Immunological Mechanisms in Pancreatic Cancer

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Immunomodulation in pancreatic cancer

PURPLESTRIDE
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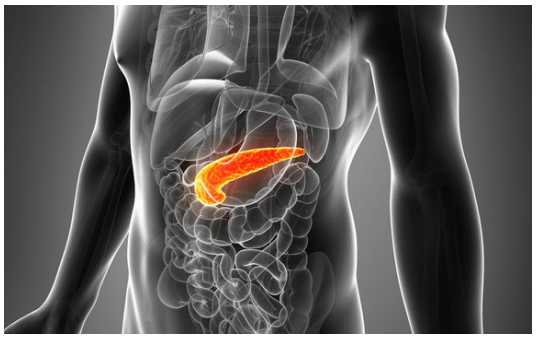
Key Objectives

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

Epidemiology



Estimated New Cases

	Males			Females	
Prostate	174,650	20%		Breast	268,600	30%
Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%		Colon & rectum	67,100	8%
Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%		Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%		Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%		Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%		Pancreas	26,830	3%
Pancreas	29,940	3%		Leukemia	25,860	3%
All Sites	**870,970**	**100%**		**All Sites**	**891,480**	**100%**

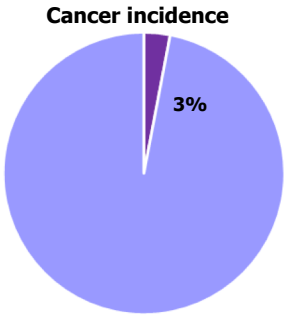
Estimated Deaths

	Males			Females	
Lung & bronchus	76,650	24%		Lung & bronchus	66,020	23%
Prostate	31,620	10%		Breast	41,760	15%
Colon & rectum	27,640	9%		Colon & rectum	23,380	8%
Pancreas	23,800	7%		Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%		Ovary	13,980	5%
Leukemia	13,150	4%		Uterine corpus	12,160	4%
Esophagus	13,020	4%		Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%		Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%		Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**		**All Sites**	**285,210**	**100%**

Siegel et al., 2019

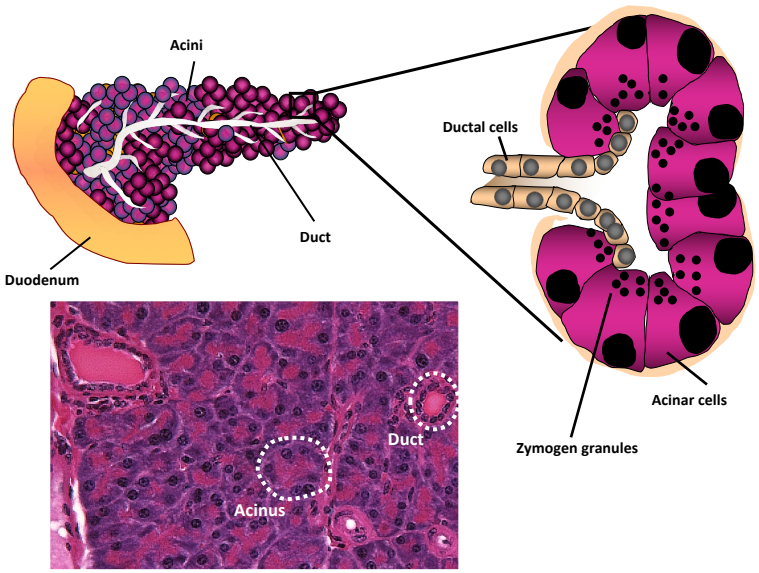
Epidemiology

- 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

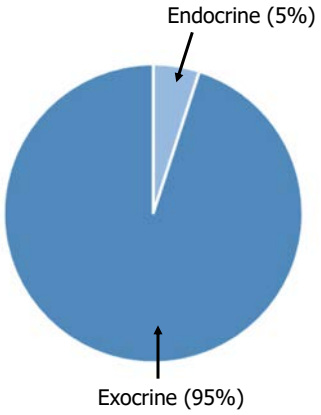


Siegel et al, 2016
SEER Cancer Statistics Review, 1975-2012, National Cancer Institute

The exocrine pancreas



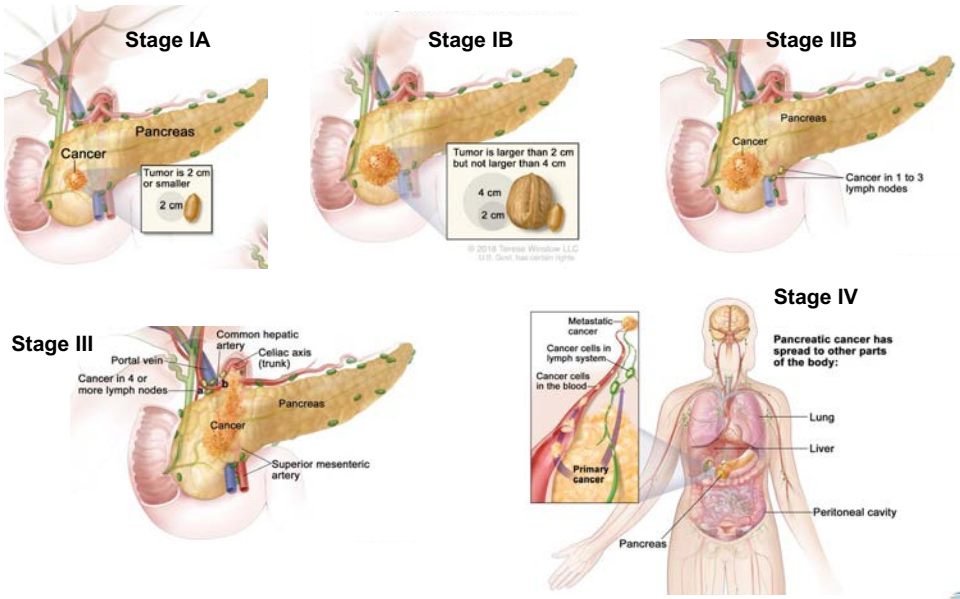
Types of pancreatic cancer



- 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

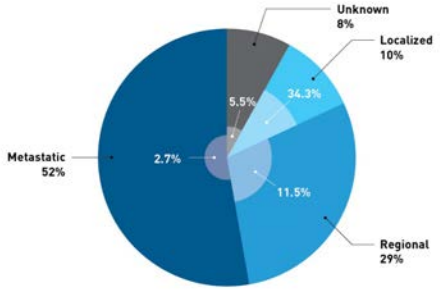


https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq

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!!

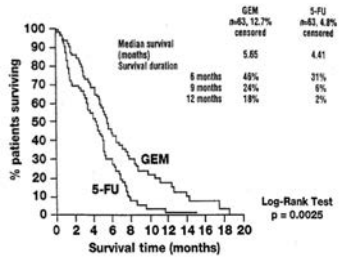
Incidence and 5-year survival at diagnosis

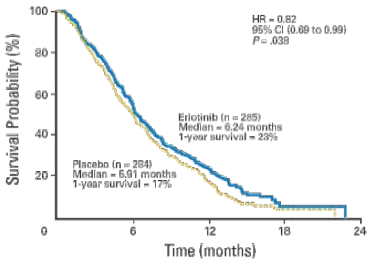


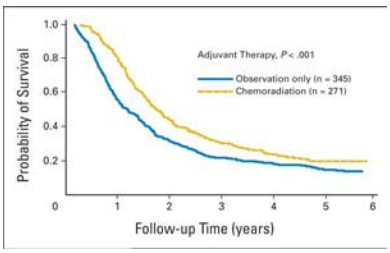
Dark: diagnosis
Light: survival of each group

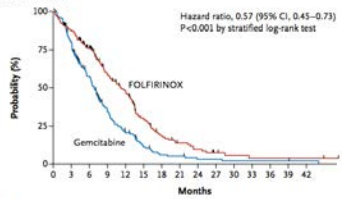
SEER Cancer Stat facts: www.seer.cancer.gov/statfacts/html/pancreas.html
Siegel et al., 2016

Advances in the treatment of pancreatic cancer

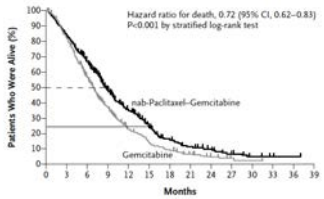








Median overall survival:
- FOLFIRINOX: 11.1 months
- Gemcitabine: 6.8 months

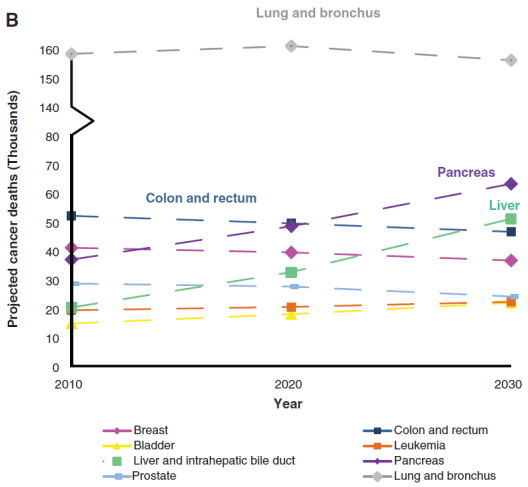


Median overall survival:
- nab-paclitaxel: 8.5 months
- Gemcitabine: 6.7 months

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

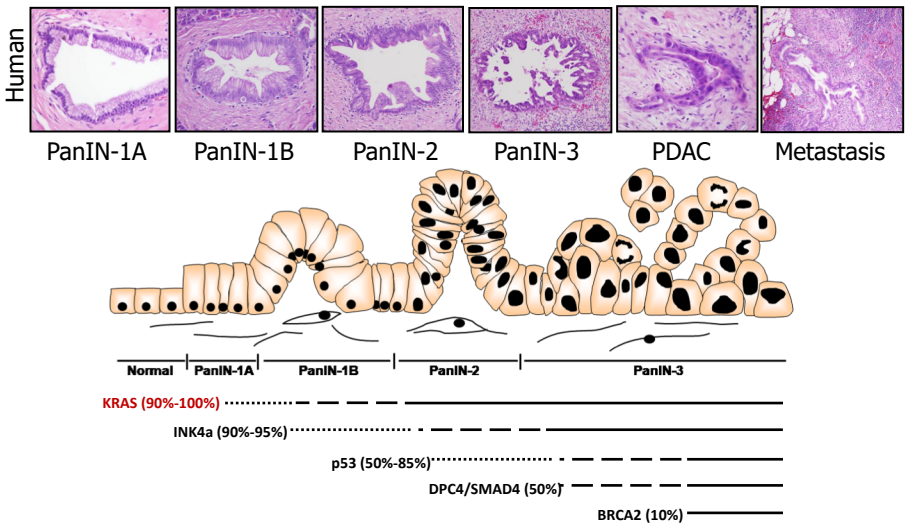
Burris III et al. JCO 1997
Moore et al. JCO 2007
Conroy et al. NEJM 2011
Von Hoff, NEJM 2013
Herman et al., J Clin Oncol.2008

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



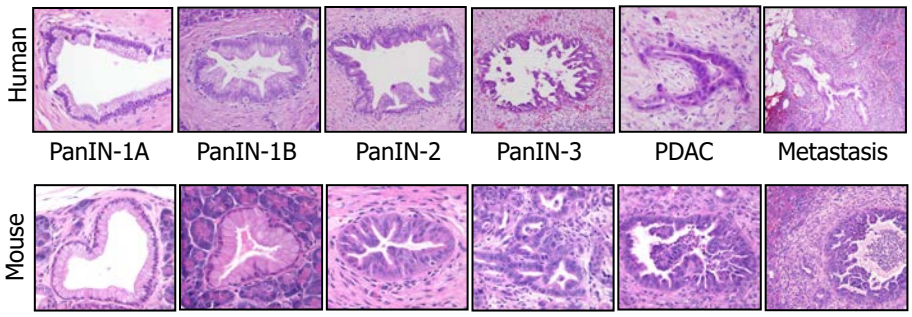
Rahib et al, 2014

Histopathological and genetic evolution of pancreatic ductal adenocarcinoma



Adapted from A. Maitra and R. Hruban, 2008

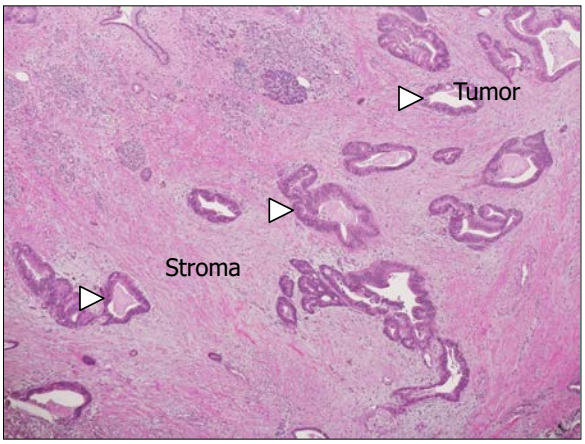
Mouse models recapitulate human histology

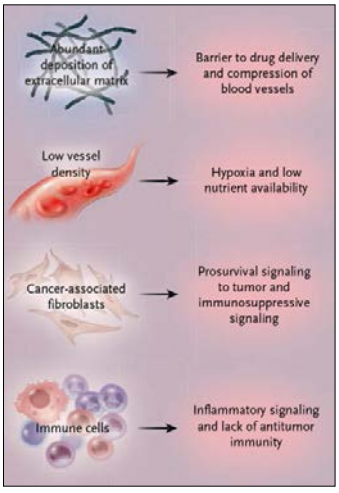


$KRas^{G12D}$;$p53^{R172H}$ mutations

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

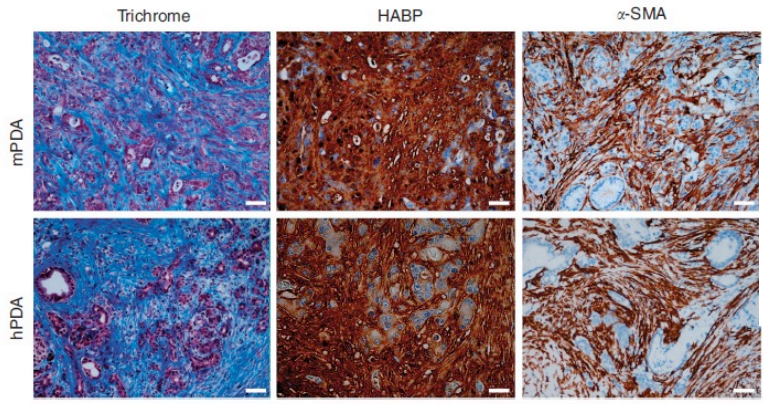
Pancreatic cancer: a paradigm for tumor-host interaction



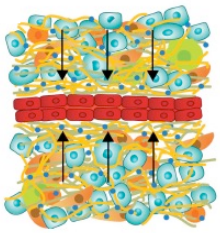


Bardeesy et al. NEJM 2014

The desmoplastic stroma in PDA



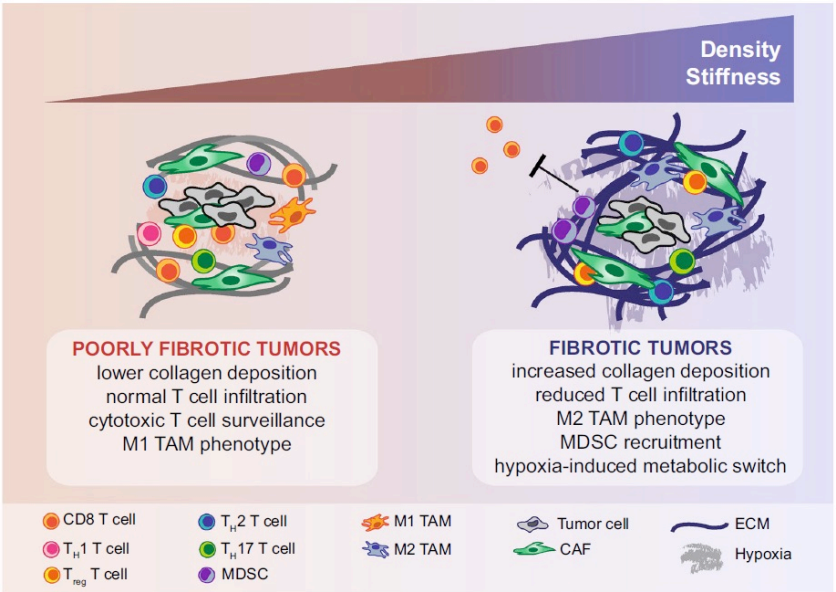
Collagen | Hyaluronic acid binding protein | Smooth muscle actin



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

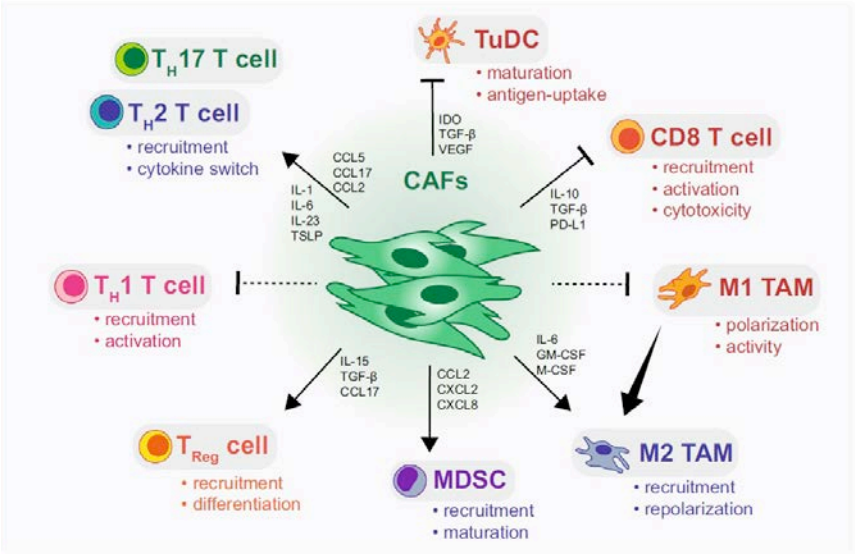
Provenzano et al., 2013

Regulation by Fibrotic ECM



Jiang et al., 2017

Regulation by Activated Fibroblasts

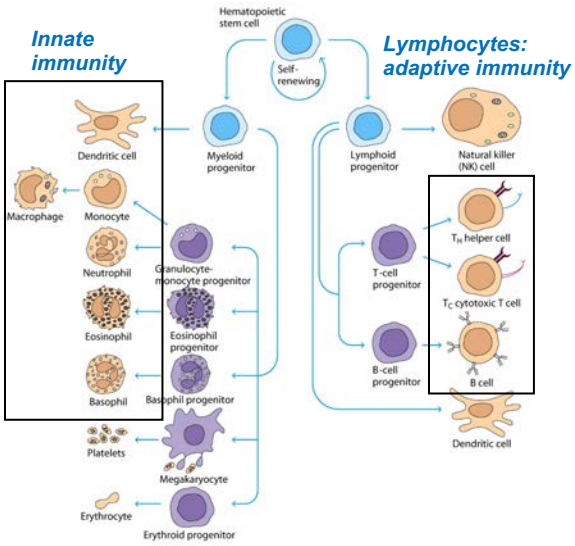


Jiang et al., 2017

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

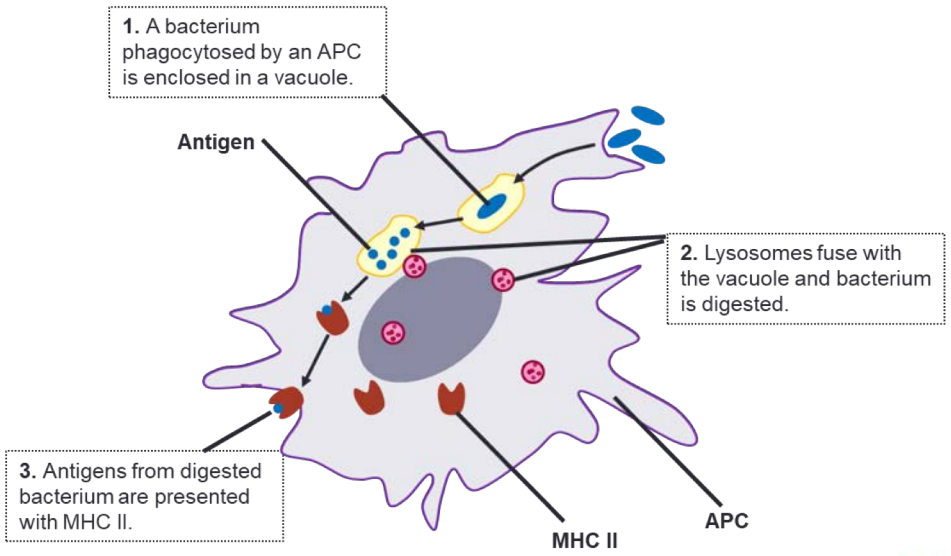
Most blood cells act to fight infection

- 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)

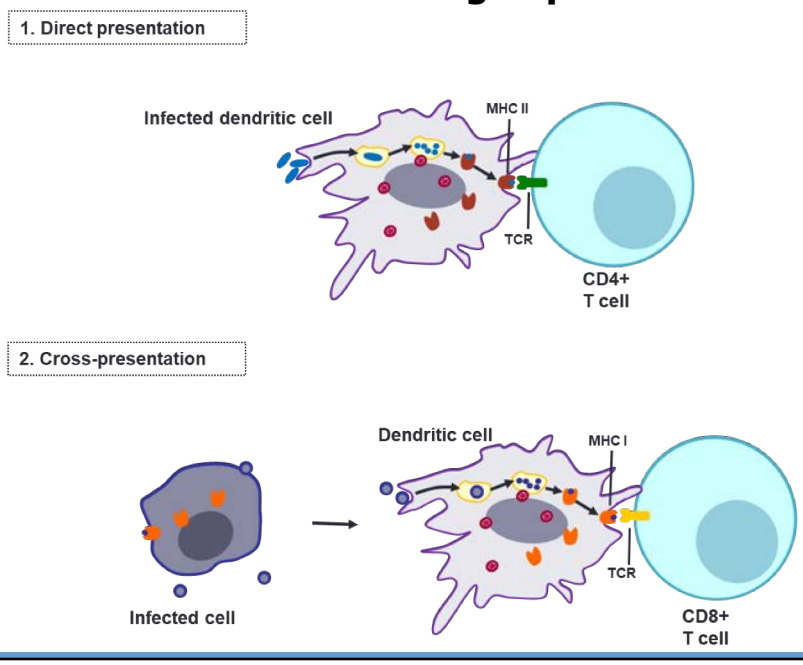


- T helper cells: regulate other immune cells
- T cytotoxic (killer) cells: kill infected cells
- B cells: produce antibodies (immunoglobulin)

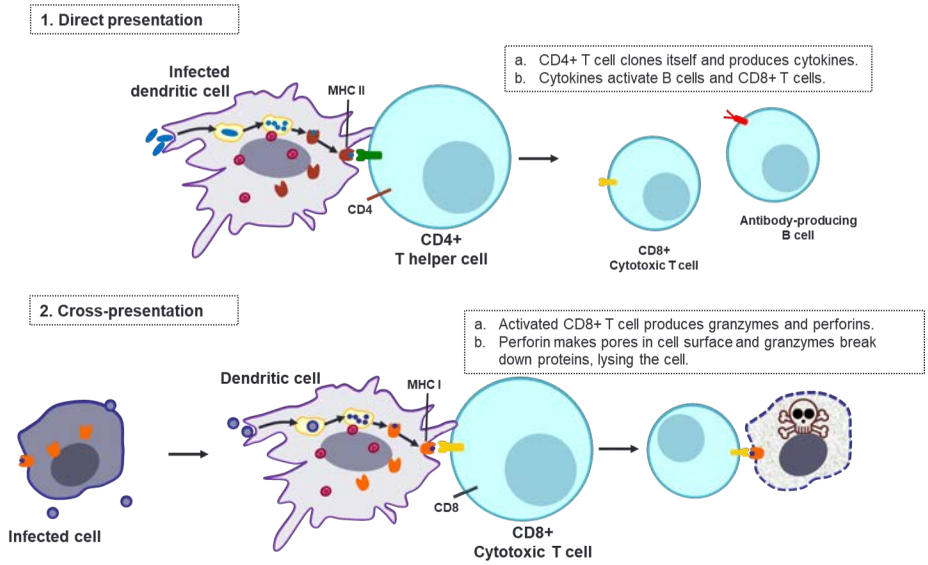
Mechanisms of antigen presentation



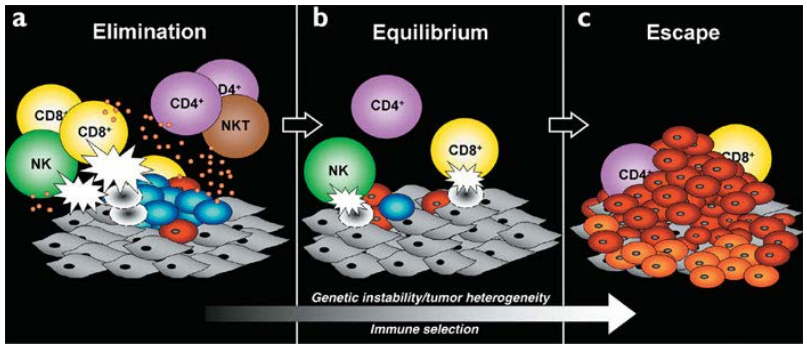
Mechanisms of antigen presentation



Mechanisms of T cell activation by antigens



The 3 E's of cancer immunoediting

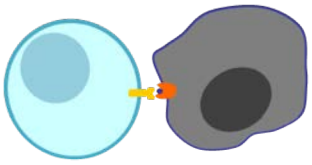


- **Recognition of cancer cells by immune system:**
  - Mutant antigen
  - Ectopic expression of a normal protein

Dunn et al., Nature Immunology 2002

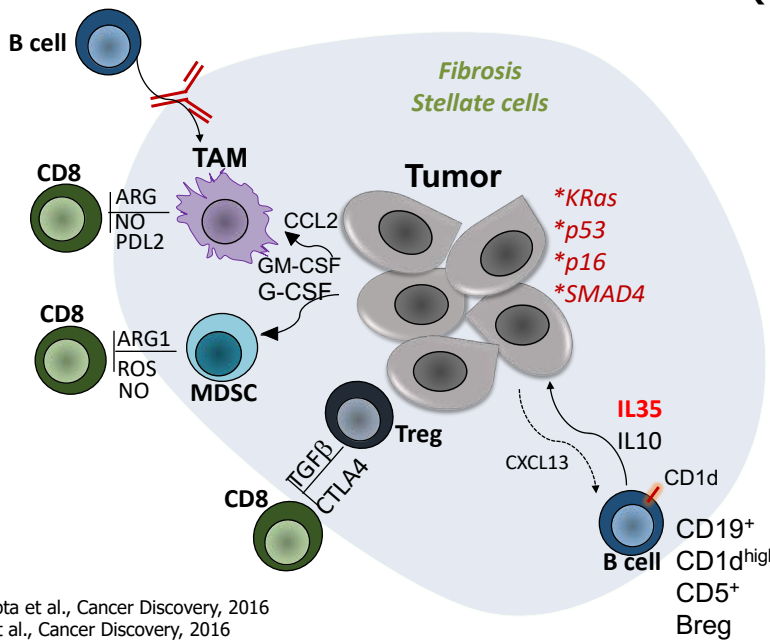
How does cancer escape immune surveillance?

- **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

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Current Immunotherapy approaches

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Drs. Allison and Honjo
Nobel prize in Medicine, 2018

Wolchok and Chan, Nature, 2014

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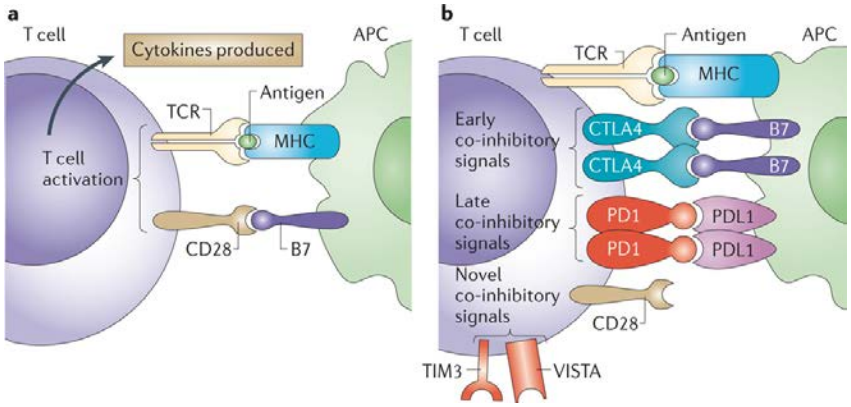
Basic mechanisms of T cell stimulation and inhibition

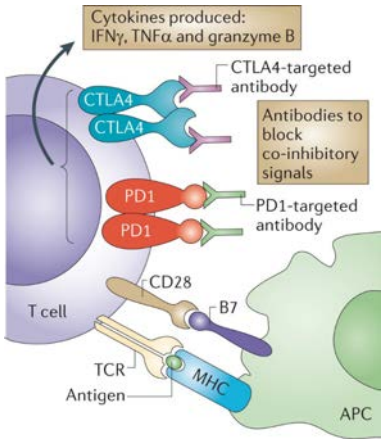


T cell activation

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

Sharma et al, Nature Reviews Cancer, 2011

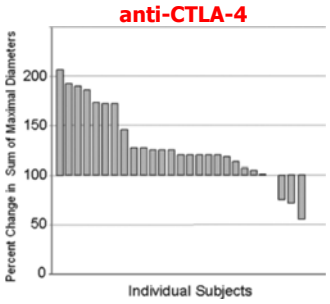
Examples of Current Immunotherapies that induce effector T cell function



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

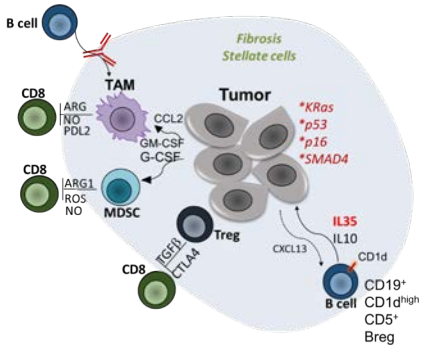
Sharma et al, Nature Reviews Cancer, 2011

Lack of therapeutic efficacy for checkpoint blockade monotherapy



Maximal response in sum of maximal diameters of index lesions

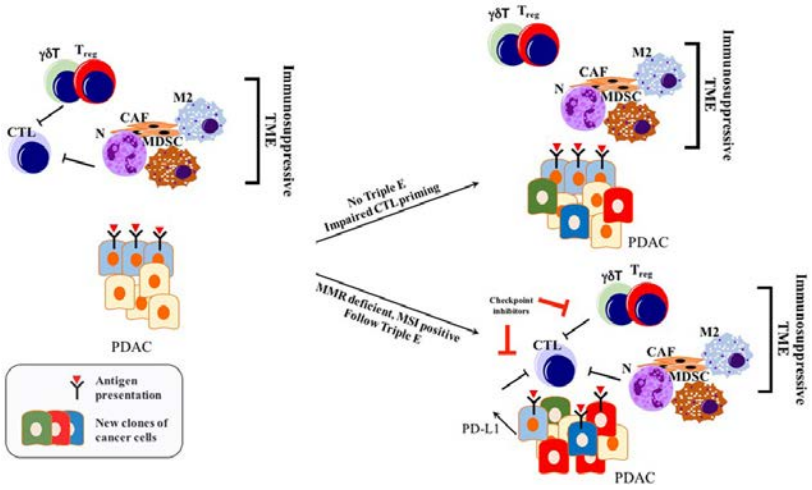
- **No objective responses in PDAC patients (14) on anti-PD-L1 monotherapy**



- **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

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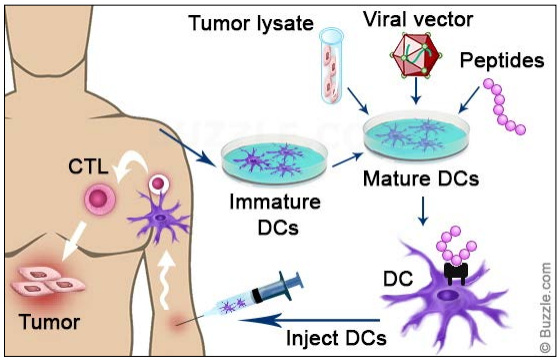
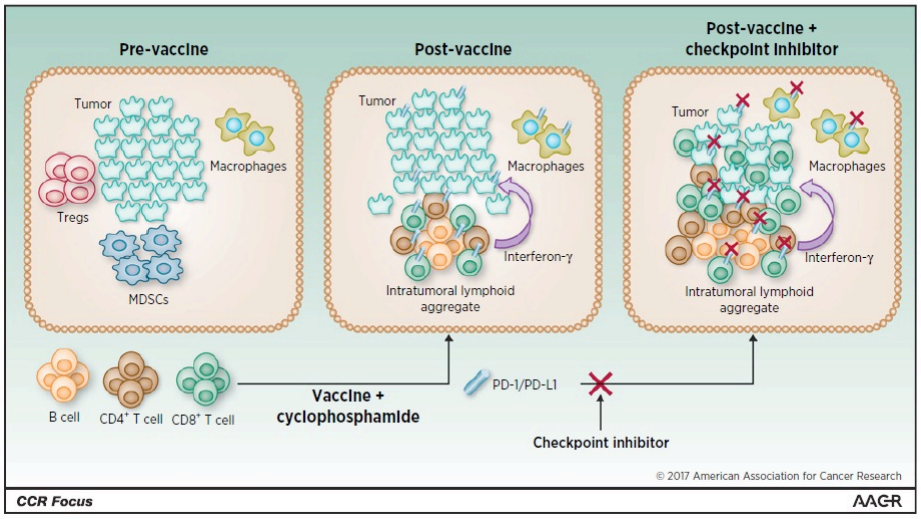


Proposed vaccine benefits in pancreatic cancer



- 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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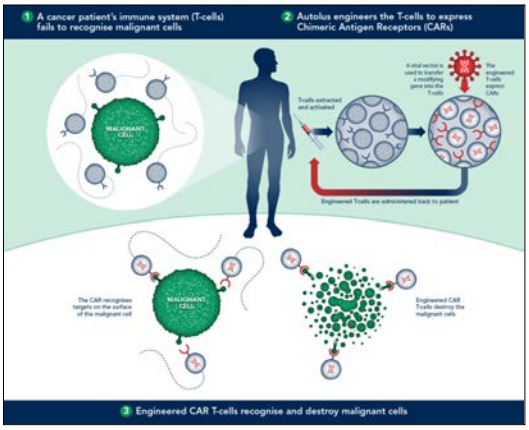

Challenges

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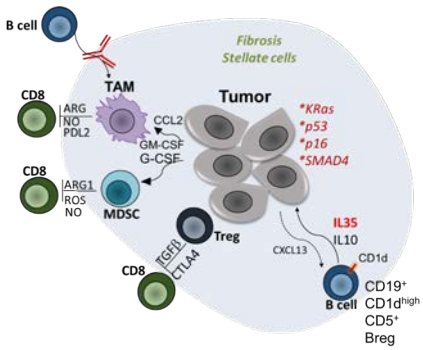
  - 'Designer' T cells (CAR T cells, enhanced TCR cells)
- **Block suppressive mechanisms:**
  - **Block or deplete immunosuppressive cells**
  - Resolve fibrosis



- 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

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 NCT02465060). 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 (NCT27037072).

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.

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Current Immunotherapy approaches in pancreatic cancer

Vaccines
- Algenpantucel-L
- GVAX
- CRS-207
- NY-ESO-1

Checkpoint Modulators
- Ipilimumab (CTLA-4)
- MEDI4736, Pembrolizumab (PD-1)
- MPDL3280A (PDL-1)
- PF-05082566, Urelumab (anti-4-1BB/CD137)
- INCB024360 (IDO-1)
- INCB39110 (JAK-1)

Cytokines
- Peg IL-10

T Reg Depletion
- Low dose cyclophophamide
- Metronomic chemotherapy
- Anti-CD25

Adaptive T Cell Transfer
- CAR T cells - mesothelin
- NY-ESO-1
- Anti-MAGE-A3-DP4

Javle et al., 2016

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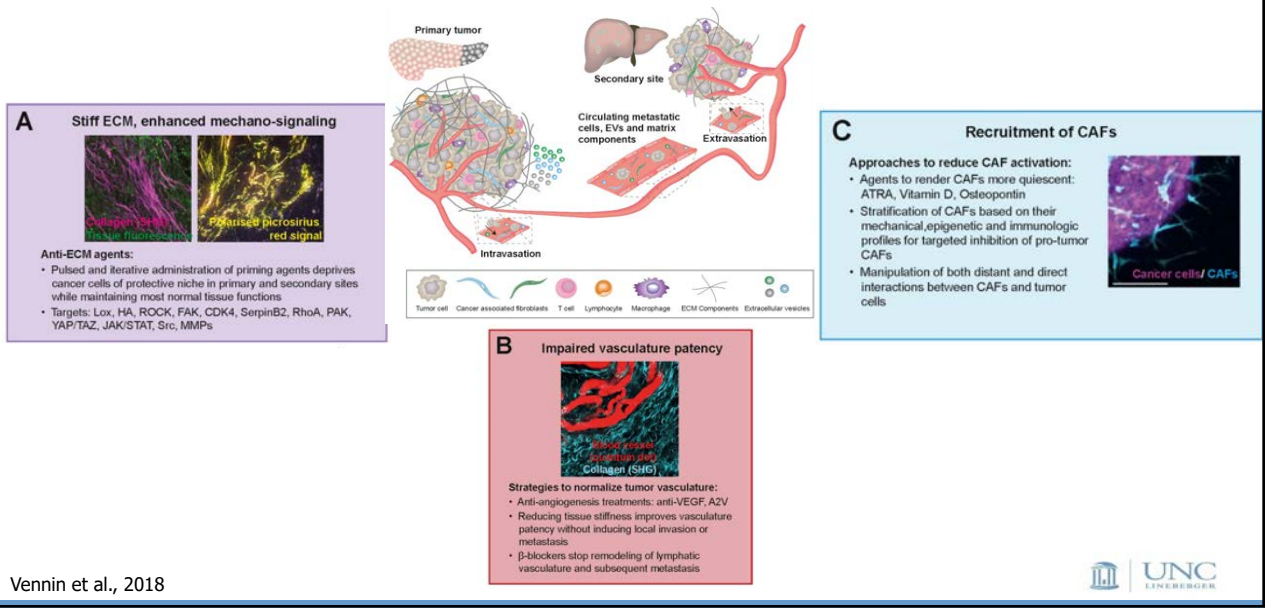
Stromal therapy in pancreatic cancer



Vennin et al., 2018

Combination of Immune Checkpoint Inhibitors With Untargeted Therapeutic Options

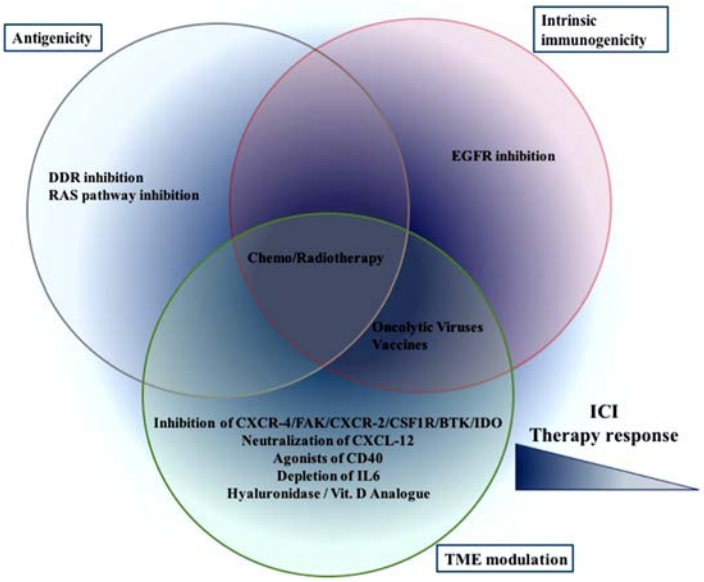


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TABLE 3 | Selection of currently ongoing clinical trials evaluating CTLA4 or/and PD1/PD-L1 checkpoint blockade in combination with untargeted and targeted options including other immunotherapeutic approaches for pancreatic cancer as indicated.

Combination strategy/target	Compounds	Entity	Phase	Trial ID
Chemotherapy	Gemcitabine + ipilimumab (CTLA-4-Ab)	Advanced pancreatic cancer	Ib	NCT01473940
	Nab-paclitaxel (±gemcitabine) + nivolumab (PD-1-Ab)	Advanced/metastatic pancreatic adenocarcinoma (next to NSCLC and mBC)	I	NCT02309177
	mFOLFOX6 + pembrolizumab (PD-1-Ab) [+celecoxib (COX-2-inh.) for non-responders]	Advanced gastrointestinal-cancer including pancreatic cancer	I	NCT02268825
Radiotherapy	SBRT 6 Gy × 5 days + durvalumab (PD-L1-Ab), vs. tremelimumab (CTLA-4-Ab) vs. both combined	Unresectable, non-metastatic pancreatic cancer	Ib	NCT02868632
	SBRT 5 Gy × 5 days vs. 8 Gy × 1 day + durvalumab (PD-L1-Ab), vs. tremelimumab (CTLA-4-Ab) vs. both combined	Unresectable pancreatic cancer	I/II	NCT02311361
	Radiotherapy (not defined) + nivolumab (PD-1-Ab) and ipilimumab (CTLA-4-Ab)	Pancreatic cancer, progressed on chemotherapy (next to CRC)	II	NCT03104439
	45–50.4 Gy + PD-1-Ab (not defined)	Unresectable pancreatic cancer	II	NCT03374293
Vaccines	GVAX/Cy ± nivolumab (PD-1-Ab)	Neoadjuvant/adjuvant for resectable pancreatic cancer	I/II	NCT02451982
	GVAX/Cy + CRS-207 ± nivolumab (PD-1-Ab)	Previously treated metastatic pancreatic adenocarcinoma	II	NCT02243371
	CRS-207 (±GVAX/Cy) + nivolumab (PD-1-Ab) and ipilimumab (CTLA-4-Ab)	Previously treated pancreatic cancer	II	NCT03190265
Chemotherapy + vaccine	Capecitabine + CV301 + durvalumab (PD-L1-Ab)	Metastatic pancreatic cancer (next to CRC)	I/II	NCT03376659
Chemotherapy + Vit. D analog	Paricalcitol (vitamin D analog) + pembrolizumab (PD-1-Ab) ± gemcitabine/nab-paclitaxel	Resectable pancreatic cancer, neoadjuvant setting	I	NCT02930902
Chemotherapy + FAK	Defactinib (FAK-inh.) + gemcitabine + pembrolizumab (PD-1-Ab)	Advanced solid tumors	I	NCT02546531
Chemotherapy + CD40	Gemcitabine/nab-paclitaxel + APX005M (CD40-ago.-Ab) ± nivolumab (PD-1-Ab)	Untreated metastatic pancreatic adenocarcinoma	II	NCT03214250
Chemotherapy + CSF1R	Cabiralizumab (CSF1R-Ab) + nivolumab (PD-1-Ab) ± different chemotherapeutic regimens	Pretreated, progressed metastatic pancreatic adenocarcinoma	II	NCT03336216
Radiotherapy + vaccine	SBRT 6.6 Gy × 5 days + GVAX/Cy + nivolumab (PD-1-Ab)	Borderline resectable pancreatic cancer, no previous therapy	II	NCT03161379
Radiotherapy + vaccine	SBRT 6.6 Gy × 5 days + GVAX/Cy + pembrolizumab (PD-1-Ab)	Locally advanced pancreatic cancer	II	NCT02648282
CSF1R + vaccine	IMC-CS4 (CSF1R-Ab) + GVAX/Cy + pembrolizumab (PD-1-Ab)	Borderline resectable pancreatic adenocarcinoma	I	NCT03153410
IDO1 + vaccine	Epacadostat (IDO1-inh.) + CRS-207 (±GVAX/Cy) + pembrolizumab (PD-1-Ab)	Metastatic pancreatic cancer progressed on prior chemotherapy	II	NCT03006302
ACT	Autologous TIL, ipilimumab (CTLA-4-Ab), nivolumab (PD-1-Ab), proleukin, Cy., fludara	Cancer patients across all diagnoses	I/II	NCT03296137

Ab, antibody; inh., inhibitor; ago., agonist; CRC, colorectal cancer; CRS-207, Listeria-based mesothelin vaccine; CV301, CEA/MUC1 prime-boost vaccine based on modified vaccinia Ankara-Bavarian Nordic (MVA-BN), a recombinant fowlpox viral vector (foe the boost) and TRICOM, which is comprised of three costimulatory molecules B7-1, ICAM-1, and LFA-3; Cy, cyclophosphamide; GVAX, irradiated pancreatic cancer cells, genetically modified to express GM-CSF; IDO1, indoleamine 2,3-dioxygenase 1; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy; ACT, adoptive cell therapy; TIL, tumor-infiltrating lymphocyte; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1.

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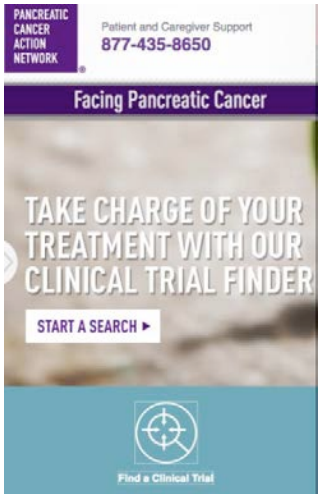

- Over 170 pancreatic cancer specific studies listed in Clinical Trial Finder
- Over 115 pancreatic cancer specific studies listed in Clinical Trial Finder for metastatic pancreatic cancer

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