Immunological Mechanisms in Pancreatic Cancer

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Immunomodulation in pancreatic cancer

PURPLESTRIDE
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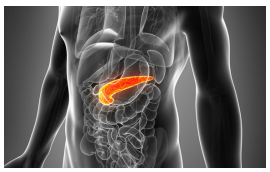
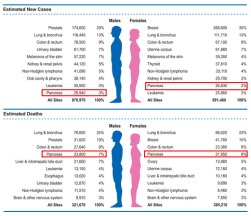
Key Objectives

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

Epidemiology

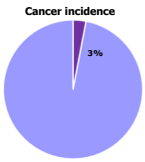




Siegel et al., 2019

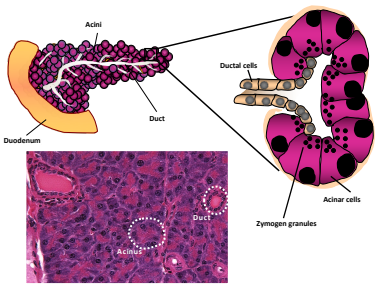
Epidemiology

- Estimated 53,000 new cases diagnosed yearly in the US.
- Males-27,670; Females –25,400
- Pancreatic Cancer Represent 3% of all new cancer cases in the U.S.
- Pancreatic Cancer is most frequently diagnosed among people aged 65-74



Siegel et al, 2016
SEER Cancer Statistics Review, 1975-2012, National Cancer Institute

The exocrine pancreas

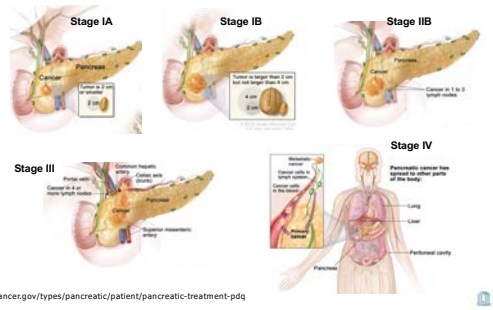


Types of pancreatic cancer

- pancreatic neuroendocrine tumors (PNETs) or islet cell tumors

- Pancreatic ductal adenocarcinoma (PDA)
- Acinar adenocarcinoma
- Intraductal papillary mucinous neoplasm (IPMN)
- Acinar cell carcinoma, adenosquamous carcinoma, colloid carcinoma, giant cell tumor, hepatoid carcinoma, mucinous cystic neoplasms, pancreatoblastoma, serous cystadenoma, signet ring cell carcinoma, solid and pseudopapillary tumors, squamous cell carcinoma, and undifferentiated carcinoma.

Pancreatic ductal adenocarcinoma



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

Challenges in PDA

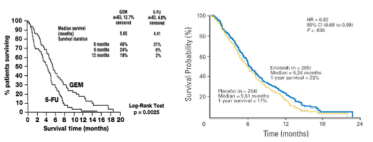
- Late diagnosis: vague symptoms, difficulty imaging/biopsy, cystic neoplasms
- Invasive surgery : resectability of the tumor
- Early metastatic spread
- Sparse options for therapy: drugs don't penetrate; >95% harbor KRAS mutations: currently UNDRUGGABLE!!

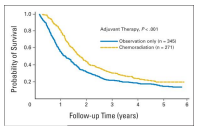
Incidence and 5-year survival at diagnosis

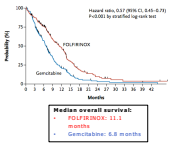
Dark: diagnosis
Light: survival of each group

SEER Cancer Stat facts: www.seer.cancer.gov/statfacts/html/pancreas.html
Siegel et al., 2016

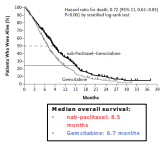
Advances in the treatment of pancreatic cancer







Median overall survival:
- FOLFIRINOX: 11.1 months
- Gemcitabine: 6.8 months



Median overall survival:
- nab-paclitaxel: 8.5 months
- Gemcitabine: 6.7 months

	1975-1977	1987-1989	2005-2011
5 year survival	3%	4%	8%

Burris III et al. JCO 1997
Moore et al. JCO 2007
Conroy et al. NEJM 2011
Von Hoff, NEJM 2013
Herman et al., J Clin Oncol.2008

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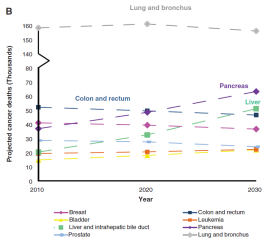
Pancreatic cancer is projected to become 2nd leading cause of death



Rahib et al, 2014

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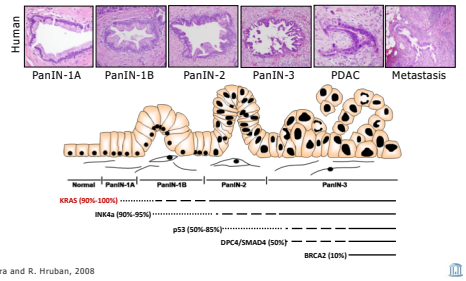
Histopathological and genetic evolution of pancreatic ductal adenocarcinoma



Adapted from A. Maitra and R. Hruban, 2008

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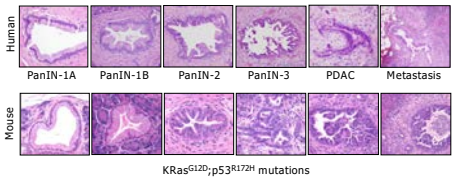
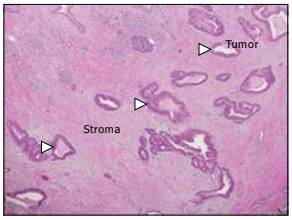
Mouse models recapitulate human histology

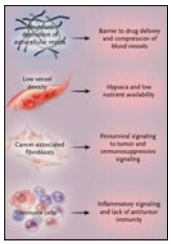


$KRas^{G12D}$;$p53^{R172H}$ mutations

Yeh & Der (2007) Expert Opin Ther Targets 11:673
Hingorani, Tuveson, Cancer Cell 2005

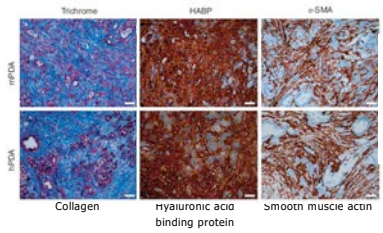
Pancreatic cancer: a paradigm for tumor-host interaction





Bardeesy et al. NEJM 2014

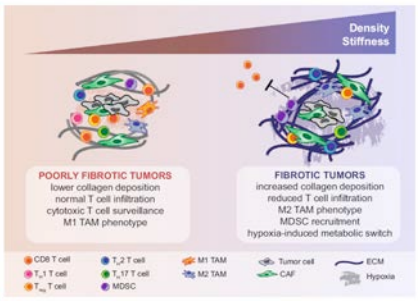
The desmoplastic stroma in PDA



- **Robust deposition of ECM**
- **Activated pancreatic stellate cells**
- **Hypovascular**
- **Collapsed vessels**
- **Interstitial fluid pressure is high**

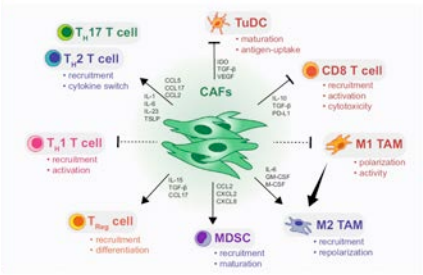
Provenzano et al., 2013

Regulation by Fibrotic ECM



Jiang et al., 2017

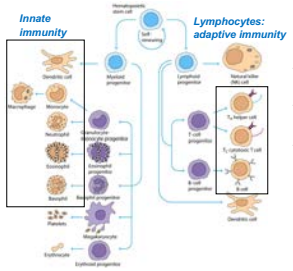
Regulation by Activated Fibroblasts



Jiang et al., 2017

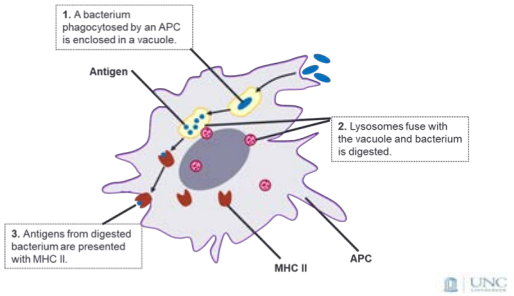
- **Promote immunosuppression - hinder anti-tumor immunity**

Most blood cells act to fight infection

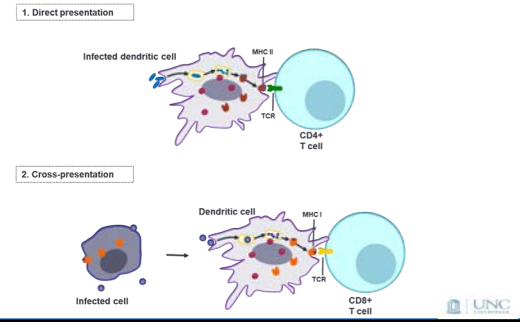


- Dendritic cells and macrophage: directly kill microbes by phagocytosis and other mechanisms.
- They also help to activate T cells (connection between innate and adaptive immunity)
- T helper cells: regulate other immune cells
- T cytotoxic (killer) cells: kill infected cells
- B cells: produce antibodies (immunoglobulin)

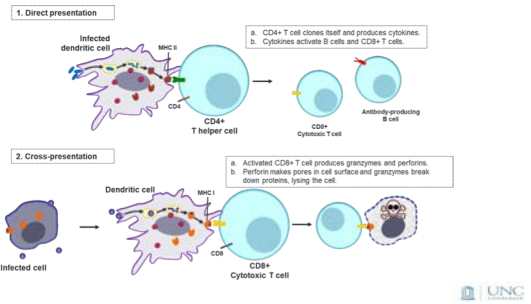
Mechanisms of antigen presentation



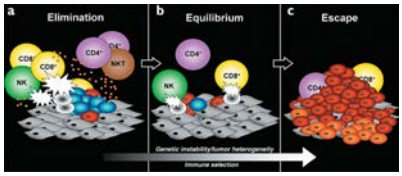
Mechanisms of antigen presentation



Mechanisms of T cell activation by antigens



The 3 E's of cancer immunoediting

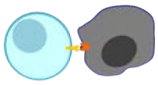


- **Recognition of cancer cells by immune system:**
  - Mutant antigen
  - Ectopic expression of a normal protein

Dunn et al., Nature Immunology 2002

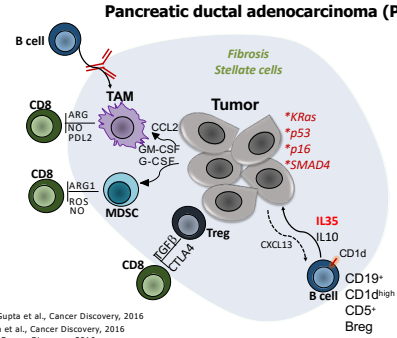
How does cancer escape immune surveillance?

- **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
  - Reduced ability to migrate/hypoxia



Cancer cell

Pancreatic ductal adenocarcinoma (PDAC)



- **Fibrosis, immunosuppression**
- **Exclusion of T cells**

- **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.

Pylayeva-Gupta et al., Cancer Discovery, 2016
Gunderson et al., Cancer Discovery, 2016
Lee et al., Cancer Discovery, 2016

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
  - Resolve fibrosis

Current Immunotherapy approaches

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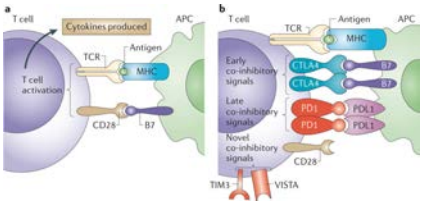
Drs. Allison and Honjo
Nobel prize in Medicine, 2018

Wolchok and Chan, Nature, 2014

Basic mechanisms of T cell stimulation and inhibition

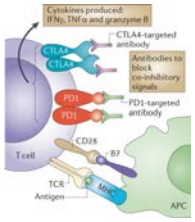


T cell activation

T cell activation is limited by CTLA-4 and PD-1

Sharma et al, Nature Reviews Cancer, 2011

Examples of Current Immunotherapies that induce effector T cell function

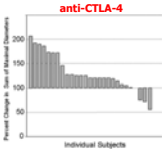


Use of anti-CTLA-4 and anti-PD-1 allows for sustained T cell response

Sharma et al, Nature Reviews Cancer, 2011

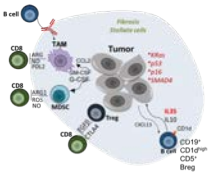
Lack of therapeutic efficacy for checkpoint blockade monotherapy

anti-CTLA-4



Maximal response in sum of maximal diameters of index lesions

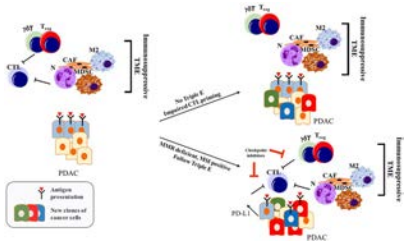
- **No objective responses in PDAC patients (14) on anti-PD-L1 monotherapy**



- **Bring the CD8+ T cells in first!**

Royal et al., 2010
Brahmer et al., 2012

Immunoediting in PDA: only tumors with genetic instability follow Triple E, while others cannot



- tumors with mismatch repair (MMR) deficiency or with more microsatellite instability (MSI) are shown to respond better to immunotherapy
- 1% of patients with PDAC showed MSI with inactivation of MLH1 and MSH2
- PD-1 antibody, was approved by the Food and Drug Administration in 2017 for solid tumors with MMR defects or MSI, including PDAC

Kabacaoglu et al., 2018
Li et al., 2017
Humphris et al., 2017

Current Immunotherapy approaches

- **To boost immune system:**
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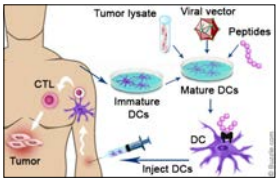
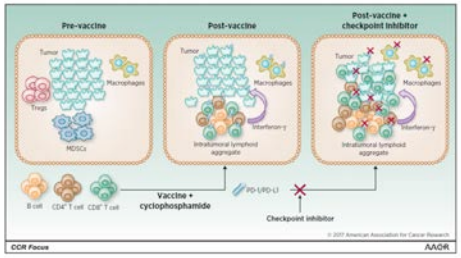
  - 'Designer' T cells (CAR T cells, enhanced TCR cells)
- **Block suppressive mechanisms:**
  - Block or deplete regulatory T cells and MDSC
  - Resolve fibrosis



Proposed vaccine benefits in pancreatic cancer



- Irradiated, granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting, allogeneic PDAC vaccine (GVAX) given as a single agent or in combination with low-dose cyclophosphamide to deplete regulatory T cells (Treg)

Lutz et al., 2014
Johnson et al., 2017

Current Immunotherapy approaches

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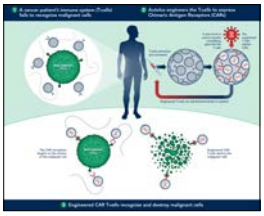

Challenges

(1) lack of ideal TSAs
(2) inefficient trafficking of CAR-T cells to tumor sites
(3) the immune-suppressive TME
(4) the risk of developing on-target/off-tumor toxicities,

- preclinical studies on various pancreatic cancer cell surface antigens, namely, MSLN, B7H3, CEA, MUC1, PSCA, CD24, HER2, and natural killer receptors

autolus.com

Current Immunotherapy approaches

- **To boost immune system:**
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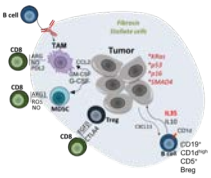
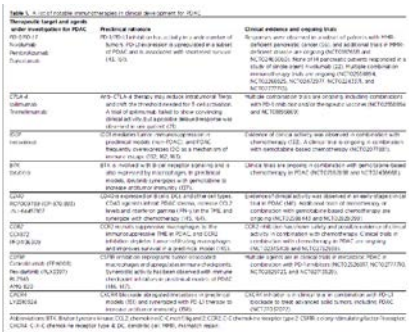
  - Vaccination
  - 'Designer' T cells (CAR T cells, enhanced TCR cells)
- **Block suppressive mechanisms:**
  - **Block or deplete immunosuppressive cells**
  - Resolve fibrosis

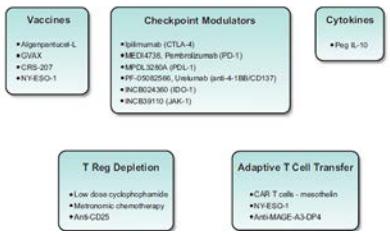


- Macrophage polarization: agonistic CD40 (FGK45)
- Inhibition of myeloid cells recruitment: anti-CXCR2, anti-CSFR1
- Inhibition of macrophage/B cell activity: ibrutinib (iBTK)
- Treg depletion:Cyclophosphamide, anti-CD25

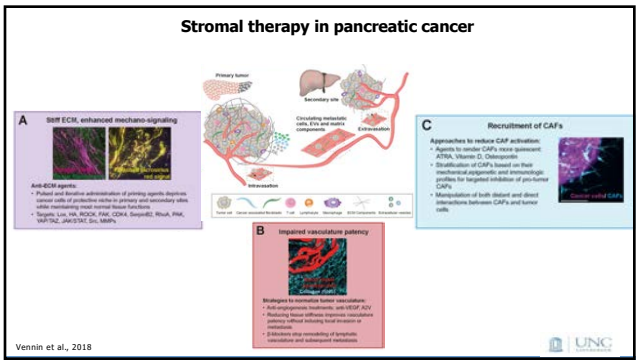


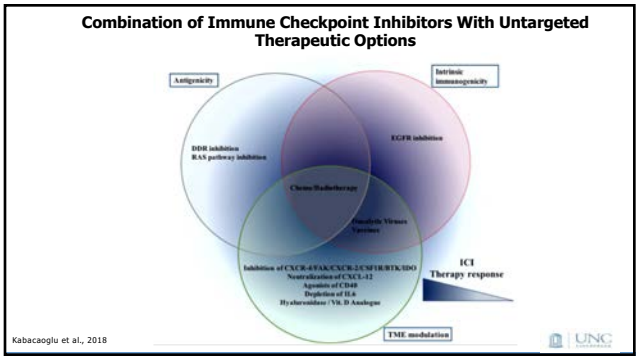
Johnson et al., 2017

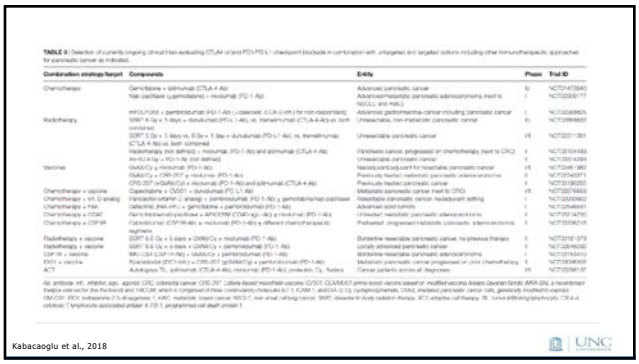
Current Immunotherapy approaches in pancreatic cancer

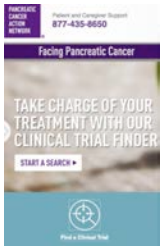


Javle et al., 2016


Stromal therapy in pancreatic cancer
A
Stiff ECM, enhanced mechano-signaling
B
Impaired vasculature patency
C
Recruitment of CAFs
Vennin et al., 2018


Combination of Immune Checkpoint Inhibitors With Untargeted Therapeutic Options
Antigenicity
Intrinsic immunogenicity
DDR inhibition
RAS pathway inhibition
EGFR inhibition
Chemo/Radiotherapy
Oncolytic Viruses Vaccines
Inhibition of CXCR-4/VAK/CXCR-2/CSF1R/IDK/IDO
Neutralization of CXCL-12
Agonists of CD40
Depletion of IL6
Hyaluronidase / Vit. D Analogue
ICI Therapy response
TME modulation
Kabacaoglu et al., 2018


Kabacaoglu et al., 2018



- Over 170 pancreatic cancer specific studies listed in Clinical Trial Finder
- Over 115 pancreatic cancer specific studies listed in Clinical Trial Finder for metastatic pancreatic cancer

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References

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2. Siegel et al., CA Cancer J Clin., 2016
3. Rahib et al., Cancer Res. 2014
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22. Kabacaoglu et al., Front Immunol., 2018
23. Li et al., 2017
24. Humphris et al., 2017
25. Lutz et al., 2014

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