Immunological Mechanisms in Pancreatic Cancer

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Key Objectives

- Etiology and common treatment options for pancreatic ductal adenocarcinoma
- Challenges imposed by tumor microenvironment
- Novel approaches to immunotherapy in pancreatic cancer

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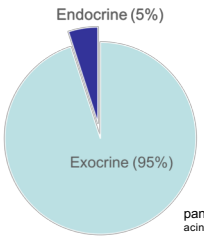
Types of pancreatic cancer



pancreatic ductal adenocarcinoma
acinar cell carcinoma
pseudopapillary
pancreaticoblastoma

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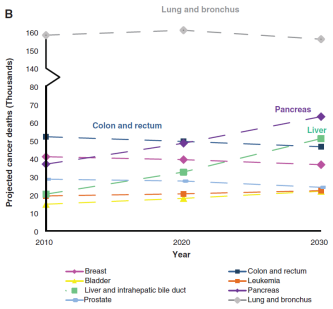
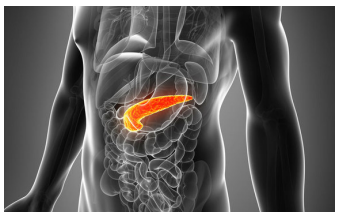
Pancreatic cancer
2nd ~~4th~~ leading cause of death



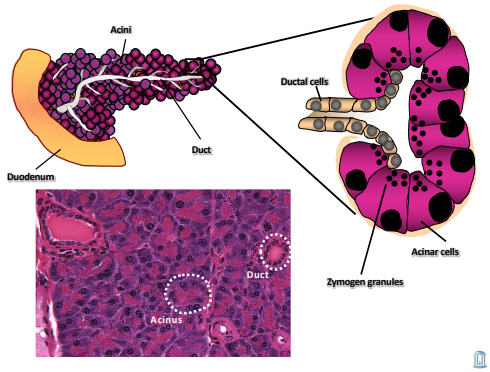
Rahib et al, 2014

Pancreatic ductal adenocarcinoma

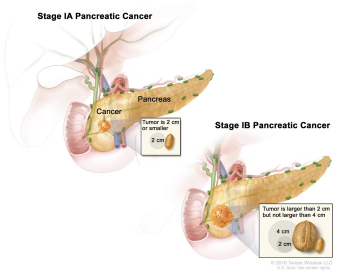


www.webmd.com

The exocrine pancreas



Pancreatic ductal adenocarcinoma

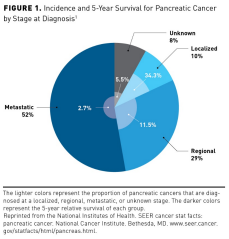


https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq

Why is pancreatic cancer such a difficult problem?

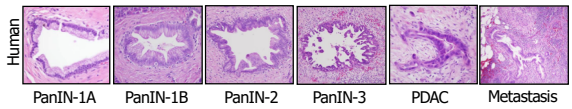
- Diagnosed late
- Difficult to see on imaging
- Difficult to biopsy
- Cystic neoplasms
  - When are they malignant?
- Biopsies may have few tumor cells
- Metastasizes early
- Surgery is a big deal
- Few therapies
  - Drugs don't penetrate?
  - Drugs don't work?

Challenges
PDAC: Stage at Diagnosis



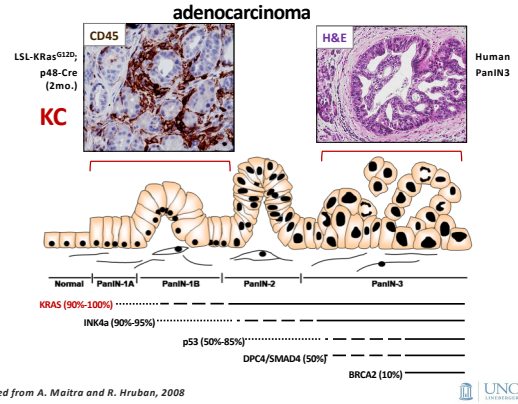
Seer.cancer.gov

Histopathological and genetic evolution of pancreatic ductal adenocarcinoma



Yeh & Der (2007) Expert Opin Ther Targets 11:673

Histopathological and genetic evolution of pancreatic ductal adenocarcinoma



Adapted from A. Maitra and R. Hruban, 2008

Pancreatic ductal adenocarcinoma (PDAC)

- 230,000 cases worldwide (2% of cancers)
- Greater than 90% mortality
- Late diagnosis
- 4 year survival rate after treatment <8%
- >95% harbor KRAS mutations: currently UNDRUGGABLE!!

Advances in the treatment of pancreatic cancer

- If the cancer is detected at an early stage when surgical removal of the tumor is possible, the 5-year survival rate is 32%.
- About 10% of people are diagnosed at this stage.
- If the cancer has spread to surrounding tissues or organs, the 5-year survival rate is 12%.
- For the 52% of people who are diagnosed after the cancer has spread to a distant part of the body, the 5-year survival rate is 3%.

https://www.cancer.net/cancer-types/pancreatic-cancer/statistics

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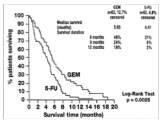
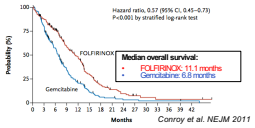
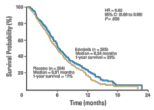
Advances in the treatment of pancreatic cancer



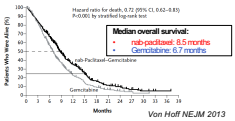
Burris III et al. JCO 1997



Conroy et al. NEJM 2011



Moore et al. JCO 2007



Von Hoff NEJM 2013

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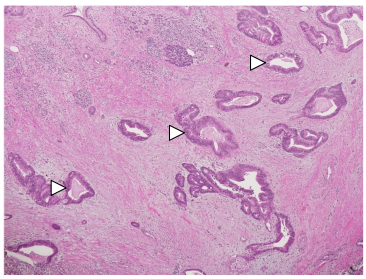
Pancreatic cancer: a paradigm for tumor-host interaction



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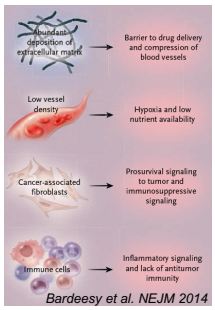
Challenges: Tumor stroma barrier

just a physical barrier?



Bardeesy et al. NEJM 2014

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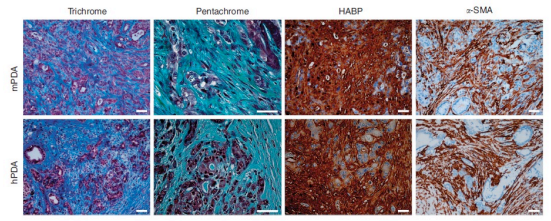

Figure 1. The desmoplastic stroma in PDA. Both mouse (top) and human (bottom) PDA display robust deposition of ECM and activated pancreatic stellate cells. Masson's trichrome reveals robust collagen content in PDA (blue) while a more complex Movat's pentachrome staining highlights the presence of GAGs and mucins (blue) co-localised with collagen (turquoise/green). Histochemistry with hyaluronic acid binding protein (HABP) confirms the abundance of HA in PDA and immunohistochemistry for α-SMA identifies activated PSC, or myofibroblasts. Scale bars = 50 μm.

Provenzano et al., 2013

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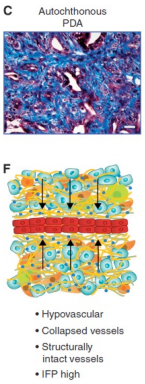

Provenzano et al., 2013

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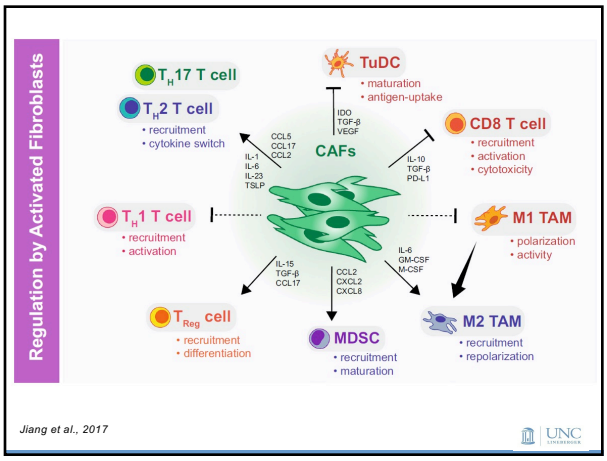
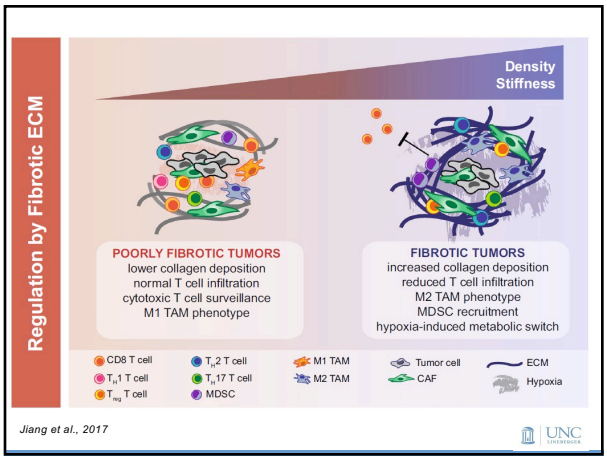
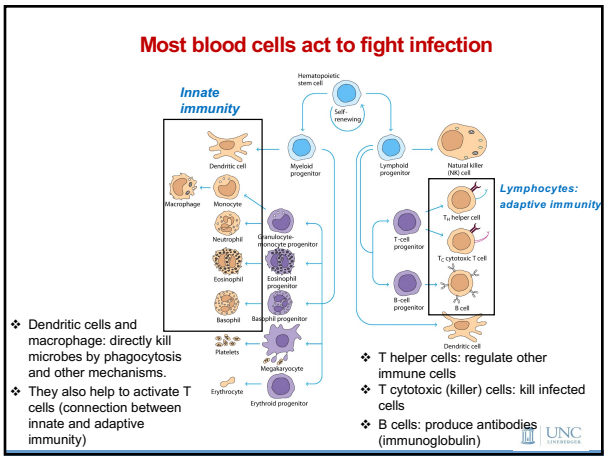


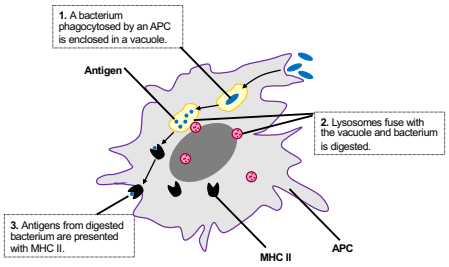
Jiang et al., 2017



Jiang et al., 2017

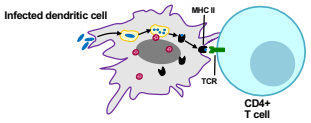


Mechanisms of antigen presentation

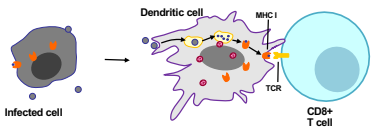


Mechanisms of antigen presentation

1. Direct presentation

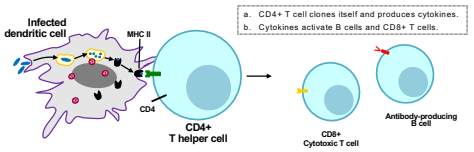


2. Cross-presentation

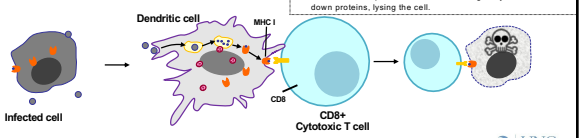


Mechanisms of T cell activation by antigens

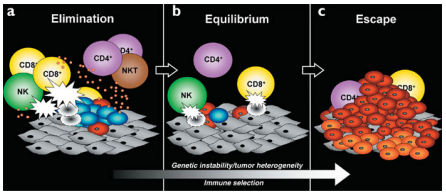
1. Direct presentation



2. Cross-presentation



The 3 E's of cancer immunoediting



- **Recognition of cancer cells by immune system:**
  - Mutant antigen
  - Ectopic expression of a normal protein

Dunn et al., Nature Immunology 2002

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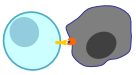
How does cancer escape immune surveillance?

- **Altering characteristics of a cancer cell:**
  - Loss of antigen
  - Downregulation of MHC I
- **Suppressing the immune response:**
  - T cell anergy
  - Release of immunosuppressive cytokines by tumor or stromal cells



Cancer cell

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Challenges: Tumor stroma barrier

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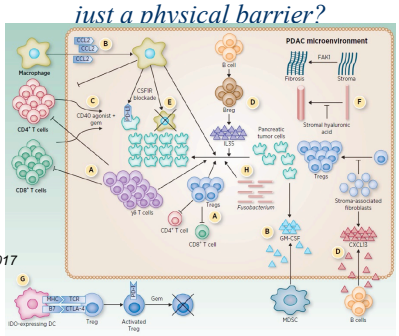

Johnson et al., 2017

- **Immunotherapy!!** Strategies to improve the tumor-associated immune response by either boosting components of the immune system that produce an effective immune response or by inhibiting components that suppress the immune response.

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Current Immunotherapy approaches in pancreatic cancer

- **To boost immune system:**
  - Checkpoint blockade antibody therapy
  - Vaccination
  - 'Designer' T cells (CAR T cells, enhanced TCR cells)
- **Block suppressive mechanisms:**
  - Block or deplete regulatory T cells and MDSC
  - Block suppressive cytokines

Current Immunotherapy approaches in pancreatic cancer

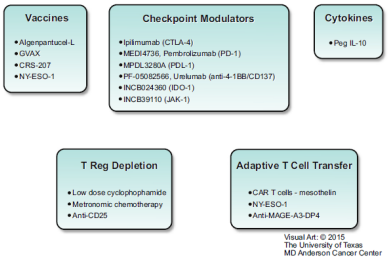
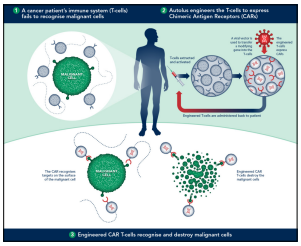


Fig. 4. Immune therapy approaches for pancreatic cancer.

Javle et al., 2016

Current Immunotherapy approaches

- **To boost immune system:**
  - Adoptive T cell transfer
  - **'Designer' T cells (CAR T cells, enhanced TCR cells)**
  - Dendritic cell vaccination
- **Block suppressive mechanisms:**
  - Block or deplete regulatory T cells and MDSC
  - Block suppressive cytokines
  - Checkpoint blockade antibody therapy



autolus.com

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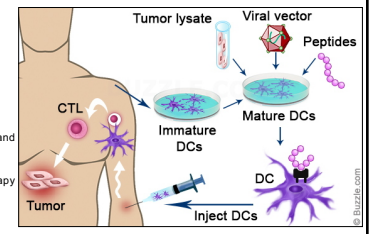

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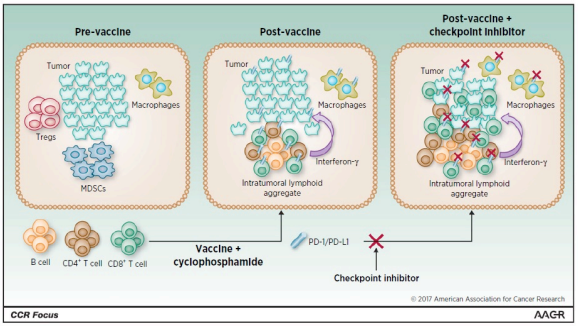
Proposed vaccine benefits in pancreatic cancer



Johnson et al., 2017

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Current Immunotherapy approaches

- **To boost immune system:**
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  - 'Designer' T cells (CAR T cells, enhanced TCR T cells)
  - Dendritic cell vaccination
- **Block suppressive mechanisms:**
  - Block or deplete regulatory T cells and MDSC
  - **Checkpoint blockade antibody therapy (anti-PD-1, CTLA-4)**

Wolchok and Chan, Nature, 2014

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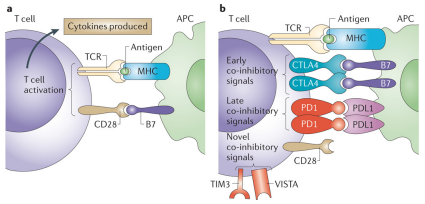
Basic mechanisms of T cell stimulation and inhibition

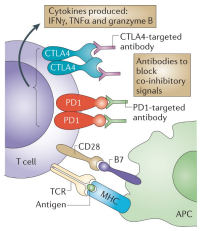


T cell activation

T cell activation is limited by CTLA-4

Sharma et al, Nature Reviews Cancer, 2011

Current Immunotherapies that induce effector T cell function



Use of anti-CTLA-4 and anti-PD-1 allows for sustained T cell response

Sharma et al, Nature Reviews Cancer, 2011

Table 1. A list of notable immunotherapies in clinical development for PDAC

Therapeutic target and agents under investigation for PDAC	Preclinical rationale	Clinical evidence and ongoing trials
PD-1/PD-L1 Nivolumab Pembrolizumab Durvalumab	PD-1/PD-L1 inhibition has activity in a wide number of tumors. PD-L1 expression is upregulated in a subset of PDAC and is associated with shortened survival (43, 161).	Responses were observed in a subset of patients with MMR-deficient pancreatic cancer (56), and additional trials in MMR-deficient disease are ongoing (NCT01876511 and NCT02460060). None of 14 pancreatic patients responded in a study of single-agent nivolumab (22). Multiple combination immunotherapy trials are ongoing (NCT02558894, NCT02268825, NCT02472977, NCT02243371, and NCT02777710).
CTLA-4 Ipilimumab Tremelimumab	Anti-CTLA-4 therapy may reduce intratumoral Tregs and shift the threshold needed for T-cell activation. A trial of ipilimumab failed to show convincing clinical activity, but a possible delayed response was observed in one patient (21).	Multiple combination trials are ongoing, including combinations with PD-1 inhibition and/or therapeutic vaccines (NCT02558894 and NCT01896869).
IDO1 Indoximod	IDO1 mediates tumor immunosuppression in preclinical models (non-PDAC), and PDAC frequently overexpresses IDO as a mechanism of immune escape (132, 162, 163).	Evidence of clinical activity was observed in combination with chemotherapy (133). A clinical trial is ongoing in combination with gemcitabine-based chemotherapy (NCT02077881).
BTK Ibrutinib	BTK is involved with B-cell receptor signaling and is also expressed by macrophages. In preclinical models, ibrutinib synergizes with gemcitabine to increase antitumor immunity (137).	Clinical trials are ongoing in combination with gemcitabine-based chemotherapy in PDAC (NCT02562898 and NCT02436668).
CD40 RO7009789 (CP-870,893) JNJ-64457107	CD40 is expressed on B cells, DCs, and other cell types. CD40 agonists inhibit PDAC stroma, increase CCL2 levels and interferon gamma (IFN-γ) in the TME, and synergize with chemotherapy (145, 164).	Evidence of clinical activity was observed in an early-stage clinical trial in PDAC (141). Additional trials of monotherapy or combination with gemcitabine-based chemotherapy are ongoing (NCT02588443 and NCT02829099).
CCR2 CCX872 PF04136309	CCR2 recruits suppressive macrophages to the immunosuppressive TME in PDAC, and CCR2 inhibition depletes tumor-infiltrating macrophages and improves survival in a preclinical model (145).	CCR2 inhibition has shown safety and possible evidence of clinical activity in combination with chemotherapy. Clinical trials in combination with chemotherapy in PDAC are ongoing (NCT02345408 and NCT02732938).
CSF1R Cabiralizumab (FPA008) Pexidartinib (PLX3397) BLZ945 AMG 820	CSF1R inhibition reprograms tumor-associated macrophages and upregulates immune checkpoints. Synergistic activity has been observed with immune checkpoint inhibitors in preclinical models of PDAC (146, 147).	Multiple agents are in clinical trials in metastatic PDAC in combination with PD-1 inhibitors (NCT02526017, NCT02777710, NCT02829723, and NCT02713529).
CXCR4 LY2510924	CXCR4 blockade abrogated metastasis in preclinical models (151) and synergized with PD-L1 therapy to increase antitumor immunity (158).	CXCR4 inhibitor is in clinical trial in combination with PD-L1 blockade to treat advanced solid tumors, including PDAC (NCT02737072).

Abbreviations: BTK, Bruton tyrosine kinase; CCL2, chemokine (C-C motif) ligand 2; CCR2, C-C chemokine receptor type 2; CSF1R, colony-stimulating factor-1 receptor; CXCR4, C-X-C chemokine receptor type 4; DC, dendritic cell; MMR, mismatch repair.

Johnson et al., 2017

Germline mutations as predictors of checkpoint blockade responsiveness

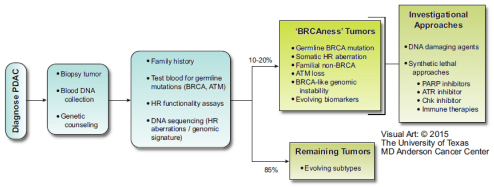
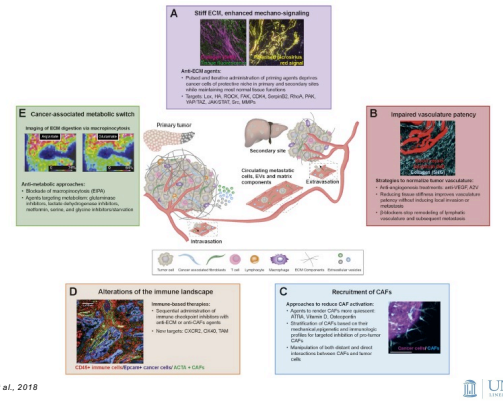


Fig. 3. BRCA and HRD beyond germline BRCA mutations.

Javle et al., 2016

Stromal therapy in pancreatic cancer



Vennin et al., 2018

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