Genomics meets immunity in pancreatic cancer: Current research and future directions for pancreatic adenocarcinoma immunotherapy

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Abstract

Pancreatic adenocarcinoma (PDAC) remains a formidable disease that needs improved therapeutic strategies. Even though immunotherapy has revolutionized treatment for various solid tumor types, it remains largely ineffective in treating individuals with PDAC. This review describes how the application of genome-wide analysis is revitalizing the field of PDAC immunotherapy. Major themes include new insights into the body’s immune response to the cancer, and key immunosuppressive elements that blunt that antitumor immunity. In particular, new evidence indicates that T cell-based antitumor immunity against PDAC is more common, and more easily generated, than previously thought. However, equally common are an array of cellular and molecular defenses employed by the tumor against those T cells. These discoveries have changed how current immunotherapies are deployed and have directed development of novel strategies to better treat this disease. Thus, the impact of genomic analysis has been two-fold: both in demonstrating the heterogeneity of immune targets and defenses in this disease, as well as providing a powerful tool for designing and identifying personalized therapies that exploit each tumor’s unique phenotype. Such personalized treatment combinations may be the key to developing successful immunotherapies for pancreatic adenocarcinoma.

Introduction

Pancreatic adenocarcinoma (PDAC) is one of the most lethal malignancies and is predicted to become the second leading cause of cancer-related deaths by 2030.1-3 Unfortunately, the vast majority of patients (>80%) present with advanced primary or metastatic disease that is unresectable.4-6 Currently, standard chemotherapy for PDAC remains either nab-paclitaxel plus gemcitabine7 or FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan and oxaliplatin) which improves the five-year survival rate a mere 8.5 to 11.1 months, respectively.8 Although patients with resectable disease typically have a better prognosis, current surgery and adjuvant chemotherapy regimens only confer a median survival of ~25 months.9 In addition, recent targeted therapy trials aimed at disrupting commonly overactive pathways in pancreatic cancers, such as KRAS and tyrosine kinase receptors, have also failed to improve survival over standard chemotherapy.10,11 While immune checkpoint modulators have demonstrated exciting efficacy in various solid tumors,12-15 these therapies have essentially failed in PDAC patients.16-19 Thus, despite the emergence of new therapies for PDAC, the five-year survival rate for patients with this cancer remains disappointingly low.20 To advance therapeutic options for PDAC patients, a greater understanding of the complex interplay between tumor genomics and the immune landscape of PDAC, including both antitumor immune responses and the suppressive defenses that protect the tumor, is needed. Recent investigations have resulted in the generation of novel immunotherapy strategies and highlight the benefit of using genomic studies to design personalized treatments that effectively address this devastating malignancy. This review highlights how genome-wide analysis is revitalizing the field of PDAC immunotherapy through improved understanding of the complex interaction between the host and PDAC.

Molecular subtypes of pancreatic adenocarcinoma

The vast majority of PDAC harbor a KRAS mutation at codon 1221,22 with the latest data suggesting a 93% prevalence of this mutation among PDAC tumors.23 Significant effort has focused on developing a successful anti-KRAS biologic therapy, yet no KRAS-targeted strategy has impacted clinical practice.24 Further investigation has revealed that this poor response is, in part, due to the tumor’s ability to acquire additional oncogenic mutations.25-27 While the diversity of these mutations initially made defining prognostic patterns difficult,28 application of whole genome and
RNA/exome sequencing indicated that these mutations tend to occur in common pathways. Among the most common are RAS/MAPK, Hedgehog, TGFβ, Wnt/Notch, G1/S phase transition, and apoptosis regulation.57,58 Studies have now defined molecular subtypes of PDAC tumors with prognostic and therapeutic indications23,31-34 (Table 1).

The first application of PDAC molecular subtypes was to delineate different sensitivities to chemotherapies. One early study found that classical subtype tumors responded more to erlotinib (an EGFR tyrosine kinase inhibitor) while the quasimesenchymal phenotype was more sensitive to gemcitabine.31 The COMPASS clinical trial recently used genome sequencing of PDAC biopsies to categorize tumors as either classical or basal-like prior to FOLFIRINOX therapy, thus highlighting the feasibility and predictive value of pre-therapy genetic analysis.32 This study also demonstrated that classical tumors were more responsive to FOLFIRINOX than basal-like tumors.33 Exploration of PDAC epigenetics has further refined these current subtypes (Table 1) and promises to identify additional therapeutic targets.23 Among these targets are histone acetyltransferases (HATs) and histone deacetylases (HDACs),36,37 and dysregulated/mutated non-coding regions of DNA.38-41

More recently, studies have correlated genetic patterns within the PDAC tumor with its susceptibility to immune attack. Mismatch Repair-Deficient (MMR-D) PDAC, like other MMR-D tumors, arise from mutations in post-replication machinery that allows for a high mutational burden and characteristic microsatellite instability.42,43 MMR-D cancers also demonstrate increased cytotoxic T cell tumor infiltration and higher tumor checkpoint protein expression.34,44 The high mutation rate and T cell infiltration in MMR-D tumors has been correlated with better prognosis45 and response to immunotherapy46 in other cancers. Studies indicate that MMR-D PDAC, particularly those which arise in patients with Lynch Syndrome, will respond to PD-1 blockade similar to other MMR-D solid tumors.47-49 In a recent study, 57% of patients with MMR-D PDAC tumors had objective response rates on PD-1 checkpoint blockade.49 Unfortunately, MMR-D PDAC represents less than 1% of all pancreatic adenocarcinomas.49 Furthermore, genetic screening is currently the only consistent method to detect MMR-D tumors since family history of inherited cancer is not necessarily predictive of risk.50 Of note, global genomic analysis can now identify tumors with high immune infiltrate and checkpoint protein expression (termed immunogenic PDAC) that could be targeted by checkpoint inhibitors or other immunotherapy.33 Further work is required to determine what percentage of tumors have this immunogenic signature and if they differ from tumors that arise from mismatch repair deficiency, particularly in their sensitivity to immunotherapies. Collectively, the identification of PDAC subtypes and their correlation with specific responses to both chemotherapy and immunotherapy is already shaping the development of more targeted and efficacious treatment regimens.

Beyond subtypes: new insights into pancreatic adenocarcinoma immunology

Unlike MMR-D PDAC, the majority of pancreatic adenocarci-
noma tumors are immunologically cold, as defined by the lack of effector T cells in the tumor. Traditionally, this phenomenon is partially attributed to the low mutational load of PDAC that yields few neoantigens for T cells to recognize.51-53 However, new genetic evidence challenges this idea as a recent investigation that profiled tumor antigens from long-term pancreatic cancer survivors revealed that neither abundance of neoantigens nor the levels of CD8+ T cells in PDAC predicted survival.54 Instead, patients with the longest survival tended to have neoantigens which imitated microbial epitopes with stronger likelihood of TCR recognition.

Another study comparing PDAC and melanoma antigen load and T cell responses further challenged the concept that a high number of neoantigens is required for robust antitumor immunity. These investigators discovered that while the number of potential neoantigens in PDAC was an order of magnitude lower than melanoma, almost every PDAC tumor had a mutation that resulted in a predicted neoantigen.55 Yet, despite the lower number of potential neoantigens, T cell infiltration in PDAC was still similar to melanoma. The tumors differed in that the infiltrating T cells in PDAC were less cytotoxic (lower IFNγ production) than in melanoma.55 The lower cytotoxicity of PDAC T cells needs to be further elucidated but is consistent with an exhausted phenotype. If true, this would explain why PD-1 blockade is not very effective in PDAC, since it only releases T cells from inhibition but doesn’t reverse their exhausted phenotype.56 A study that sequenced T cell receptors in PDAC tumors offered further corroboration that PDAC can be immunogenic. In this study, PDAC-infiltrating T cells had an elevated level of T cell receptor clonality,57 a marker of an antigen-specific adaptive immune response and favorable prognosis.58,59 Importantly, the clonality and ex vivo expansion rate of PDAC-derived T cells was similar to that found in melanoma biopsies, suggesting that they are equally capable of mounting a disease-specific immune response.57 Additionally, since PDAC tumors have low rates of mutagenesis, the likelihood that common mutations (such as KRAS codon 12 mutations59 or MUC1664) are shared by both the primary and metastatic tumors might improve chances of disease clearance.60

The pro-neoplastic pancreatic adenocarcinoma immune landscape

The dissonance between the seemingly robust T cell infiltra-
tion and lack of tumor clearance in PDAC may be explained, at least in part, by to the hostile immune landscape within the tumor. Efforts to understand PDAC at the molecular level have revealed key components to its immunosuppressive environment leading to immune evasion, suppression and exclusion.

PDAC tumors have a variety of protective mechanisms that help them to avoid immune detection (Figure 1A). In addition to yielding few neoantigens,51,52,55 PDAC tumors also downregulate MHC I molecules on their cell surface, thereby rendering them invisible to CD8+ T cells.61,62 Another mechanism to avoid immune recognition is through the release of pancreatic exosomes, which transfer miRNA to neighboring dendritic cells (DCs) decreasing MHC II expression.63 Thus, PDAC tumors conceal their already low antigen signal further by reducing the expression of MHC molecules on both the tumor and antigen presenting cells (APCs). In parallel, the anti-phagocytic molecule CD47 is highly expressed in PDAC tumors, sending a don’t eat me signal that prevents both recognition and phagocytosis by macrophages.64 CD47 blocking antibodies alleviate this inhibition, thus restoring tumor detection and clearance via phagocytosis65 (Figure 1A).

PDAC also suppresses the T cell anti-tumor response by creating a favorable tumor microenvironment through multiple strategies including the recruitment of suppressive cell subsets, production of enzymes/ cytokines, and upregulation of immune checkpoint proteins (Figure 1B). Molecular drivers of immunosuppression include Yes-associated protein (YAP) which signals down-
stream from KRAS to recruit myeloid-derived suppressor cells (MDSCs) to inhibit adaptive immune responses.\(^{66,67}\) Similarly, cytokine signaling through KRAS and STAT3 drives the production of Indoleamine-2,3-dioxygenase (IDO) at the tumor site.\(^{68-70}\) IDO, an enzyme involved in tryptophan metabolism, drives immunosuppression and correlates with poor clinical outcomes in several malignancies such as breast,\(^{71}\) gastric,\(^{72}\) and liver\(^{73}\) cancer. A recent study reported that IDO is upregulated in 59% of PDAC tissues and that its elevation correlates with poor prognosis, poor tumor differentiation, and higher metastatic burden.\(^{74}\) Targeting of this pathway via the IDO inhibitor indoximod resulted in greater cytotoxic T cell infiltration and tumor reduction in mice,\(^{75}\) identifying IDO as a potential target for future combination therapies.

While monotherapy with PD-1 blockade has proven ineffective in PDAC, evidence suggests that PD-L1 still plays a role in the immunosuppressive landscape of PDAC. Specifically, PD-L1 expression has been reported to be upregulated by the epigenetic modifier H3K4me3 in pancreatic cancer\(^{76}\) and KRAS in lung cancers.\(^{77,78}\) The fact that both H3K4me3 and KRAS are highly active in the majority of PDAC cancers supports the notion that PD-L1 may indeed be more commonly expressed among PDAC tumors than previously thought.\(^{76,79,80}\) High PD-L1 expression supports the use of checkpoint therapy for PDAC patients in a combinatorial strategy. Furthermore, the multitude of additional immunosuppressive signals in the PDAC microenvironment besides checkpoint proteins, including YAP, IDO and H3K4me3, asserts the benefit of genomic analysis to determine which signals are present in a tumor for optimal therapy design.

Another major barrier to successful anti-PDAC immune responses is the dense extracellular matrix (ECM). Fibrosis in PDAC is directly correlated with aggressiveness of the tumor,\(^{81}\) and this may be due, in part, to passive exclusion of T cells from the tumor.\(^{82}\) Multiple pathways are known to encourage the desmoplastic environment of PDAC and represent possible thera-

### Table 1. Genetic subtypes.

| Collisson et al., 2011 |
|-----------------------|
| **Subtype** | **Genetic signature** | **Histology** | **Clinical implications** |
| Classical | Adhesion-associated and epithelial genes; GATA6\(^{#}\) | Highly differentiated | Sensitive to erlotinib |
| QM-PDA* | Mesenchymal Genes | Poorly differentiated | Sensitive to gemcitabine |
| Exocrine-like | Digestive enzyme genes | ELA3\(^{#}\) and CFTR\(^{#}\) | |

| Moffitt et al., 2015 |
|---------------------|
| **Subtype** | **Genetic Signature** | **Histology** | **Clinical implications** |
| Classical | GATA6\(^{#}\) and SMAD4\(^{#}\) | >10% mucin expression | 1 year survival of 70% |
| Basal-like | Laminins and Keratins | <10% mucin expression | 1 year survival of 44% |
| Stromal factors | Collisson’s mesenchymal genes and stroma histology likely from CAF\(^{#}\) cells not neoplastic cells | Activated stroma = worse prognosis |

| Bailey et al., 2016 |
|---------------------|
| **Subtype** | **Genetic signature** | **Histology** | **Clinical implications** |
| Pancreatic progenitor | high PD1X, MUC1 and MUC5AC expression | Includes mucinous non-cystic (colloid) and mucinous IPMN |
| Squamous | TP53, KDM6A, TP53 N mutations | Includes adeno-squamous carcinomas | Poor prognostic factor |
| ADEX\(^{#}\) | Endocrine and exocrine pancreas genes, subclass of pancreatic progenitor | Includes rare acinar cell carcinomas |
| Immunogenic | B and T cell genes, upregulation of CTLA4 and PD1 | Includes mucinous non-cystic (colloid) and mucinous IPMN |

| Cancer Genome Atlas Network, 2017 |
|----------------------------------|
| **Subtype** | **Genetic signature** | **Histology** | **Clinical implications** |
| Classical/pancreatic progenitor | GNAS mutations common; high EVAD, DEANR1, and GATA6-AS1 lncRNAs |
| Squamous/basal-like | TP53 mutations common; high CAV1, low miR-192-5p and miR-194-5p |
| ADEX\(^{#}\) | Genetic signature may be due to non-neoplastic infiltrate rather than unique neoplasm | Low neoplastic cellularity |

\(^{#}\text{Quasi mesenchymal pancreatic ductal adenocarcinoma; }^{#}\text{cancer associated fibroblast; }^{#}\text{aberrantly differentiated endocrine exocrine.}
peutic targets. KRAS signaling drives PDAC fibrosis through the recruitment and activation of both tumor-associated fibroblasts (TAF) and stellate cells to further support PDAC progression. However, crosstalk between the ECM and the immune microenvironment also plays a role in fibrotic development. For example, inflammatory signaling due to IL-1β, nitrous oxide, and IRAK4 signaling downstream of toll-like receptors are also implicated in fibrosis and resultant chemoresistance. Further studies that lend a better understanding of the relationship between the desmoplastic microenvironment and the antitumor immune response will be key to unleashing the full potential of PDAC-targeted immunotherapies.

Collectively, genotyping and histopathologic characterization of PDAC tumors has deepened our understanding of three key immunoresistant mechanisms: immune evasion, immunosuppression, and immune cell exclusion (Figure 1). These findings lay the groundwork for novel therapies focused on either driving T cell responses to PDAC or subduing its immunosuppressive microenvironment.

Figure 1. Key immunosuppressive mechanisms of PDAC. A) Immune evasion tactics include 1) low levels of mutation resulting in few non-self antigens, 2) KRAS signaling lowers MHC I expression by tumor cells, 3) exosomes containing miRNA silence dendritic cell (DC) expression of MHC II molecules, and 4) increased expression of anti-phagocytic molecules like CD47 prevent APC processing and tumor clearance. B) The tumor suppresses immune responses through PD-L1 expression, MDSC recruitment, and high IDO expression. C) The highly fibrotic extracellular matrix of the tumor creates a physical barrier preventing T cell infiltration into the tumor.
Novel immunotherapies for generating T cell responses to pancreatic adenocarcinoma

The majority of immunotherapies for PDAC have focused primarily on inducing or enhancing tumor-specific T cell responses. These therapies fall into three major categories, including: increasing antigen-specific responses (via vaccination), improving T cell recognition of tumor-associated proteins (via T cell receptor selection or design), and targeting the immunosuppressive tumor microenvironment.

Vaccines produced early evidence that an antitumor immune response could be generated against common, previously non-immunogenic PDAC tumor antigens. As a proof of concept, an early study using the GVAX vaccine (irradiated allogeneic PDAC cells that express the immunostimulatory cytokine GM-CSF) revealed a correlation between clinical response and an increase in antigen-specific CD8+ T cells. In subsequent preclinical and clinical trials, the GVAX vaccine has been reported to induce cytotoxic T cell infiltration and increased PD-L1 expression in the tumor. In mouse models, the addition of PD-1 checkpoint blockade following GVAX vaccination increased survival by 38% and curative responses by 25.5%. These data suggest that combination therapy of vaccination and PD-L1 inhibition could have a synergistic effect to enhance clinical responses. Several trials have been or are currently ongoing based on a combinatorial strategy with GVAX (NCT02243371, NCT03161379, NCT03190265, NCT02451982, NCT03767582). Additionally, vaccination using peptide-pulsed, patient-derived DCs given concurrently with the (TLR)-3 agonist poly-ICLC in a phase 1 trial was well tolerated with a median overall survival of 7.7 months.

A better understanding of specific genetic alterations in PDAC such as unique post-translational modifications has expanded vaccine strategies. A classic example is MUC1, which is aberrantly glycosylated in a wide number of cancers including PDAC. In a phase 1 clinical trial in which advanced pancreatic cancer patients were vaccinated with dendritic cells carrying the abnormal MUC1 antigen demonstrated an immunological response in two of seven patients. In these patients, there was significantly increased IFNγ and granzyme B production, but the treatment did not slow disease.

![Figure 2. Advances in immunotherapy informed by genomic analysis of PDAC tumors. A) Vaccine strategies can take advantage of either natural (Muc1 and α-enolase) or man-made (α-gal) post-translational modifications of self-proteins. B) PDAC tumors express high levels of aberrant surface proteins, which can be targeted by T cells with chimeric antigen receptors (CARs). C) Both immunosuppressive (1&2) and desmoplastic (3&4) features of the PDAC immune environment are being targeted by novel immunotherapies.](image-url)
Figure 3. Developing personalized therapies for patients with pancreatic cancer. Sequencing of excised tumor or biopsies may one day allow physicians to categorize a patient's cancer into therapeutic groups based on expression of tumor and immunologic markers. This will allow for the intelligent selection and design of combination immunotherapies for more successful treatment.

Antigenicity can also be induced through synthetic modification of peptides. As an example, a recent study synthetically modified pancreatic lysates with the α-gal epitope from non-primate mammals to take advantage of naturally occurring anti-Gal antibodies specific for that epitope. This vaccination strategy increased not only anti-Gal antibody responses, but also expanded lymphocytes specific for MUC1 and mesothelin antigens. Overall, the expanding experience with vaccination therapies has demonstrated that this approach may boost T cell responses against PDAC tumors and serve as a compelling partner in immunotherapy combination strategies (Figure 2A).

Adoptive cell therapy with either naturally arising tumor-infiltrating lymphocytes (TILs) or with T cells genetically redirected with antigen receptors (TCRs or CARs, respectively) produce some of the highest response rates and odds of complete responses in patients with various solid tumors and leukemias. Although TIL/TCR therapy can target any non-self antigen from either surface or intracellular peptides, this strategy is dependent on MHC presentation, which, as previously discussed (Figure 1A), is often downregulated in PDAC tumors. CAR T cells were designed, in part, to address these limitations. CARs are comprised of an antigen-specific scFv antibody linked to the CD3ζ TCR signaling domain as well as costimulatory domains (such as CD28 or 4-1BB). Because CAR T cells are antibody based, this strategy does not depend on antigen presentation by MHC molecules, but rather recognizes the unprocessed protein on the cell surface. An additional benefit of CAR T cells is the potential to turn a wide array of non-immunogenic, or even immunosuppressive, proteins into reliable targets for an antitumor response (Figure 2B).

CAR T cell therapy was recently FDA approved to treat patients with B cell malignancies based on initial evidence that up to ~89% of these patients have a complete response from their disease. CAR T cell therapy has also been developed for PDAC with early notable success. In a recent preclinical study, investigators isolated two highly specific TCRs against KRAS codon 12 mutations G12V and G12D from mice immunized with human PDAC cells. Infusion of human T cells redirected with these TCRs resulted in slowed tumor growth in xenograft mouse models.

Multiple additional CAR T cells have been developed against highly expressed molecules on the surface of PDAC cells, including: mesothelin, MUC1, and the prostate cancer antigen PSCA. A phase 1 clinical trial reported that infusion of mesothelin-targeted CAR T cells led to tumor debulking in three of six PDAC patients as noted by decreased metabolically active tumor on PET-CT (NCT01897415). Additional phase 1 clinical trials targeting mesothelin (lentiviral transduced; NCT03323944) and...
PSCA (NCT02744287) are also currently underway. CAR T cells targeting CD47 have also shown promise in early preclinical studies. Interestingly, this strategy transforms a basic cloaking defense of the tumor into a reliably expressed target antigen. In a xenograft mouse model, CD47-specific CAR T cells limited growth of PDAC tumors by greater than 50%.\(^\text{111}\) These novel therapies underscore that our growing understanding of tumor genomics can not only guide molecular therapies, but can also suggest targets for future cellular therapies.

Novel immunotherapies for disabling the immunosuppressive pancreatic adenocarcinoma microenvironment

Growing evidence suggests that in order for patients to fully benefit from T cell enhancing immunotherapies, the immunosuppressive microenvironment of their tumors will also need to be targeted. Major advancements have been made in therapies that target the immunosuppressive defenses of PDAC. For example, intratumoral delivery of nanoparticles loaded with the immune-activating chemotherapeutic oxaliplatin and the IDO inhibitor indoximod resulted in the decrease of FoxP3\(^+\) regulatory T cells, increased recruitment and expansion of effector T cells, and enhanced tumor regression.\(^\text{75}\) Another study combined GVAX with IDO inhibition, which resulted in enhanced T cell infiltration and function and increased survival from ~40% to ~90%.\(^\text{112}\)

In addition to IDO and checkpoint inhibitors, alternative methods of breaking down the immunosuppressive defenses of PDAC using chemotherapeutic agents have been reported. Combination of gemcitabine with a CD40 agonist results in a T cell-dependent regression of subcutaneous murine PDAC tumors.\(^\text{113}\) The depletion of extratumoral macrophages in these mice increased T cell infiltration into spontaneous tumors, demonstrating a potential future target for enhancing T cell-mediated PDAC regression. CD40 agonists have also improved penetration of chemotherapy into the tumor through macrophage-dependent depletion of tumor stroma.\(^\text{114}\) A recent phase 1 study determined that the combination of CD40 agonists and gemcitabine was well tolerated and capable of producing a therapeutic response in four out of 22 PDAC patients\(^\text{115}\) (NCT00711191). A new phase 1 trial testing the combination of CD40 agonist and gemcitabine/Nab-Paclitaxel with or without Nivolumab is currently ongoing (NCT03214250).

Reducing tumor fibrosis is another powerful strategy to induce tumor sensitivity to immunotherapy. For example, blocking focal adhesion kinase (FAK) decreased stromal activity and fibrosis, halting overall growth and metastasis of the tumor.\(^\text{116}\) Combining checkpoint inhibition with FAK inhibition doubled survival time in mice whose tumors were previously unresponsive to checkpoint blockade.\(^\text{117}\) In another study, depletion of fibroblast activation protein (FAP)-expressing fibroblasts in the tumor rendered pancreatic tumors sensitive to checkpoint therapy.\(^\text{118}\) To this end, CAR T cells have also been developed against the FAP\(^+\) fibroblasts, which are a key component of PDAC tumors.\(^\text{119}\) Blockade of cholecystokinin receptor signaling also reduces tumor growth and fibrosis. Similar to FAK inhibition, it enhances survival outcomes of mice treated with checkpoint inhibition.\(^\text{120}\) These examples indicate that inhibition of the tumor stroma may represent a critical strategy for sensitizing PDAC tumors to immunotherapies (Figure 2C).

While preclinical work has identified a multitude of single therapies that successfully generate immunity to PDAC, these agents in isolation are largely ineffective when translated to patients. The efficacy of the combinatorial approach vs. monotherapy has borne out in a couple of recent clinical trials\(^\text{121,122}\) (UMIN000005248, UMIN000000769). Many of the other studies discussed in this review have also indicated the power of multimodal immunotherapies, and the majority of current NIH clinical trials in PDAC immunotherapy are examining a combinatorial approach to treating this disease (Table 2). Furthermore, the success of combinations of single agents that on their own were not effective in PDAC also advocates for revisiting therapies previously determined obsolete. For example, as single agents, KRAS inhibitors have failed to make a marked improvement in patient survival despite the near universality of KRAS mutation in PDAC. However, KRAS inhibitors may prove powerful additions to T cell activating immunotherapies as KRAS is now known to be central to driving the immunosuppressive microenvironment (Figure 1).

Conclusions

Early genomic studies were used in PDAC to define mechanisms of tumorigenesis and chemoresistance. The application of genome-wide analysis to PDAC immunology has revealed that PDAC patients either possess effective tumor-antigen specific T cells for the cancer or have the capacity to generate an anti-tumor T cell response. However, we have also learned that PDAC can mount a robust immunosuppressive response at both the cellular and molecular level. Thus, to enhance the success of PDAC immunotherapy, treatment strategies will need to not only elicit immune responses, but also overwhelm the tumor’s defenses which counter them. In addition, the diversity of potential tumor antigens and defense mechanisms discovered in PDAC tumors yields a vast array of possible tumor phenotypes, each one with its own sensitivities and resistance to treatment. Genomic analysis can determine these key factors in an individual’s cancer and assist with guiding future therapy strategies.\(^\text{123}\) Pre-treatment genomic assessment of PDAC has already proven feasible\(^\text{125}\) and has the power to inform personalized immunotherapies strategies (Figure 3).

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| Category | Interventions | Clinical trial ID |
|----------|--------------|------------------|
| anti-CTLA-4 | Ipilimumab (anti-CTLA-4) + Gemcitabine | NCT01473940 |
| anti-CTLA-4/anti-PD-1 | Tremelimumab (anti-CTLA-4) + Durvalumab (anti-PD-L1) | NCT02527434 |
| & anti-PD-1 | Ipilimumab (anti-CTLA-4) or Nivolumab (anti-PD-1) + YVXS2503 (anti-SEM4D antibody) | NCT03372318 |
| & Niraparib (PARP inhibitor) + Nivolumab (anti-PD-1) or Ipilimumab (anti-CTLA-4) | NCT03404860 |
| anti-PD-1/ PD-L1 | Pembrolizumab (anti-PD-1) + ACP-196 | NCT02650485 |
| & Pembrolizumab (anti-PD-1) + Vaccinia virus (p53 vector) | NCT02529563 |
| & Nivolumab (anti-PD-1) + Cabiralizumab (anti-CSFR-1) | NCT02509017 |
| & Pembrolizumab (anti-PD-1) + AMG820 (anti-CSF-1R) | NCT02713259 |
| & Durvalumab (anti-PD-L1) + Galunisertib (TGFBeta inhibitor) | NCT02734160 |
| & Nivolumab (anti-PD-1) + Paricalcitol (Vitamin D analog) + Chemotherapies | NCT02754726 |
| & Pembrolizumab (anti-PD-1) + BL-8040 (CXR4 analog) | NCT02624586 |
| & Pembrolizumab (anti-PD-1) + BL-8040 (CXR4 analog) | NCT02670799 |
| & Nivolumab (anti-PD-1) + IRE | NCT01808974 |
| Pembrolizumab (anti-PD-1) + XL888 (hspp90 inhibitor) | NCT03095781 |
| Nivolumab (anti-PD-1) + Duratumumab (anti-CD38) | NCT03096559 |
| Pembrolizumab (anti-PD-1) + Olaptesed (anti-CXCL12) | NCT03168139 |
| Atezolizumab (anti-PD-L1) + BL-8040 (CXR4 antagonist) + RO6874281 (anti-FAP) | NCT03193190 |
| Nivolumab (anti-PD-1) + APX005M (CD40 agonist) + Gemcitabine and Nab-Paclitaxel | NCT03214550 |
| Durvalumab (anti-PD-L1) + Stereoreactive Ablative Body Radiotherapy | NCT03258275 |
| Nivolumab (anti-PD-1) + Entinostat (HDAC inhibitor) | NCT03257761 |
| Durvalumab (anti-PD-L1) + Guadecitabine (DNA methyltransferase inhibitor) | NCT03331562 |
| Pembrolizumab (anti-PD-1) + Paricalcitol (Vitamin D analog) | NCT03331562 |
| Durvalumab (anti-PD-L1) + Radiation Therapy | NCT03490769 |
| Nivolumab (anti-PD-1) + BMS-81360 (CCR2/CCR5 antagonist) + Chemotherapies | NCT03496682 |
| Olecumab (anti-CD73) + Durvalumab (anti-PD-L1) + Chemotherapies | NCT03613550 |
| Pembrolizumab (anti-PD-1) + PEGPH20 (pegylated hyaluronidase) | NCT03634332 |
| Pembrolizumab (anti-PD-1) + Palereorep (Oncolytic Reovirus) | NCT03723915 |
| Pembrolizumab (anti-PD-1) + Defactinib (FAK inhibitor) | NCT03727880 |
| anti-PD-1/vaccine | GVAX Vaccine (With CY) and CRS-207 Vaccine + Nivolumab (anti-PD-1) | NCT02243371 |
| Nivolumab (anti-PD-1) + GVAX Vaccine + Urelumab (anti-CD137) + Cyclophosphamide | NCT02451982 |
| Peptide Vaccine + Pembrolizumab (anti-PD-1) | NCT02600849 |
| GVAX Vaccine + Pembrolizumab (anti-PD-1) + Cyclophosphamide + SBRT | NCT02648392 |
| Epacadostat (anti-IDO) + Pembrolizumab (anti-PD-1) + GVAX vaccine + CRS-207 vaccine | NCT02600302 |
| Pembrolizumab (anti-PD-1), GVAX vaccine, IMC-CS4 (anti-CSF-1R) | NCT03153410 |
| Nivolumab (anti-PD-1) + GVAX vaccine + SBRT + Cyclophosphamide | NCT03161379 |
| GVAX Vaccine (With CY) and CRS-207 Vaccine + Nivolumab (anti-PD-1) + Iiplimumab (anti-CTLA4) | NCT03190265 |
| Durvalumab (anti-PD-L1) + anti-CEA- & MUC1 vaccine | NCT03376659 |
| GVAX Vaccine + Nivolumab (anti-PD-1) and BMS-81360 (CCR2/CCR5 antagonist) | NCT03767582 |
| Vaccine | Allogenic GM-CSF plasmid- transfected tumor cell vaccine | NCT00638910 |
| Falimare (anti-CEA vaccine) + Inalimare (anti-CEA and MUC1 vaccine) + Sargramostim (recombinant GM-CSF) | NCT00669734 |
| GVAX vaccine + Cyclophosphamide | NCT01277411 |
| GVAX vaccine + Cyclophosphamide + SBRT + FOLFRINOX | NCT01555321 |
| NPC-1C vaccine + Gemcitabine + Nab-Paclitaxel | NCT01834235 |
| Tumor derived gp96 vaccine | NCT02123079 |
| anti-DC1 vaccine + interferon alpha-2b + Rintatolinodim (immunomodulatory RNA drug) | NCT02151448 |
| ETBX-011 Vaccine + ALT-803 (IL-15 complex) | NCT03127098 |
| ETBX-011 Vaccine + ALT-803 (IL-15 complex) | NCT03392494 |
| MDCS8 (dendritic cell KRAS vaccine) | NCT03592888 |
| CAR T-cell therapy | Mesocar T cells | NCT01897415 |
| anti-CEA CAR-T cells + Sir Spheres | NCT02416466 |
| BFX-601 (anti PSMA CAR-T cells) + Rimiducid | NCT02744827 |
| anti-CEA CAR-T cells | NCT02858536 |
| anti-CLD18 CAR-T cell | NCT03159819 |
| anti-Meso CAR-T cells | NCT03233944 |
| anti-Meso CAR-T cell vs anti-CD19 CAR-T cells + Cyclophosphamide | NCT03497135 |
| Other T cell therapy | FOLFOX8 + Anti-CD38 Activated T cells | NCT01435874 |
| Bispecific Antibody T cells + Aledesma11 (recombinant IL-2) + Sargramostim (recombinant GM-CSF) + Chemotherapies | NCT02608086 |
| Gemcitabine with CD8+ NK/G2D+ AKT cells | NCT02929797 |
| Oncolytic virus | VCN-01 (Oncolytic Adenovirus) | NCT02045602 |
| LOAd703 (Oncolytic Adenovirus) | NCT03235989 |
| CadVEC Oncolytic Adenovirus | NCT03749256 |
| Other | CD40 agonist monoclonal antibody + Gemcitabine | NCT06711191 |
| Indoximod (IDO inhibitor) + Nab-Paclitaxel + Gemcitabine | NCT02077881 |
| TG01 injection + Gemcitabine | NCT02617714 |
| CCX872-B (CCR2 antagonist) | NCT02454086 |
| ALT-803 (IL-15 complex) + Gemcitabine + Nab-paclitaxel | NCT02539674 |
| Ibrutinib (BTK inhibitor) + pacitaxel and gemcitabine | NCT03629886 |
| Ibrutinib (BTK inhibitor) | NCT02753500 |
| Plexixafor (CXR4 antagonist) | NCT03772700 |
| CDX-145 (anti-BD4) + CDX-301 (anti-flt3L) | NCT03329550 |

SBRT, stereotactic body radiation therapy; IRE, irreversible electroporesis; CSF-1R, colony-stimulating factor-1 receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
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