of the tumor microenvironment represents a promising strategy in order to improve the penetration and efficacy of systemic chemotherapeutics and/or nanomedicines and may provide important therapeutic outcomes. Such strategies are especially attractive because these pathophysiological barriers cannot be overcome through nanomedicine design alone. One of the approaches used to address the stroma is to target the noncellular components. In this setting, one promising drug is a (polyethylene glycol, PEG) PEGylated version of Halozyme's proprietary recombinant human hyaluronidase enzyme, rHuPH20 (PEGPH20) that is able to degrade hyaluronan, which is an abundant component of the ECM in pancreatic stroma. Preclinical studies in a genetically engineered mouse model of PDAC have demonstrated that enzymatic depletion of hyaluronan by PEGPH20 induced the re-expansion of tumor blood vessels as well as an unexpected selective change in tumor endothelial ultrastructure and macromolecular permeability, which resulted in increasing the intratumoral delivery of two chemotherapeutic agents, doxorubicin and GEM. These changes in tumor vasculature and drug delivery also prolonged the survival of the mouse model treated with the PEGPH20 and GEM combination compared with GEM monotherapy (Jacobetz et al., 2013). In a phase Ib study (NCT01453153) in patients with stage IV untreated pancreatic cancer, the PEGPH20 plus GEM combination was well tolerated and showed promising clinical activity, particularly in patients with tumors expressing high hyaluronic acid levels (Hingorani et al., 2016). Consistent with preclinical studies, the imaging analyses in selected patients demonstrated a rapid increase in tumor perfusion within 24 hours after PEGPH20 dosing, which resulted in higher intratumoral concentration of subsequently administered chemotherapy. The promising results of this trial warranted follow-up studies combining PEGPH20 with other agents. A combination of PEGPH20 plus GEM/nab-PTX was evaluated versus GEM/nab-PTX in an open-label randomized phase 2 trial (HALO 2020) in patents with untreated metastatic PDAC (Hingorani et al., 2018). The study results demonstrated an overall improvement in PFS for patients receiving PEGPH20 plus GEM/nab-PTX. With the limited number of patients, the greatest treatment benefit with the PEGPH20 plus GEM/nab-PTX treatment was observed in patients with high-hyaluronan tumors (median PFS of 9.2 month and overall RR of 71%) compared with the GEM/nab-PTX control arm (median PFS of 4.3 months and overall RR of 29%). Currently, PEGPH20 is under investigation in the phase III randomized HALO-109-301 trial given in combination with GEM/nab-PTX (NCT02715804) in a biomarker-selected patient population with high hyaluronic acid levels (Fig. 1). The limitations of this therapy include thromboembolic events; therefore, anticoagulation is now administered in conjunction with PEGPH20 in active clinical

TABLE 3
Nab-PTX/GEM–based combination therapy in clinical trials (ongoing)

Regimen	Target	Clinic Trial	Phase	Status
PCSC targeting				
Sonidegib	SMO	NCT02358161	I/II	U
		NCT01431794	I/II	ANR
Napabucasin	STAT3	NCT02993731	III	R
Kinase or signaling pathway targeting				
Afatinib	ErbB2 and EGFR	NCT02975141	I	ANR
Ficlatuzumab	HGF	NCT03316599	I	R
FG-3019	CTGF	NCT02210559	I/II	ANR
Ibrutinib	BTK	NCT02562898	I/II	ANR
		NCT02436668	III	ANR
Adavosertib	WEE1	NCT02194829	I/II	ANR
Nintedanib	VEGFR, FGFR, and PDGFR	NCT02902484	I/II	R
Ceritinib + cisplatin	ALK	NCT02227940	I	R
BYL-719	PI3K	NCT02155088	I	ANR
TGR-1202	PI3K-δ	NCT02574663	I	ANR
9-ING-41	GSK-3β	NCT03678883	I/II	NR
Ulixertinib	ERK	NCT02608229	I	R
Cisplatin + BGB324	AXL	NCT03649321	I/II	NR
Olaratumab	PDGFR-α	NCT03086369	I/II	R
Immune system targeting				
Tocilizumab	IL-6R	NCT02767557	II	R
Indoximod	IDO	NCT02077881	I/II	ANR
ALT-803	IL-15 superagonist	NCT02559674	I	ANR
Selicrelumab	CD40 antigen stimulants	NCT02588443	I	R
Durvalumab + tremelimumab	PD-1L + CTLA-4	NCT02879318	II	ANR
Nivolumab + paricalcitol + cisplatin	PD-1	NCT02754726	II	R
Oleclumab + durvalumab	PD-1 + PD-L1	NCT03611556	I/II	R
Cabiralizumab + nivolumab	CSF1R + PD-L1	NCT03336216	II	R
BMS-813160 + nivolumab	CCR2/5 + PD-L1	NCT03184870	I/II	R
APX005M + nivolumab	CD40 agonist + PD-L1	NCT03214250	I/II	R
BMS-813160 + nivolumab	CCR2/5 + PD-L1	NCT03496662	I/II	R
Pembrolizumab + paricalcitol	PD-1 + VD receptor activator	NCT02930902	I	R
Other targets				
Nal-Iri/5-FU + folinic acid	DNA and Top I	NCT03703063	I	R
Enzalutamide	AR antagonist	NCT02138383	I	ANR
CPI-613	TCA cycle	NCT03435289	I	R
SGT-53	p53 gene	NCT02340117	II	R
ARQ-761	NQO1	NCT02514031	I	R
Selinexor	SINE	NCT02178436	I/II	ANR
Hydroxychloroquine	TLR	NCT01978184	II	ANR
PEGPH20	HA	NCT02487277	II	R
		NCT02715804	III	R
PEGPH20 + rivaroxaban	HA and Factor Xa	NCT02921022	U	R
ensituximab	MUC5AC	NCT01834235	I/II	ANR
VCN-01	pRB	NCT02045602	I	R

ALK, anaplastic lymphoma kinase; ANR, active, not recruiting; AR, androgen receptor; AXL, cell surface receptor tyrosine kinase, part of the TAM family of kinases; BTK, Bruton's tyrosine kinase; CCR2/5, C-C chemokine receptor type 2/5; CD40, cluster of differentiation 40; CSF1R, colony stimulating factor 1 receptor; CTGF, connective tissue growth factor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; ErbB2, receptor tyrosine-protein kinase (also known as human epidermal growth factor receptor 2); ERK, extracellular signal-regulated kinase; Factor Xa, activated form of Stuart-Prower factor; FGFR, fibroblast growth factor receptor; GSK-3β, glycogen synthase kinase 3β; HA, hyaluronic acid; HGF, hepatocyte growth factor; IDO, indoleamine-pyrrole 2,3-dioxygenase; IL-15, interleukin-15; IL-6R, interleukin 6 receptor; MUC5AC, mucin 5AC (a protein that in humans is encoded by the MUC5AC gene); NQO1, NADPH dehydrogenase (quinone) 1; NR, not recruiting; P53, transformation-related protein 53 (any isoform of a protein encoded by homologous genes in various organisms); PD-1, programmed cell death protein; PD-1L, programmed cell death protein ligand; PDGFR, platelet-derived growth factor receptors; PDGFR-α, platelet-derived growth factor receptor α; PI3K, phosphoinositide 3-kinase; pRB, phosphorylated retinoblastoma protein; R, recruiting; SINE, short interspersed nuclear element; SMO, smoothened [a class frizzled (Class F) G protein-coupled receptor]; STAT3, signal transducer and activator of transcription 3 (a transcription factor); TCA cycle, tricarboxylic acid cycle; TLR, Toll-like receptor; Top I, topoisomerase I; U, unknown; VEGFR, vascular endothelial growth factor receptor; WEE1, nuclear kinase belonging to the Ser/Thr family of protein kinases.

trials (Hingorani et al., 2015; Adiseshaiah et al., 2016; Meng and Nel, 2018). Collagen is another ECM component that contributes to solid stress and vessel compression in tumors. Jain and his colleagues (Chauhan et al., 2013) have demonstrated that the angiotensin inhibitor losartan reduces stromal collagen and hyaluronan production, which is associated with decreased activity of cancer-associated fibroblasts. Consequently, losartan reduces solid stress in tumors, resulting in increased vascular perfusion and drug and oxygen delivery and potentiates chemotherapy in PC models. Losartan also increased the efficacy of the liposomal formulation of doxorubicin, Doxil (Diop-Frimpong et al., 2011). Interestingly, the administration of losartan or Doxil alone did not affect the growth of pancreatic tumors, but the tumors were significantly smaller in mice treated with the losartan plus Doxil combination. These observations are in good agreement with previously reported results of clinical evaluation of liposomal doxorubicin in patients with unresectable PDAC where no complete or

partial responses were seen (Halford et al., 2001). Thus, losartan shows potential to enhance the intratumoral penetration and efficacy of small and large therapeutics in patients with PDAC. In parallel, retrospective clinical data suggested that patients with PDAC receiving GEM monotherapy and treated with angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors to manage hypertension survived approximately 6 months longer than those who were only on GEM therapy (Nakai et al., 2010). Collectively, these findings formed the basis of an ongoing phase II clinical trial investigating the combination of losartan and FOLFIRINOX and then chemoradiotherapy in unresectable locally advanced PDAC (NCT01821729) (Fig. 1).

Hedgehog signaling has been shown to be active in pancreatic carcinogenesis (Bailey et al., 2008) and its inhibition caused tumor growth suppression associated with reduction in the expression of Hedgehog target genes in the stroma compared with control-treated xenograft tumors (Feldmann et al., 2008; Yauch et al., 2008; Mills et al., 2013). Preclinical studies in genetically engineered mouse models have demonstrated that inhibition of Hedgehog pathway signaling transiently increases intratumoral vessel diameter, which results in stromal disruption and enhanced drug delivery (Olive et al., 2009). Unfortunately, a recent phase II trial (NCT01130142) of GEM plus the sonic Hedgehog inhibitor (HHI) saridegib versus GEM plus placebo in previously untreated patients with metastatic PDAC resulted in a disappointing outcome. The trial had to be halted due to progressive disease and decreased median OS in patients treated with GEM and saridegib (Richards et al., 2012). Furthermore, recently reported data on the clinical evaluation of vismodegib (another smoothened inhibitor) and a GEM combination failed to demonstrate its benefits over GEM (Catenacci et al., 2015). The reasons for the failure of those drugs in the clinical setting are not entirely clear. Perhaps the stroma is contributing to some tumor control; therefore, permanent stroma depletion may also increase the opportunity for cancer cells to metastasize and alleviate stress associated with hypoxia (Özdemir et al., 2014). These results emphasize the need to invest more effort in the identification of markers of sensitivity during patient selection as well as in the development of rational therapeutic combinations and dosing regimens. Overall, pharmacologic inhibition of tumor stroma in combination with chemotherapy is a promising strategy as a means to potentiate delivery of therapeutics to the tumor. However, the ECM is a complex network having both pro- and antitumor effects and a deeper knowledge of the interactions between stroma and cancer cells is required to translate this strategy into clinical success.

Normalization of tumor vasculature using antiangiogenic agents is another approach that enhances extravasation of therapeutic agents at tumor sites. The tumor vasculature is abnormal in the architecture and morphology of the vascular wall. Tumor vessels are often tortuous and irregular, with poorly aligned defective endothelial cells, detached pericytes, and lack of a smooth muscle layer (Whipple and Korc, 2008). The leaky nature of tumor vasculature coupled with a dysfunctional lymphatic system forms the physiologic basis of the enhanced permeability and retention effect, which is beneficial to nanocarriers in order to extravasate from vessels and accumulate in tumors (Duncan, 2006). However, the low tumor perfusion, unevenly distributed blood flow, and heterogeneous vessel permeability hinder the homogeneous distribution and deep penetration of the drugs and nanomedicines throughout the tumor (Jain, 2012; Miao et al., 2015). Correction of excessive angiogenesis signaling to repair abnormalities in vascular structure and function may enhance drug delivery, thereby increasing chemotherapy activity. The vascular-normalization concept was evaluated in several clinical trials, in which vascular endothelial growth factor–targeted agents (bevacizumab, axitinib, and aflibercept) were added to GEM in the treatment of patients with advanced-stage PDAC (Kindler et al., 2010; Rougier et al., 2013; Tian et al., 2013; Sahora et al., 2014). The addition of an agent against vascular endothelial growth factor receptors to GEM-based chemotherapy resulted in higher overall RR but no survival advantage. It is possible that the inhibition of vascular endothelial growth factor receptors was quickly overwhelmed by the signaling forces coming from the other major pathways (e.g., epidermal growth factor receptors). Therefore, it is conceivable that simultaneous targeting of multiple pathways may prevent the rapid emergence of resistance. As an additional consideration, the chemotherapeutics should be administered during the window of normalization to obtain improved delivery, since vascular normalization is a transient process (Goel et al., 2011).

With respect to the nanocarrier systems, it is well established that the size of the nanomaterial affects the kinetics and extent of tumor accumulation and penetration. Kataoka and colleagues (Cabral et al., 2011) compared the tumor deposition of drug-loaded polymeric micelles of different sizes (30–100 nm) that exhibited similar circulation profiles and comparable tumor accumulation. It was found that the micelles with diameters above 50 nm mostly accumulated at the periphery of tumors and were not able to efficiently penetrate into the interstitium of poorly permeable, hypovascular tumors such as the human pancreatic cancer BxPC3 model; consequently, this resulted in very limited antitumor activity (Choi et al., 2007, 2011; Longmire et al., 2008; Cabral et al., 2011). Conversely, very small nanoparticles with size below 10 nm are often associated with a shorter blood half-life and fast clearance through renal filtration. In general, the vasculature of pancreatic tumors is moderately permeable, with pore sizes in the range of 50–60 nm (Chauhan and Jain, 2013). Thus, a size range of 15–50 nm would be preferable in order to exploit the leakiness of the tumor vasculature as far as transport is concerned. Consistent with this concept, cisplatin-incorporated polymeric micelles composed of polyethylene glycol/poly(glutamic acid) block copolymers with a size of about 30 nm (under the development name NC-6004; NanoCarrier Co., Ltd.) were designed to provide sustained release of cisplatin and utilize the enhanced permeability and retention effect to target the release of platinum to tumors (Nishiyama et al., 2003). Preclinical studies have indicated that NC-6004 exhibited prolonged blood circulation, preferential distribution to tumors, significantly lowered toxicity levels (compared with cisplatin at equivalent doses), and increased antitumor activity (Uchino et al., 2005; Cabral et al., 2011; Baba et al., 2012). These characteristics have been demonstrated in both a phase I study, where NC-6004 was used as monotherapy for patients with solid tumors, and a phase Ib/II study, where NC-6004 was used in combination with GEM in patients with pancreatic cancer (Plummer et al., 2011; Doi et al., 2017; Subbiah et al., 2018). Based on these results, a phase III trial is currently ongoing in Asia on the combination therapy of NC-6004 and GEM versus GEM monotherapy in the treatment of patients with locally

advanced or metastatic PDAC (NCT02043288) (Fig. 1). Another nanomedicine, Genexol-PM, a 20–50 nm polyethylene glycol/poly(D,L-lactide) copolymer micellar formulation of paclitaxel, was evaluated as monotherapy in treatment-naive advanced PDAC patients in a single-arm phase II study and demonstrated a median OS (6.5 months) and other efficacy parameters preferable to those seen historically with GEM (Saif et al., 2010). The formulation is currently under evaluation in combination with GEM in patients with recurrent and metastatic PDAC (NCT02739633) (Fig. 1).

The contradictory size requirements for prolonged blood circulation and improved tumor penetration have aided the development of multistage systems that could maintain relatively large sizes during blood circulation but convert to smaller particles possessing favorable tissue penetration and diffusivity once accumulated at the tumor site (Wong et al., 2011; Sunoqrot et al., 2014). For example, Li et al. (2016) fabricated pH-sensitive nanoparticles through amphiphilic polymer–directed assembly of platinum prodrug-conjugated polyamidoamine (PAMAM) dendrimers. At physiologic pH, these hybrids had a size of around 100 nm, which favored long blood circulation and enhanced tumor accumulation. Then, the acidic tumor microenvironment triggered the release of small PAMAM prodrugs with sizes of approximately 5 nm, which enabled deep and uniform tumor penetration. Finally, the PAMAM prodrugs were rapidly reduced in the reductive cytosol to release active and potent cisplatin. A proof-of-principle in vivo efficacy study conducted in a BxPC-3 human pancreatic tumor model demonstrated that delivery of cisplatin prodrug via a multistage delivery system resulted in superior tumor shrinkage and prolonged survival time compared with free cisplatin or PAMAM prodrugs loaded in similarly sized, pH-stable nanoparticles. Moreover, intravital confocal laser scanning microscopy analyses confirmed that the released PAMAM enables efficient extravasation and penetration into deep tumor space (Fig. 1). These results emphasize the importance of size on the interstitial diffusivity of particles and suggest that tumor microenvironment–based size switching is a viable strategy for improving drug penetration and therapeutic efficacy, especially in tumors with poor permeability.

Targeting Cancer Stem Cells

As previously mentioned, current PDAC treatments ultimately fail, partially owing to the late diagnosis and dismal prognosis, but also as a result of tumor relapse at local or distant locations after treatment. Recent evidence has demonstrated that a small subpopulation of tumor cells (1%–5%) with extremely high tumorigenic potential, pancreatic cancer stem cells (PCSCs), are responsible for the disease progression, its resistance to chemotherapy and radiation, and driving relapse after treatment in PDAC patients (Hidalgo, 2010; Lonardo et al., 2010; Zhan et al., 2015; Batlle and Clevers, 2017). Moreover, when PCSCs are identified in surgical samples from patients with resectable disease, they confer a shorter survival rate (Rasheed et al., 2010). Of note, conventional therapies have been found to enrich stem cell fraction in tumors (Batlle and Clevers, 2017). Indeed, several studies have demonstrated that monotherapy with GEM increases the relative proportion of PCSCs (Hermann et al., 2007; Li et al., 2011; Zhang et al., 2016c). For example, Hermann et al. (2007) reported that PCSCs were enriched by >2 times in the orthotopic L3.6pl pancreatic tumor model following 3-week GEM treatment. Thus, strategies aimed at specific targeting and eradication of PCSCs may have important clinical implications. One of the most promising approaches to targeting and depleting this cell population is certainly the inhibition of stem cell–associated pathways (e.g., wingless-related integration site, Hedgehog, mTOR, and Notch), and multiple preclinical studies have provided compelling rationale for several phase I and II trials (Tables 2 and 3). However, according to the reported data, these trials have shown very limited positive outcomes with low responses and comparable rates in both PFS and OS. Given these results and our current understanding that all signaling pathways—including those used by PCSCs—function as a coordinated network, it is possible that PCSCs are heterogeneous and able to escape inhibition of an individual signaling pathway (Nimmakayala et al., 2019). It is likely that PCSC targeting will require the design of mechanism-based combination regimens. Funding from the preclinical studies suggest that this hypothesis is worthy of further exploration. For example, Heeschen and colleagues (Mueller et al., 2009) have shown that neither cyclopamine (a Hedgehog pathway inhibitor) nor rapamycin (an mTOR inhibitor) alone or as supplements to GEM chemotherapy were capable of effectively diminishing the PCSC pool. Only combined inhibition of these two pathways together with GEM, resulted in the desired targeting of the PCSCs. Importantly, administration of this triple combination in mice with established patient-derived pancreatic tumors was reasonably tolerated and translated into significantly prolonged long-term survival. Despite the great efficacy of this combination exhibited in the preclinical setting, the most concerns in the clinic are still the drug-related side effects. In this context, utilization of drug delivery systems to overcome some limitations related to drug solubility, stability as well as mitigating off-target toxicity might be beneficial at maximizing drug potentials in eliminating PCSCs. However, the number of reports on nanocarriers as a drug delivery system targeting PCSCs in PDAC is rather limited. For instance, Hedgehog pathway inhibitor 1 (HPI1) is a potent HHI based on in vitro evaluation. To overcome the limitations related to HPI1 poor aqueous solubility, its nanoparticle-based formulation (Nano-HHI) was developed using polyethylene glycol/poly(lactic-co-glycolic acid) copolymers. Nano-HHI particles of approximately 60 nm in size formed stable aqueous dispersions, and improved systemic bioavailability compared with the parent compound. Nano-HHI in combination with GEM suppressed tumor growth in orthotopic Pa03C pancreatic xenografts compared with GEM alone. Importantly, Nano-HHI, either as a single agent or in combination therapy arms, can cause a marked decrease in PCSCs within the tumor, suggesting its potential for further translational development (Fig. 1). Most recently, Mahato and coworkers (Kumar et al., 2017) designed and evaluated a new analog of vismodegib, MDB5, which was shown to be more potent in depleting PCSCs. In a pancreatic tumor mouse model, treatment with MDB5 containing nanoparticles resulted in significant inhibition of tumor growth and was well tolerated. These results suggest that nanoformulations of MDB5 can be further explored as a platform for monotherapy and/or combination therapy. Drug repurposing for oncology indication has recently been realized due to existing preclinical and clinical data and fast Food and Drug Administration approval (Fig. 1). In this context,

anthothecol, an antimalarial compound, and its nanoparticle-based formulation were shown to inhibit cell proliferation and colony formation, and induced apoptosis in PCSCs and cancer cell lines, but appeared to have little effect on nonmalignant pancreatic ductal cells. It was found that anthothecol inhibits the Hedgehog signaling pathway by disrupting binding of Gli to DNA, thus acting as a Gli inhibitor (Fig. 1). The other formulations of agents that are effective against PCSCs require further careful evaluation in relevant PDAC animal models to confirm whether their use could potentially improve the treatment outcomes and reduce recurrence of the disease. Other intriguing possibilities include immunotherapy directed against PCSC markers; however, a cautious approach is required because many of these markers can be found on normal stem cells in the hematopoietic system (Batlle and Clevers, 2017). Furthermore, regeneration of the PCSC pool by plasticity of non-PCSCs upon treatment cessation presents another challenge in therapy design targeting. The development of anti-PCSC therapies is in a relatively early stage, and along with the great promise of drug delivery technologies many issues remain unresolved or unknown; therefore, more basic and applied research is needed to translate these therapeutic designs into clinical approaches (Zhao et al., 2013).

Closing Remarks

PDAC remains one of the most devastating cancers with a dismal response to the existing therapies. Despite intensive research over the past decades, the development of effective chemotherapeutic treatments has been slow, with only modest improvement in patients' survival. Intrinsic and acquired drug resistance extremely shortens the period of effectiveness of drugs, whereas drugs proven to be efficient in other type of cancers (e.g., taxanes and anthracyclines) fail in treating PDAC, indicating that PDAC possesses uniquely challenging characteristics that are not yet completely understood. Combination therapies demonstrate improved outcomes in patients' survival and quality of life; nevertheless, the overall improvement is still marginal, especially for patients diagnosed with late stages of the disease. With a more comprehensive understanding of the physiology and pathology of PDAC, the expansion of treatment beyond conventional chemotherapies to specific and targeted strategies including nanomedicine-based drug delivery platforms holds great therapeutic promise in combating PDAC. Since a proper drug combination can target multiple pathways, promote synergistic drug action, and suppress the development of drug resistance, the use of multiple therapeutic agents in a treatment regimen has become the primary strategy in treating PDAC. However, this remains a challenging task due to the possible cumulative toxicities as well as the differences in pharmacokinetics and biodistribution profiles that result in inconsistent drug uptake and suboptimal combinatorial effects at the sites of action, which are sensitive to both dosing and scheduling of multiple drugs. Indeed, nanomaterials offer several advantages as therapeutic tools due to design flexibility and small size, and can be engineered to interact with specific biologic components in targeted diseased tissues. Such carriers can simultaneously allow mixing different drugs in one carrier particle, control drug retention, and reconcile the pharmacokinetics, ratiometric delivery of drug combination, and sequential drug release, which are important determinants for better tailored combinatorial regimens in cancer treatment. This, in principle, can open very broad possibilities in designing synergistic drug combinations that could affect multiple aberrant pathways in PDAC (Meng et al., 2015; Lu et al., 2017). The selected studies described herein clearly emphasize that nanomedicines can improve the therapeutic responses observed with standard therapies and achieve accelerated clinical translation. However, the complexity of these systems compared with conventional small molecule drugs and intricate structural properties demands careful engineering of the nanocarriers to achieve the desired effect. Challenges exist in terms of efficient delivery of the cargo to the tumor as well as clearance of the nanomaterials once they have accomplished their mission in vivo. Moving forward, further thorough characterization and understanding of nanomaterial interactions with biologic milieus that drive both their intended action and possible toxicological responses and immunogenicity will be critical in the design and optimization of future cancer nanomedicines and will help in eventually taking them from bench to bedside.

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Authorship Contributions

Participated in research design: Lei, Xi, Bronich.

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