TRACO-2018

Pancreatic Cancer: Current Understanding and Future Challenges

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Laboratory of Human carcinogenesis
Center for Cancer Research

Cancer incidence and mortality

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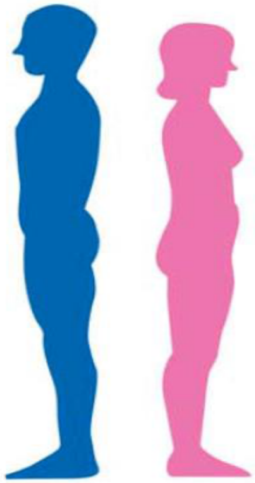
Pancreatic Cancer Incidence and Mortality

Estimated Deaths

Siegel R et. al., CA Cancer J Clin, 65, 2015

Males				Females		
Lung & bronchus	86,380	28%		Lung & bronchus	71,660	26%
Prostate	27,540	9%		Breast	40,290	15%
Colon & rectum	26,100	8%		Colon & rectum	23,600	9%
Pancreas	20,710	7%		Pancreas	19,850	7%
Liver & intrahepatic bile duct	17,030	5%		Ovary	14,180	5%
Leukemia	14,210	5%		Leukemia	10,240	4%
Esophagus	12,600	4%		Uterine corpus	10,170	4%
Urinary bladder	11,510	4%		Non-Hodgkin lymphoma	8,310	3%
Non-Hodgkin lymphoma	11,480	4%		Liver & intrahepatic bile duct	7,520	3%
Kidney & renal pelvis	9,070	3%		Brain & other nervous system	6,380	2%
All Sites	**312,150**	**100%**		**All Sites**	**277,280**	**100%**



- **4th Leading Cause of Cancer Deaths in the United States.**
- **Median Survival < 6 Months.**
- **Estimated 48,960 New Cases and 40,560 Deaths in 2015.**
- **No Effective Treatment.**

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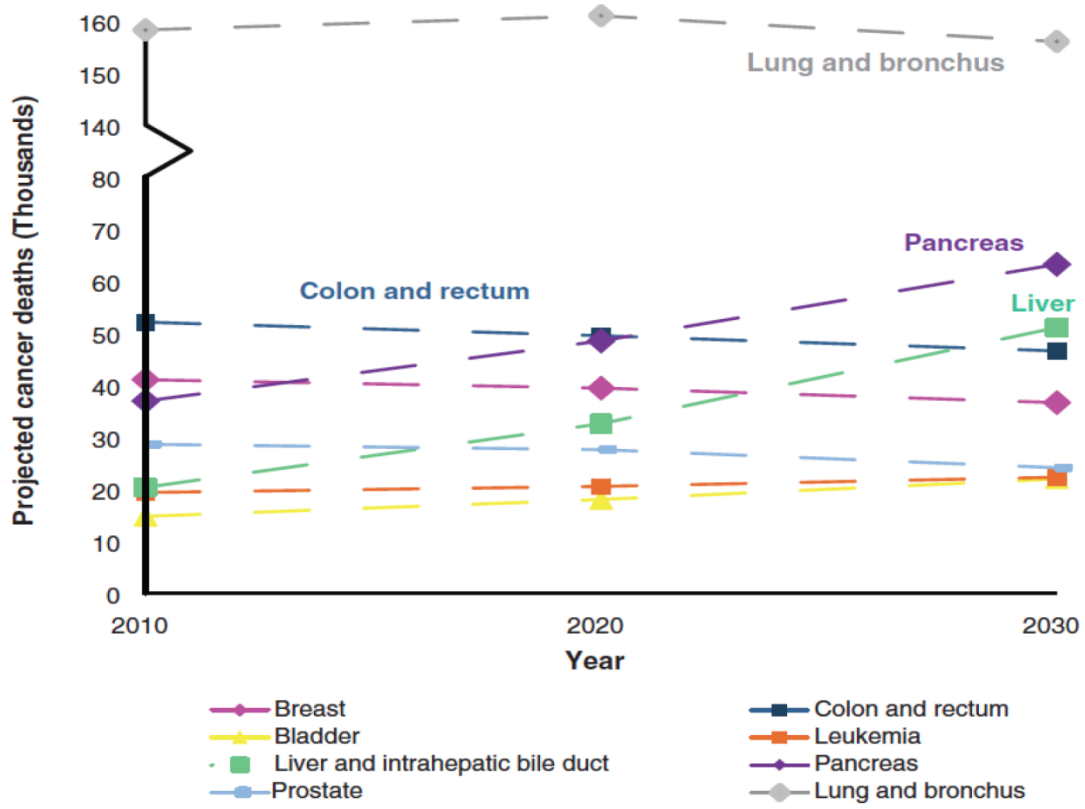
Pancreatic cancer deaths are increasing

Pancreatic Cancer: Second Leading Cause of Cancer-related Death by 2030



Rahib, L., et. al., Cancer Res., 74, 2913-21, 2014

Risk factors

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Risk Factors and Inherited Syndromes

Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

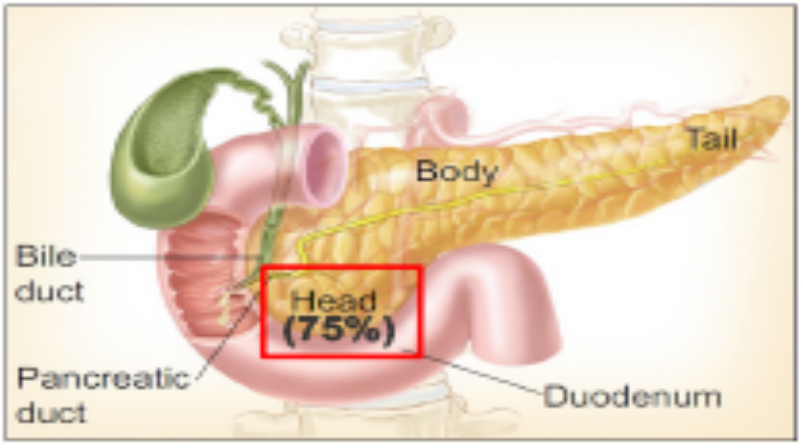
Variable	Approximate Risk
Risk factor	
Smoking[3]	2–3
Long-standing diabetes mellitus[4]	2
Nonhereditary and chronic pancreatitis[5]	2–6
Obesity, inactivity, or both[6]	2
Non–O blood group[7]	1–2
Genetic syndrome and associated gene or genes — %	
Hereditary pancreatitis (*PRSS1, SPINK1*)[8]	50
Familial atypical multiple mole and melanoma syndrome (*p16*)[9]	10–20
Hereditary breast and ovarian cancer syndromes (*BRCA1, BRCA2, PALB2*)[10,11]	1–2
Peutz–Jeghers syndrome (*STK11* [*LKB1*])[12]	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (*MLH1, MSH2, MSH6*)[13]	4
Ataxia–telangiectasia (*ATM*)[14]	Unknown
Li–Fraumeni syndrome (P53)[15]	Unknown

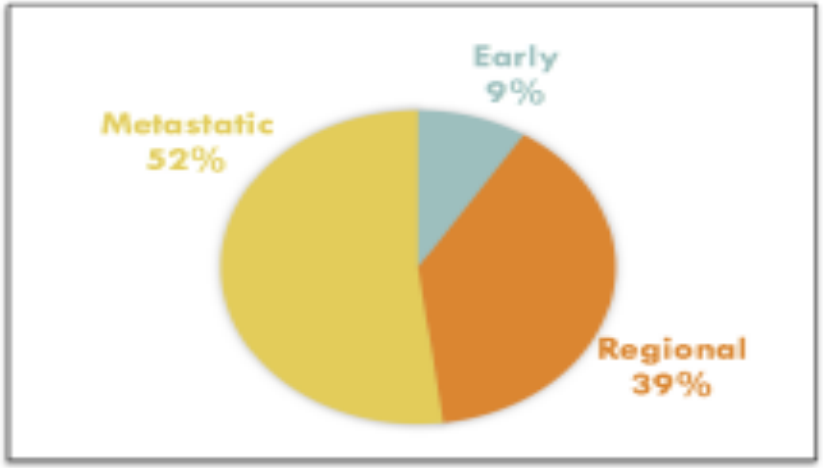
* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

Ryan, Hong and Bardeesy, NEJM, 371, 2014

Pancreatic cancer types

Pancreatic Cancer: Types and Stage at Diagnosis





American Cancer Society, *Cancer Facts and Figures 2017*

- Adenocarcinoma (~90%)
- Neuroendocrine (<5%)
- Mucinous
- Acinar Cell Carcinoma

Most patients have advanced disease at diagnosis

Cancer of the Pancreas, NIH Publication No. 10-1560, 2010

Pancreatic cancer patient treatment

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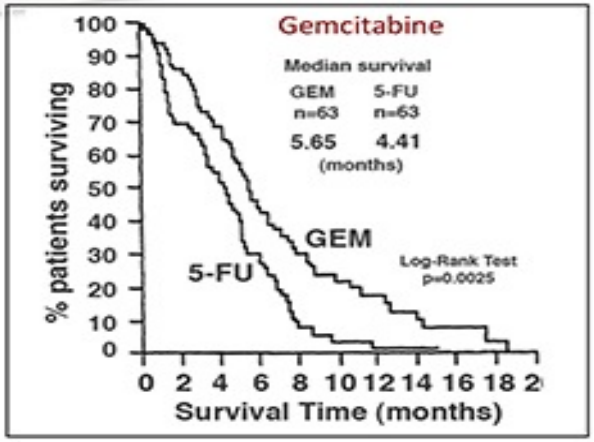
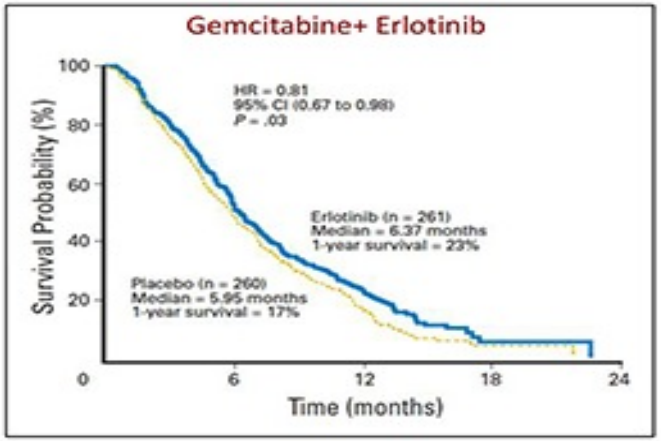
Disappointing Progress in the Treatment of Pancreatic Cancer

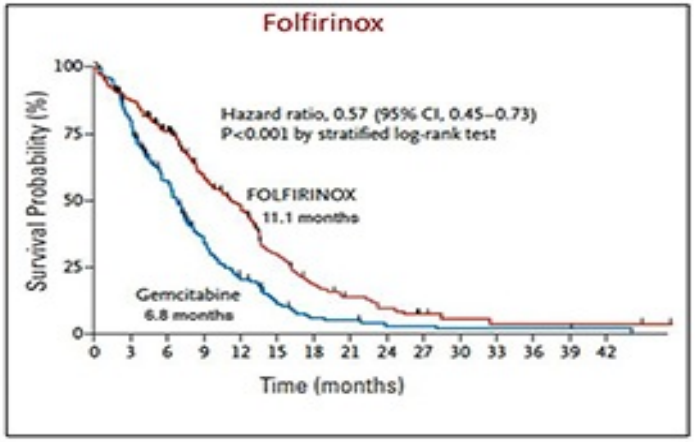
Burris et. al., J. Clin. Oncol., 15, 1997



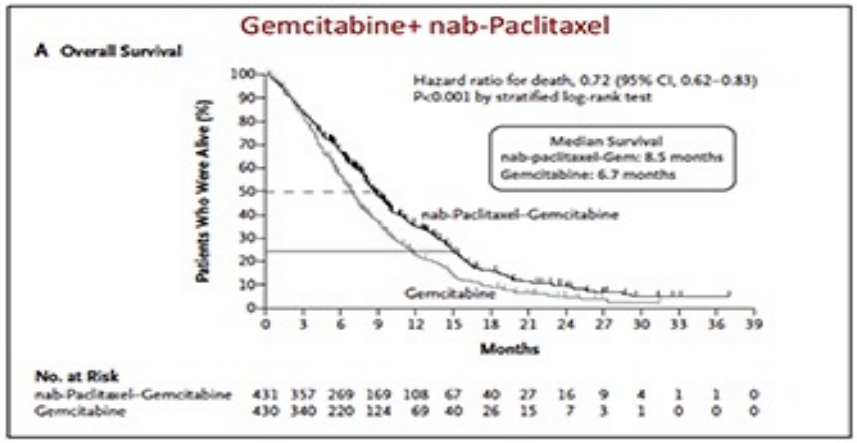
Moore et. al., J. Clin. Oncol. 25, 2007



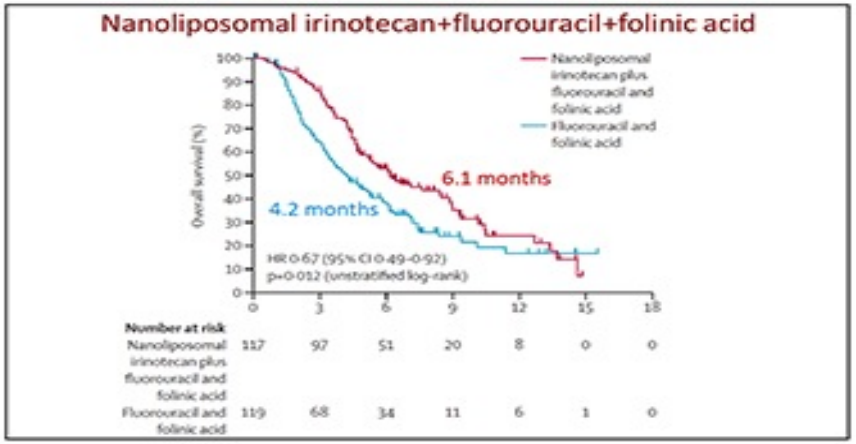
Conroy et. al., NEJM, 36, 2011



Von Hoff, D.D. et. al, NEJM, 369, Oct, 2013



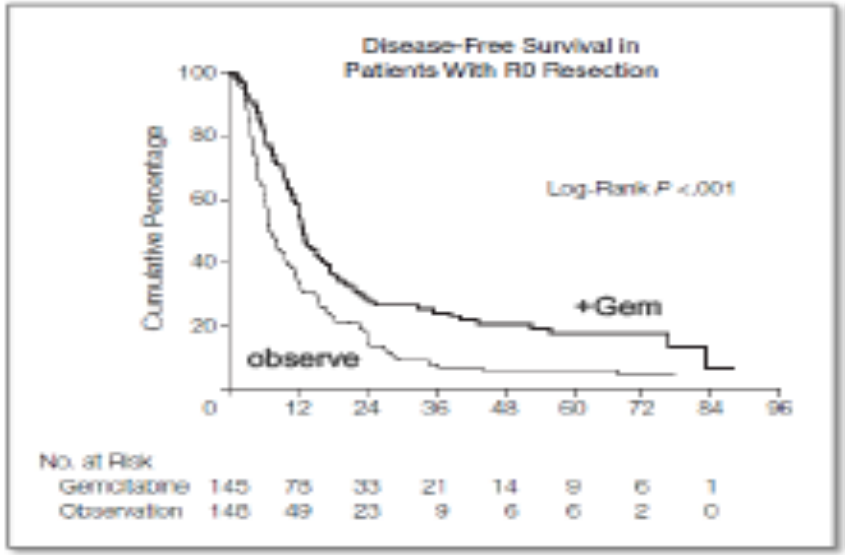
Wang-Gillam A., et. al., Lancet, Nov 20, 2015



Early stage disease

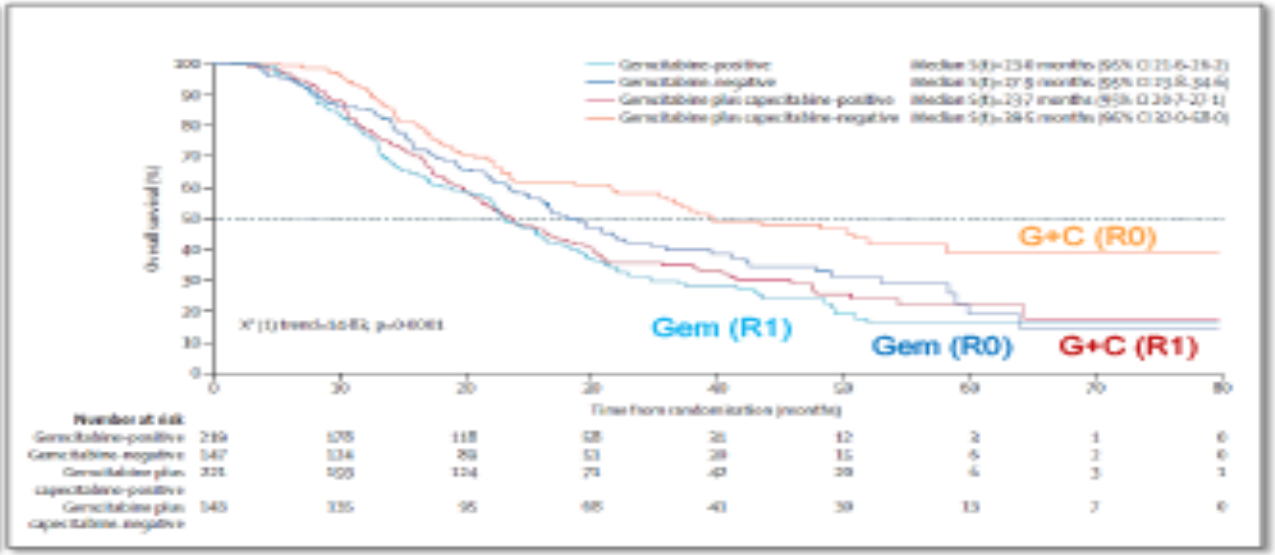
Early Stage Disease: Surgery + Chemotherapy

CONKO-001



Oettle et al, *JAMA*, 2007

ESPAC-4



Neoptolemos et al, *Lancet*, 2017

CONKO-001: Charite Onkologie 001
ESPAC-4: European study Group for Pancreatic Cancer

Resected pancreatic cancer

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Improved Survival in Resected Pancreatic Cancer Cases

Late Diagnosis

Poor Therapeutic Response

Dismal Outcome
(Median Survival < 6 mo)

(18-20%)

Resectable Cases
(Median Survival < 2 yrs)

- Stage
- Grade
- Lymph Node Spread
- Resection Margin

(~12%)

5 yr Survival

Molecular Differences in Tumors Determine Patient Outcome?

Neoantigens and pancreatic cancer

LETTER

doi:10.1038/nature24462

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

Vinod P. Balachandran[1,2,3], Marta Łuksza[4], Julia N. Zhao[1,2,3], Vladimir Makarov[5,6], John Alec Moral[1,2,3], Romain Remark[7], Brian Herbst[2], Gokce Askan[2,8], Umesh Bhanot[8], Yasin Senbabaoglu[9], Daniel K. Wells[10], Charles Ian Ormsby Cary[10], Olivera Grbovic-Huezo[2], Marc Attiyeh[1,2], Benjamin Medina[1], Jennifer Zhang[1], Jennifer Loo[1], Joseph Saglimbeni[2], Mohsen Abu-Akeel[9], Roberta Zappasodi[9], Nadeem Riaz[6,11], Martin Smoragiewicz[12], Z. Larkin Kelley[13,14], Olca Basturk[8], Australian Pancreatic Cancer Genome Initiative*, Mithat Gönen[15], Arnold J. Levine[4], Peter J. Allen[1,2], Douglas T. Fearon[13,14], Miriam Merad[7], Sacha Gnjatic[7], Christine A. Iacobuzio-Donahue[2,5,8], Jedd D. Wolchok[3,9,16,17,18], Ronald P. DeMatteo[1,2], Timothy A. Chan[3,5,6,11], Benjamin D. Greenbaum[19], Taha Merghoub[3,9,18]§ & Steven D. Leach[1,2,5,20]§

- Highest neoantigen number
- Abundant CD8+ T Cell Infiltrate
- Neoantigen quality promotes T Cell Activity in Long-term survivor

Balachandran et. al., Nature 551, Nov 2017

Tumor biology

Understanding Pancreatic Tumor Biology is Key to Improving Disease Outcome

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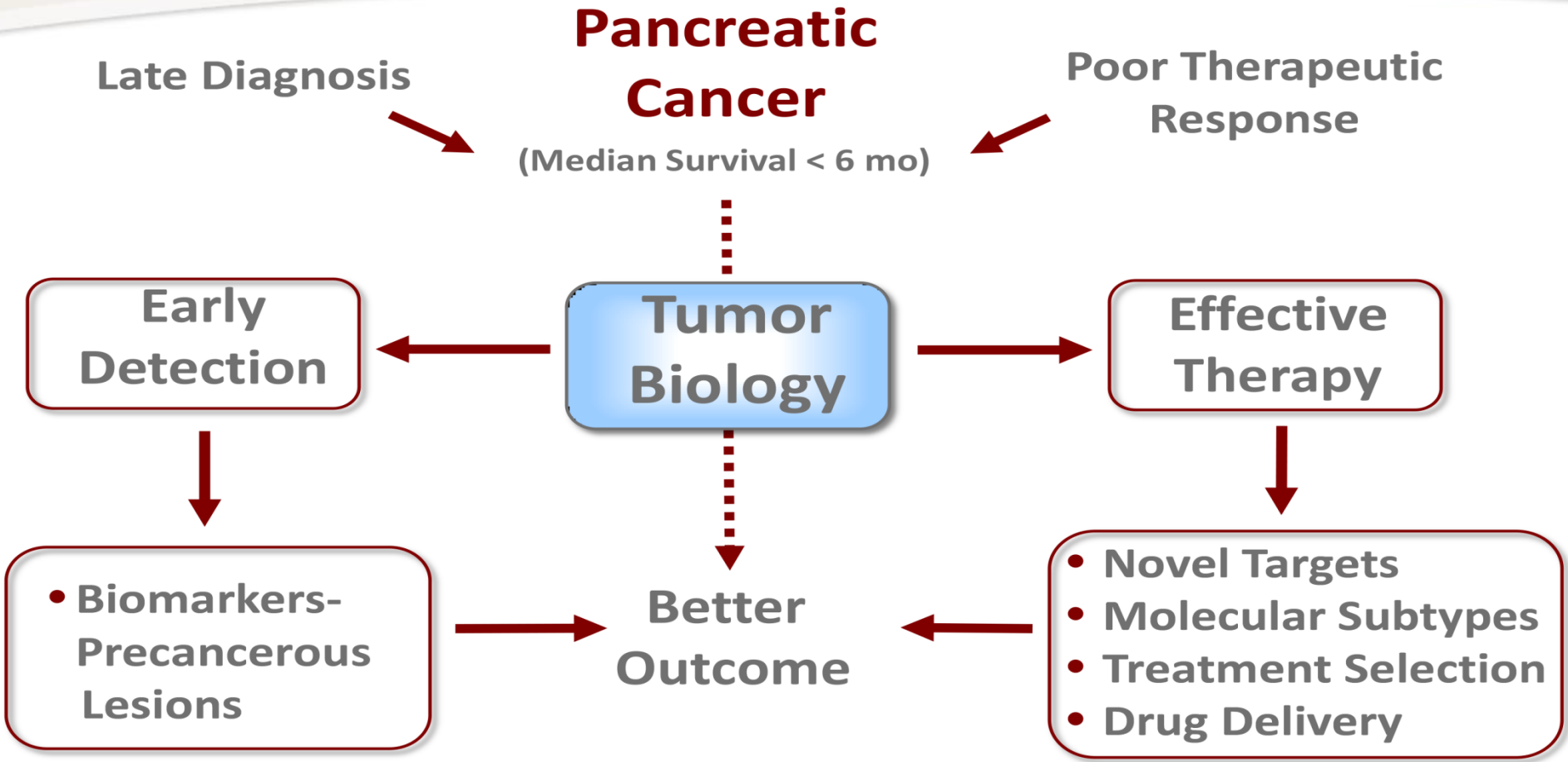

CA19-9

Carbohydrate Antigen 19-9 (CA19-9)

Serum CA19-9 >37 U/ml

Pancreatic Cancer vs Healthy Individual

Sensitivity: 80.3% (95% CI 77.2-82.6)
Specificity: 80.2% (95% CI 78-82.3)

Malignant vs Benign Pancreatic Disease

Sensitivity: 78.2%
Specificity: 82.2%

Pancreatic carcinogenesis

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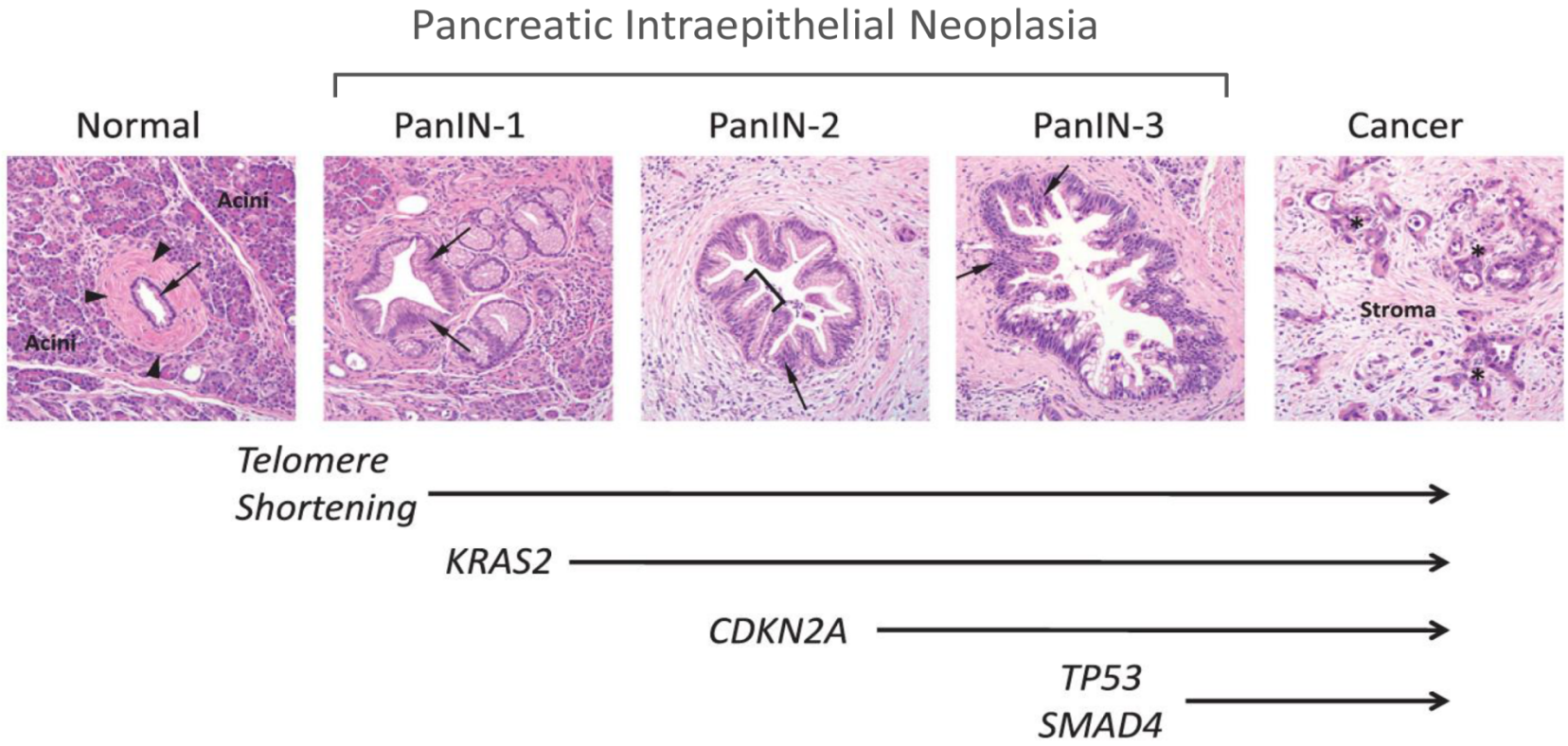
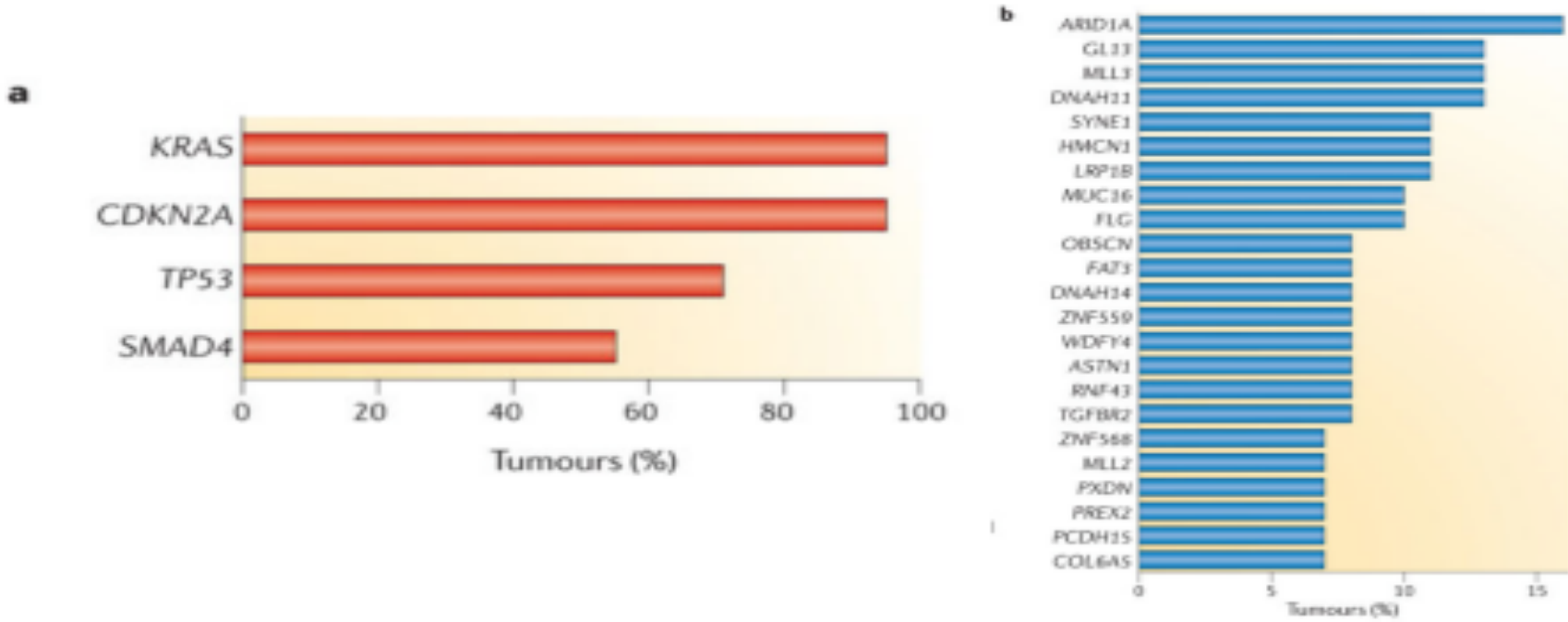
Progression Model of Pancreatic Carcinogenesis



Gene alterations in pancreatic cancer

Gene Alterations in Pancreatic Cancer



Kleeff, J. *et al.* (2016) Pancreatic cancer
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.22

Desmoplastic stroma

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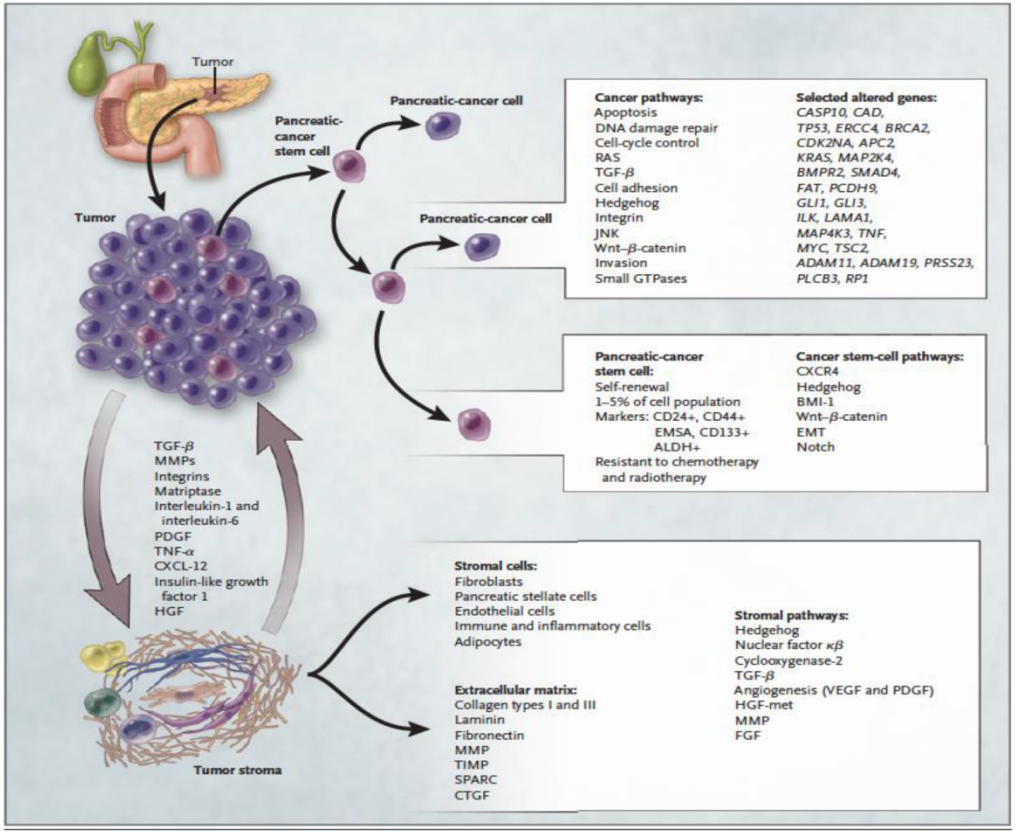
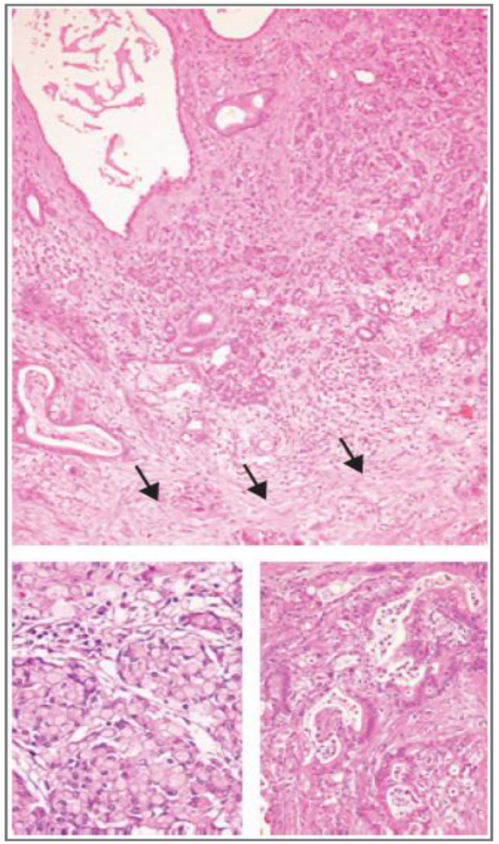
Prominent, Desmoplastic Stroma in Pancreatic Cancer



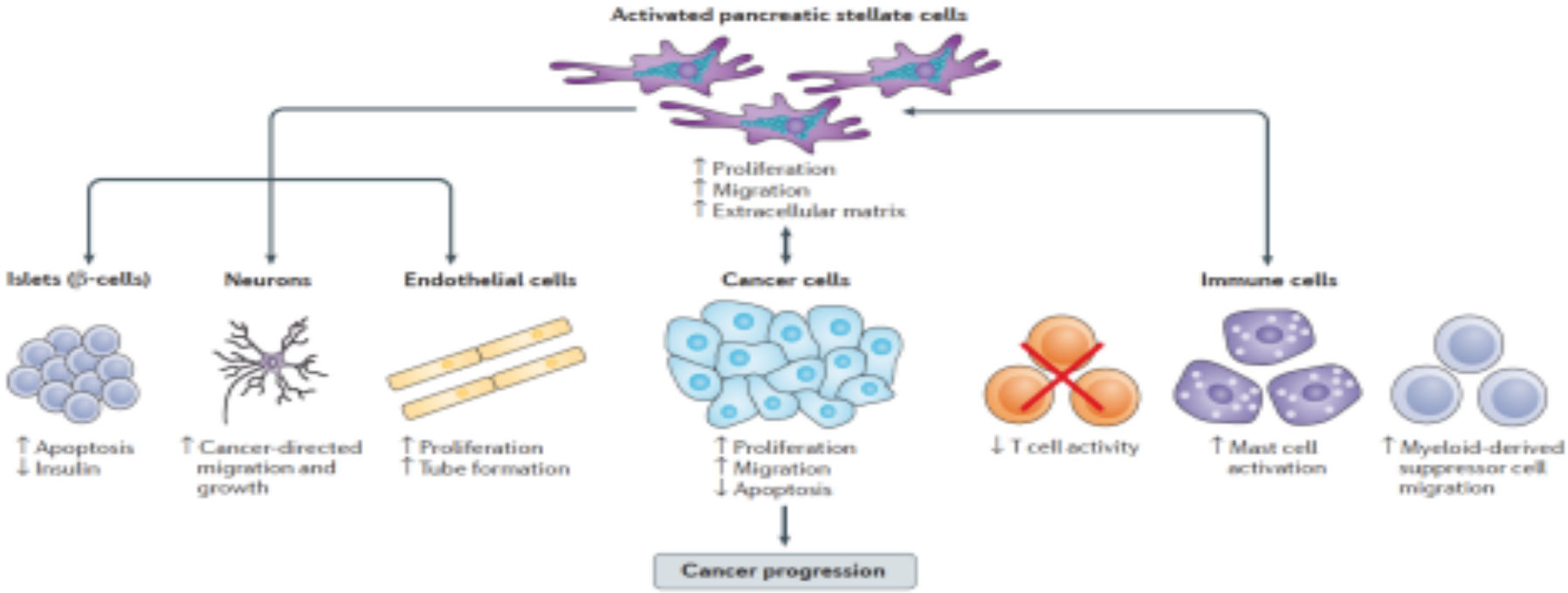


H/E

From: Hidalgo, M., N Engl J Med, 2010

Pancreatic stellate cells

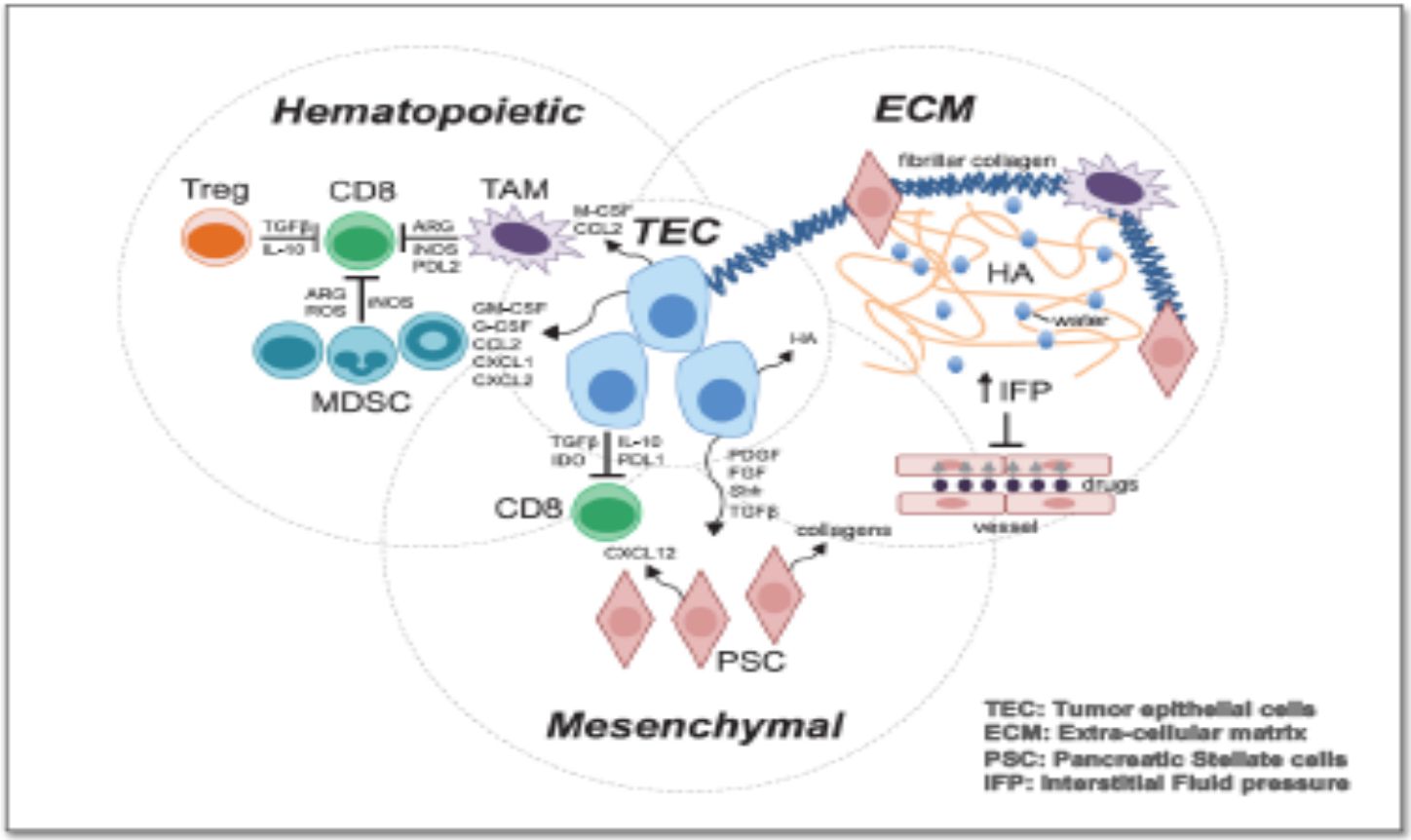
Pancreatic stellate cells regulates desmoplastic stroma



Kleeff, J. *et al.* (2016) Pancreatic cancer
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.22

Complex stromal networks

Complex Stromal Networks Supporting Pancreatic Cancer Progression and Therapeutic Resistance



Stromnes, I.M., et. al., Carcinogenesis, 35, 2014

Biomarkers

Lack of any reliable marker for early detection of Pancreatic Cancer

Glycan-1 positive exosomes

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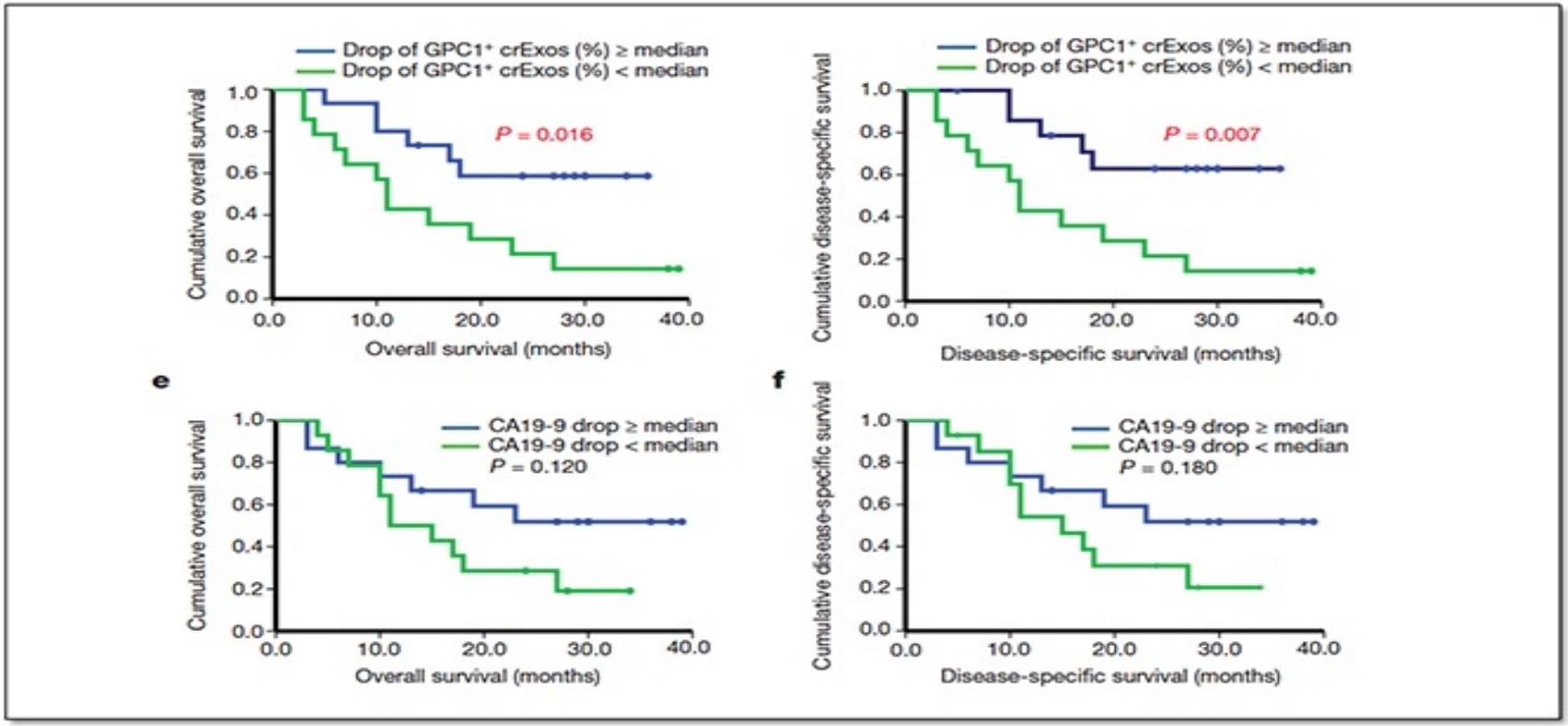
Glypican-1 Positive Circulating Exosomes Predicts Prognosis in Resected PDAC Patients



Melo, S.A., et al., Nature, 523, 2015

Pancreatic cancer and tumor heterogeneity

Tumor heterogeneity and molecular subtyps.

Heterogeneity

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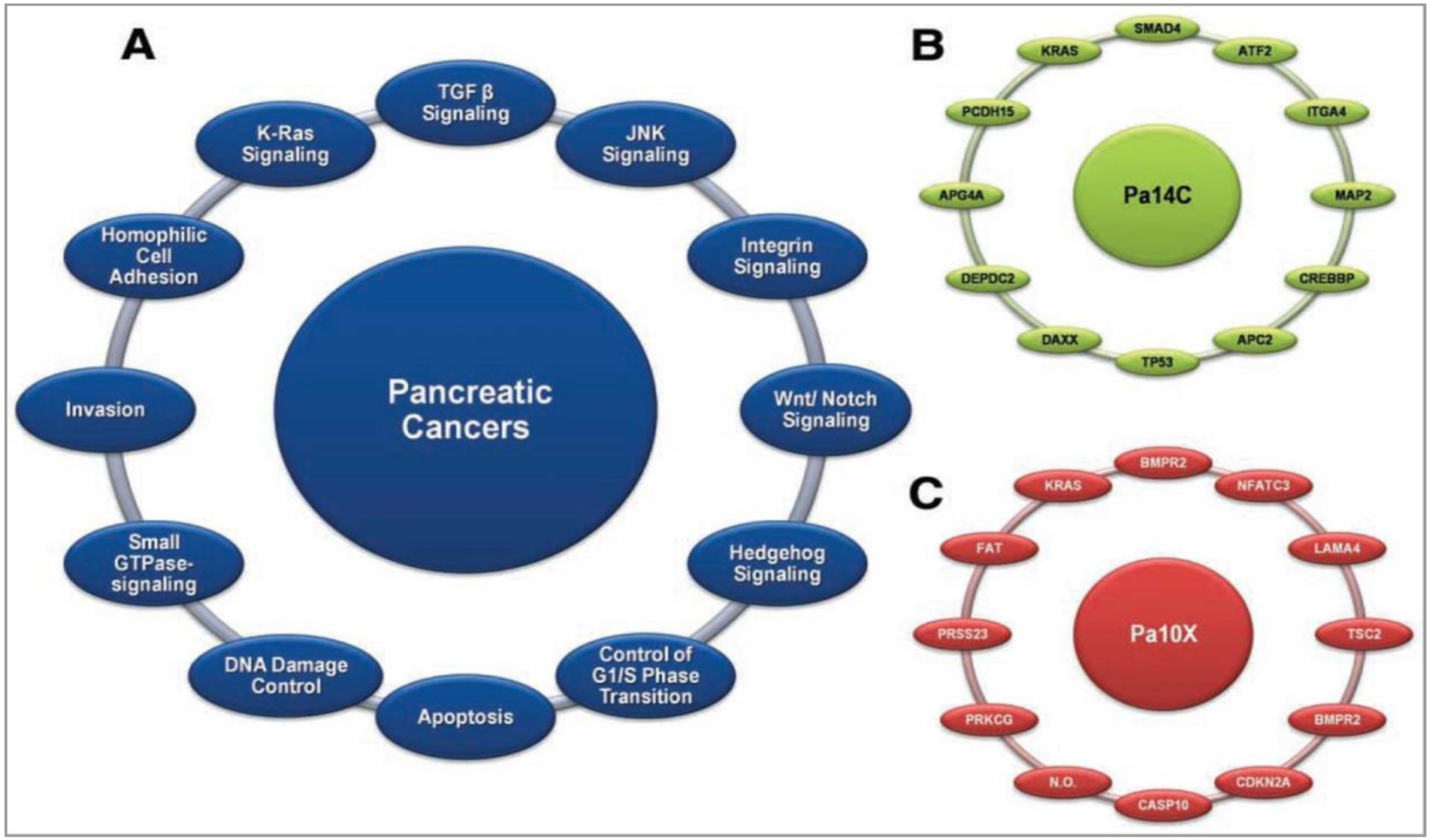
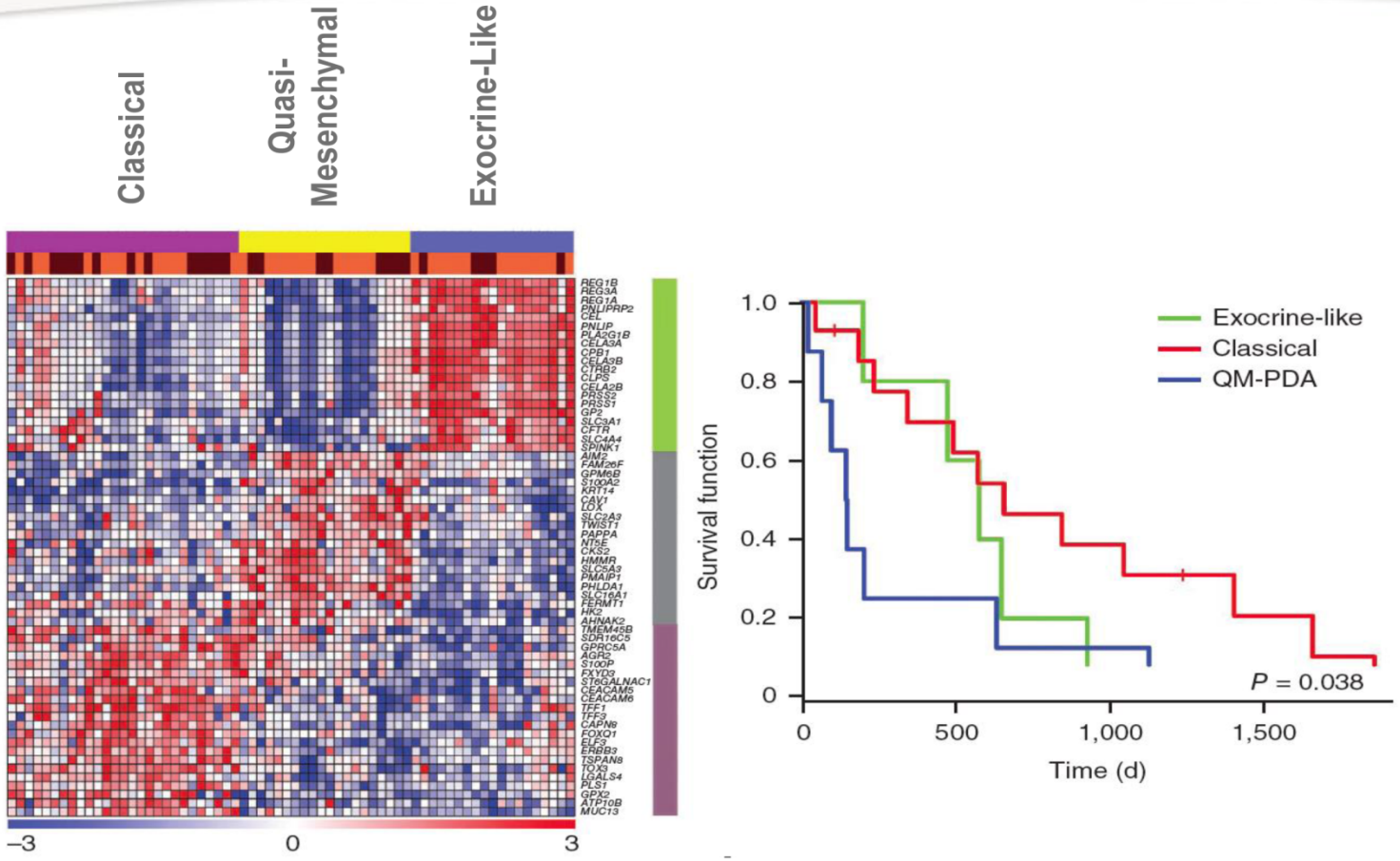
Pancreatic Cancer is Highly Heterogenous



From: Jone, S. et al., Science, 321, 2008

Molecular subtypes

Are There Different Molecular Subtypes of PDAC?



Collison et. al., Nat. Med., 17, 2011

Chromosomal structure

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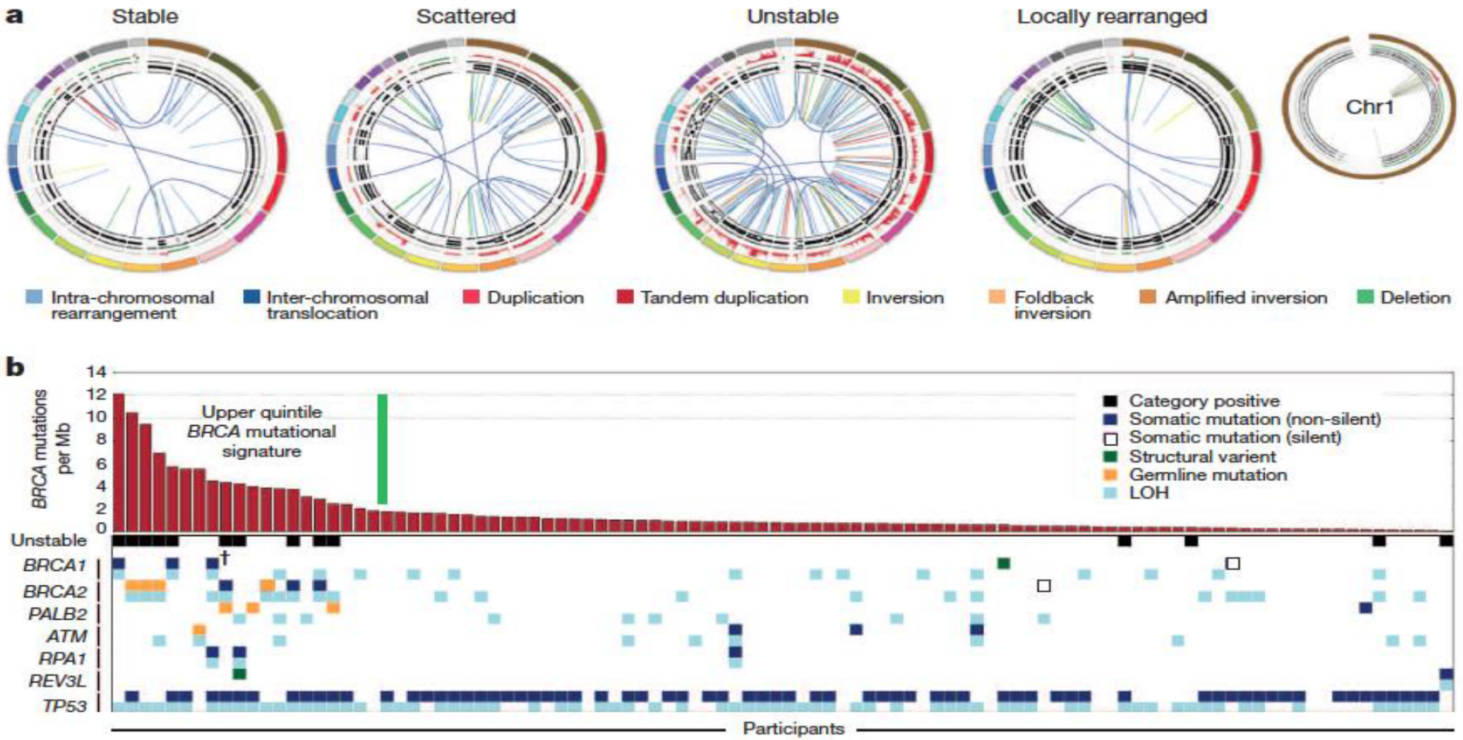
Variations in Chromosomal Structure and PDAC Subtypes



Waddell et. al., Nature, 518, 2015

Stroma specific subtypes

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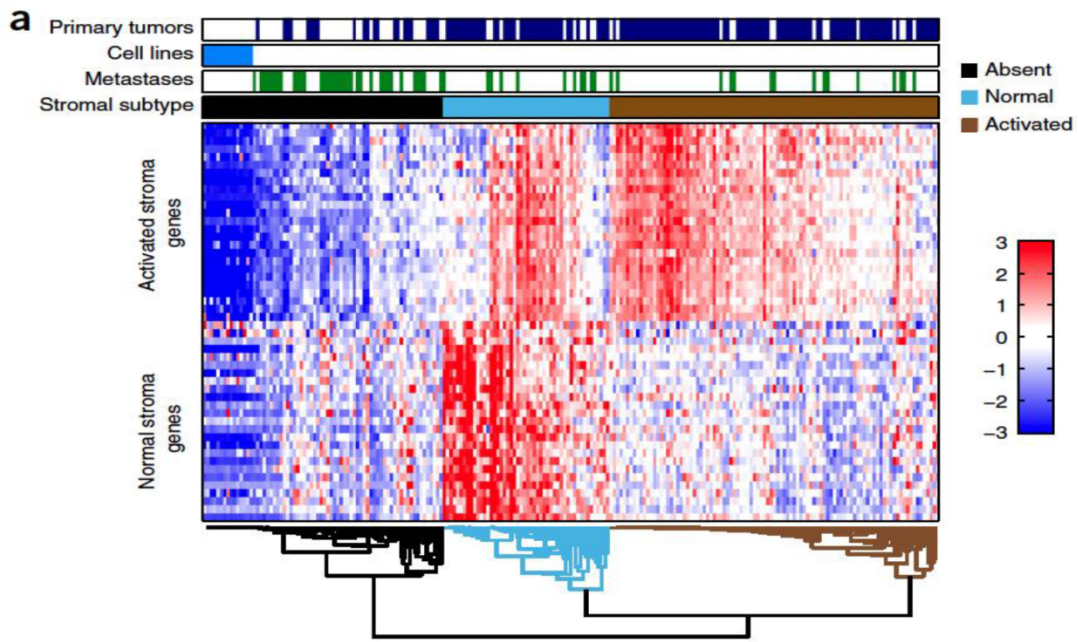
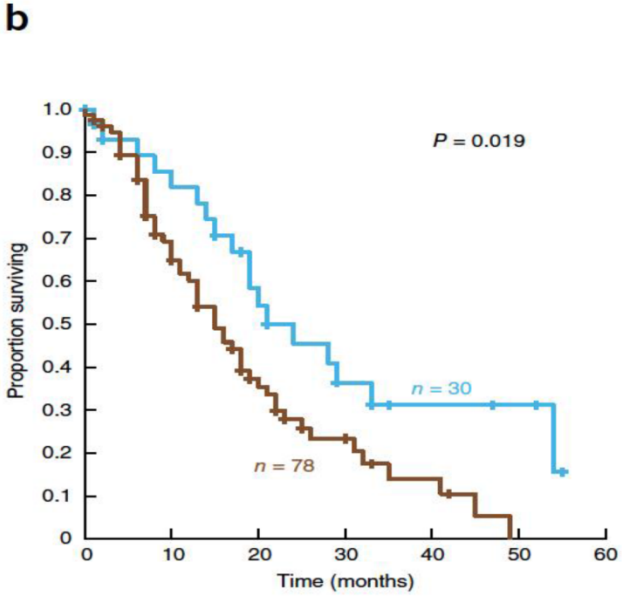
Stroma-Specific Subtypes in Pancreatic Cancer





Moffitt et. al., Nature Genetics, 2015

Four PDAC subtypes

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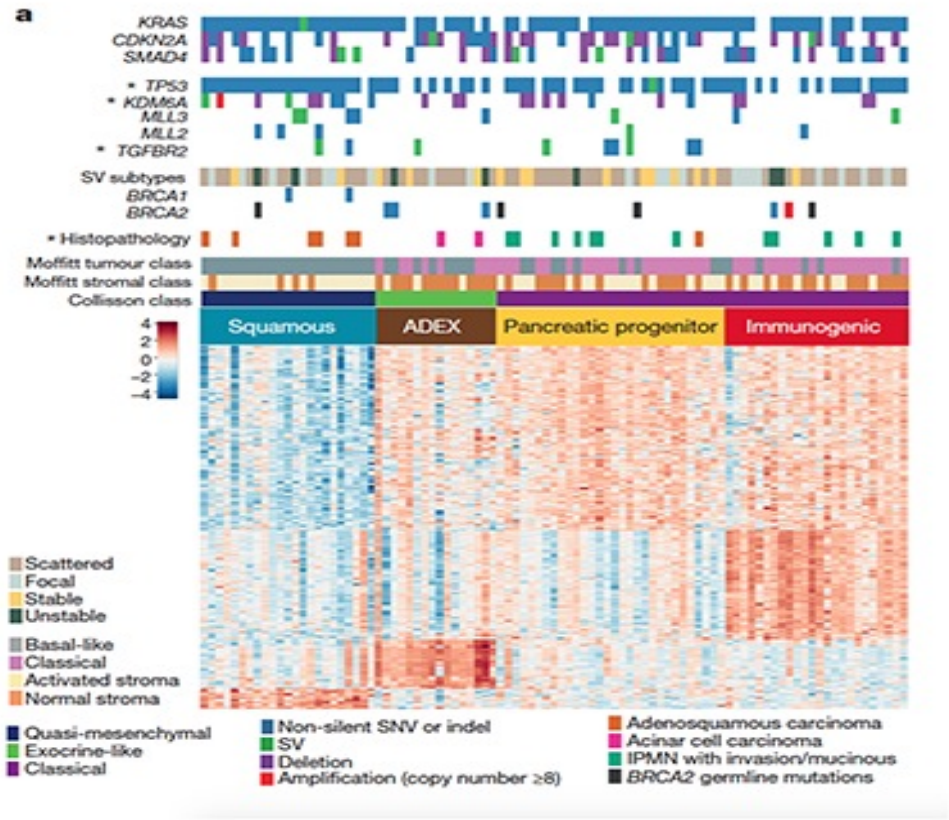
Gene Expression Analysis Identified 4 PDAC Subtypes



(N=456)

Bailey et. al., Nature, 2016

ADEX: Aberrantly differentiated exocrine and endocrine

PDAC subtypes

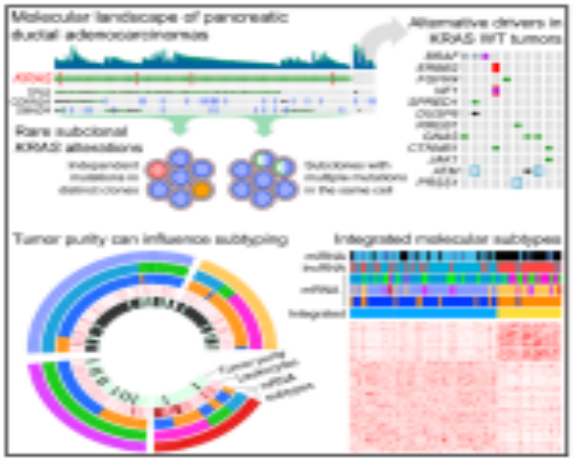
Two Major PDAC Subtypes: Neoplastic Cellularity is important

Article

Cancer Cell

Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma

Graphical Abstract



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The Cancer Genome Atlas Research Network

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In Brief

This TCGA study reveals the complex molecular landscape of PDAC, with a small number of tumors carrying multiple KRAS mutations, KRAS wild-type PDACs harboring alterations in other RAS pathway genes or alternate oncogenic drivers, and integrated RNA and protein subtypes indicating clinically significant subsets of disease.

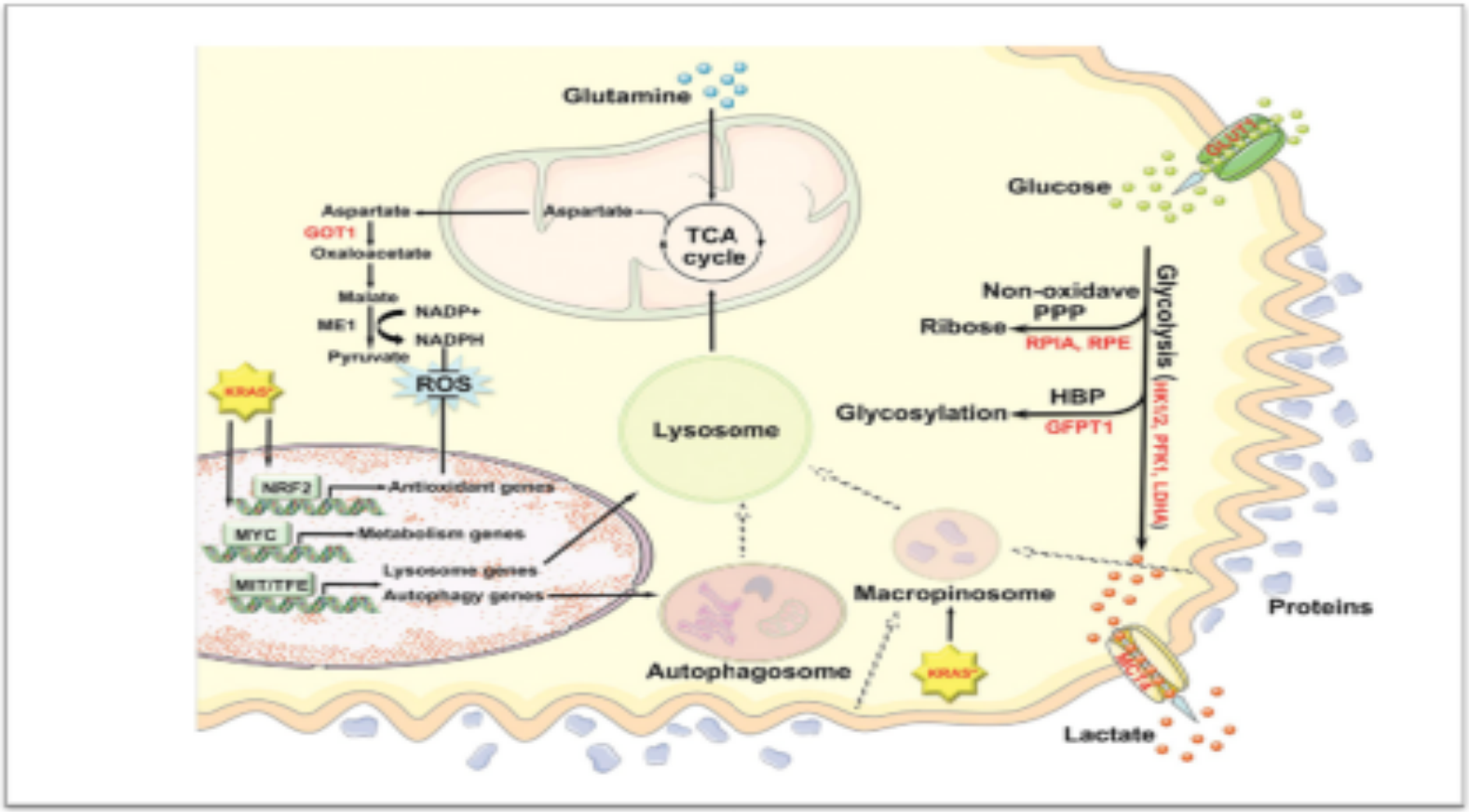
Highlights

- Multi-platform study of 150 pancreatic cancers accounting for neoplastic cellularity
- Identify *KRAS* mutational heterogeneity and alternate drivers in *KRAS* wild-type tumors
- Identify proteomic subtypes with prognostic significance and therapeutic implications
- Integrated analysis of mRNA and non-coding RNA suggests consensus subtypes

Cancer Cell, 32, 185-203, 2017

Metabolic reprogramming

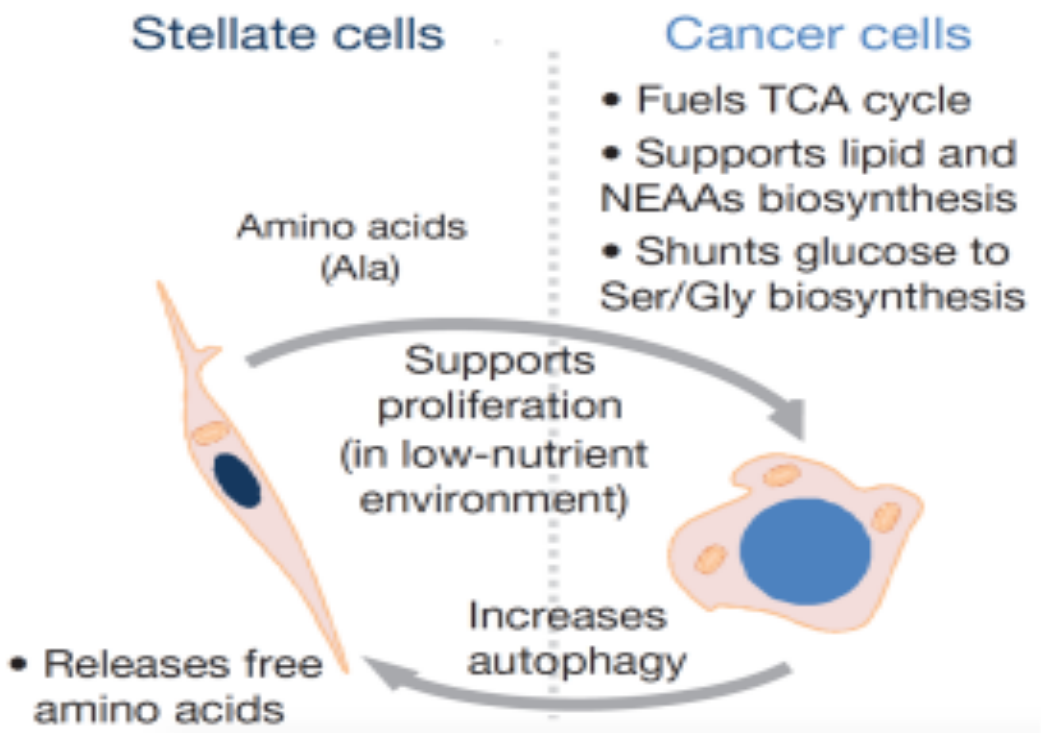
Metabolic Reprogramming in Pancreatic Cancer



Ying H et.al., Genes and Dev., 2016

Pancreatic stellate cells

Pancreatic stellate cells support tumor metabolism



Sousa, et. al., Nature, 2016

Metabolic subtypes

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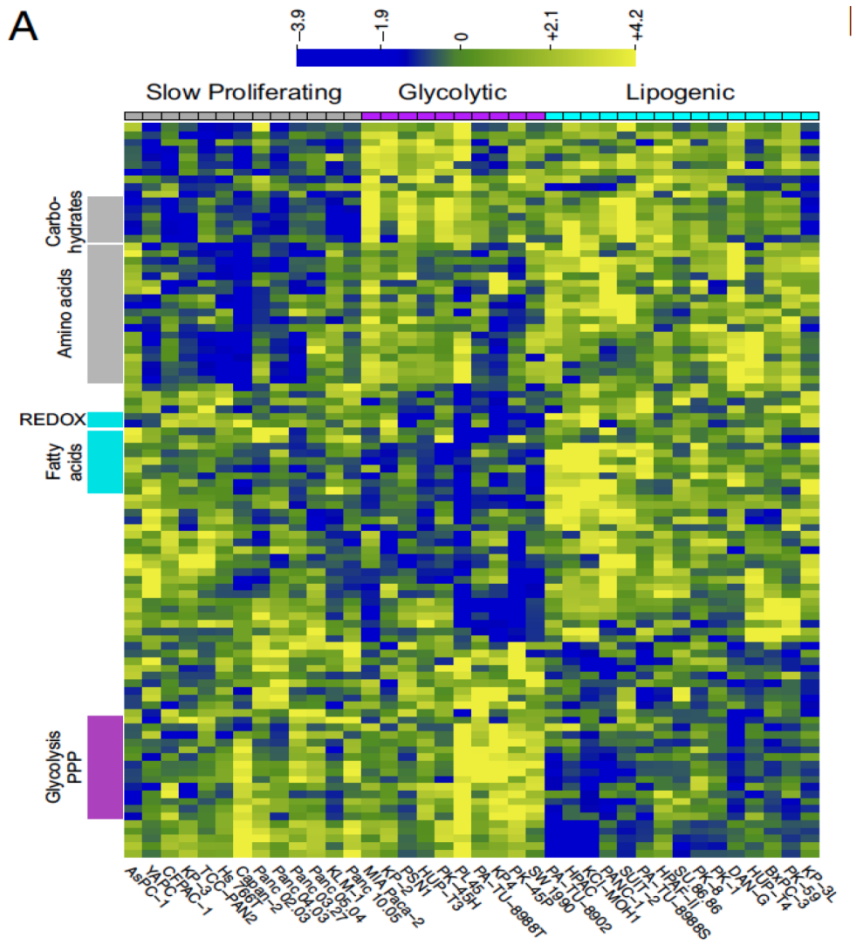
Metabolic Subtypes in Pancreatic Cancer



Daemen et. al., PNAS, 2015

Targeting stroma

Treatment Strategies to Improve Disease Outcome

Drug Delivery
and
Effectiveness of Systemic Therapy

↓

Targeting Stroma

Mouse models

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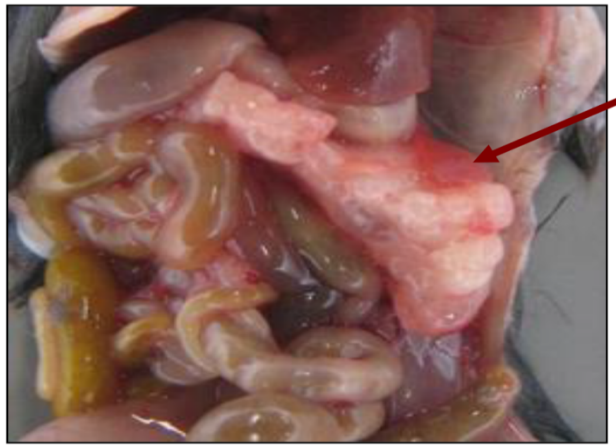
Pancreatic Cancer Mouse Model (KPC)

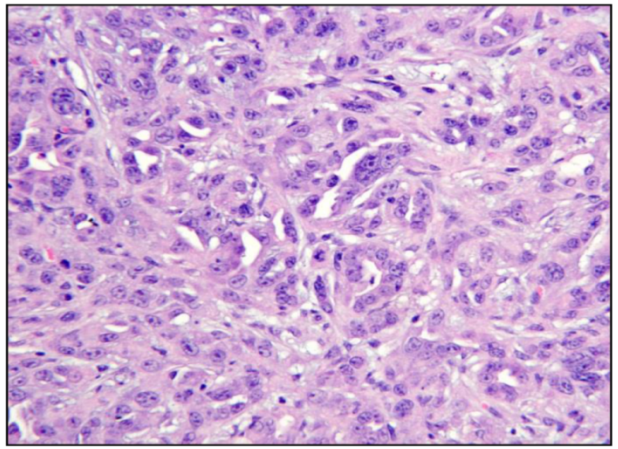
*LSL-Kras-G12D X p53 LSL R172H X Pdx-Cre 1

↓

Pancreatic Ductal Adenocarcinoma (PDAC)

(Median Survival = 4-5 months)





H&E

*Hingorani, S. et. al., Cancer Cell, 2005

Hedgehog signaling

Inhibition of Hedgehog Signaling Depleted Stroma, Enhanced Drug Delivery and Improved Survival in Mice

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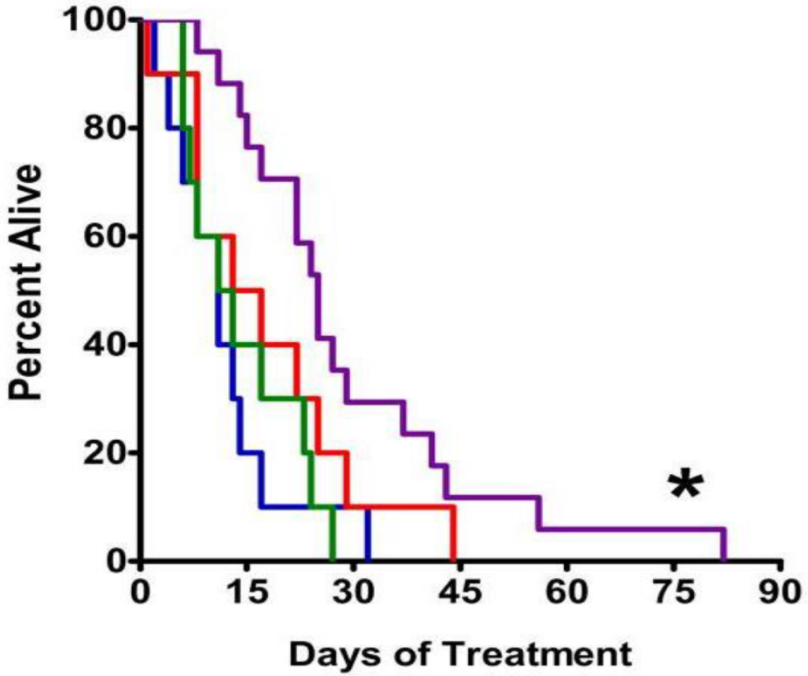

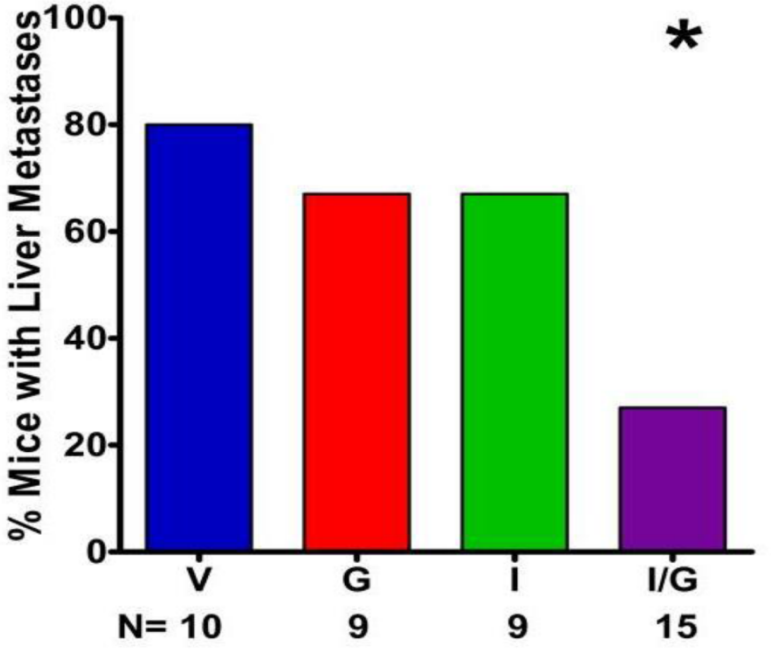

V=Vehicle
G=Gemcitabine
I= IPI-926 (Hedgehog Inhibitor)
I/G= IPI-926/Gem

Olive KP et. al., Science, 324, 2009

Stroma targeting

Enzymatic Targeting of Stroma Enhances Therapeutic Response

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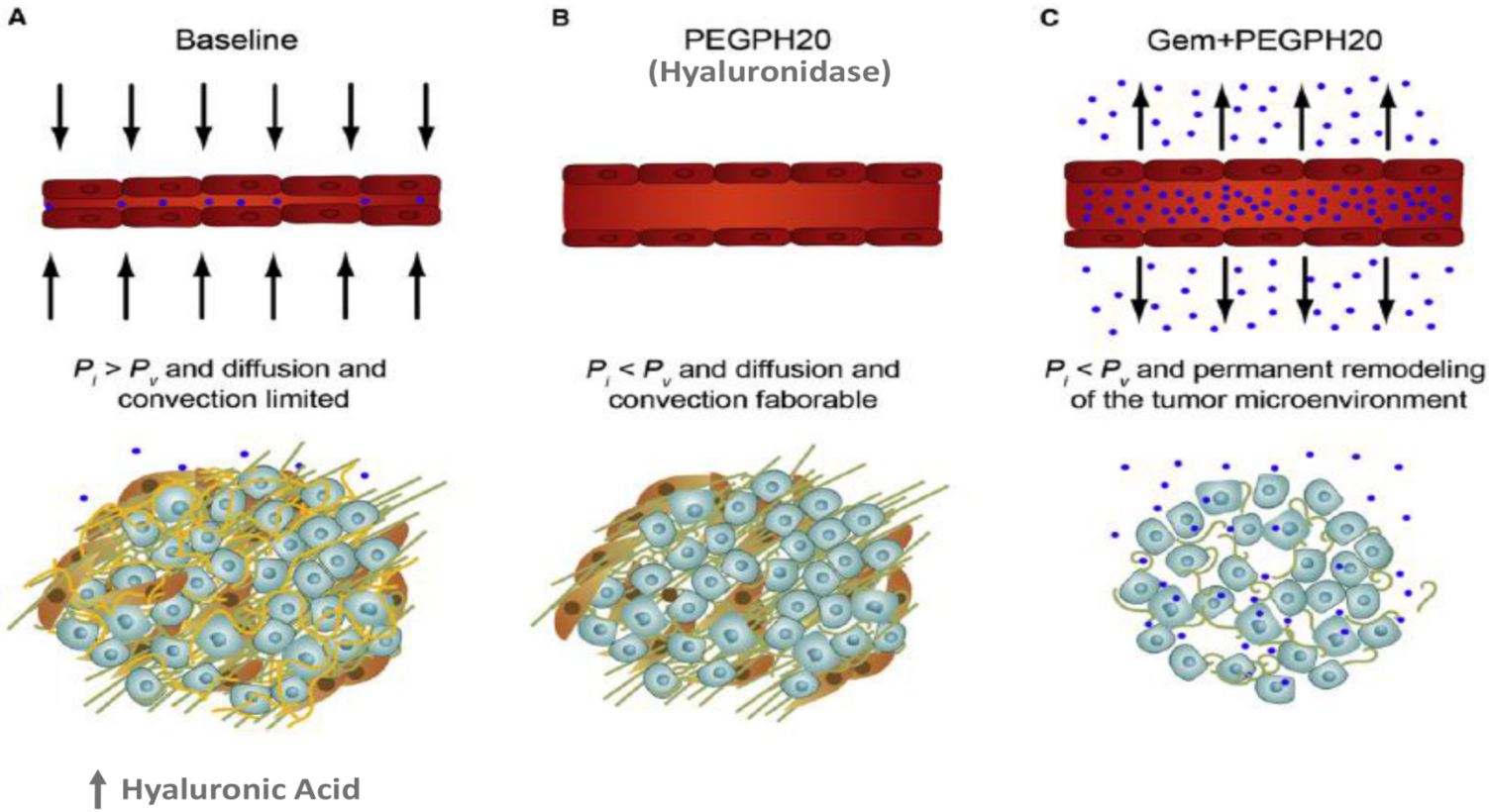

Provenzano et. al., Cancer Cell, 21, 2012

Therapeutic response

Enzymatic Targeting of Stroma Enhances Therapeutic Response

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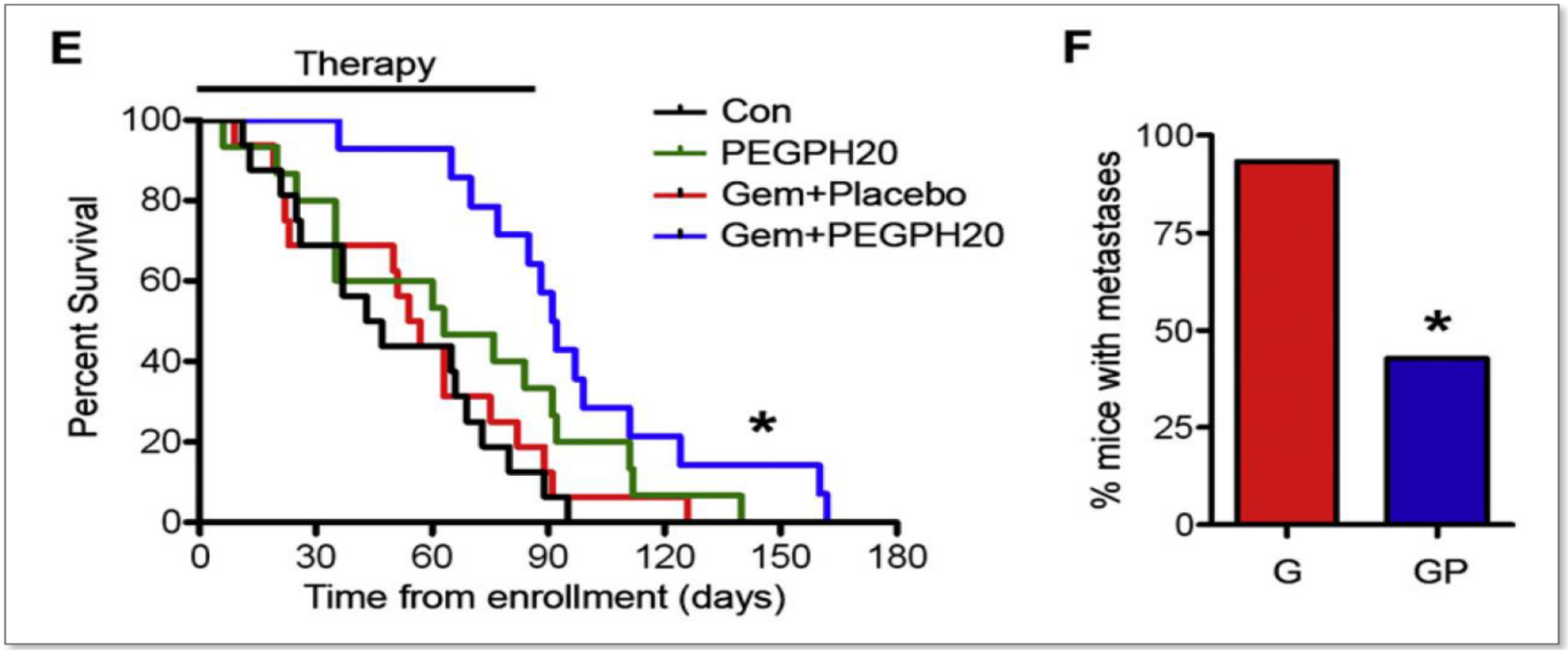

Provenzano et. al., Cancer Cell, 21, 2012

Two Faces of Anti-Stromal Therapy

Stromal-targeting may not (always) have beneficial therapeutic response

Sonic Hedgehog

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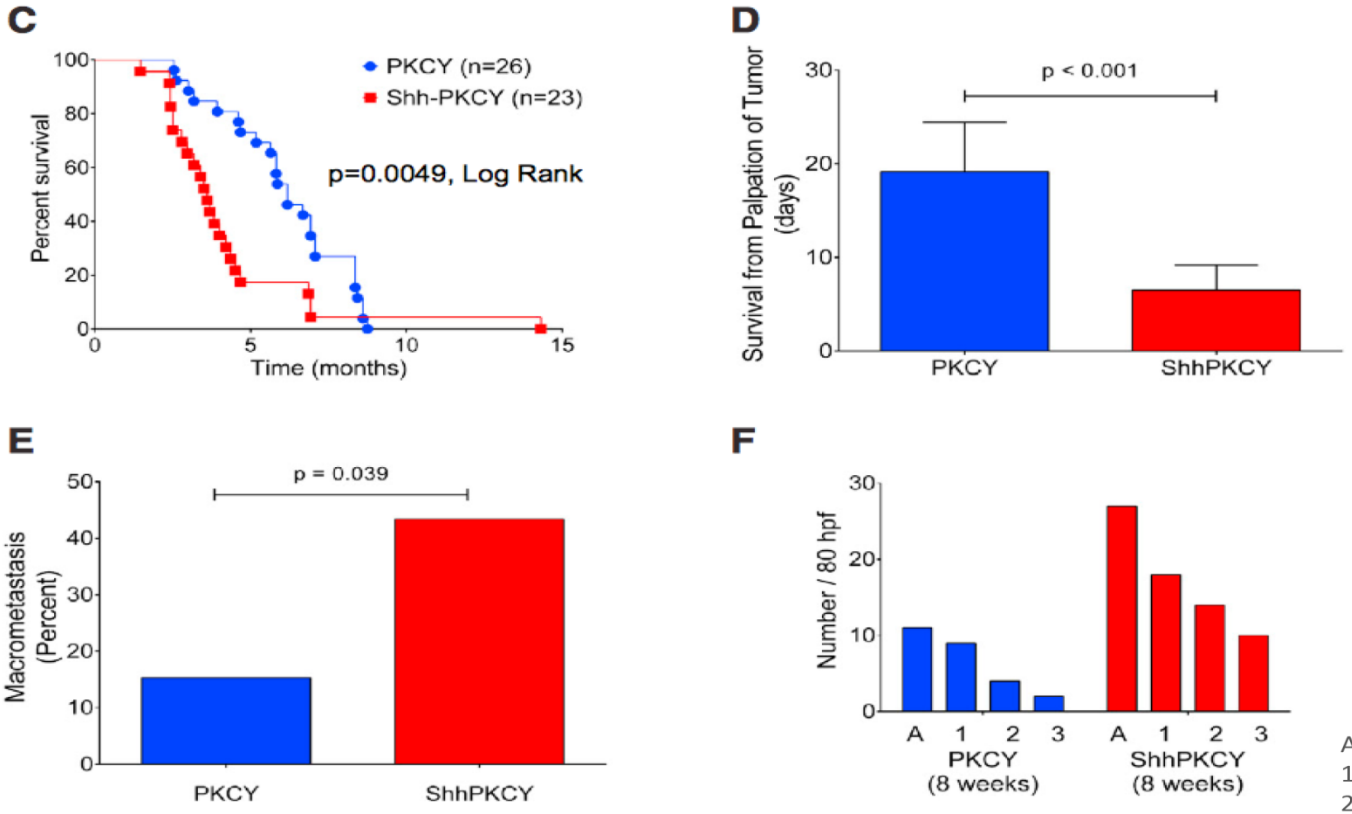
Sonic Hedgehog as a Tumor Suppressor in PDAC

Genetically Engineered Mouse Model



A= Acinar to Ductal Metaplasia
1= PanIN1
2= PanIN2
3= PanIN3

Rhim AD et. al., Cancer Cell, 25, 2014

Myofibroblast Depletion Enhances PDAC

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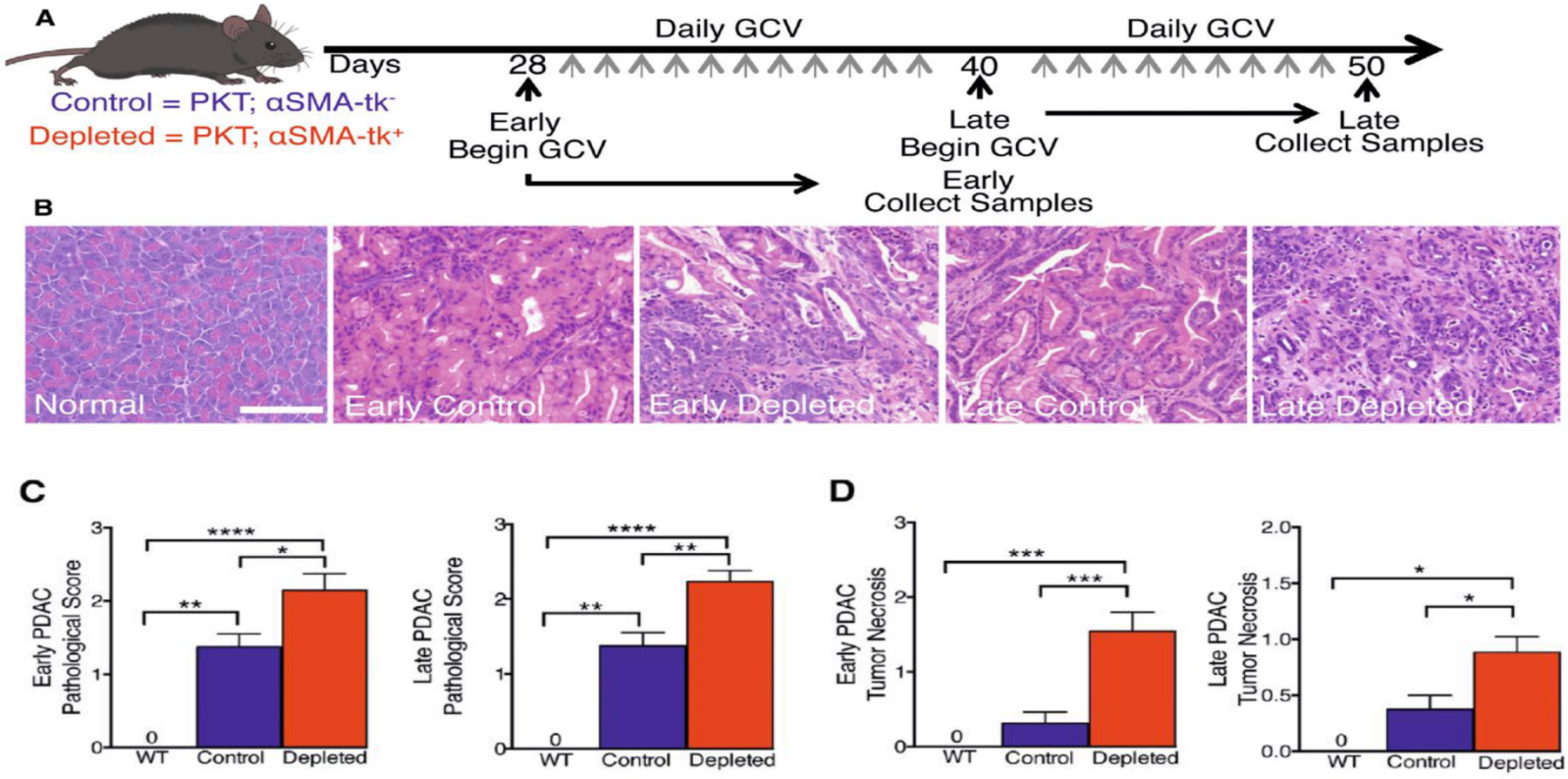
Myofibroblast Depletion Enhances PDAC



Ozdemir, BC et. al., Cancer Cell, 25, 2015

Myofibroblast depletion

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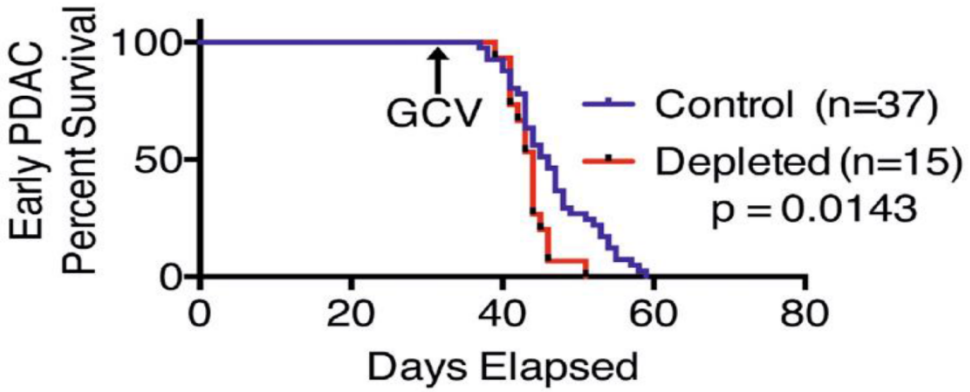
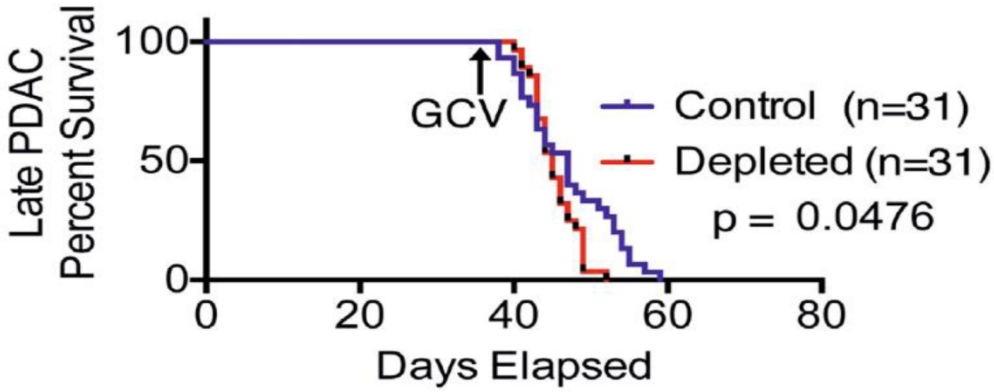
Myofibroblast Depletion Reduces Overall Survival





GCV= genciclovir (Depletes Myofibroblasts in PKT;αSMA-tk+ Mice)

Treatment strategies

Treatment Strategies to Improve Disease Outcome

Drug Delivery

and

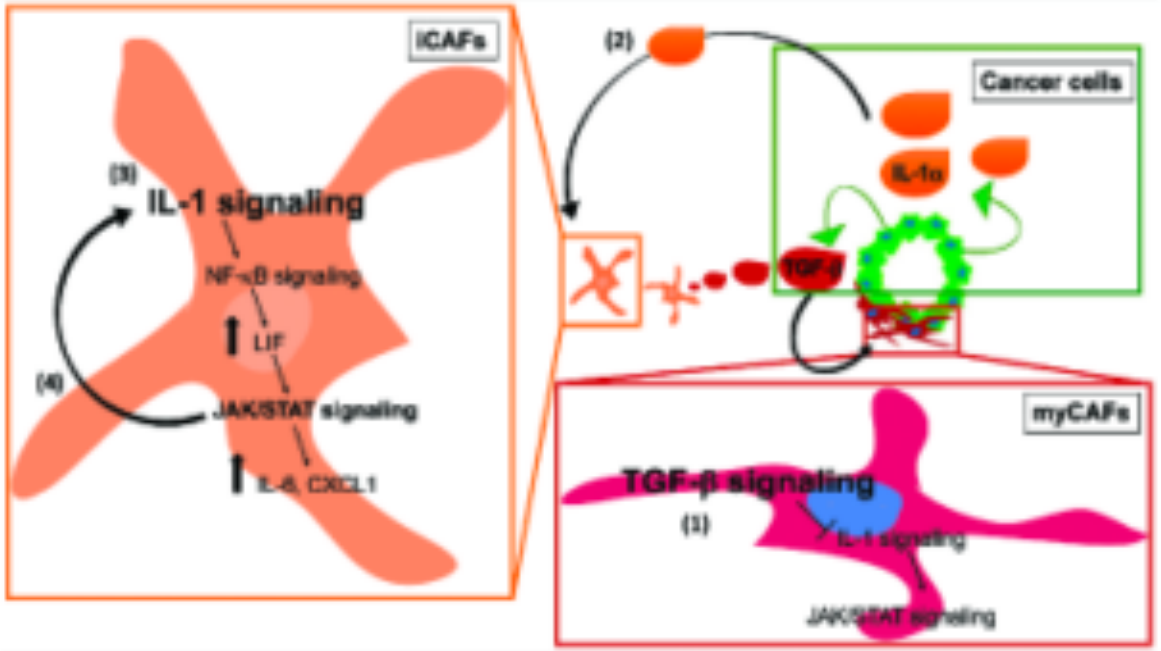
Effectiveness of Systemic Therapy

↓

CAF heterogeneity

Cancer associated fibroblast (CAF) heterogeneity and stromal targeting in PDAC

Tumor Promoting



Tumor Restraining

Tumor secreted Ligands TGF-β and IL-1 promotes CAF heterogeneity

Patient sensitivity

Patient's organoid and therapeutic sensitivity

RESEARCH ARTICLE

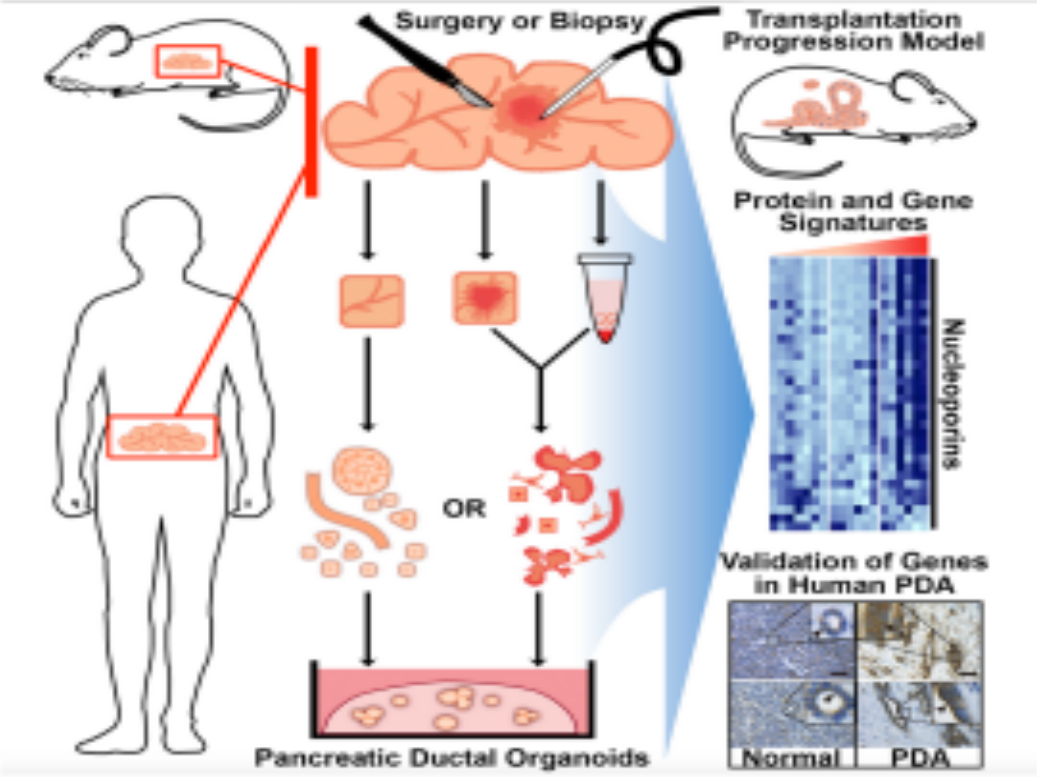
Organoid Profiling Identifies Common Responders to Chemotherapy in Pancreatic Cancer

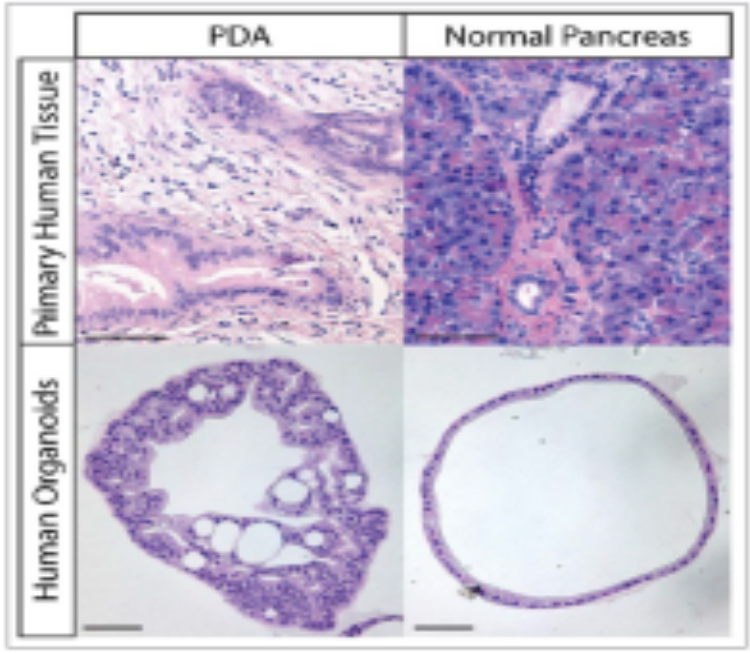
Hervé Tiriac[1], Pascal Belleau[1], Dannielle D. Engle[1], Dennis Plenker[1], Astrid Deschênes[1], Tim D. D. Somerville[1], Fieke E. M. Froeling[1], Richard A. Burkhart[2], Robert E. Denroche[3], Gun-Ho Jang[3], Koji Miyabayashi[1], C. Megan Young[1,4], Hardik Patel[1], Michelle Ma[1], Joseph F. LaComb[5], Randze Lerie D. Palmaira[6], Ammar A. Javed[2], Jasmine C. Huynh[7], Molly Johnson[8], Kanika Arora[8], Nicolas Robine[8], Minita Shah[8], Rashesh Sanghvi[8], Austin B. Goetz[9], Cinthya Y. Lowder[9], Laura Martello[10], Else Driehuis[11,12], Nicolas LeComte[6], Gokce Askan[6], Christine A. Iacobuzio-Donahue[6], Hans Clevers[11,12,13], Laura D. Wood[14], Ralph H. Hruban[14], Elizabeth Thompson[14], Andrew J. Aguirre[15], Brian M. Wolpin[15], Aaron Sasson[16], Joseph Kim[16], Maoxin Wu[17], Juan Carlos Bucobo[5], Peter Allen[6], Divyesh V. Sejpal[18], William Nealon[19], James D. Sullivan[19], Jordan M. Winter[3], Phyllis A. Gimotty[20], Jean L. Grem[21], Dominick J. DiMaio[22], Jonathan M. Buscaglia[5], Paul M. Grandgenett[23], Jonathan R. Brody[9], Michael A. Hollingsworth[23], Grainne M. O'Kane[24], Faiyaz Notta[3], Edward Kim[7], James M. Crawford[25], Craig Devoe[26], Allyson Ocean[27], Christopher L. Wolfgang[2], Kenneth H. Yu[5], Ellen Li[5], Christopher R. Vakoc[1], Benjamin Hubert[8], Sandra E. Fischer[28,29], Julie M. Wilson[3], Richard Moffitt[16,30], Jennifer Knox[24], Alexander Krasnitz[1], Steven Gallinger[3,24,31,32], and David A. Tuveson[1]

Tiriac et. al., Cancer Discov., 8, 1112-9, 2018

Organoid

Organoid: A highly promising model for PDAC

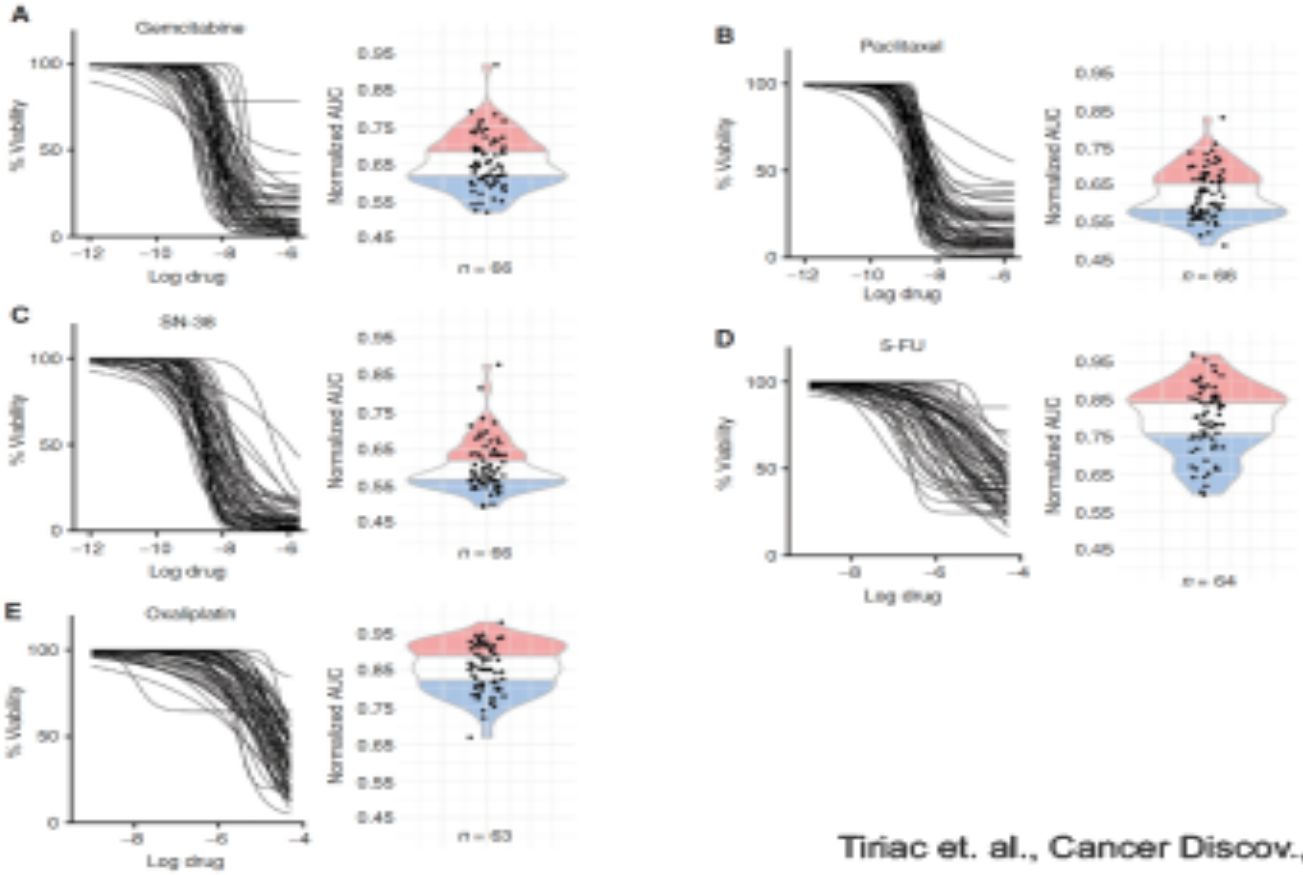




Boj et. al., Cell, 160, 2015
Boj et. al., Mol. Cell. Onc., 2016
Hwang et. al., J. Pathology, 238, 2016

Chemotherapeutic response

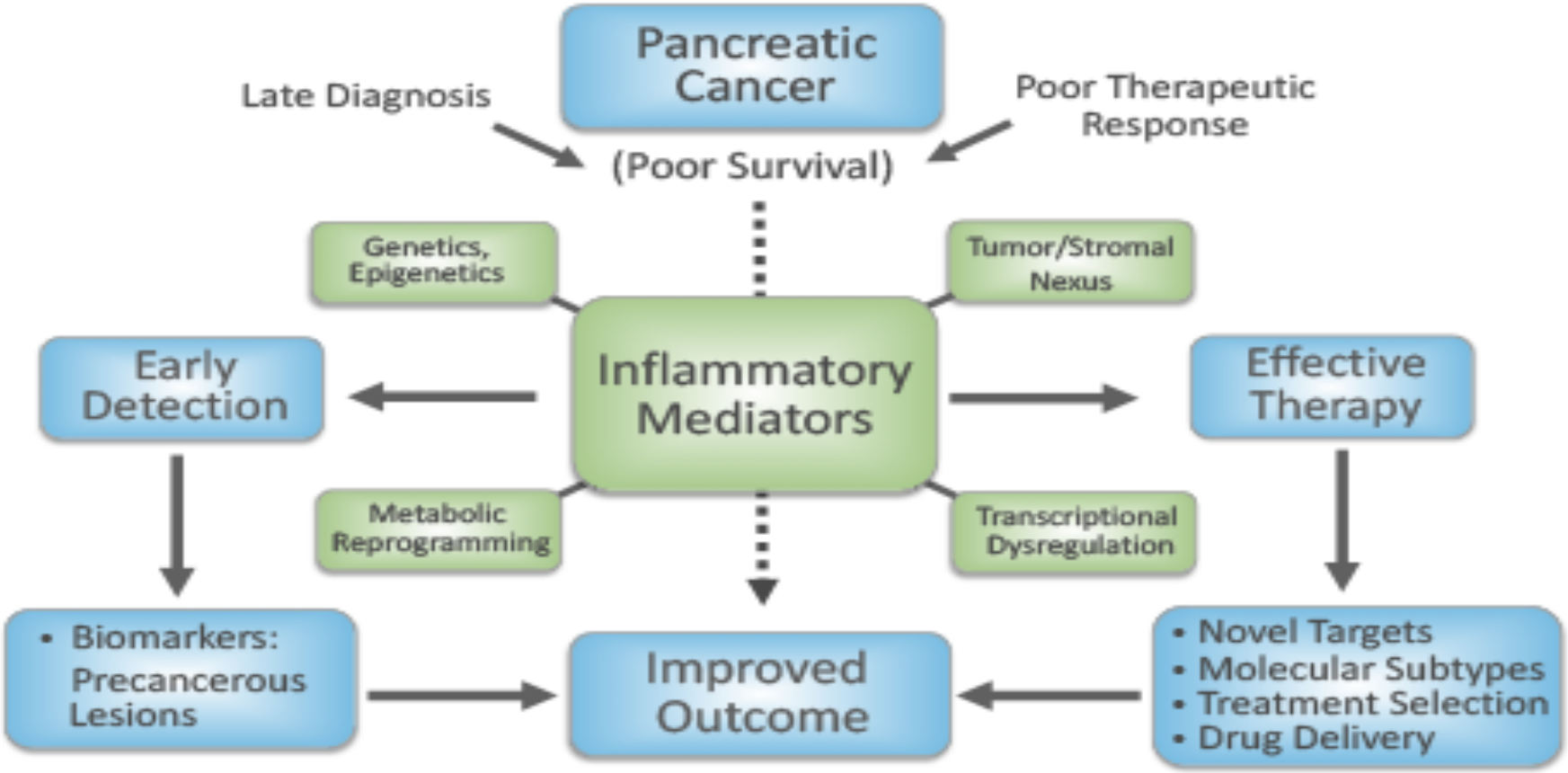
Heterogeneity of chemotherapeutic response



Tiriac et. al., Cancer Discov., 8, 1112-9, 2018

Pancreatic tumor biology

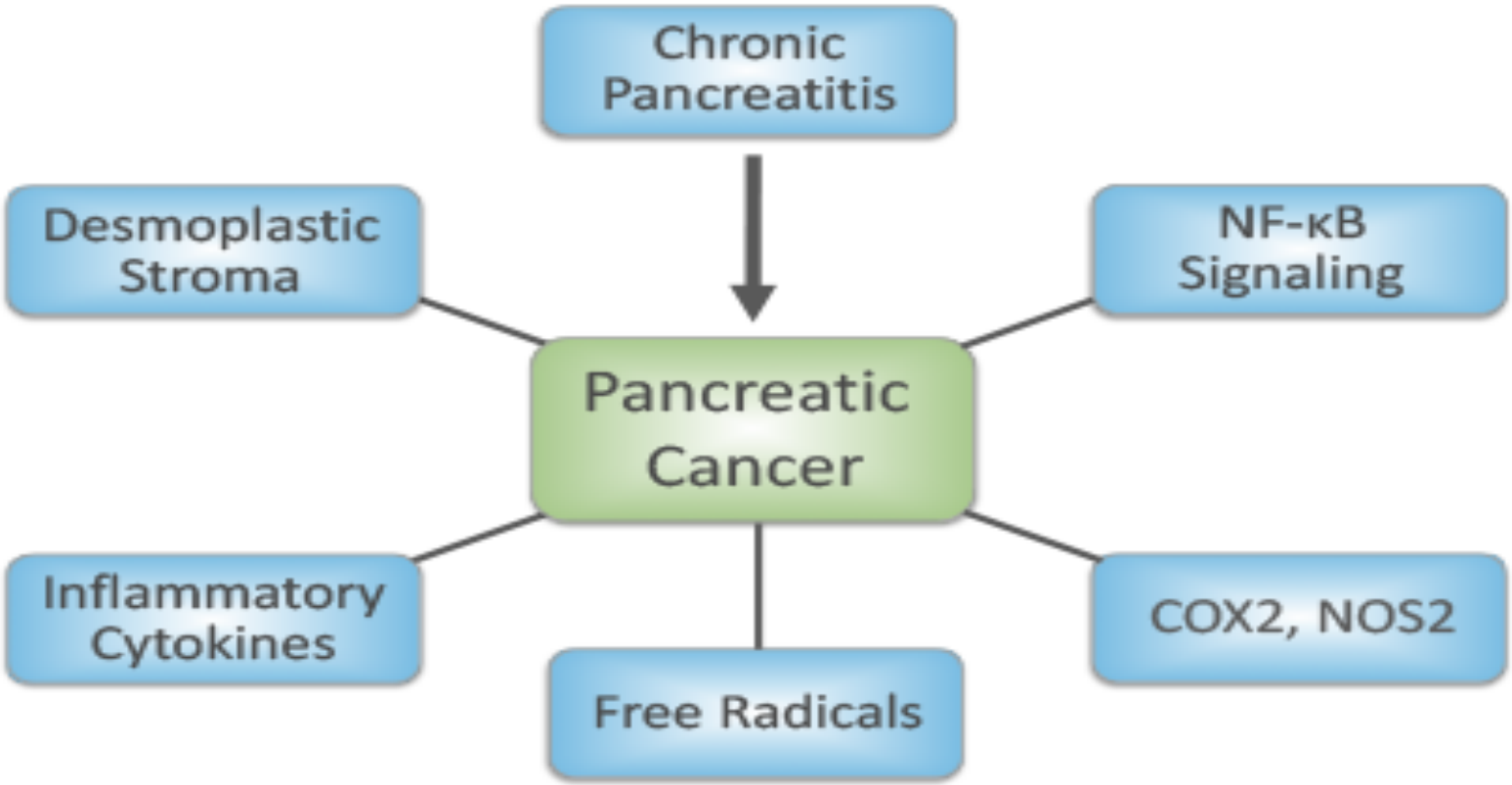
Understanding Pancreatic Tumor Biology is Key to Improving Disease Outcome in Patients



Hussain, S.P., Int J Biol Sci,12, 2016

Inflammation

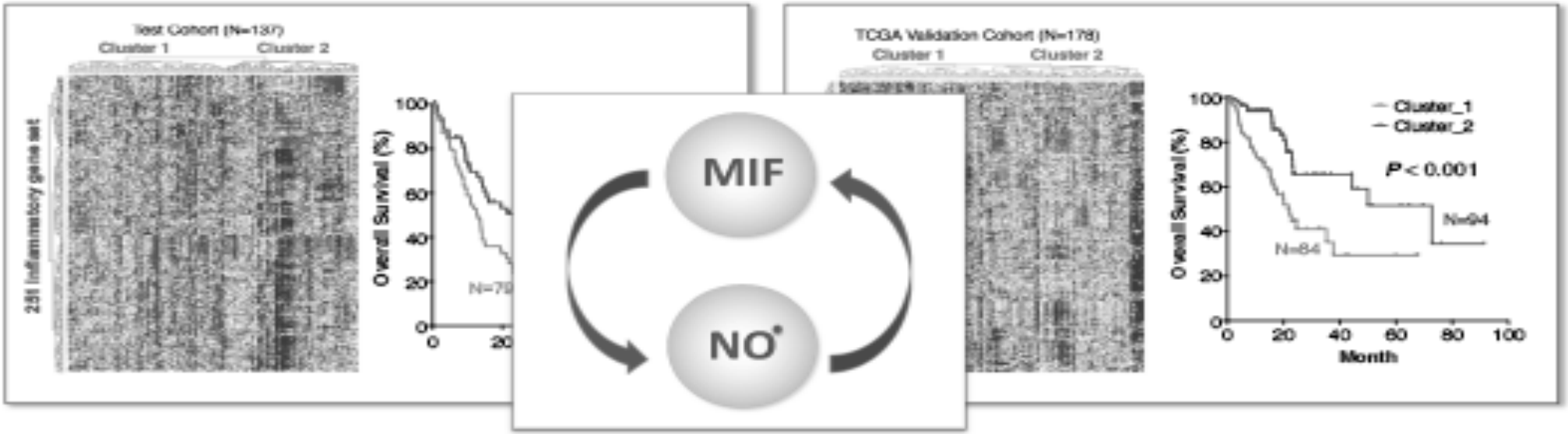
Inflammation and Pancreatic Cancer



Inflammatory mediators

Role of Inflammatory Mediators in the progression of PDAC

Hypothesis: Inflammatory gene signature is associated with pancreatic cancer progression and disease aggressiveness



MIF and NOS2

- Higher expression in tumors as compared with adjacent nontumor pancreas
- Highly expressed in patients with worst prognosis

MIF: Macrophage Migration Inhibitory Factor
NOS2: Inducible Nitric Oxide Synthase

MIF and Cancer

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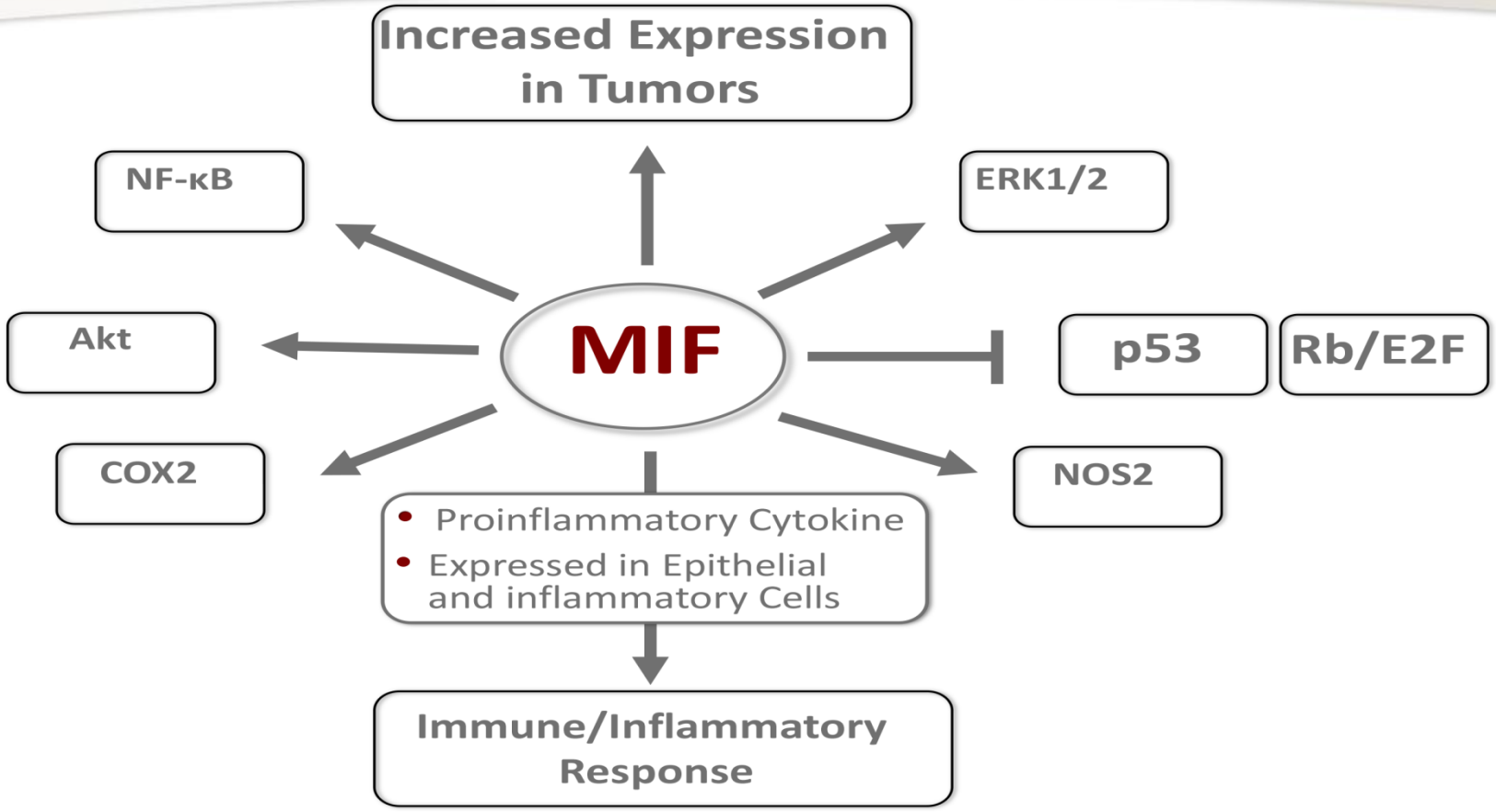
Macrophage Migration Inhibitory Factor (MIF)



HYPOTHESIS

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MIF Contributes to Pancreatic Cancer Progression and Predicts Disease Outcome.

MIF and PDAC

Increased expression of MIF in tumors from pancreatic ductal adenocarcinoma cases

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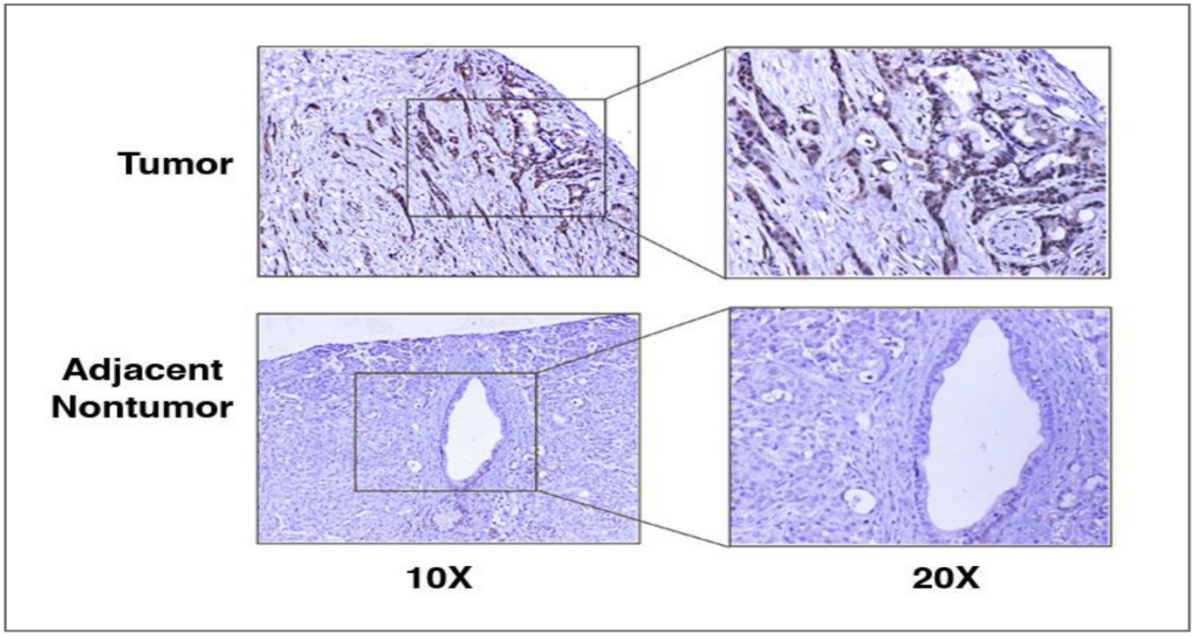

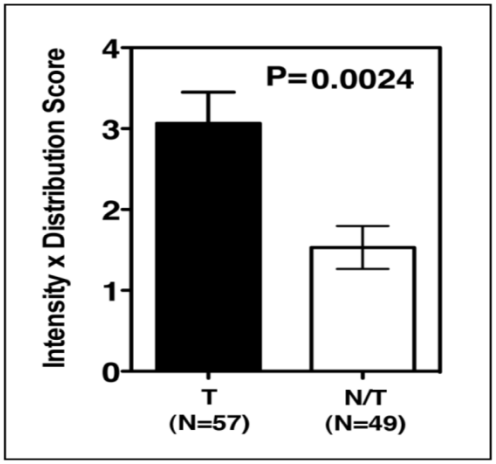

MIF expression and poor PDAC survival

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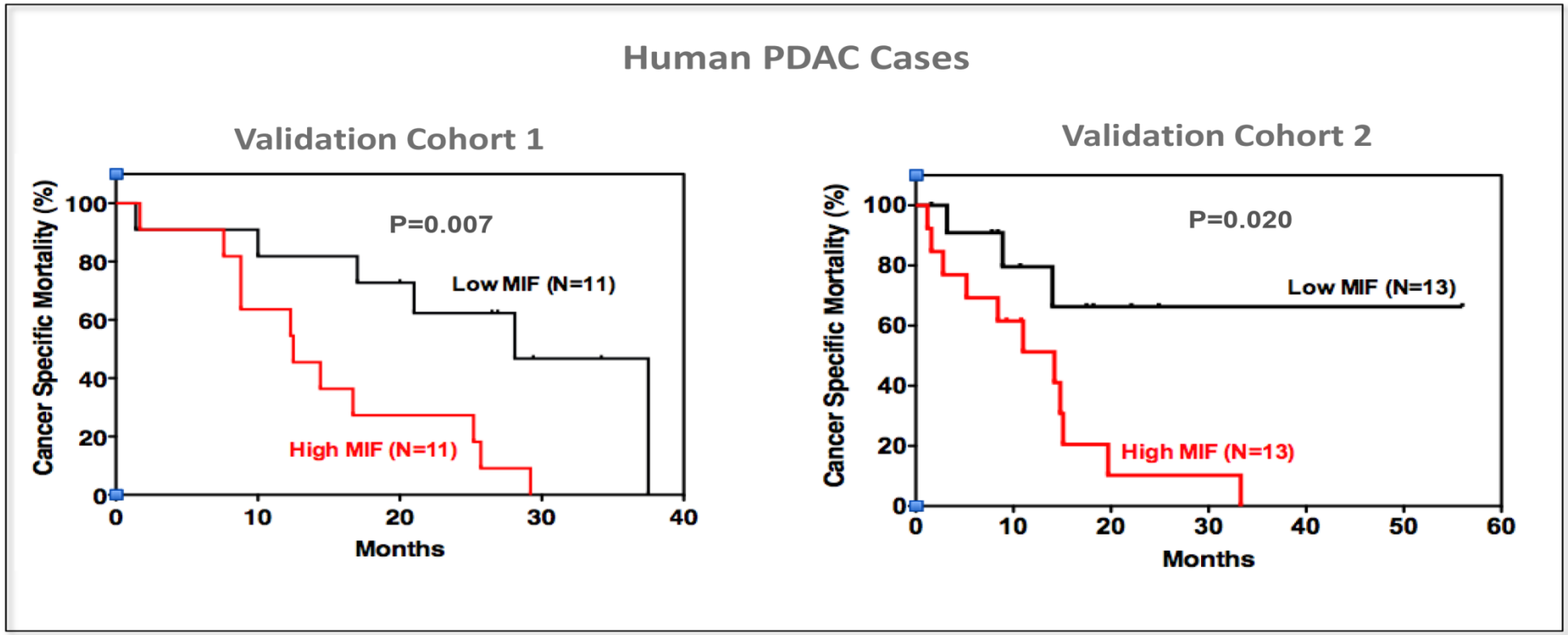
A higher expression of MIF is associated with poor survival in human PDAC

Validation in Independent Cohorts



MIF accelerates tumor growth

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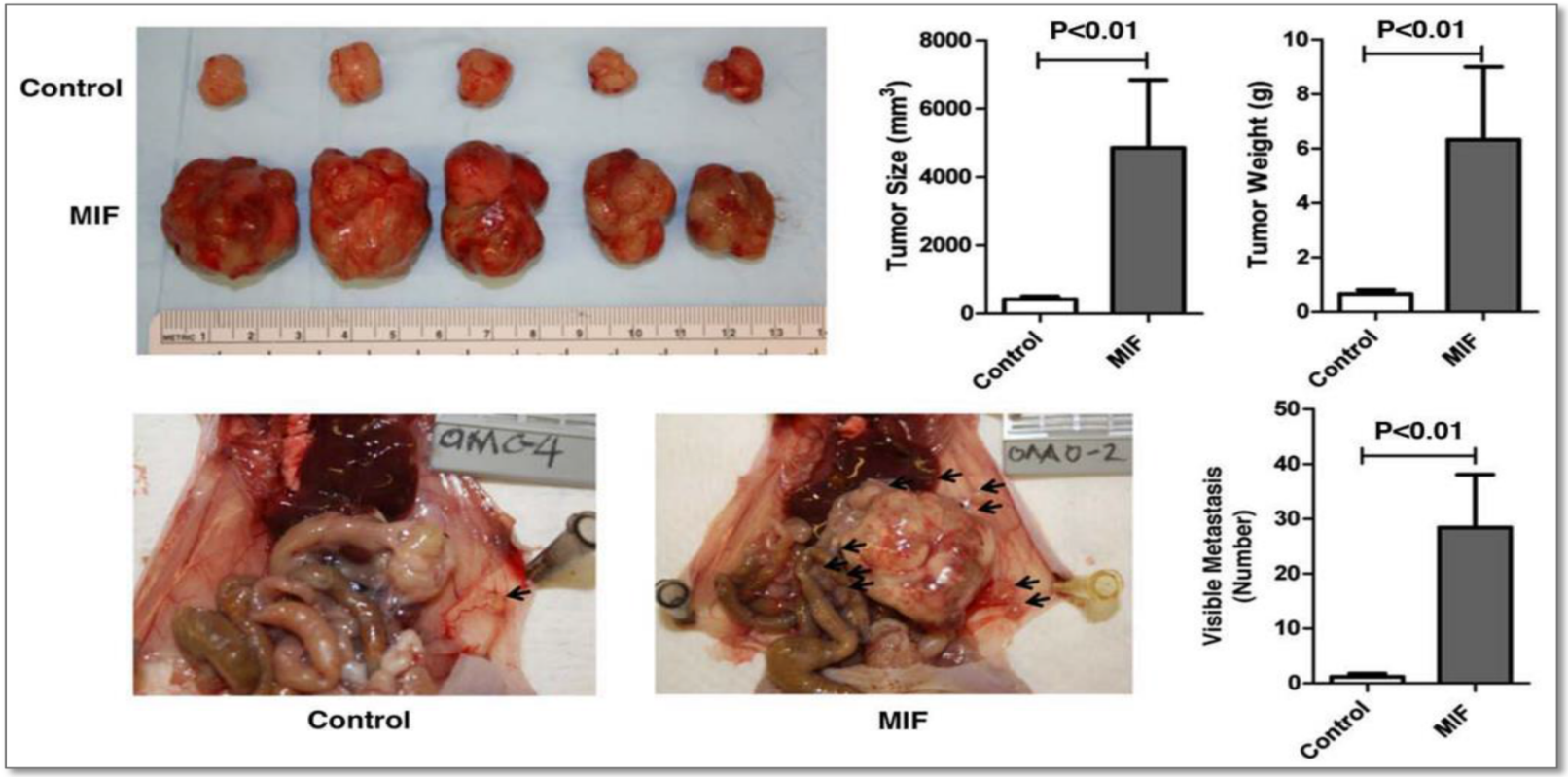
MIF accelerates tumor growth and metastasis In orthotopic xenografts in mice



MIF and gene expression

MIF Induces a marked change in global gene expression profile including EMT-related genes in orthotopic tumors

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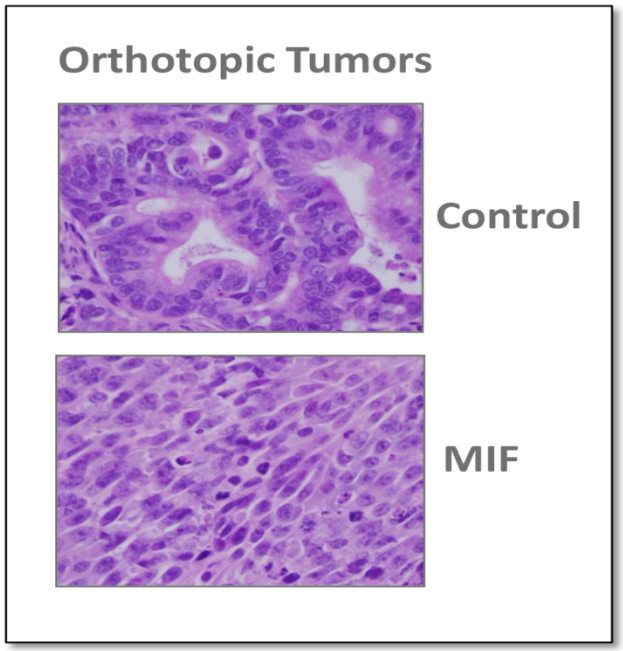

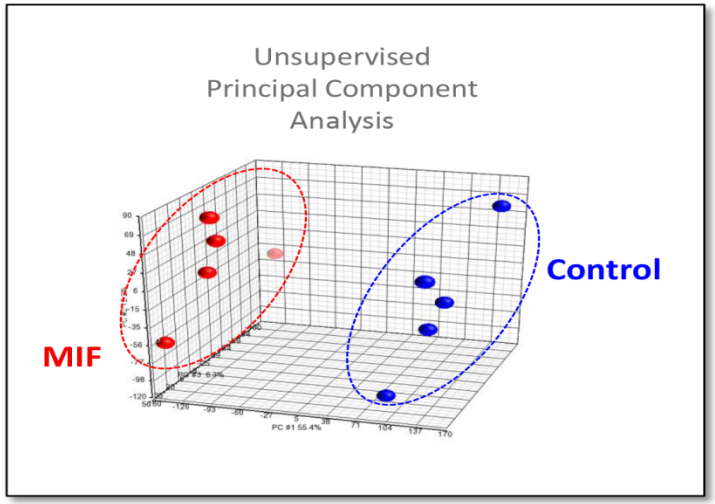

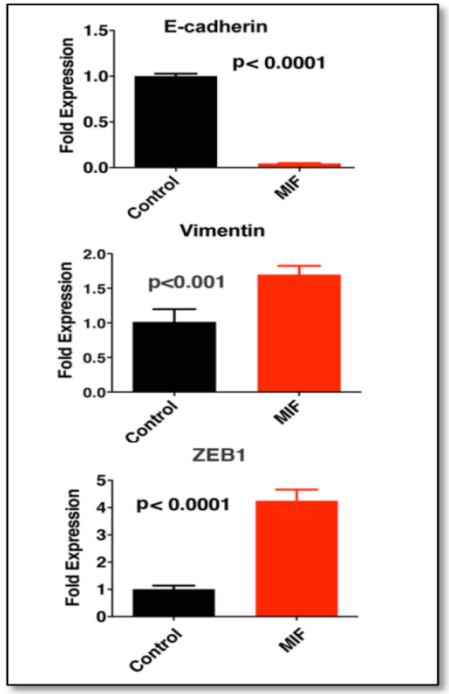

- MIF over-expressing tumors are poorly differentiated.
- MIF induces a change in global gene expression profile.
- MIF over-expressing tumors showed expression of EMT-marker genes.

MIF-induced disease

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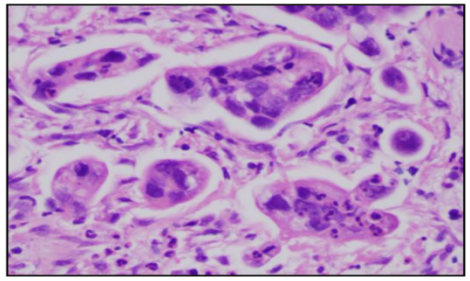
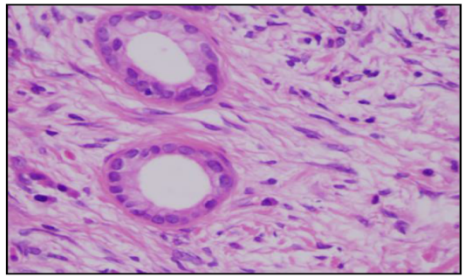
MIF-induced disease aggressiveness in pancreatic cancer

Human PDAC Cases

H/E



High MIF



Low MIF

Shouhui Yang

Questions

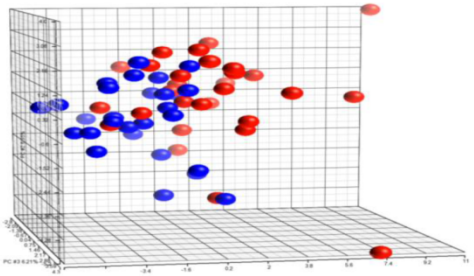
- Molecular Distinctions
- Mechanistic and Functional Role of MIF in Tumor Progression

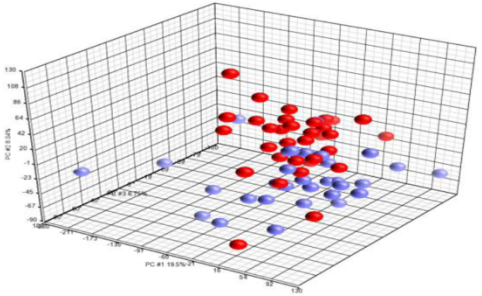
OMICS

miRNA

mRNA

- High MIF
- Low MIF





MIF axis in Pancreatic Cancer

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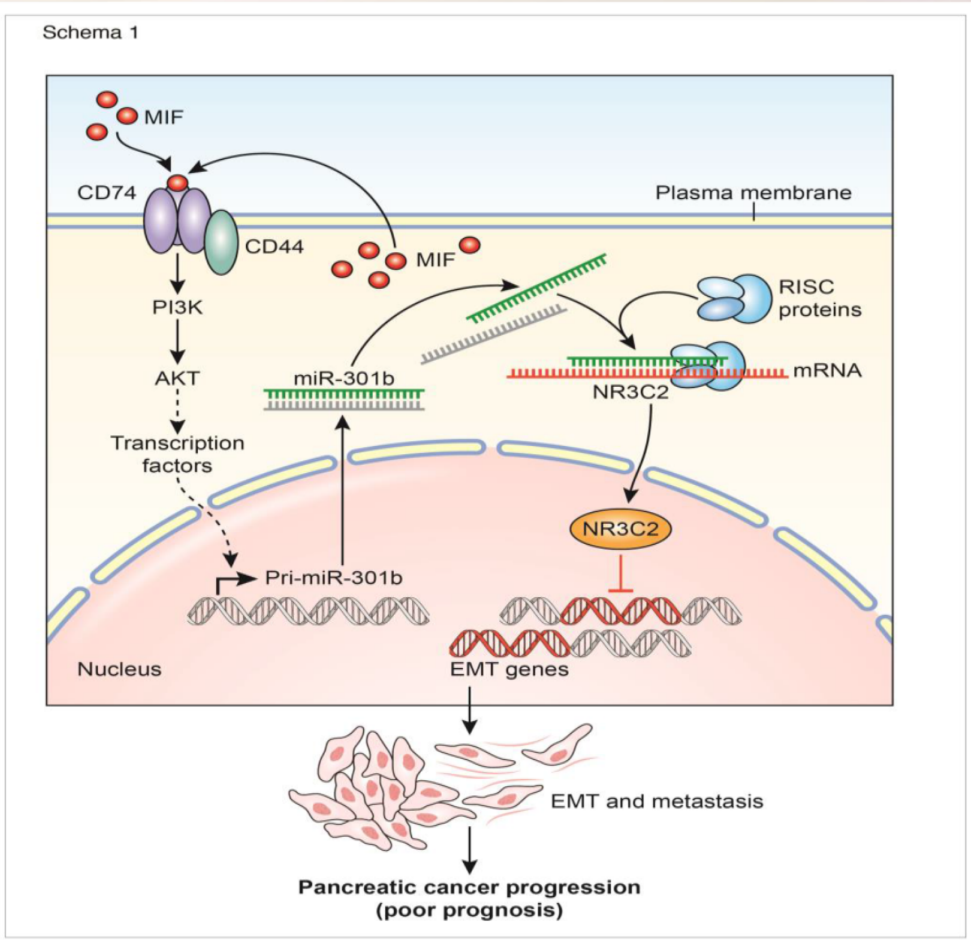
MIF/miR-301b/NR3C2 Axis in Pancreatic Cancer



Pancreatic Tumors Express MIF

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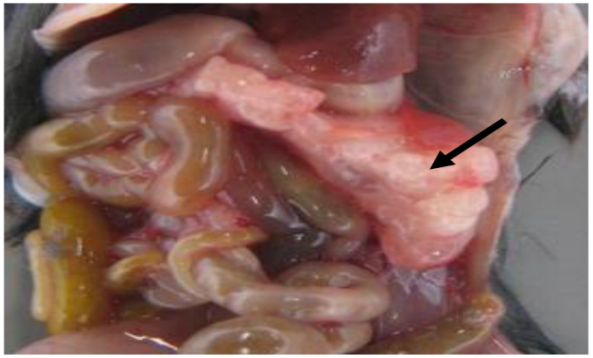
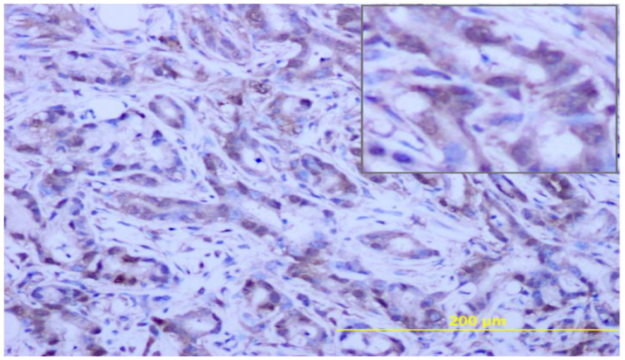
Pancreatic tumors in KPC mice express a high level of MIF

(KPC: $KRAS^{G12D}$; $P53^{R172H}$; Pdx-1-Cre)

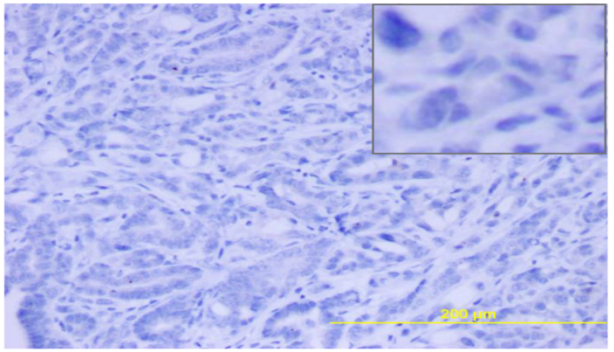
MIF Immunostaining



KPC



KPC



KPC/$MIF^{-/-}$

MIF deletion in genetically engineered mouse model of pancreatic cancer

MIF deficiency enhances survival

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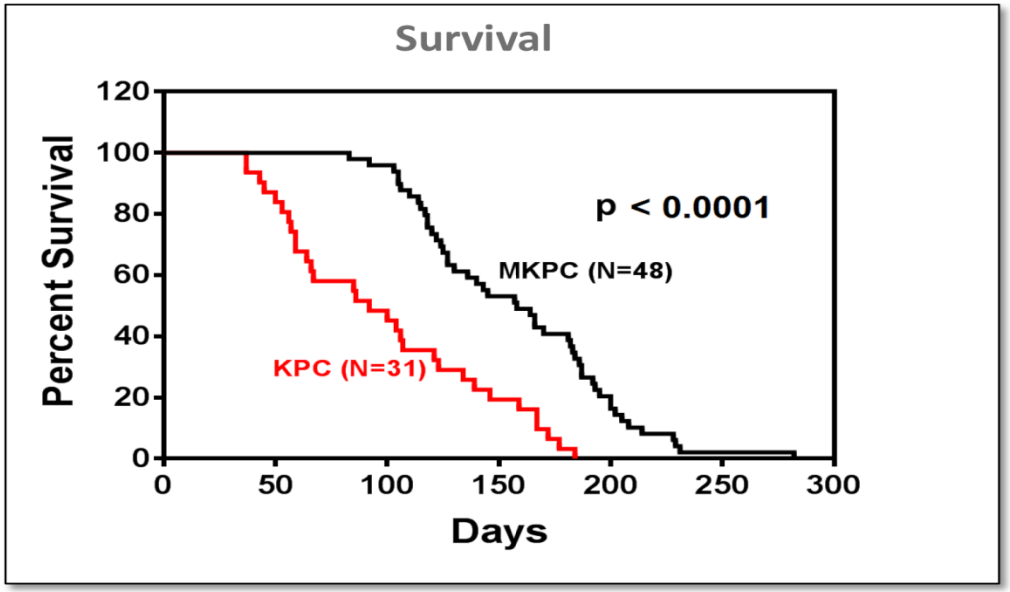
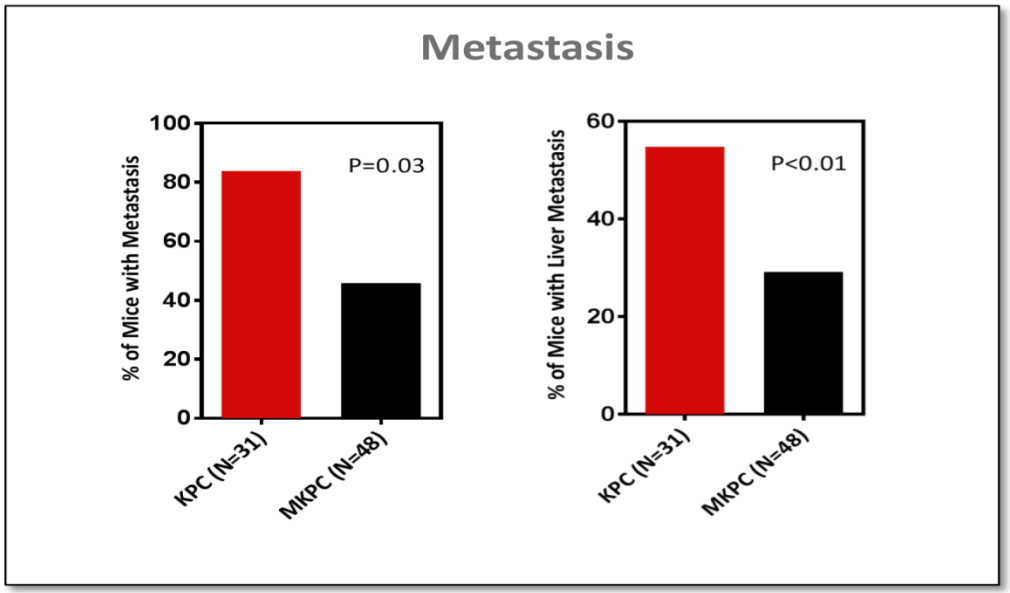
MIF-deficiency enhanced survival and reduced metastasis in KPC mice

KPC Mouse Model

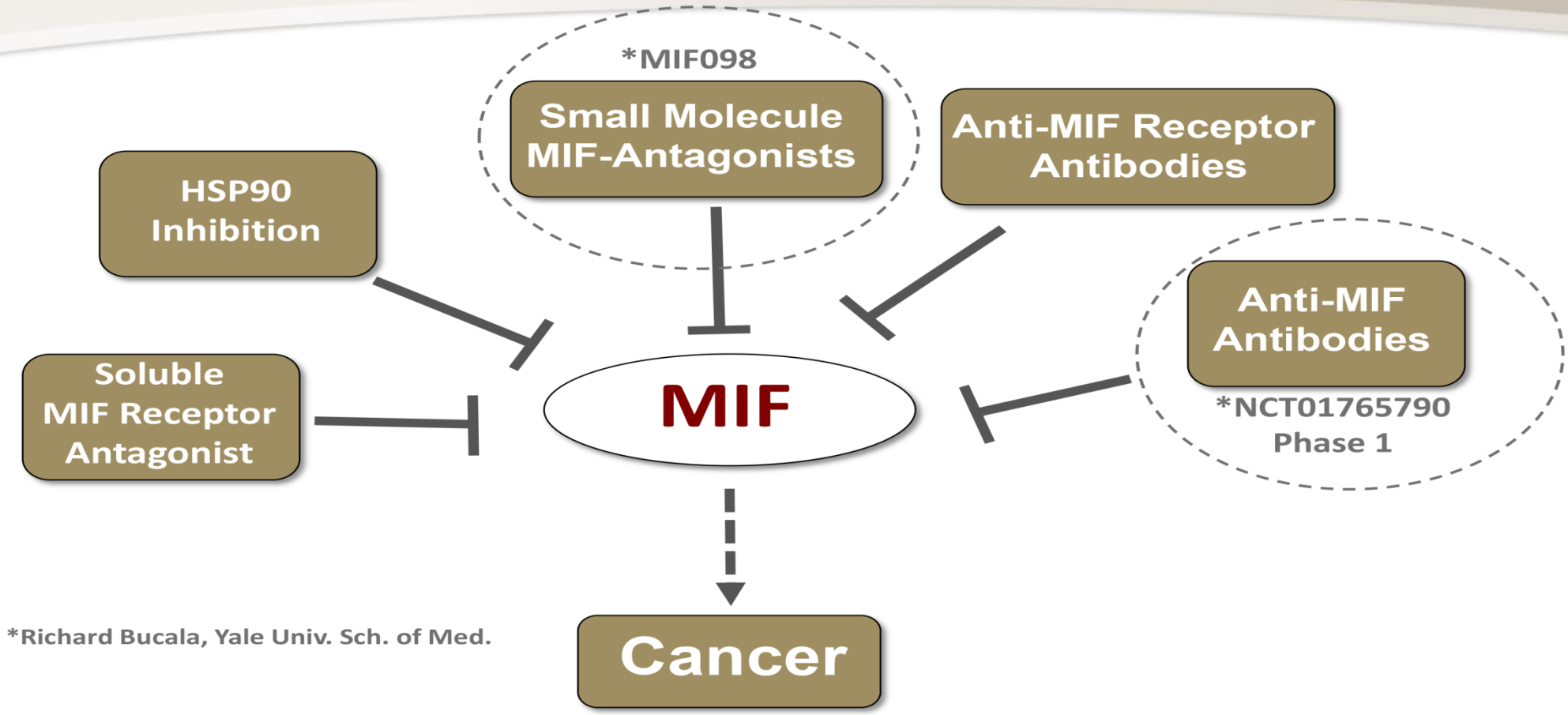




MKPC= MIF-deficient KPC mice

MIF inhibition strategies

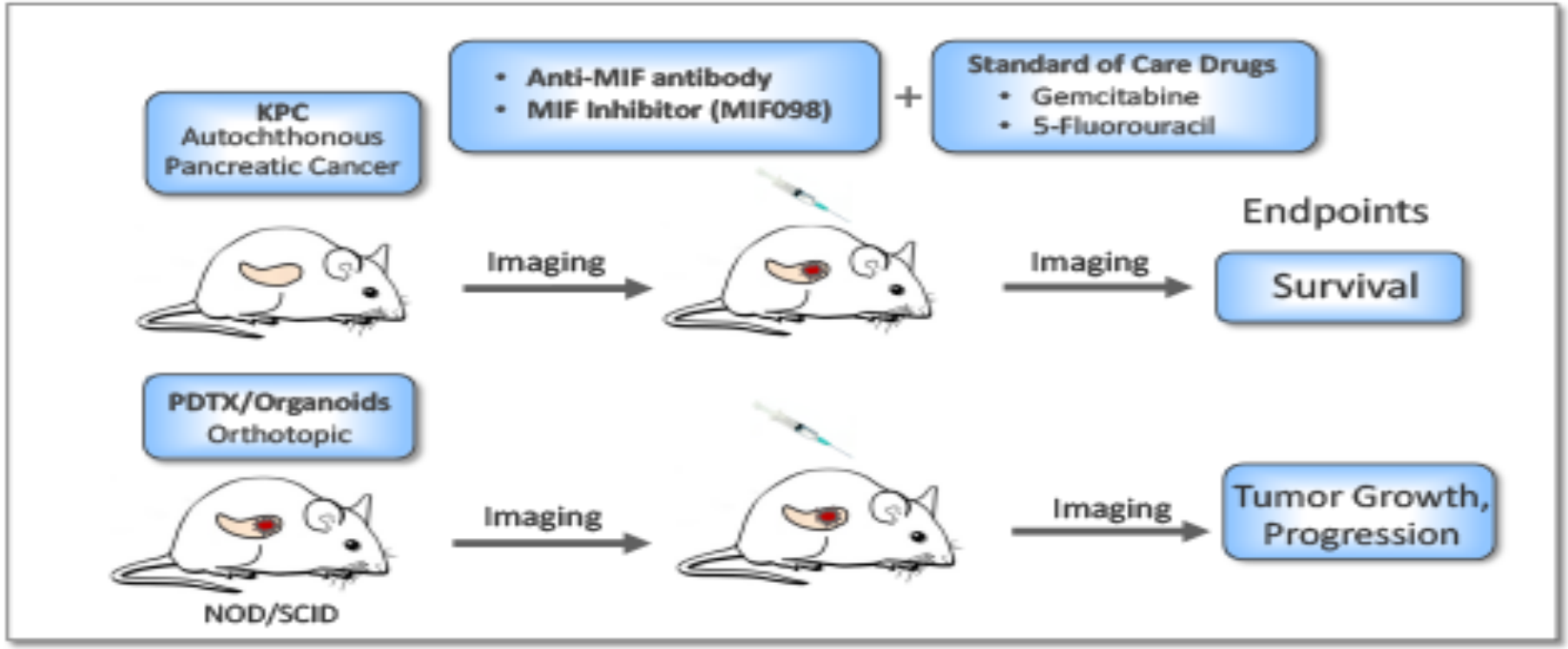
Strategies for MIF inhibition



*Richard Bucala, Yale Univ. Sch. of Med.

Targeting MIF

Pharmacological Targeting of MIF



Understanding pancreatic tumor biology

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Understanding Pancreatic Tumor Biology is Key to Improving Disease Outcome