Published in final edited form as:

Expert Rev Anticancer Ther. 2018 February ; 18(2): 131–148. doi:10.1080/14737140.2018.1417844.

The evolution into personalized therapies in pancreatic ductal adenocarcinoma: challenges and opportunities

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Abstract

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is projected to be the second leading cause of cancer related mortality in the United States in 2030, with a 5-year overall survival of less than 10% despite decades of extensive research. Pancreatic cancer is marked by the accumulation of complex molecular changes, complex tumor-stroma interaction, and an immunosuppressive tumor microenvironment. PDAC has proven to be resistant to many cytotoxic, targeted and immunologic treatment approaches.

Areas covered: In this paper, we review the major areas of research in PDAC, with highlights on the challenges and areas of opportunity for personalized treatment approaches.

Expert commentary: The focus of research in pancreatic cancer has moved away from developing conventional cytotoxic combinations. The marked advances in understanding the molecular biology of this disease especially in the areas of the microenvironment, metabolism, and DNA repair have opened new opportunities for developing novel treatment strategies. Improved understanding of molecular abnormalities allows the development of personalized treatment approaches.

Keywords

targeted therapy; personalized therapy; pancreas cancer; tumor microenvironment; DNA repair pathways

1. Introduction

It is estimated that 53,670 people would be diagnosed with pancreatic ductal adenocarcinoma (PDAC) in 2017, while approximately 43,090 people would die because of

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Declaration of interest

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it. PDAC is the third leading cause of cancer related mortality and is projected to become the second leading cause of cancer dead by 2030. [1] Progress in the treatment of PDAC has been painfully slow over the past several decades. In the period 1975 – 1977, the 5-year relative survival rate of patients diagnosed with pancreas cancer in the United States was 3%, while in the period 2006–2012 the 5-year survival rate was at 9%. [2]

At this time, there is no proven method for screening and early detection of PDAC which largely explains why most patients are diagnosed at an advanced stage of the disease. [3] The relative anatomic inaccessibility of the pancreas [4] challenges the development of early detection strategies. Only 10–15% of patients present at an early stage that is amenable to a curative surgical resection. This underscores the need to develop reliable screening methods that will enable detection of the disease at its early and potentially curable stage. Even though surgical resection is the only potentially curative treatment, the median overall survival of patients who undergo radical resection is 11–23 months [5, 6] because most patients who undergo surgical resection will ultimately develop metastatic disease. This readily explains the systemic nature of the disease at presentation even in those with apparent localized stage. A significant number of patients whose disease progresses on front line therapy will not receive further treatment because of rapid clinical deterioration. [7] There is an urgent unmet need in the treatment of this disease, which is often coupled with frustration stemming from the lack of treatments with durable response.

There is also a need for reliable prognostic and predictive biomarkers to appropriately select patients for the available treatment options. The only biomarker approved for clinical use at this time is serum levels of CA19–9, which is used as a prognostic marker and to follow the activity of PDAC. However, this biomarker lacks specificity and sensitivity [8] and the level of CA19–9 doesn't reliably predict drug response or resistance to treatment. [9].

In this article, we discuss the opportunities and challenges in furthering the development of newer and improved personalized treatment strategies for this deadly cancer.

2. Molecular Biology of Pancreatic ductal adenocarcinoma

A better understanding of the molecular biology of PDAC is the foundation for the development of personalized therapies. The molecular basis of pancreatic carcinogenesis was extensively studied using genetically engineered animal models (GEMM) of pancreatic adenocarcinoma. These models have shown that carcinogenesis is a multi-step process associated with the accumulation of signature mutations along the way. Table 1 summarizes examples of such GEMM models. Frequently encountered mutations and their affected downstream pathways in PDAC are summarized in Table 2.

2.1. Oncogene activation

Activating mutations of the *KRAS* oncogene are the earliest genetic changes in transformation to pancreatic cancer. [10] These mutations are seen in over 90% of diagnosed pancreatic cancers. [11] Activating *KRAS* mutations compromise the ability of the *RAS* protein to hydrolyze GTP to GDP, thus locking the protein in an active conformation. [12] The activation of *KRAS* in the pancreatic epithelium promotes the formation “pancreatic

intraepithelial neoplasia” (PanIN), which is considered a precursor lesion for future pancreatic carcinogenesis. [13] Though these mutations are key steps in PanIN initiation, they are not sufficient for the development of pancreatic adenocarcinoma which needs additional genetic changes including loss of tumor suppressor genes. [14]

2.2. Tumor suppressor gene inactivation

Tumor suppressor genes code for key cellular proteins that prevent malignant transformation of normal cells. As such, tumor suppressor genes inhibit cellular proliferation. They also induce apoptosis when there is a critical damage that cannot be readily repaired by the DNA repair machinery. Consequently, inactivating mutations of tumor suppressor genes lead to the loss of their regulatory function in cell division, senescence and detection of DNA damage. In pancreatic cancer, frequently inactivated tumor suppressor genes include *Ink4A* (*p16/CDKN2A*), *TP53*, *SMAD4* (*DPC4*) and *BRCA2*. Inactivating mutations of the *Ink4A* (*p16/CDKN2A*) tumor suppressor gene are seen in up to 95% of pancreatic adenocarcinoma. [15] It is shown that *KRAS* mutations may induce the expression of *Ink4A* and the induction of cellular death. *Ink4A* loss therefore may be required to override the cellular senescence induced by constitutively activated *KRAS*. [16] The *TP53* tumor-suppressor gene is mutated in 50–75% of pancreatic adenocarcinomas. [17, 18] *TP53* mutations arise in later-stage PanINs that have acquired significant features of dysplasia, reflecting the possible function of *TP53* in preventing malignant progression. [10] Following *p53* loss, the rate of genomic aberrations increases drastically. This possibly contributes to the immense heterogeneity of pancreatic tumors and their resistance to multiple chemotherapeutic agents. [18] *SMAD4* (*DPC*) mutations are seen in approximately 50% of all pancreatic adenocarcinomas. Similar to *p53* mutation, loss of *SMAD4* occurs late in the process of PanIN progression to carcinoma. *SMAD4* loss is likely to contribute to tumor progression by influencing tumor-stroma interactions. [19]

2.3. DNA repair pathways

DNA damage repair (DDR) pathways are critical to the survival of the cell. To maintain the integrity of the genome, the cell relies on a significant functional overlap in the base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombinant (HR) and non-homologous end joining (NHEJ) pathways. [20, 21, 22, 23, 24] The presence of seemingly redundant repair pathways ensure genomic stability in that if one pathway is lost, the cell becomes increasingly dependent on the others. [25]

There has been an increasing interest in targeting the DNA damage repair pathways because of the recognition of synthetic lethality. In a cell with redundant pathways, the inactivation of one function may be compensated for by another. Inactivating the alternative pathway(s) can be lethal to the cell, hence the phenomenon of synthetic lethality. There is an interest in the development of drugs that target the single strand DDR pathways in cancers with a defective double strand DDR pathway.

Mutations in *BRCA* gene account for approximately 5% of all pancreatic adenocarcinomas. However, *BRCA2* gene mutation account for up to 20% of all cases of familial PDAC. [26] Somatic *BRCA2* mutations are also seen in sporadic cases of pancreatic adenocarcinoma.

Similar in function to *BRCA1*, *BRCA2* is involved in the repair of double stranded breaks in DNA. Loss of *BRCA2* leads to the rapid accumulation of double strand DNA breaks and chromosomal aberrations. [27] Mutation in *BRCA2* is typically seen late in tumorigenesis, probably reflecting the requisite inactivation of mediators of DNA-damage-response pathways, like *TP53*. [10] Heterozygous germline mutation of *PALB2* has been shown to cause a defect in DNA replication and damage response. [28] Anecdotal experience showed inactivating mutation of *PALB2* gene lead to a favorable tumor response to mitomycin C treatment, as the mutation leads to disturbed *BRCA1* and *BRCA2* interactions and result in defective DNA double strand break repair. [29] Ataxia telangiectasia mutated (*ATM*) is another gene involved in the DNA double strand break repair. [30] In a study of 166 familial pancreatic cancer probands, 2.4% (4/166) carried deleterious *ATM* mutations. [31] In an integrated genomic analysis of 456 cases of pancreatic adenocarcinoma, the frequency of DNA repair genes (*BRCA1*, *BRCA2*, *ATM*, *PALB2*) mutation was 17% (5% germline, and 12% somatic). [32]

2.4. Tumor Microenvironment

The role of tumor microenvironment in carcinogenesis, disease progression, metastasis, drug resistance, and immunosuppression has become increasingly recognized in the past decade. [33] It has been reported that up to 80% of the tumor mass in pancreatic adenocarcinoma may be contributed by the dense desmoplastic stroma with various cellular components. [34] The stroma consists of pancreatic stellate cells (PSCs), extracellular matrix (ECM), fibroblasts, macrophages, blood vessels, pericytes, lymphatic vessels, bone marrow-derived cells (BMDCs), stem cell-like cells and inflammatory cells. [35, 36] Studies have shown that the microenvironment-tumor cross talk is complex, dynamic and rapidly changing.

Pancreatic stellate cells, whose exact origin is unknown, play an important role in this network. In the normal pancreas, they make up 4% of all parenchymal cells. [37] These cells are activated by paracrine signaling from the surrounding cancer cells, immune or endothelial cells in the context of benign inflammation or malignancy. [38] Upon activation, these cells undergo transformation into myofibroblast-like cells expressing the cytoskeletal protein alpha smooth muscle actin (aSMA). In this conformation, the stellate cells increase their proliferation, migration and extracellular matrix protein synthesis. [39] Activated pancreatic stellate cells can induce cancer cell proliferation, while decreasing cancer cell apoptosis. They can also stimulate cancer cell migration, through increased epithelial mesenchymal transition (EMT) of cancer cells. [40] Pancreatic stellate cells have chemotactic effect on CD8+ T cells through secretion of CXCL12 [41] and on myeloid derived suppressor cells (MDSCs) through the secretion of IL 6. [42] MDSCs are known to suppress immune response to the tumor, and hence lead to immune evasion by cancer cells. Pancreatic stellate cells also produce VEGF and the hepatocyte growth factor (HGF) and activate cMET pathway hence promoting angiogenesis. [43, 44] It has been proposed that pancreatic stellate cells can also travel to metastatic site and facilitate seeding, survival and proliferation of the metastatic cancer cells at their new sites. [43] It is important to note that these findings are derived from in vitro studies and in vivo murine models and that there are species as well as donor-dependent variances between murine and human pancreatic stellate cells

2.5. Tumor infiltrating immune cells

An immunosuppressive tumor microenvironment is one of the hallmarks of pancreatic cancer. This is characterized by the presence of activated immunosuppressive and tumor supportive immune cells like myeloid derived suppressive cells (MDSCs), regulatory T cells (Tregs), tumor associated macrophages (TAM), and the presence of tumor-supportive immune cells with lack of effector immune cells.[45, 46] MDSCs can suppress effector CD8+ T-lymphocytes and promote initial tumor growth. [47] Tregs can secrete suppressive cytokines such as interleukin 10 (IL-10) and tumor growth factor β (TGF β) and function through immune check-point inhibitors. [48] The M2 subtype of TAMs has been shown to be immunosuppressive in pancreatic carcinoma. [49] Effector cells such as CD4+, CD8+ T cells and NK cells are found to be minimal or nonfunctional in the pancreatic carcinoma stroma. This phenotype of pancreatic carcinoma tumor microenvironment is considered to be induced by the tumor cells, pancreatic stellate cells and their interaction with each other and with other cells of the stroma. [50, 51]

2.6. Angiogenesis

Angiogenesis is complex process of forming new blood vessel formation to support the growing needs of tumors and is mediated by many cell types and growth factors. [52] Angiogenesis can be independent of vascular endothelial growth factor (VEGF). Angiopoietin-Tie and Delta-Notch family are examples of other systems mediating angiogenesis in tumors. [53] Considering the pancreatic cancer molecular heterogeneity and complexity of stroma, it is not surprising that VEGF-inhibitors have not shown therapeutic benefits in pancreas cancer. [54, 55] The inhibition of angiogenesis has been speculated to increase the aggressiveness of the tumor through the hypoxia induced transcription factor pathway, in which the active HIF transcription factor binds to its promoter, and turns on the *cMET* gene. The *cMET* gene has been shown to be one of the major promoters of the epigenetically driven epithelial-mesenchymal transitions that convert closely packed epithelial cancer cells into chemotherapy resistant mesenchymal type cells. [56, 57, 58] Inhibiting *cMET* was shown to abrogate oncogenic signaling in vitro and impair tumor growth in vivo. [59, 60]

3. Challenges in the treatment of pancreatic ductal adenocarcinoma

3.1. Disease biology

Finding an effective systemic treatment has been extremely challenging largely because of de novo or rapidly acquired resistance to cytotoxic therapy. The lack of a driver genetic mutation that can be inhibited and the molecular heterogeneity of the disease make it difficult to effectively target molecular pathways. [61, 62] Abundant and complex tumor stroma functions more than a physical barrier to therapeutic interventions. This tumor microenvironment has been characterized to be immunosuppressive thereby enabling the cancer to evade the immune system and be unresponsive to immunotherapy. [63, 64]

As the *KRAS* mutation plays a key role in the oncogenesis in more than 90% of pancreatic cancer cases, it is a rational target for drug development. Unfortunately, this has met with little success because of RAS's molecular structure. [65] As there is no therapeutic

intervention that can target the activated *KRAS* mutation, blocking the pathways downstream to *KRAS* has been attempted, but with little success, if any. [66]

3.2. Tissue acquisition for research

Obtaining tissue from pancreatic masses for diagnostic and research purposes may be challenging due to the location of the organ. Percutaneous image guided needle biopsy of pancreas masses has been safely used in humans as early as 1975. [67] Core needle biopsy was introduced in the late 1980s. [68] Both methods have comparable accuracy in establishing the diagnosis. [69, 70, 71] Endoscopic ultrasound (EUS) has changed the way we obtain diagnostic tissue specimens. With increasing focus on personalized therapy and search for predictive biomarkers there has been an increased need for bigger sized core biopsies in the last few years [72] and modified needles are being evaluated for acquisition of such specimens. [73]

Circulating tumor cells (CTCs) in the peripheral blood is being studied as means of noninvasive tissue acquisition. However, isolation of cancer cells from the blood may be challenging. [74] Circulating cells are likely to be detected with higher disease burden, although there are reports of CTC detection in early disease stage. [75] The presence of CTC in the blood has generally been linked to worse prognosis. [75, 76, 77] The detection techniques and procedures are rapidly developing. The sensitivity of these tests are currently relatively low, and their place in the clinic or research remains to be established. [78] It is believed that with further development, CTCs may provide valuable diagnostic, prognostic or predictive information in the treatment of pancreatic adenocarcinoma. Furthermore, mutational analysis of CTCs and serial monitoring of CTCs and CTC burden might serve as means of monitoring treatment response/emergence of resistance. [75] Circulating cell free DNA (cfDNA) is another resource under investigation. Its utility as a biomarker for pancreatic cancer is similarly being determined. [79]

3.3. Genomic profiling

The use of targeted Next Generation Sequencing (NGS) has been proposed to improve the diagnostic value of fine needle aspiration derived material by detecting key somatic and germline genetic alterations that are unique to pancreatic cancer. [80, 81] The findings of germline mutations may also have implication for unaffected family members. It can also help identify patients at risk of developing pancreatic adenocarcinoma and help define future therapeutic options. [82] NGS in exceptional responders may identify subset of patients that might benefit from specific treatments. Furthermore, NGS may identify potential targets that may help tailor treatments to a specific mutation. However, next generation sequencing has not been prospectively validated for clinical use in patients with pancreatic cancer and remains experimental at this point. There is currently no available drug that can directly target the four most common mutations, *KRAS*, *CDKN2A*, *TP53* and *SMAD4* in pancreatic cancer. All the mutations that can be therapeutically exploited in pancreatic cancer have an exceedingly low prevalence [83] and as such are not interrogated in clinical practice unless enrolled in a clinical trial that is enriched for a particular molecular abnormality. [84] NGS results can also be used to risk stratify patients. In a recent study, a composite of 25-gene

signature from NGS in pancreas cancer patients has been shown to identify patients with short and long-term survival benefits after surgical resection of the primary tumor. [85]

3.4. Preclinical models

Preclinical models of pancreatic cancer are important for the investigation of carcinogenesis, progression and therapy. These include *in vitro* models (pancreatic cancer cell lines, spheroids and organoid) and *in vivo* models including cancer cellular models subcutaneously or orthotopically transplanted into mice, genetically engineered mouse models (GEMMs) and patient-derived xenografts (PDXs). Among them, the *in vivo* models especially PDXs are more important for testing the efficacy of novel therapeutics because of assumed similarity with the pathology of the disease in humans.

3.4.1. *In vitro* Models—Pancreatic cancer cells lines have been widely used in basic research for pancreatic cancer biology and therapy. So far, more than 25 pancreatic cancer cell lines have been established for *in vitro* studies (<http://www.creative-bioarray.com/Products/Pancreatic-Tumor-Cells-list-106.htm>) [86]. Among them, MiaPaCa-2, PANC-1, AsPC-1, HPAC and BxPC-3 cell lines have been most frequently used in the studies of signaling transduction pathway, biomarkers, novel drug screen, and targeting drug resistance in pancreatic cancer. Pancreatic cancer cell lines are cultured in 2-D monolayer pattern and provide a relatively easy tool to conduct any *in vitro* experiments. However, cells in 2-D structure behave differently than cells in 3-D structure which better mimic cells grown in physiological condition *in vivo*. [87]

To overcome the limitation of 2-D cell culture, scientists have created 3-D spheroid culture models. [88] This model was originally developed and used for testing novel agents and their combinations. Building further on these the field has recently focused on the development of organoids using pancreatic cancer cells grown in a semi-solid environment. [89, 90] Studies found that organoids maintained same genetic and phenotypic features of source cells. [89] Moreover, organoids have the similar structure and function compared to the *in vivo* counterparts, suggesting that organoids have great potential for preclinical investigations. [90] The development of pancreatic organoid preclinical models to study the molecular basis of pancreatic cancer and discover targeted therapies supports the enthusiasm for improved drug development.

3.4.2. *In -vivo* Models—Before the emergence of GEMMs and PDXs, human pancreatic cancer cell lines have been subcutaneously or orthotopically transplanted into mice for preclinical research. However, these models lack the interaction between human cancerous cells and human stromal cells. Also, the cancer cells grow in the environment without human immunity. Therefore, the models do not physiologically mimic the human pancreatic cancer. [91] Nevertheless, with the advantage of gene engineering and xenograft techniques, GEMMs and PDXs mouse models (Table 1), which are more suitable for preclinical research, have been developed.

As discussed earlier, multiple gene mutations contribute to the development and progression of PDAC. Based on this information, GEMMs were developed that cover the most commonly found mutations in pancreatic cancer. *KRAS* mutation is the most frequent

genetic alteration in pancreatic cancer. Therefore, transgenic mice have been designed to carry *PDX-1-Cre/Lox-Stop-Lox (LSL)-KRAS*. [13] PDX-1 (Pancreatic duodenal homeobox 1, also known as insulin promoter factor 1) is a critical transcription factors in the developmental program of the pancreas. The Cre/Lox is site-specific recombination system. *PDX-1-Cre/Lox-Stop-Lox (LSL)-KRAS* ensures *KRAS* mutation and activation in pancreatic cells in the mouse model. [13] The pancreas of this transgenic mouse develops ductal lesions identical to all three stages of human PanINs. [13] However, *KRAS* mutation is not sufficient to induce progression to the invasive pancreatic adenocarcinoma. Therefore, more GEMMs have been designed to have activated *KRAS* with one or more other gene mutations such as *p53*, *Ink4a*, *Smad4* and *TGF- β* mutations commonly found in pancreatic cancer. [92, 93, 94, 95, 96, 97, 98] Recent study shows that *LSL-KrasG12D; LSL-Trp53R172H/+; Ink4flox/+; Ptf1/p48-Cre* mouse model with multiple mutations is a more applicable model for preclinical investigation of locally invasive and metastatic pancreatic cancer. [99] The activated *KRAS* together with other gene mutations in pancreatic cells promotes PanINs to progress to invasive pancreatic cancers, making the models more relative to clinical pancreatic cancer. However, the GEMMs harbor same mutations in all pancreatic cells and they are homogeneous. Nonetheless, pancreatic cancer is highly heterogeneous and significantly affected by the tumor microenvironment. Thus, patient-derived xenografts (PDXs) have been developed to overcome the disadvantages of GEMMs,

Pancreatic PDXs are increasingly used in preclinical investigation of efficacy of novel therapeutics. So far, more than 22 PDXs have been developed (Mouse Tumor Biology Database). [100] PDXs are created by the transplantation of a human tumor mass into an immunocompromised mice such as athymic nude mice. PDXs can maintain the original genetic profiles of original cancers from patients even after passaging *in vitro* and *in vivo*. Cancer cells in PDX models grow in their original human stroma. These advantages allow testing for efficacy of novel therapeutics in an *in vivo* setting which mimics the original tumor and environment. The *in vivo* experiments using these models provide valuable information that can help to design more effective human clinical trials to further test the novel therapeutics for treatment of pancreatic cancer. Recently, a gemcitabine-resistant pancreatic cancer patient-derived orthotopic xenograft (PDOX) has been used to demonstrate that MEK inhibitors more significantly inhibit pancreatic cancer growth compared to other therapies. [101] A limitation of PDX models is that PDXs are created in immunocompromised mice, which are not suitable for testing immunotherapy. Recently, humanized NOD SCID gamma mouse models engrafted with human hematopoietic stem cells have been developed and used for investigation of immunotherapy. [102] We believe that by development of conditional control of human immune system engrafted in the mice, the humanized NOD SCID mouse models could be utilized for creating pancreatic cancer PDXs models which could be used for preclinical investigation of immunotherapy.

3.5. Prioritization of molecular targets

It is a disappointment to many that we still don't have a cutting-edge target for effective therapy despite decades of research in pancreatic cancer. The very modest advance in patient outcome from the systemic therapy of pancreatic cancer during the era of targeted therapies was still with conventional cytotoxic drugs. Success of personalized therapy in other

malignancies was a result of discovering “actionable” molecular targets that can be used in patient selection. This illusive actionable treatment target may be discovered with the use of newer molecular technologies, and advanced computing power that can sift through the extensive databases generated from extensive work in genomics, proteomics and metabolomics. [103, 104]

There is a need for more powerful computing power, and even artificial intelligence, to sift through the plethora of information being generated constantly. Although most models still lack clinical validity, different computational models are being used to identify and validate anticancer drug targets on a genome-wide scale. [105] Before large human studies can be performed on the proper selection of targets and drugs that can affect them, a thorough preclinical evaluation along with clinical validation is needed. Establishing efficacy of new targeted therapies in multiple models would increase the level of confidence for possible eventual clinical benefit. With better design of early stage clinical trials and focus on meaningful clinical benefit, rather than a mere statistical significance of findings, it may be possible to avoid conducting a costly phase III study that winds up being unnecessary. [106] The use of predictive algorithms to incorporate existing and future knowledge to best match therapeutic intervention to the molecular signatures of the tumor needs to be implemented to bring about a meaningful breakthrough treatments for this deadly disease. [107]

3.6. Clinical trial design

The design of trials based on rare molecular abnormalities remains challenging due to the difficulty of patient accrual. Such challenges have led to development of innovative designs of clinical trials. Umbrella study typically enrolls patients with a single tumor type. Patients are directed towards different therapeutic arms of the study based on the molecular characteristic of their tumor. Basket study, on the other hand, enrolls patients with different tumor types. Tumors sharing common biomarkers are stratified to receive certain drugs regardless of their tissue of origin. In other words, in the context of basket trial what matters is the tumor’s molecular signature, rather than tissue of origin. Master or tent protocol uses a single multiplex diagnostic assay to assign participants to different arms of a trial within the same trial or network of trials. In this approach after the initial molecular profiling patients and clinicians are presented with different options for standard therapy versus all possible options of available clinical trials. This type of study would ideally need to be conducted in collaboration of a network of organizations. [84] Adaptive trials use information obtained while trial is ongoing (interim analyses) to modify the course of trial. Depending on the emerging results, a study can be extended or stopped. If no benefit is seen within a specific arm of study, that arm can be dropped. In addition, it allows for change of randomization proportion, and rate of accrual. [84, 107]

Considering, the failure of many of our traditional approach to clinical trials in finding an effective therapy in this disease and the complexity of the above measures, a more comprehensive coordination of the available trials is needed to guide patients to the best available clinical trials.

4. Opportunities for personalized therapy for the near future

Although there has been a great interest in personalizing pancreatic cancer therapy, this has been a very elusive goal to achieve. There is also a significant amount of interpatient variability seen in treatment outcomes of patients receiving the current standard of care in the clinic that is also in need of predictive biomarkers. Consequently, clinical trials continue to be largely based on empiric drug combinations and are minimally dependent on predictive biomarkers. Recent work identified several potential areas of developing targeted therapy strategies that may be coupled with predictive biomarkers. Table 3 illustrates select clinical trials exploring the therapeutic utility of such biomarkers.

4.1. Targeting DNA Repair: *BRCA* and beyond

DNA damage may result from base modifications, double-strand DNA breaks, single strand DNA breaks, intrastrand and interstrand DNA cross links. DNA is repaired by distinct pathways to maintain genetic stability and integrity. Two main double strand break repair pathways are prevalent: the more efficient homologous recombination and the error prone non-homologous end joining pathway. [108] The *BRCA* genes encode proteins essential for the homologous recombination pathway of double strand DNA break repair. They also play a key role as a key cell cycle checkpoint in response to DNA damage. [27, 108] *BRCA1/2*-deficient cells that lack homologous recombination activity accumulate inefficiently repaired double-strand DNA breaks, resulting in genomic instability and an increased predisposition to malignant transformation and progression. [109] Although the risk of pancreatic cancer in carriers of *BRCA1* gene mutation is not well quantified, it is estimated to be a 2 to 3 fold increased over the general population. [110, 111] *BRCA1* gene mutation was not seen in a cohort of familial pancreatic cancer patients, raising the question of its significance in familial pancreatic cancer syndromes. On the contrary, *BRCA2* gene mutation has been seen in about 6% of patients with familial pancreatic cancer syndromes. [112] The risk of pancreatic cancer in *BRCA2* gene mutation carriers is reported to be 3 to 6 fold increased over the general population. [113, 114] Patients with impaired DNA repair pathways have been shown to respond better than those with intact DNA repair pathways to therapeutic interventions that induce DNA damage, such as platinum-based chemotherapy drugs and radiation therapy. [115, 116] In a retrospective study of 58 *BRCA*-associated advanced pancreatic cancer patients, there was a significant overall survival advantage in patients treated with platinum when compared to those treated with non-platinum chemotherapy agents (22 vs 9 months; P: 0.039). [117] Small sized studies in patients with *BRCA1/2* mutation related pancreatic cancer showed improved response rates and survival outcome after treatment with platinum-based chemotherapy. [116, 118, 119]

Single strand breaks are by far the most common DNA damages in a cell. If single strand damages are not repaired efficiently, they evolve into a double strand break. [108, 120] Base excision repair (BER) pathway is an important repair mechanism for single strand DNA breaks. Poly-ADP ribose polymerase (PARP-1) is a critical component of the BER pathway and plays a key role in sensing and binding to single strand DNA damages and results in the activation of catalytic proteins including topoisomerases, histones, and PARP-1 itself for the repair of the damage. [108, 121, 122] When a cell that has a defective homologous

recombination pathway loses ability to repair single strand DNA damages, the combination could be lethal to the cell hence the phenomenon of synthetic lethality. To exploit this vulnerability, different studies are looking into using *PARP* inhibitors in patients with *BRCA* gene mutation related pancreatic cancers.

The *PARP* Inhibitor rucaparib was studied in a phase II single arm treatment of 19 patients with known germline or somatic *BRCA* mutation and relapsed pancreatic cancer, with more than 1 prior systemic treatment. There were 2 partial responses and 1 complete response of the 19 patients, response rate of 15%. [123] There are ongoing clinical trials evaluating the benefit of *PARP* inhibitors in treatment of pancreas cancer in patients with *BRCA* gene mutations (NCT01078662, NCT01989546, NCT02042378, NCT01489865). Ataxia telangiectasia mutated (*ATM*) deficiency is associated with responsiveness to the *PARP* inhibitor olaparib in gastric cancer. [123]

With increased understanding of the disease and the involved genetic alterations, the *PARP* inhibitors need to be evaluated further in patients with aberrant genes involved in the DNA repair pathway, beyond the *BRCA* genes.

4.2. Hyaluronan in the tumor stroma

Hyaluronic acid (HA) is a highly abundant mucopolysaccharide in the body synthesized by HA synthases (HAS1–3) and degraded by hyaluronidases (HYAL1–4, HYALP1 and PH20). [124] There is high level of hyaluronic acid in up to 40% of patients with pancreas cancer, due to tumor-stroma interaction, and resulting upregulation of HAS. [125, 126] The accumulation of hyaluronic acid in the stroma leads to increased interstitial fluid pressure due to its water binding capacity leading to collapse of intra-tumoral vasculature, which is considered as a barrier to the delivery of drugs. [127, 128] Hyaluronic acid has also been shown to bind surface receptors RHAMM and CD44, possibly promoting tumor proliferation, adhesion, migration, invasion and immune resistance. [129, 130, 131] Hence, hyaluronic acid has been an interesting therapeutic target in pancreas cancer. Contrary to inhibiting synthesis, blocking receptor signaling or depleting the stromal content of hyaluronic acid is the most studied strategy so far.

Recombinant human hyaluronidase (PH20) has a very short half-life in vivo, which is prolonged to weeks by conjugating it with polyethylene glycol (PEGPH20). [131] In preclinical models, systemic administration of PEGPH20 lead to intratumoral depletion of hyaluronic acid, reduction of interstitial fluid pressure, and improved penetration of chemotherapeutic drugs to the tumor cells. [127, 132, 133] Furthermore, PEGPH20 was shown beneficial effect in improving delivery of monoclonal antibodies into the tumor microenvironment in vitro. [134] A recently completed phase II study investigated whether the addition of PEGPH20 to standard gemcitabine and nab-paclitaxel improved outcomes in untreated metastatic pancreatic adenocarcinoma. Though the final study outcomes are yet to be published, interim analysis of 146 patients showed improved median PFS in patients with HA-high tumors treated with PEGPH20 (9.2 vs 4.3 months; $P = .05$). [135] PEGPH20 is currently being tested in a Phase III clinical trial in combination with gemcitabine and nab-paclitaxel that is the current standard of care. [NCT02715804]

4.3. DNA mismatch repair protein deficiency

Immunotherapy is a rapidly advancing field in cancer treatment. Among the recent immunotherapy modalities, immune check point inhibition has shown significant success in several solid malignancies, but with no meaningful benefit in pancreatic cancer. Checkpoint inhibition has been shown to be promising in mismatch repair deficient colorectal and other cancers. [136, 137] In a more recent publication, Dung et al showed that solid tumors with mismatch repair deficiency are sensitive to immune checkpoint blockade with pembrolizumab. Objective radiographic response was seen in 53% of patients with mismatch repair deficiency and complete response was seen in 21%. The responses were durable and the median PFS and OS was not reached at the time of publication. [138] Pembrolizumab has recently been FDA approved for solid tumor with mismatch repair deficiency, irrespective of tissue of origin. Although small studies have reported a higher incidence rate of mismatch repair enzyme deficiency in pancreatic cancer ranging 11 to 22%, [139, 140] After testing 12019 cancers, the prevalence of microsatellite instability was seen to be around 5% in many solid tumors, while in pancreatic adenocarcinoma it was about 2%. [138] There is an ongoing study (COMPASS study) to improve molecular and genetic characterization of pancreatic cancer and help identify who might benefit from immunotherapy. [NCT02750657]

4.4. Metabolic pathways

Pancreatic adenocarcinoma cells have developed metabolic flexibility to survive given the unique challenges of their microenvironment including hypoxia and nutrient deprivation, through metabolic reprogramming within the cancer cell and the tumor microenvironment. [141, 142]

Aerobic glycolysis switch is one of the well described adaptation in pancreatic cancer cells, regulated by PI3K, hypoxia inducible factor (HIF), p53, MYC, and AMP-activated protein kinase and liver kinase B1 pathways. [141, 143, 144] CPI-613, a highly selective blocker of pyruvate dehydrogenase (PDH) and α -ketoglutarate dehydrogenase (KGDH), was found to be safe in combination with chemotherapy (FOLFIRINOX), and phase III trial is being developed. [145]

Glutamine is used by pancreatic cancer cells for lipid biosynthesis, as a nitrogen donor for amino acids and nucleotide biosynthesis, as a carbonic substrate for the tricarbic acid (TCA) cycle, and even as fuel for energy production. Other metabolic adaptations seen in pancreatic cancer cells include activation of hexosamine biosynthetic pathway, lipid metabolism, autophagy and pinocytosis. [142] Targeting tumor specific metabolic pathways has gained attention for development of innovative therapies.

4.5. Mesothelin

Mesothelin is a surface glycoprotein, normally expressed by mesothelial cells, but also overexpressed by several solid tumors including pancreatic adenocarcinoma. [146, 147] Although its exact role in normal cells is not well established, mesothelin has been implicated in tumor adhesion and metastasis through its ability to bind to MUC16 (CA125). [148, 149] Mesothelin is implicated in tumor progression and resistance to chemotherapy.

[150, 151, 152, 153, 154] Given the overexpression of mesothelin in several human malignancies relative to normal cells, it has been regarded a potential target for antibody based therapies. SS1P (CAT-5001) is a recombinant immunotoxin consisting of anti-mesothelin antibody Fv fragment linked to a truncated *Pseudomonas* exotoxin that mediates cell killing. [155, 156] Two separate phase I studies have established the safety of SS1P. [157, 158] MORAb-009 is a high affinity monoclonal antibody against mesothelin. This antibody is cytotoxic to mesothelin expressing cell lines via antibody dependent cell toxicity. Clinical safety of MORAb-009 is established in two phase I clinical trials. [159, 160] Further clinical studies would be needed to define the clinical utilities of these mesothelin targeted novel therapies. Mesothelin has also been explored in cancer vaccine development. The vaccine CRS-207 is a live-attenuated *Listeria monocytogenes* strain expressing mesothelin. Although earlier phase studies showed that it induces mesothelin specific T-cell responses [161], but a phase II vaccine study were negative. [162]

4.6. HER/ErbB family

The human epidermal growth factor (HER)/Erythroblast leukemia viral oncogene homologue (ErbB) family of proteins consists of: HER1 (ErbB1/EGFR), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). All of the HER-family receptors are transmembrane tyrosine kinases that activate and regulate diverse processes, including cell survival, proliferation, differentiation and migration. [163, 164] Multiple studies so far have tried to target these pathways with little success in PDAC. The empiric addition of erlotinib to gemcitabine was shown to have a marginal improvement in survival outcomes over single agent gemcitabine that led to the approval of the regimen by FDA. [165] However, this regimen is not considered to offer any clinically meaningful benefit, especially after the introduction of modern chemotherapy regimens, considering its cost and added toxicity. The addition of the either antiEGFR antibody cetuximab or the antiHER2 antibody trastuzumab to gemcitabine did not improve outcomes over single agent gemcitabine. [166, 167, 168] The addition of the tyrosine kinase Her2 inhibitor lapatinib to gemcitabine also did not add any benefit compared to gemcitabine alone and the trial was stopped early for futility. [169]

Combining antiEGFR and AntiHER2 antibodies have shown synergism in preclinical studies pancreatic cancer models. [170]. But phase II clinical trials of combined trastuzumab, erlotinib and gemcitabine did not show survival benefit over single agent gemcitabine. [171] A phase II study of pertuzumab and erlotinib for refractory adenocarcinoma of the pancreas was also terminated early due to extreme toxicity in combination therapy. [NCT01108458]

The phase I/II study of combination trastuzumab and cetuximab in patients with advanced pancreatic cancer after failure of gemcitabine based chemotherapy showed stable disease in 9 of 39 patients. Treatment was discontinued due to toxicity (skin rash). OS and PFS were positively correlated with skin toxicity severity. [172] Afatinib is an irreversible EGFR, HER2 and HER4 inhibitor. The combination of afatinib and gemcitabine versus gemcitabine alone is being studied in a phase II clinical trial for untreated metastatic pancreatic cancer. [NCT01728818] The combination of afatinib plus capecitabine is being evaluated study in patients with advanced refractory pancreatic or biliary cancer. [NCT02451553]

A common shortcoming in all the above targeted therapies is the lack of predictive marker of response. In the absence of a predictive biomarker to select these treatments, it might be difficult to see benefits from treatment selected on pure empiricism.

4.7. Adoptive cell therapy

Immunogenicity of Her-2 derived peptides has been demonstrated in In vitro studies. [173, 174] Chimeric antigen receptor-modified T cell (CART) therapy represents a novel approach to treatment of many malignancies. There is an ongoing phase I/II clinical trial is studying effectiveness of CAR T cells targeting HER-2 antigen in patients with different HER-2 positive solid cancers including pancreas cancer. [NCT02713984] Feasibility targeting the EGFR molecule for the development of CAR T cells has been previously shown in vitro and in animals. [175] There is also an ongoing Phase I/II study of genetically engineered lymphocyte therapy in treating patients with EGFR positive advanced/unresectable solid tumors including pancreatic cancer tumors. [NCT01869166] Regardless of their outcomes, these studies represent a novel treatment approach and there is an important lesson that can be gained out of them.

4.8. Role of Natural Compounds

It is estimated that approximately 60% of anti-cancer drugs are either purely natural or are inspired by natural products. [176]. While some natural products are accepted as alternative medicine in western countries, these products are commonly combined with standard chemotherapy in countries like China. It is estimated that around 90% of patients with PDAC in China at some point receive Chinese herbal medicine as an adjunct to their cancer treatment. Therapeutic role of multiple natural compounds is currently under investigation in vitro, in vivo and in the context of clinical trials. [177, 178]. There are several natural compounds under investigation for their potential role against PDAC pre-clinically and in Phase I/II clinical studies. BMS-247550, a novel epothilone derivative, is being developed as an anticancer agent for the treatment of patients with malignant tumors especially pancreatic cancer. [179] BMS-247550 is a semisynthetic analogue of the natural product epothilone B and its mode of action is analogous to that of paclitaxel (i.e., microtubule stabilization). BMS-247 550 was tested in a Phase II study [NCT00016965]. Although the study was completed the outcome of this trial is still awaited. Another natural product triptolide, a diterpenoid, that was shown to be effective against pancreatic cancer cells in vitro as well as in vivo. [180] A water-soluble analog of triptolide, named minnelide had similar potency in preclinical models of pancreatic cancer. Minnelide was shown to reduce the growth and spread of tumors and improving survival in xenograft models of human PDAC. [181] Based on these data, minnelide is currently under Phase II evaluation for pancreatic cancer [NCT03117920].

4.9. Biomarkers of drug effect and toxicity

4.9.1. UGT1A1—Irinotecan is currently being used for treatment of metastatic pancreatic cancer, both in the front-line (as part of the FOLFIRONOX regimen) and in the second line (in the form of Nano liposomal irinotecan in combination with 5FU) settings. [182, 183] A subset of patients receiving irinotecan experience severe hematologic and/or gastrointestinal

toxicities. These are patients who may be deficient in the UDP-glucuronosyltransferase 1A1 (UGT1A1) enzyme that catalyzes the glucuronidation of the active irinotecan metabolite, SN-38. Different studies have shown that *UGT1A1* gene polymorphism, resulting in the deficient activity of the UDP-glucuronosyltransferase 1A1 enzyme, is a predictor of severe irinotecan toxicity. [184, 185] Different levels of dose reduction have been recommended by different authors. [123] There are different ongoing studies that aim to determine the safety profile of irinotecan in patients with advanced gastrointestinal malignancies based on their *UGT1A1* gene status. [NCT01963182, NCT02256800, NCT01643499] As most patients with advanced pancreatic cancer have limited physiologic reserve, avoiding a drug with potentially severe toxicity will be of paramount importance.

4.9.2. Gemcitabine transport molecule: hENT1—Gemcitabine (2, 2 - difluorodeoxycytidine) remains a cornerstone in the systemic treatment of patients with PDAC, especially in the adjuvant setting. It is a nucleoside analogue that inhibits ribonucleotide reductase and DNA polymerase. [186] Gemcitabine is a polar molecule and therefore does not readily diffuse across the cell membrane. The human equilibrative nucleoside transporter (hENT) 1 is the main transporter protein for cellular uptake of gemcitabine in pancreatic cancer cells. [187, 188]

Retrospective studies demonstrated that patients with pancreatic cancers that have increased expression of hENT1 had higher response and survival outcomes when treated with gemcitabine relative to those with low hENT1 expression. These included treatments in the adjuvant setting. [189, 190, 191] However, there is discordance in the predictive value of increased hENT1 expression. Some prospective studies have shown increased expression of hENT1, both by immunohistochemistry and gene sequencing, in the patients treated with gemcitabine, was predictive of increased overall and disease-free survival, in patients treated with gemcitabine. [192, 193, 194] On the other hand, the prospective CONKO-001 trial that investigated the role of adjuvant gemcitabine versus observation in pancreatic cancer, showed that hENT1 was not predictive of response to gemcitabine [195]. The difference in the types of the antibody used in the CONKO-001 study was given as a possible explanation for this discordance. [196] There is no real consensus on the cut off level for low and high expression levels. The transport and metabolism of the drug is very likely to be more complex than the use of single transporter. Additionally, the magnitude of therapeutic benefit from gemcitabine is not sufficient to maintain excitement around this biomarker. Hence the hENT1 was not accepted as a predictive biomarker worthy of further development for the standard clinical practice.

4.9.3. SMAD4—*SMAD4/DPC4* (deleted in pancreatic carcinoma, locus 4) encodes a key intracellular messenger in the transforming growth factor (TGF) signaling cascade. As TGF is a potent inhibitor of growth of epithelial cells, loss of *SMAD4* releases this inhibition and accelerate *KRAS* mediated pancreatic neoplastic transformation. [197] SMAD4 is also considered to have anti-angiogenesis activity, decreasing expression of VEGF and increasing expression of thrombospondin-1. [198] In a retrospective study of 76 patients with pancreatic cancer, 30% were found to have died with locoregional disease progression, while 70% with widespread metastasis. Only 22% of patients with locally advanced carcinomas at

autopsy showed loss of *SMAD4*, compared to 78% of patients with metastatic disease with loss of *SMAD4*. [199] Unlike pancreatic cancers with intact *SMAD4* who have more local pattern of disease progression, tumor with *SMAD4* loss commonly have distant disease progression. [200] The combination of *RUNX3* and *SMAD4* status was proposed as a better predictor of disease progression compared to *SMAD4* alone. Loss of *SMAD4/DPC4* by immunohistochemistry correlated with metastatic pattern of disease progression. On the other hand, *SMAD4/DPC4* intact tumors with high level of *RUNX3* are seen to have high metastatic potential. [201] The roles of *SMAD4* or *SMAD4/RUNX3* as a biomarker in the care of patients with PDAC should be further tested in prospective studies before it can be widely applied in the clinic, especially in situations where radiation therapy is being considered.

4.9.4. MicroRNAs—MicroRNAs (miRNAs) are small non-coding RNAs consisting of 18–24 nucleotides which regulate the stability and translation of their target mRNAs by binding to their 3'UTR region. [202, 203] They are part of the cellular regulatory network that control cell functions such as cell growth, proliferation, differentiation, development and apoptosis. [203] Studies have shown that several miRNAs are aberrantly expressed in pancreatic tumor, contrary to their adjacent normal tissue. [204, 205] It has been shown that miRNAs could elicit oncogenic or tumor-suppressive functions by directly targeting oncogenes or tumor suppressor genes. [206] The inhibition of oncogenic miRNAs and restoration of expression of tumor suppressor miRNAs are therefore potential therapeutic strategies. MicroRNAs are also linked to resistance and sensitivity to chemotherapeutic agents and targeted therapies. [207, 208] Most studies of miRNAs in pancreatic cancer are still in the pre-clinical phase. The better identification, validation and selective delivery of miRNAs could help in their clinical application.

5. Prospects of Molecular Classification of Pancreatic Adenocarcinoma

Recent biotechnological advances give us the ability to perform comprehensive genomic, transcriptomic, proteomic and metabolomic studies at a faster rate and for a much cheaper cost. However, these tests are not ready for wide clinical application. A large amount of data is generated from these new tests, which with the application of advanced bioinformatics can be used to better understand the disease process and possibly be used to design better treatment strategies.

Hoadley et al used five genome-wide platforms and one proteomic platform on 3257 specimens from 12 cancer types to examine how much is shared across tissues. [209] This study revealed that tissues can be classified into common subtypes regardless of their tissue of origin and stage. As an example, subset of bladder cancer, lung squamous and head and neck could be classified as a subtype with TP53 alterations, TP63 amplifications and high expression of immune and proliferation pathway. This innovative system of reclassifying tumors could guide novel treatment decisions and open the door for studying regimens that are considered nonstandard on the current disease classification based on tissue of origin. While such studies can find shared features among different cancers, there is also a great deal of interest in understanding the differences between different cancer types and even among different tumors of the same tissue of origin.

Bailey et al performed integrated genomic analysis of 456 cases of pancreatic adenocarcinoma and identified 32 recurrently mutated genes that aggregate into 10 pathways: *KRAS*, *TGF- β* , *WNT*, *NOTCH*, *ROBO/SLIT* signaling, G1/S transition, *SWI-SNF*, chromatin modification, DNA repair and RNA processing. [32] The authors categorized pancreatic adenocarcinoma into four molecular subtypes based on the genetic mutations observed: squamous, pancreatic progenitor, immunogenic; and aberrantly differentiated endocrine exocrine. Within each subtype, tumors share certain pathways that might have therapeutic implications. Clinical utility of such new classifications is yet to be evaluated in prospective studies. Other authors also have proposed different molecular classification system for pancreatic cancer based genomic analysis of tumor specimens. [210, 211] Collisson et al proposed classification of PDACs in to three subtypes of Classical, quasimesenchymal (QM) and exocrine like. Exploring the predictive role of this classification in PDAC cell lines, they proposed differential response to Gemcitabine and erlotinib in the classical and QM subtype. Mofitt et al expanded molecular profiling from primary tumor to metastatic lesions and normal tumors. They classified PDAC tumors in to 2 subtypes of classical and basal like. Stroma was also classified to normal and activated. Wadell et al has proposed a classification mechanism with reliance on structural variation events. [116] They classified tumors to 4 subtypes. Unstable subtype (subtype 4) which accounted for 14% of samples in this study is possibly what is currently known as pancreatic cancer with BRCAness. These classifications need to be prospectively evaluated and be used in the design of scientifically rational treatment strategies.

6. Conclusion

Pancreatic cancer remains a very challenging disease. Despite decades of research, there is no good treatment strategy that offers meaningful and durable outcomes at this time. Several areas of research are showing some promising results such as targeting the stroma, exploiting DNA repair deficiencies and immune modulation. However, it is very unlikely that a single treatment option will be effective in the treatment of this disease, given the cellular and microenvironment complexity of the tumor that has endowed it with resistance to multiple treatment strategies. A better understanding and characterization of the molecular composition and cellular cross talk in the tumor microenvironment is needed to design scientifically rational novel treatment strategies for tumors that have specific molecular profiles. Combination of targeted therapies guided by predictive biomarkers will be the ultimate therapeutic goal.

7. Expert commentary

Pancreatic ductal adenocarcinoma remains a disease with very poor outcome because of late stage disease in the majority of newly diagnosed patients. A fifth or less of the patients are diagnosed with localized disease that may be amenable to radical and potentially curative surgical resection. However, only a fifth of the resected patients survive long term making the long-term survival of the entire population of pancreatic cancer patients less than 10 percent. There is major concern with the rising incidence of this disease and the projected mortality from pancreas cancer being second to lung cancer by 2030. Improvements in systemic therapy are essential to prolong survival of patients with this disease. However,

thus far, active drugs have been very limited to a handful of conventional cytotoxic drugs. The benefit of therapy is very much limited by drug resistance. Successful developments of targeted and other novel therapies was limited by the poor understanding of the disease biology. However, in the last decade there has been a rapid increase in our knowledge of the molecular aspects of this disease with the development of better preclinical models that mimic human disease. New opportunities for targeted and personalized therapies are now being actively pursued along several fronts including exploitation of DNA repair abnormalities, disrupting the hyaluronan, targeting mesothelin, and blocking certain enzymes involved in metabolism unique to the cancer cell. Immunotherapy is still at its infancy in this disease. Unlike some other cancers, driver gene mutations are very scarce in pancreatic cancer. So far there are no molecular biomarkers to help direct, choose therapy or select patients but several may be emerging and include those involved in DNA repair, hyaluronan and mesothelin.

8. Five-year view

Pancreatic ductal adenocarcinoma is a drug resistant disease. Only few conventional cytotoxic agents have shown activity in this cancer. There is a continued work being done to optimize the delivery of these drugs, especially how they should be sequenced to improve the outcome of patients. The cytotoxic chemotherapy platforms of either gemcitabine/nab-paclitaxel or FOLFIRINOX will continue to be used especially in frontline setting to which will be added any newly developed agent. A number of targeted and novel agents are currently in phase I-III clinical trials. Within the next 2–3 years we may be able to see the clinical activities of these agents. High interest agents include PEGPH20 targeting hyaluronan, and platinum compounds with or without PARP inhibitors in patients with defective DNA repair pathways. PARP inhibitors may be used as maintenance therapy following the use of combination cytotoxic therapy in select patients with BRCA mutations. Biomarkers that may be of high interest in the next few years and be part of the everyday clinical practice include BRCA and other DNA repair gene mutations, hyaluronan expression and mesothelin expression. Innovative immunotherapy approaches are currently being actively pursued. No major immunotherapeutic breakthrough is anticipated in the near future for this disease. Molecular profiling of pancreatic cancers will expand in clinical practice and to guide clinical trial eligibility. Microsatellite testing, BRCA and related gene testing (e.g., PALB2, ATM) are examples of tests that are increasingly adopted by oncologists. Improvements in tissue collection and capture of circulating tumor cells and cell free DNA are to be expected.

Acknowledgments

Funding

The authors are grateful for support from the SKY Foundation, James H Thie Foundation and Perri Family Foundation and the National Institute of Health R21 grant 1R21CA188818–01A1

8.: Appendix: Tables and figures

Table 1.

Pancreatic cancer GEMMs and PDXs

Mouse Models	Mutation	Ref
<i>Genetically engineered mouse models (GEMMS)</i>		
Genetically engineered mouse models (GEMMS)		
PDX-1-Cre/Lox-Stop-Lox (LSL)-Kras or p48/LSL-Kras	K-ras mutation in pancreatic cells	[13]
PDX-1-Cre, LSL-KrasG12D, LSL-Trp53R172H/-	K-ras and p53 mutations	[92]
PDX-1-Cre, Brca2F11, LSL-KrasG12D, Trp53 F2–10	K-ras, BRCA2, and p53 mutations	[93]
Mist1 KrasG12D/+ transgenic model	KrasG12D into ORF of Mist1	[95]
PDX1-Cre, KrasG12D, Ink4a/Arfflox/flox transgenic model	K-ras and Ink4a mutations	[96]
PDX1-Cre, KrasG12D, Smad4flox/flox transgenic model	K-ras and Smad4 mutations	[97]
Ptf1acre/+, LSL-KrasG12D/+, Tgfr2flox/flox transgenic model	K-ras and TGF-β mutations	[98]
LSL-KrasG12D; LSL-Trp53R172H/+; Ink4flox/+;	K-ras, p53, and Ink4	[99]
Ptf1/p48-Cre	mutations	
<i>Patient derived Xenografts (PDXs)</i>		
TM00310	K-ras and p53 mutations	[100]
TM00312	p53 mutation	[100]
TM00314	K-ras mutation	[100]
More PDX models can be found in Mouse Tumor Biology Database		[100]

Table 2

Frequency of altered intracellular molecular pathways in pancreatic cancer [32]

Altered Pathways	Mutated Genes	Reported frequency
KRAS Activation	<i>KRAS, MAPK4</i>	92%
Cell Cycle, G1/S Checkpoint Disruption	<i>TP53, CDKN2A, TP53BP2</i>	78%
TGF Beta Signaling	<i>SMAD3, SMAD4, TGF, TGPBR1, TGFBR2, ACVR1B and ACVR2A</i>	47%
Histone Modification	<i>KDM6A, SETD2, ASCOM Complex members MLL2 and MLL3</i>	24%
DNA Repair	<i>BRCA1, BRCA2, ATM, PALB2, SATF2</i>	17% (5% germline, 12% somatic)
RNA Processing	<i>SF3B1, U2AF1, RBM10</i>	16%
SWI/SNF Complex	<i>ARID1A, ARID1B, PBRM1 and SMARCA4</i>	14%
WNT Signaling	<i>RNF43, MAPK2, TLE4</i>	5%

Table 3:

Select clinical trials with targets of interest

Mechanism	Target	Agent	Combined with	Phase	N	N
Stroma	Hyaluronan	PEGPH20	mFOLFIRINOX	1/2	<170	019

Mechanism	Target	Agent	Combined with	Phase	N	N
			Gemcitabine/nabpaclitaxel	3	420	018
Tumor infiltrating monocytes or macrophages	CCR2	PF-04136309	Gemcitabine/nabpaclitaxel	1b/2		027
			FOLFIRINOX	1b	47	014
	CCR2/CCR5	BMS-813160	FOLFIRINOX	1b	54	023
			Nivolumab	1/2	260 *	031
	CSF-1R	AMG 820	pembrolizumab	1/2	197 *	027
			Durvalumab	1	58 *	027
DNA repair	PARP inhibitor	Veliparib	Gemcitabin/Cisplatin	2	107	015
			FOLFOX	1/2	79	014
			FOLFIRI	2	143	028
		Olaparib	none	3	145	021
		Olaparib	Cediranib	2	126 *	024
Tumor metabolism	PDH/KGDH	CPI-613	Low dose FOLFIRINOX	1b	21	018
Mesothelin targeted	Mesothelin	anetumab	ravtansine	1	348 *	031
			ravtansine	2	30	030
		CAR T cells	none	1	30	027
		CAR T cells	none	1/2	136	015
		Antibody/LMB-100	none	1/2	100	028
Sternness	STAT3	Napabucasin	Gemcitabine/nabpaclitaxel	1b/2	71	022
			Gemcitabine/nabpaclitaxel	3	1132	022
Cell death	NQ01	ARQ-761	Gemcitabine/nabpaclitaxel	1/1b	20	025
Immune modulation	Check point inhibitors/vaccines	Nivolumab	GVAX/CRS-207	2	108	022
		Pembrolizumab	ACP-196	2	76	023
			Epacadostat/CRS-207	2	70	030
			T remelimumab/SBRT	1	60	023
		Durvalumab	Pexidartinib	1	58	027
			Gemcitabine/Nabpaclitaxel/Teremlimumab	2	180	028

*Includes other cancers

References

Reference annotations

* *Of interest*

** *Of considerable interest*

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This paper presents molecular subtyping of pancreas cancer based on the gene signatures of the cancer cells and their stromal cells.

[PubMed: 26343385]

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Key issues

- Pancreas adenocarcinoma has proven resistant to various treatment strategies and is projected to become the second leading cause of cancer related mortality in few years. There is a strong unmet need to advance systemic therapy for this disease. More effective treatments are tightly linked to better understanding of the disease biology.
- Gene mutations that can be effectively targeted by single agent therapy are extremely low in this disease. Advances in systemic therapy have been limited to conventional cytotoxic drugs at this time resulting in a very modest benefit.
- Defective DNA repair pathways is seen in minority of patients but has a potential for becoming an effective treatment for those patients using platinum compounds with or without PARP inhibitors. Examples include patients with *BRCA*, *PALB2*, or *ATM* mutations. Multiple trials are addressing this area of research.
- The disease is also characterized by complex interaction between the cancer cells and their microenvironment posing major challenges to design effective therapies. Targeting hyaluronic acid in the tumor stroma is a promising strategy when combined with gemcitabine and nab-paclitaxel. There is ongoing phase III trial in patients with tumors that overexpress hyaluronan. Other approaches include targeting the cellular component of the microenvironment responsible for disease progression and resistance to therapy
- Immunotherapy with checkpoint inhibitors has not been effective in pancreas cancer in general. In very few patients with defective mismatch repair enzymes, this treatment is a very good treatment option.
- Personalizing cancer treatment may be achieved by the use of biomarkers to guide the selection of therapeutic agents. Better molecular characterization of the disease coupled with increasing capabilities in molecular techniques may help develop more personalized treatment options.