Pancreatic Cancer: Current Understanding and Future Challenges

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Connecting the Cancer Community

TRACO, 2014

Pancreatic Cancer: Current Understanding and Future Challenges

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Pancreatic Cancer: Incidence and Mortality

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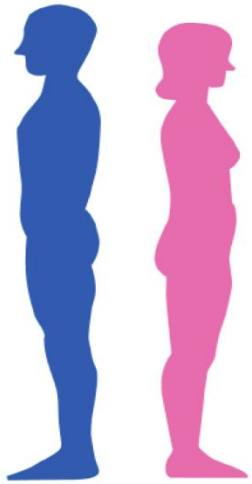
Pancreatic Cancer Incidence and Mortality

Estimated Deaths

Siegel R et. al., CA Cancer J Clin, 64, 2014

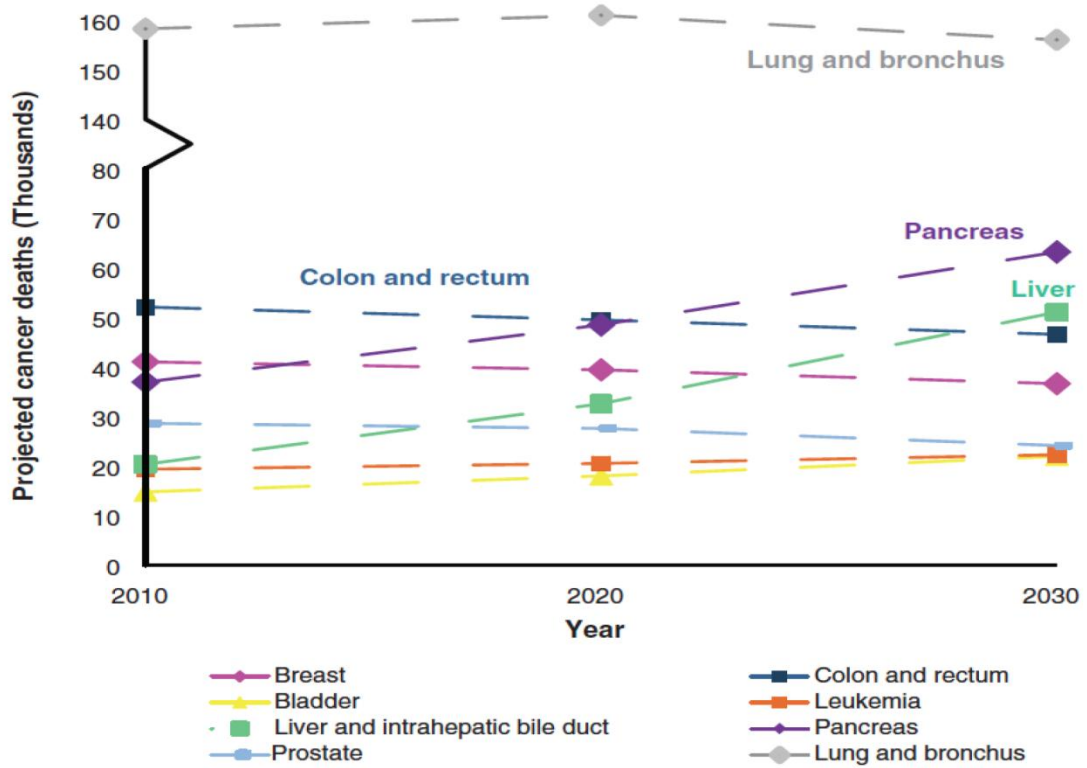
Males			Females		
Lung & bronchus	86,930	28%	Lung & bronchus	72,330	26%
Prostate	29,480	10%	Breast	40,000	15%
Colorectum	26,270	8%	Colorectum	24,040	9%
Pancreas	20,170	7%	Pancreas	19,420	7%
Liver & intrahepatic bile duct	15,870	5%	Ovary	14,270	5%
Leukemia	14,040	5%	Leukemia	10,050	4%
Esophagus	12,450	4%	Uterine corpus	8,590	3%
Urinary bladder	11,170	4%	Non-Hodgkin lymphoma	8,520	3%
Non-Hodgkin lymphoma	10,470	3%	Liver & intrahepatic bile duct	7,130	3%
Kidney & renal pelvis	8,900	3%	Brain & other nervous system	6,230	2%
All Sites	**310,010**	**100%**	**All Sites**	**275,710**	**100%**



- 4th Leading Cause of Cancer Deaths in the United States.
- Median Survival < 6 Months.
- Estimated 46,420 New Cases and 39,590 Deaths in 2014.
- No Effective Treatment.

Pancreatic Cancer and 2030

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



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

Risk Factors and Inherited Syndromes

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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 Treatment

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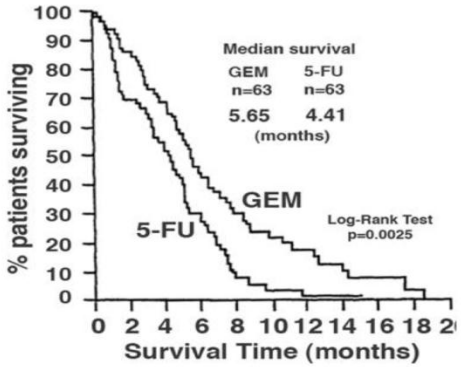
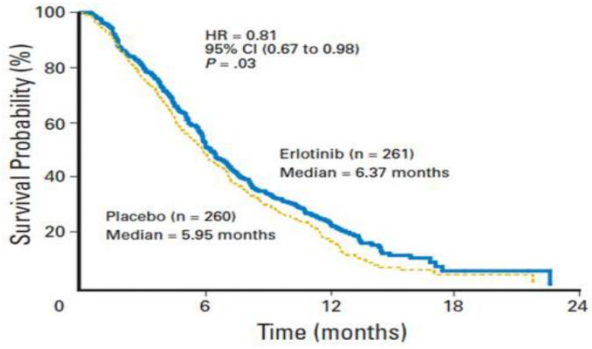
Disappointing Progress in the Treatment of Pancreatic Cancer

1997



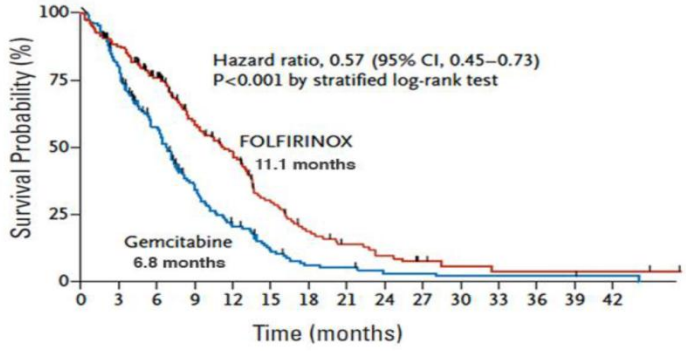
Burris et. al.,
J. Clin. Oncol., 15, 1997

2007



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

2011



Conroy et. al.,
NEJM, 36, 2011

Pancreatic cancer treatment

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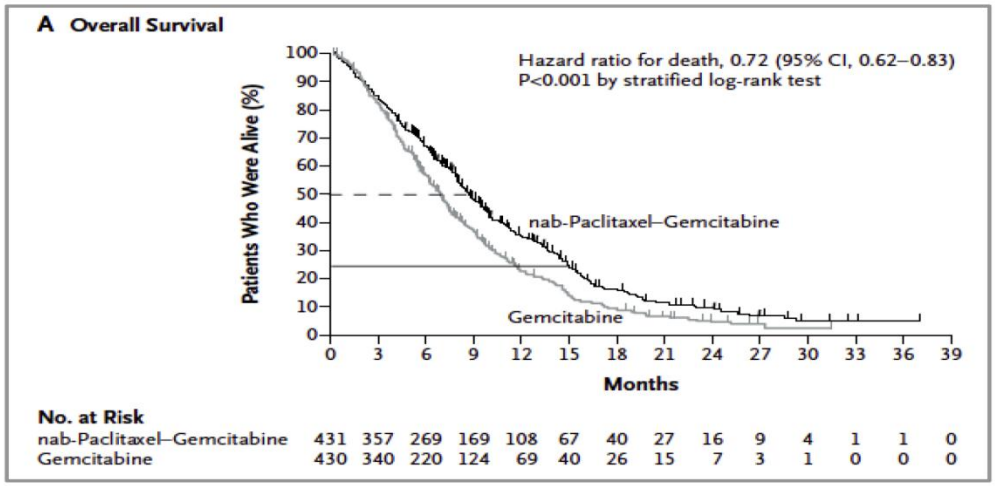
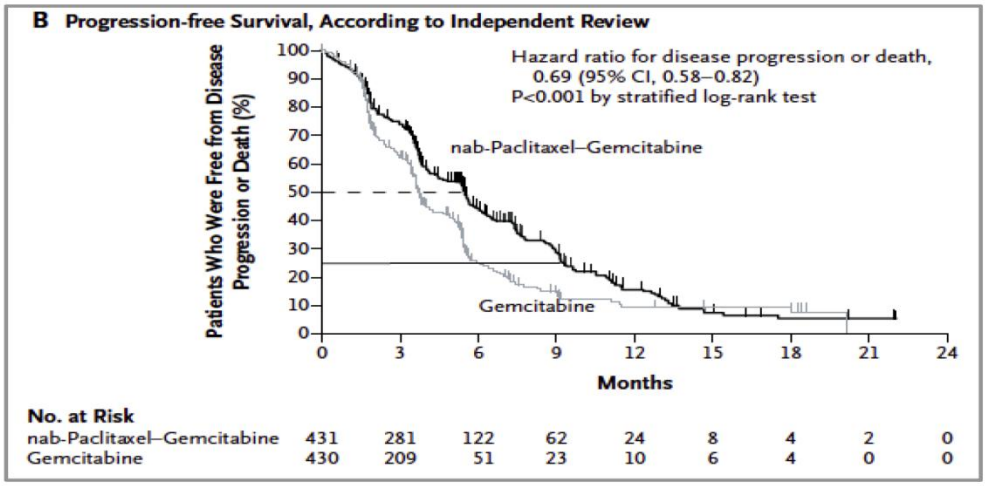
Disappointing Progress in the Treatment of Pancreatic Cancer

- A Combination of nab-Paclitaxel and Gemcitabine Improved Survival in Advanced Pancreatic cancer

2013





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

Improved Survival

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?

Progression Model

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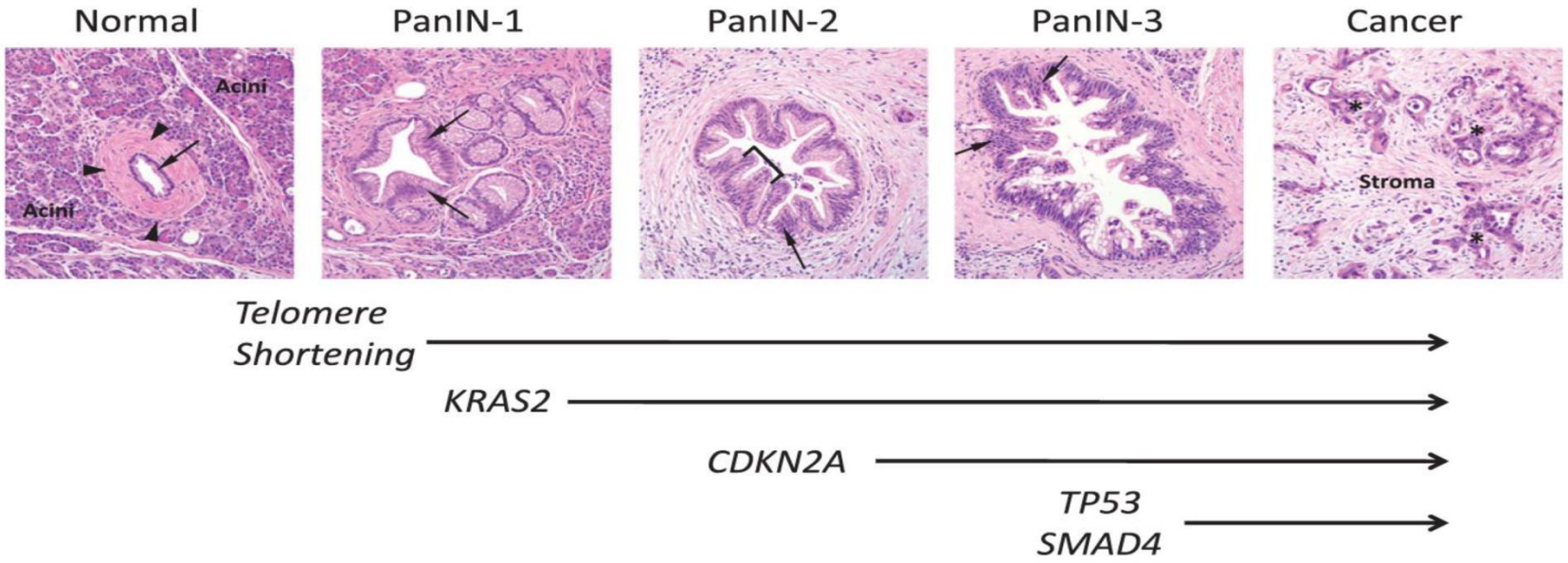
Progression Model of Pancreatic Carcinogenesis



Iacobuzio-Donahue, C.A., Gut, 61, 2012

Desmoplastic stroma

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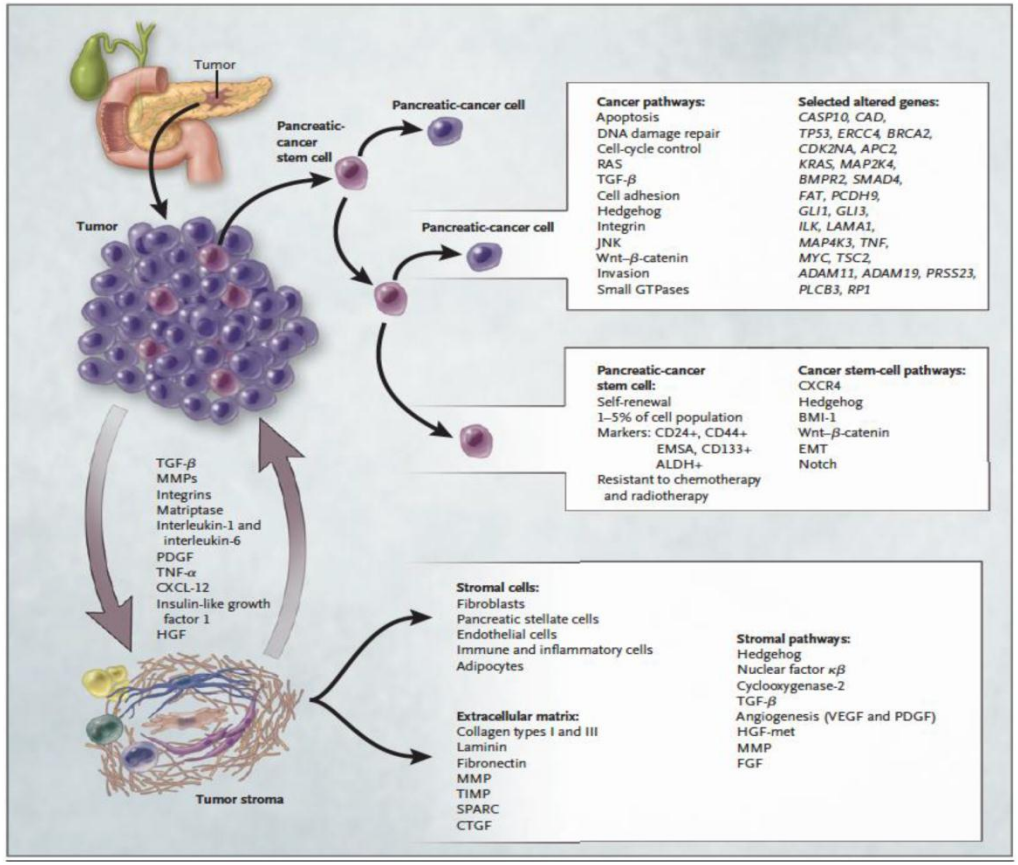
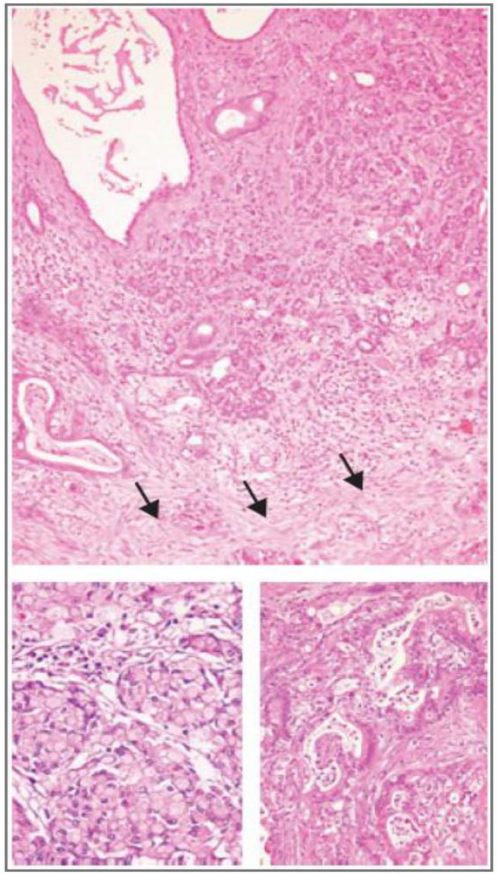
Prominent, Desmoplastic Stroma in Pancreatic Cancer





H/E

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

Pancreatic cancer heterogeneity

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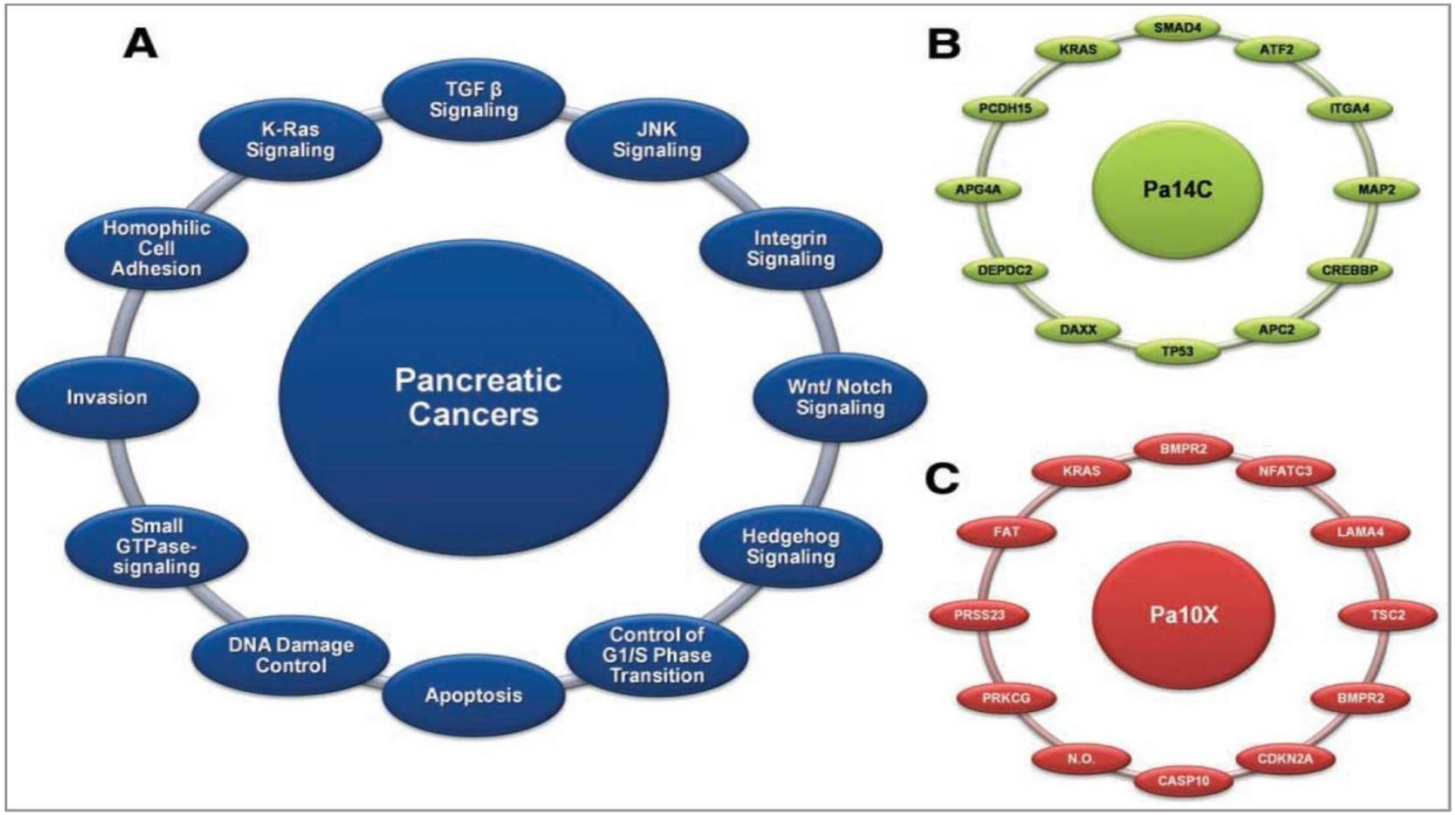
Pancreatic Cancer is Highly Heterogenous



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

PDAC subtypes

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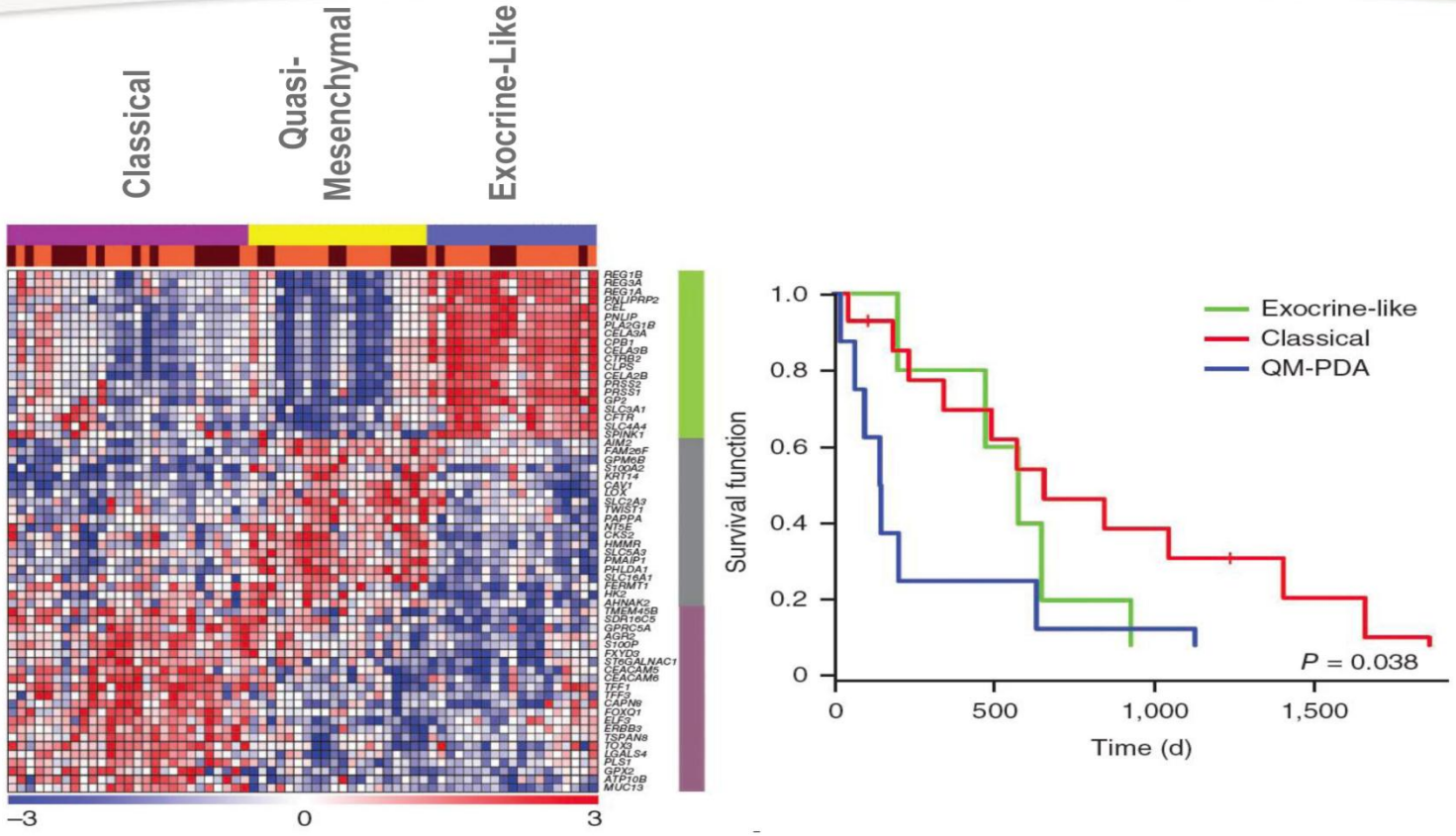
Are There Different Molecular Subtypes of PDAC?



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

Metabolic Reprogramming

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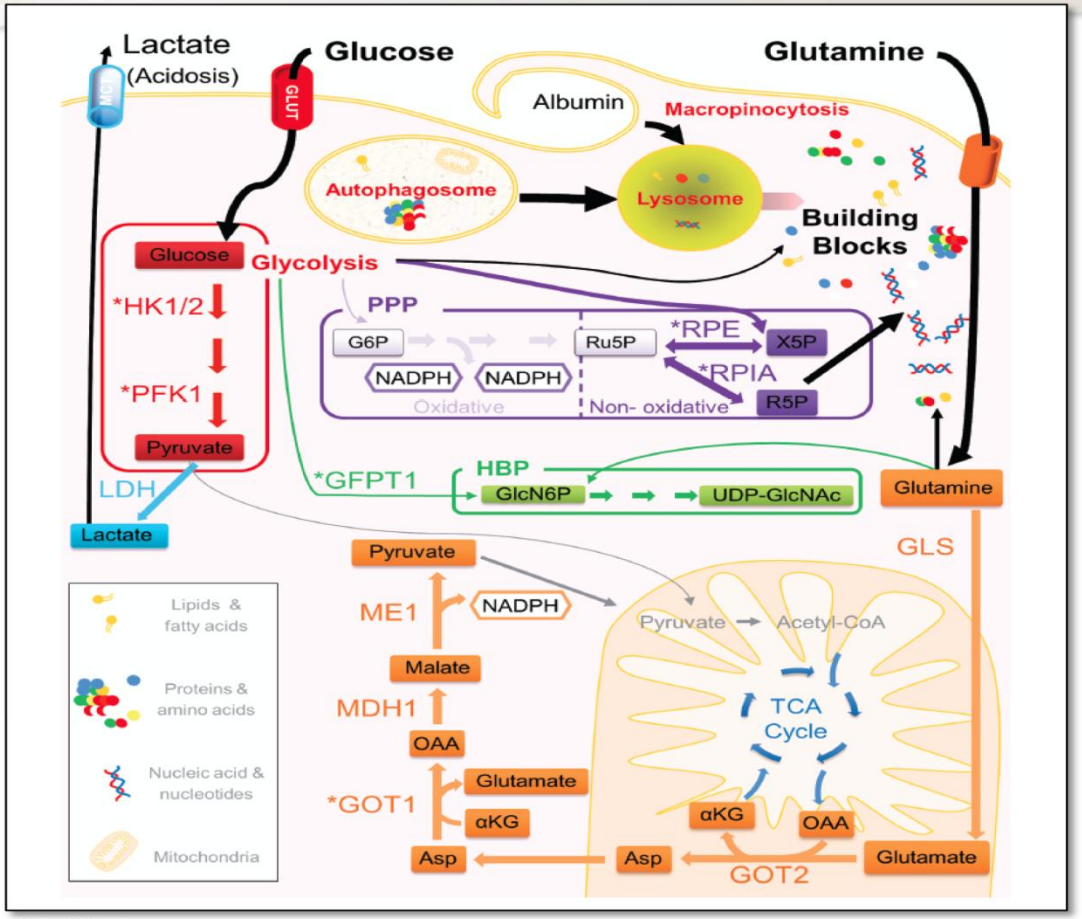
Metabolic Reprogramming in Pancreatic Cancer



Sousa and Kimmelman, Carcinogenesis, 35, 2014

Stromal networks

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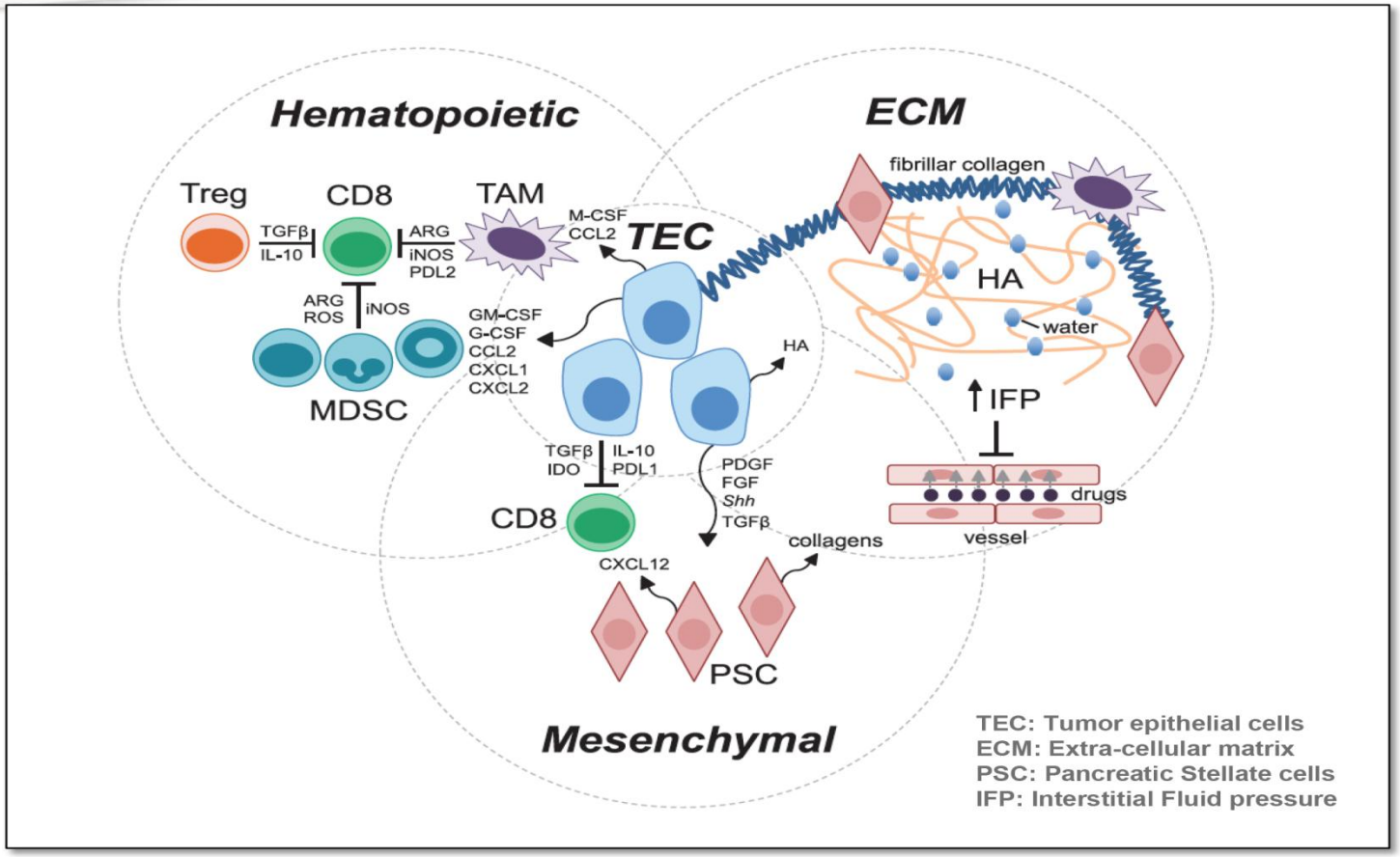
Complex Stromal Networks Supporting Pancreatic Cancer Progression and Therapeutic Resistance



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

Disease outcome

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Treatment Strategies to Improve Disease Outcome

Drug Delivery
and
Effectiveness of Systemic Therapy

↓

Targeting Stroma

Mouse model

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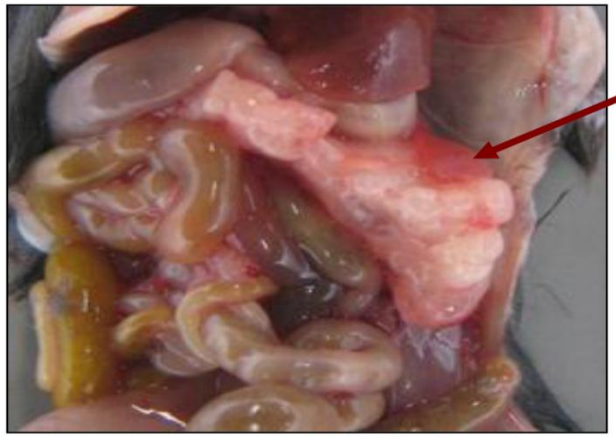
Pancreatic Cancer Mouse Model (KPC)

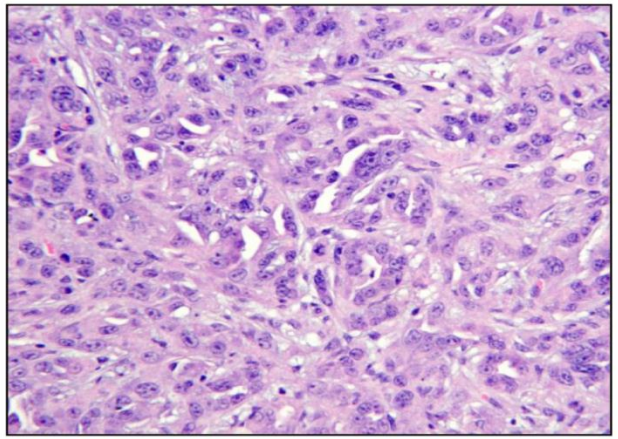
*LSL-Kras-G12D X p53 LSL R172H X Pdx-Cre 1

↓

Pancreatic Ductal Adenocarcinoma (PDAC)

(Median Survival = 4-5 months)





H&E

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

Inhibition of Hedgehog signaling

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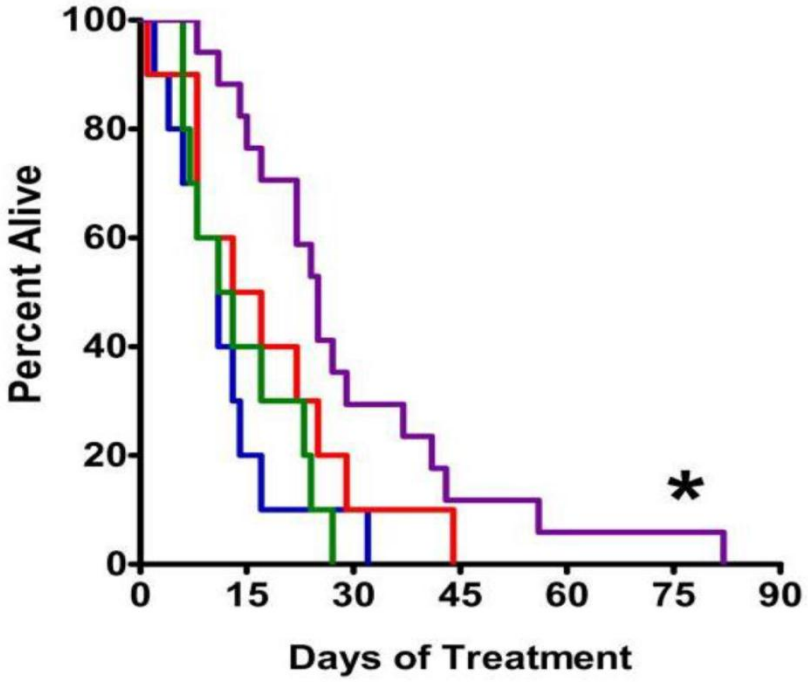
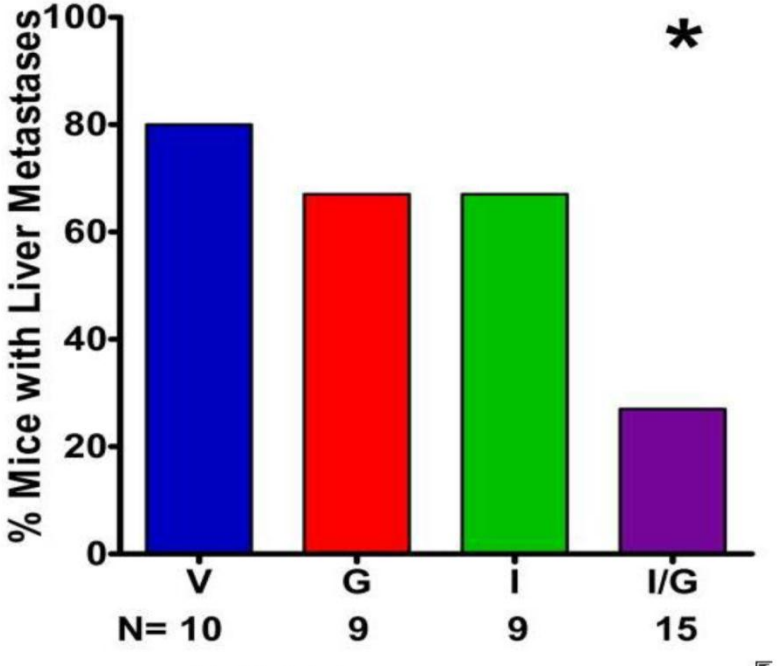
Inhibition of Hedgehog Signaling Depleted Stroma, Enhanced Drug Delivery and Improved Survival in Mice





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

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

Enzymatic targeting

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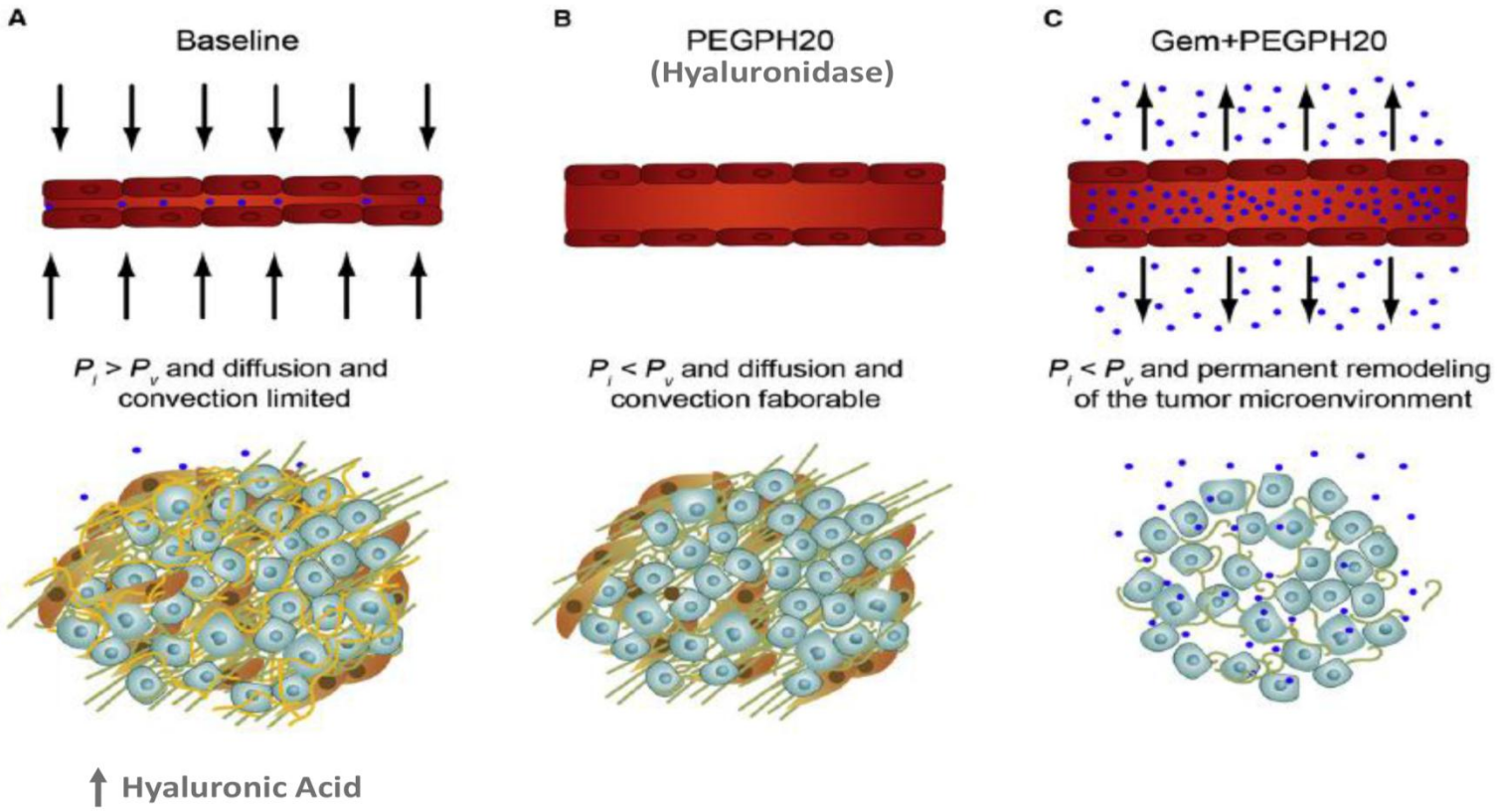
Enzymatic Targeting of Stroma Enhances Therapeutic Response



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

Enzymatic targeting

Enzymatic Targeting of Stroma Enhances Therapeutic Response

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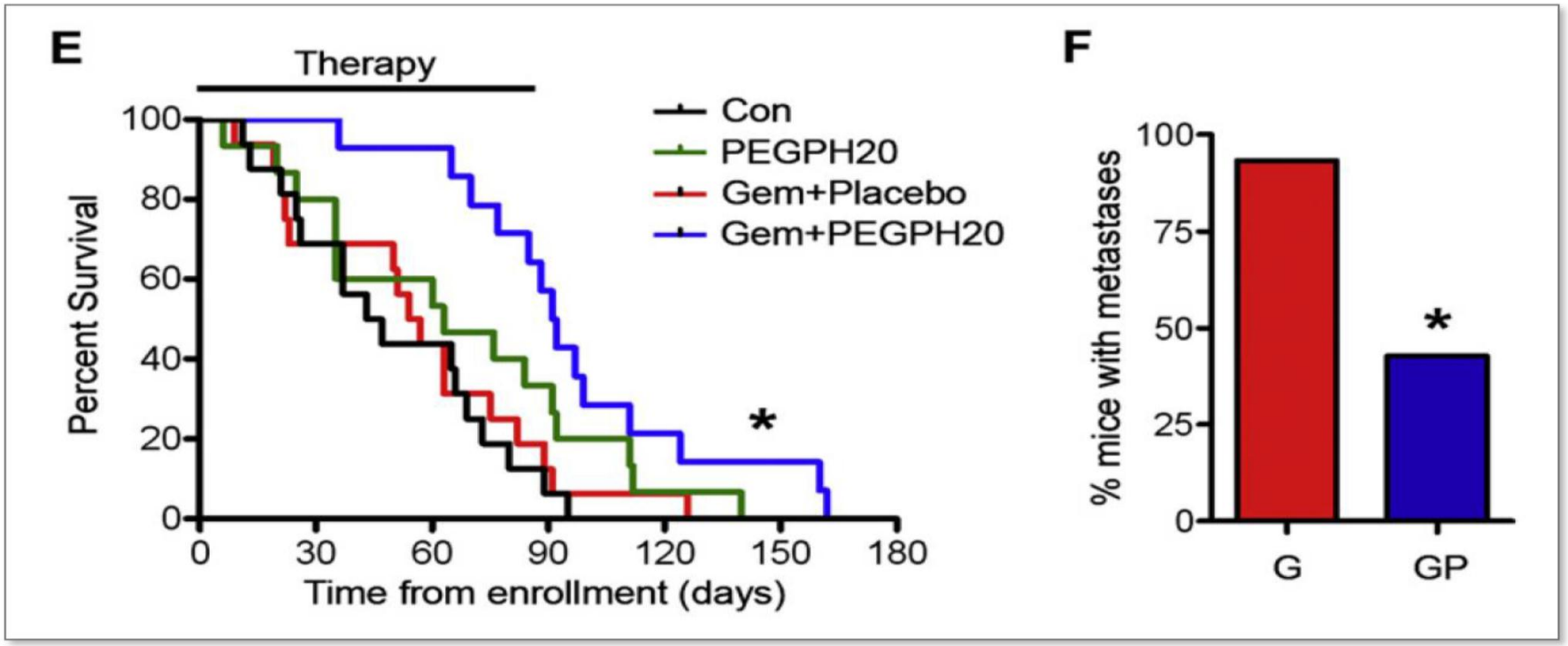

Provenzano et. al., Cancer Cell, 21, 2012

Two Faces of Anti-Stromal Therapy

Two faces of anti-stromal therapy. Stromal-targeting may not (always) have beneficial therapeutic response

Sonic Hedgehog as a tumor suppressor

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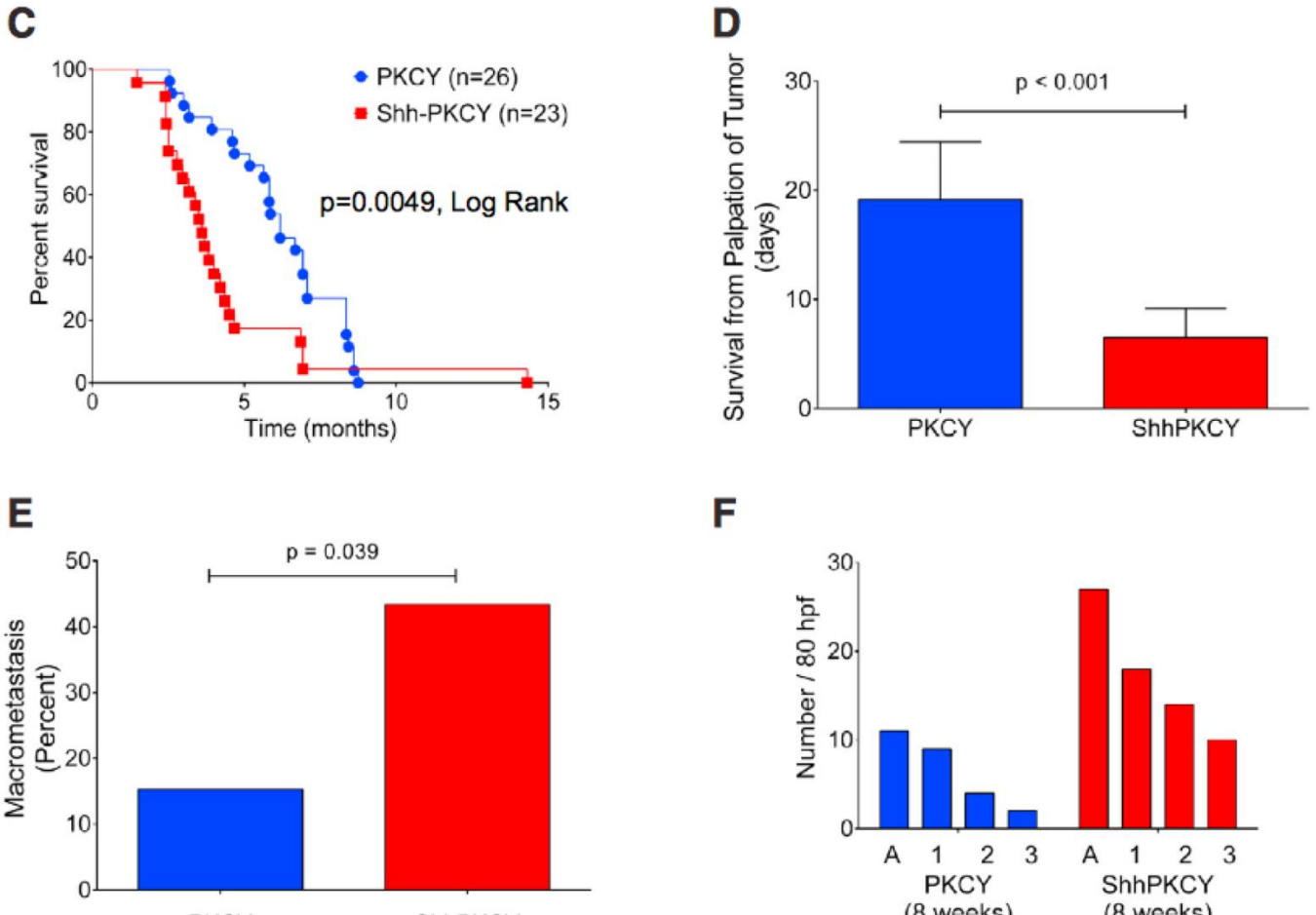
Sonic Hedgehog as a Tumor Suppressor in PDAC

Genetically Engineered Mouse Model



Myofibroblast depletion

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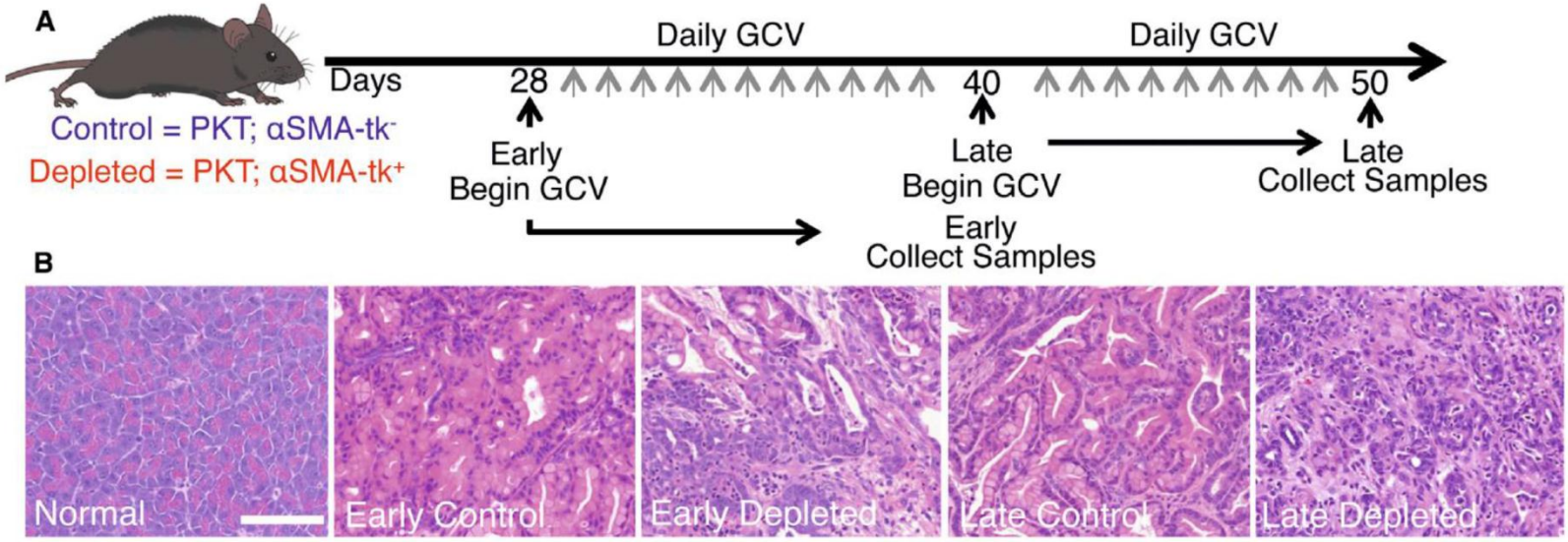
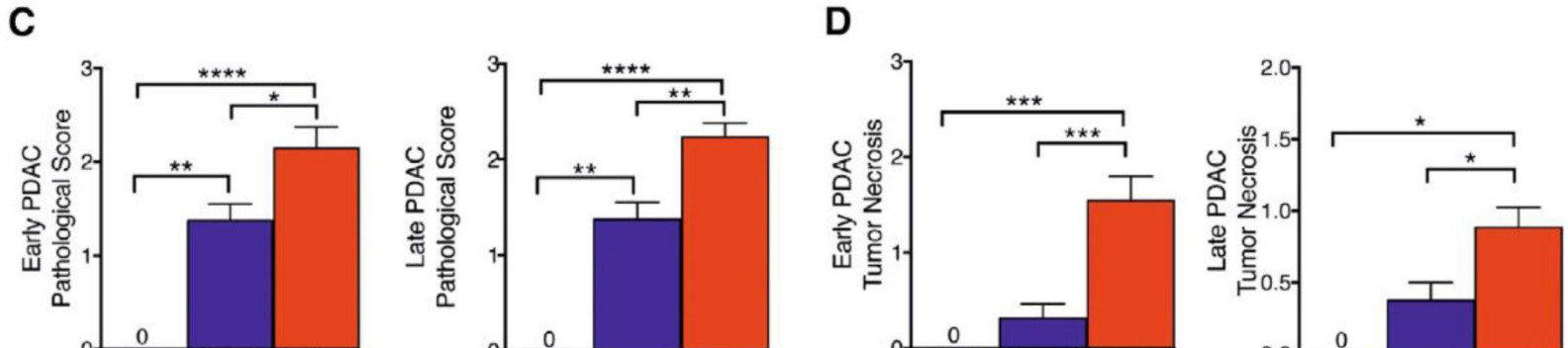
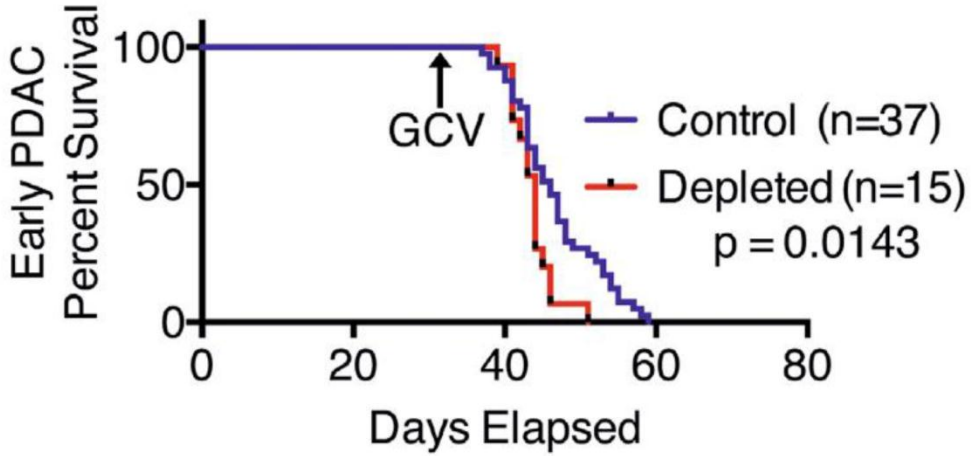
Myofibroblast Depletion Enhances PDAC

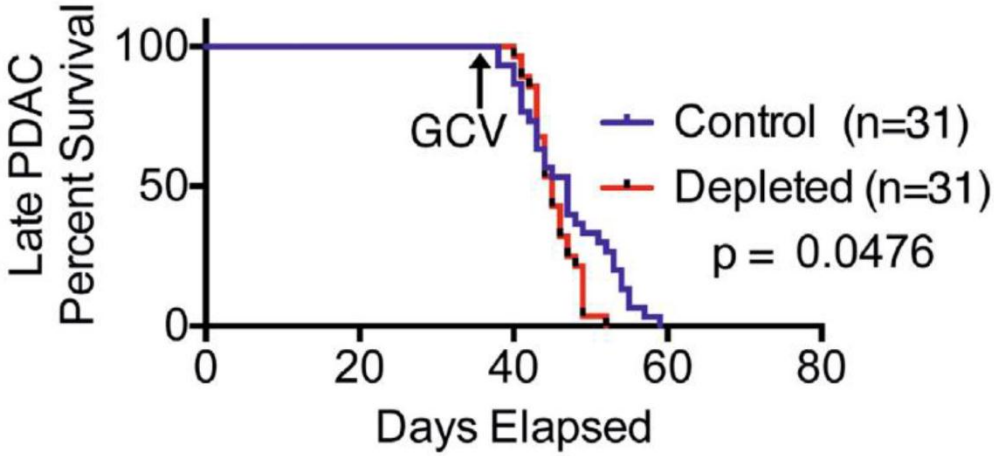




Myofibroblast depletion

Myofibroblast Depletion Reduces Overall Survival





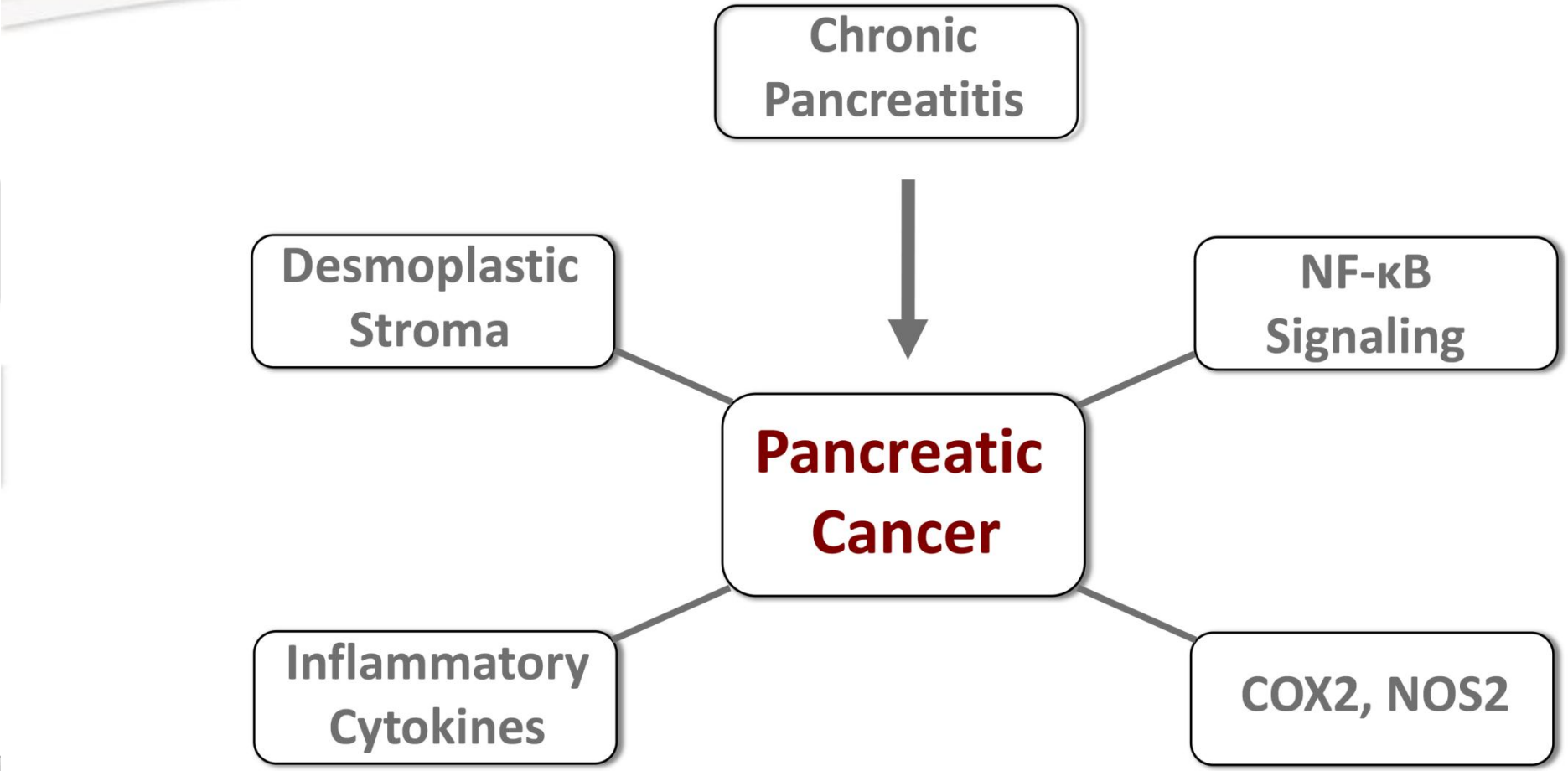
GCV= genciclovir (Depletes Myofibroblasts in PKT;αSMA-tk+ Mice

Complex Tumor-Stromal Interaction in PDAC

Complex tumor-stromal interaction in PDAC Tumor-Stromal interaction is complex and therapeutic approaches targeting stroma may require new molecular taxonomy in pancreatic cancer

Inflammation and pancreatic cancer

Inflammation and Pancreatic Cancer



Inflammatory changes

Inflammatory Changes During Development and Progression of Pancreatic Cancer

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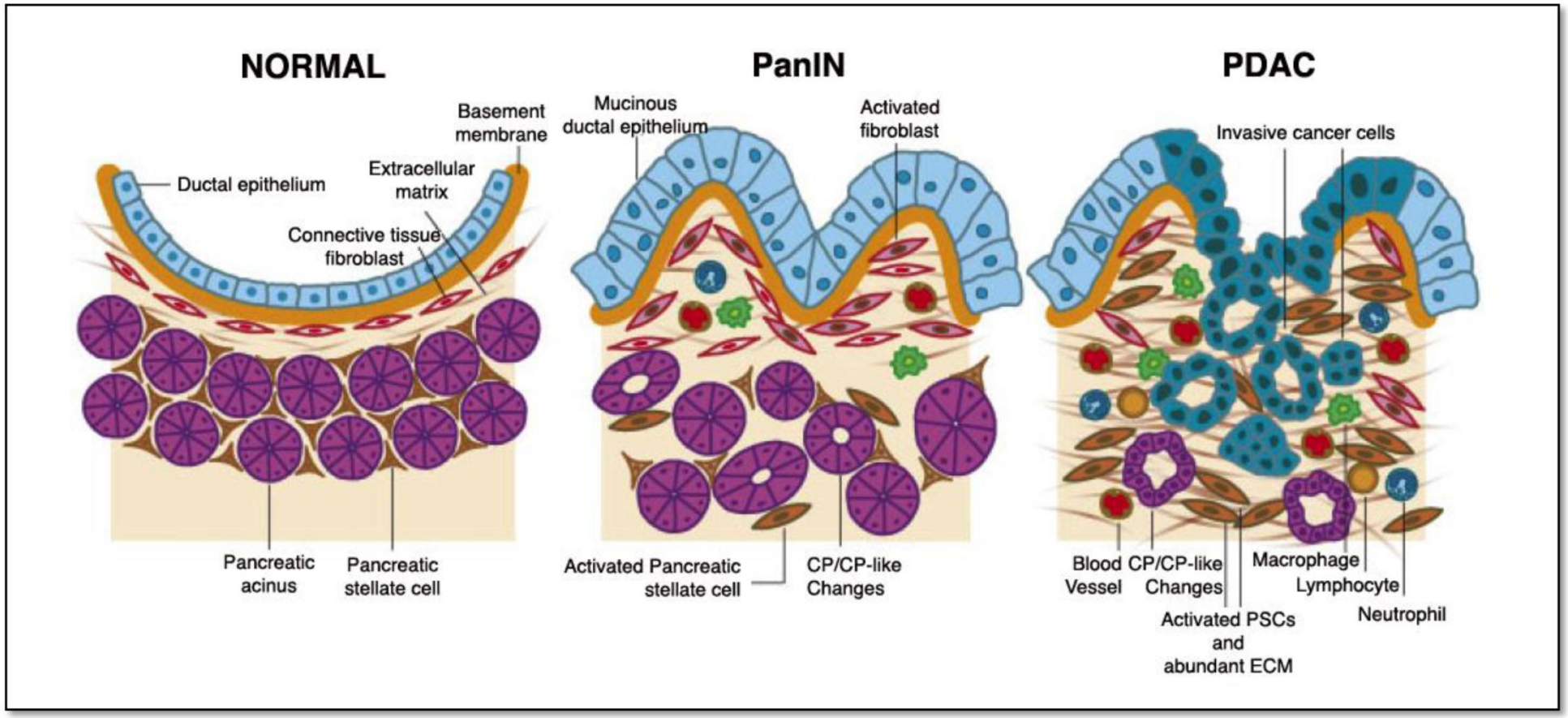

Kras in pancreatic cancer

Inflammation Enhances and Maintains a Pathologic Level of Oncogenic KRAS in Pancreatic Cancer

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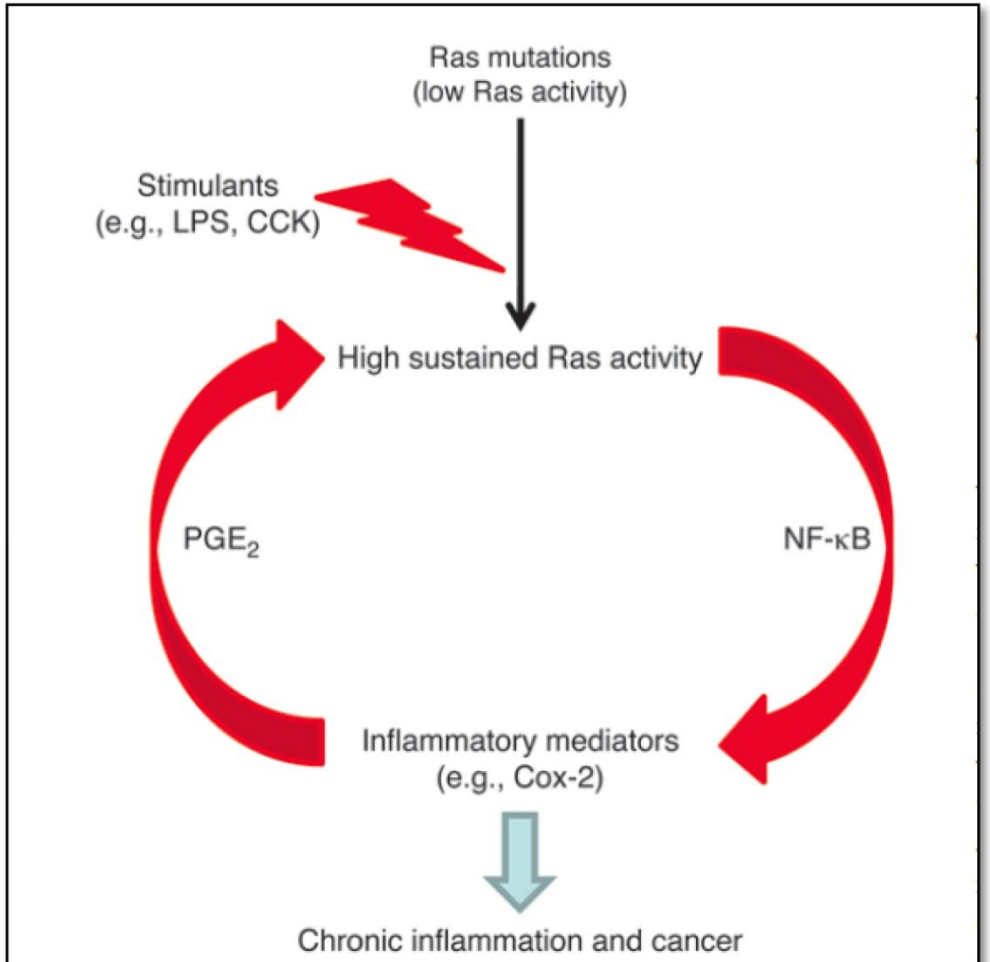

Macrophage inhibitory factor (MIF)

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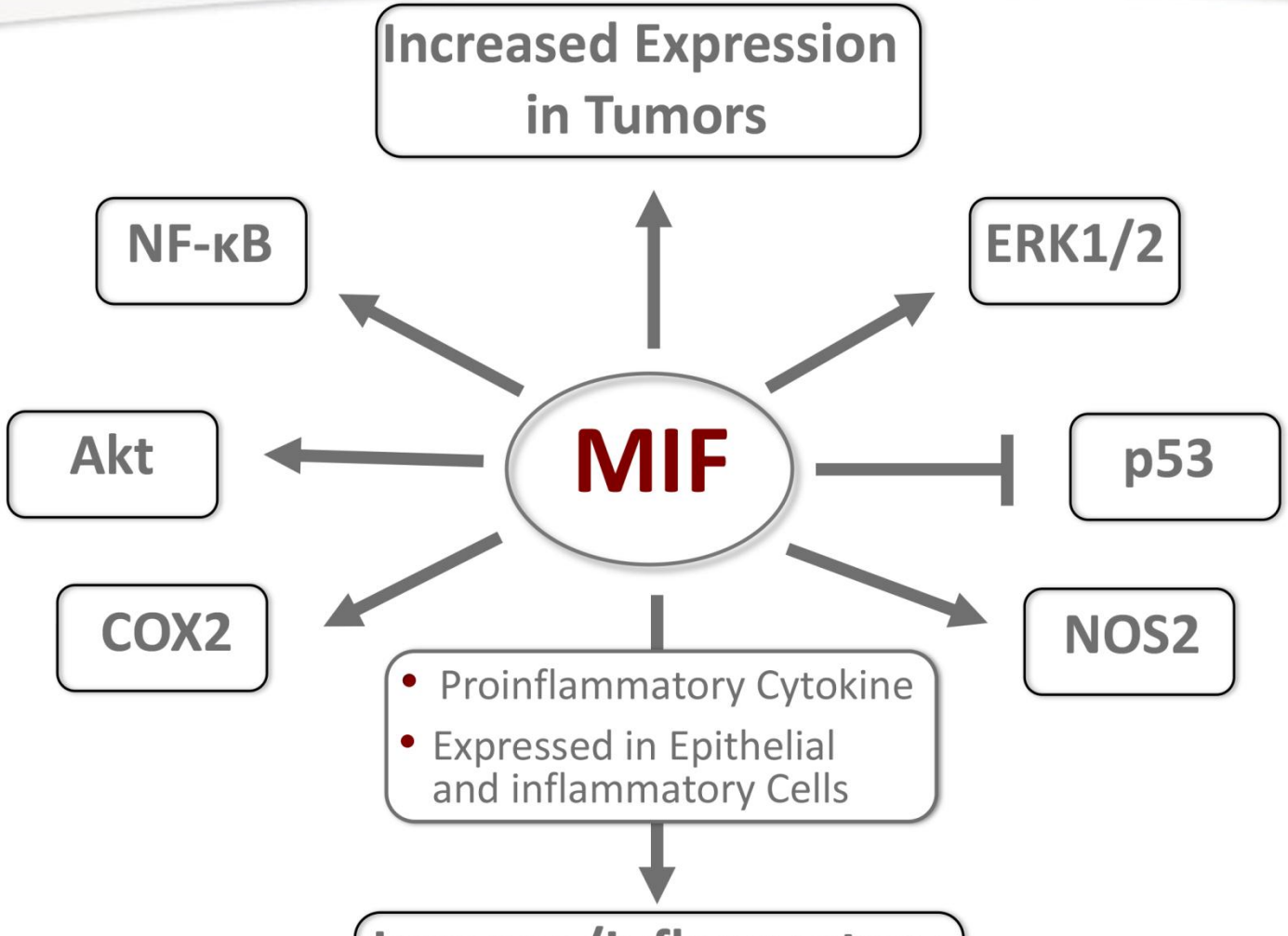
Macrophage Migration Inhibitory Factor (MIF)



MIF, Inflammation and Cancer

MIF, Inflammation and Cancer

J. Exp. Med., 190, 1999

At the Crossroads of Inflammation and Tumorigenesis

By Carlos Cordon-Cardo* and Carol Prives‡

*From the *Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021; and the ‡Department of Biological Sciences, Columbia University, New York, New York 10027*

Molecular Cell, Vol. 17, 225–236, January 21, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.molcel.2004.11.052

Macrophage Migration Inhibitory Factor MIF Interferes with the Rb-E2F Pathway

Oleksi Petrenko* and Ute M. Moll*

Immunity, 26, 2007

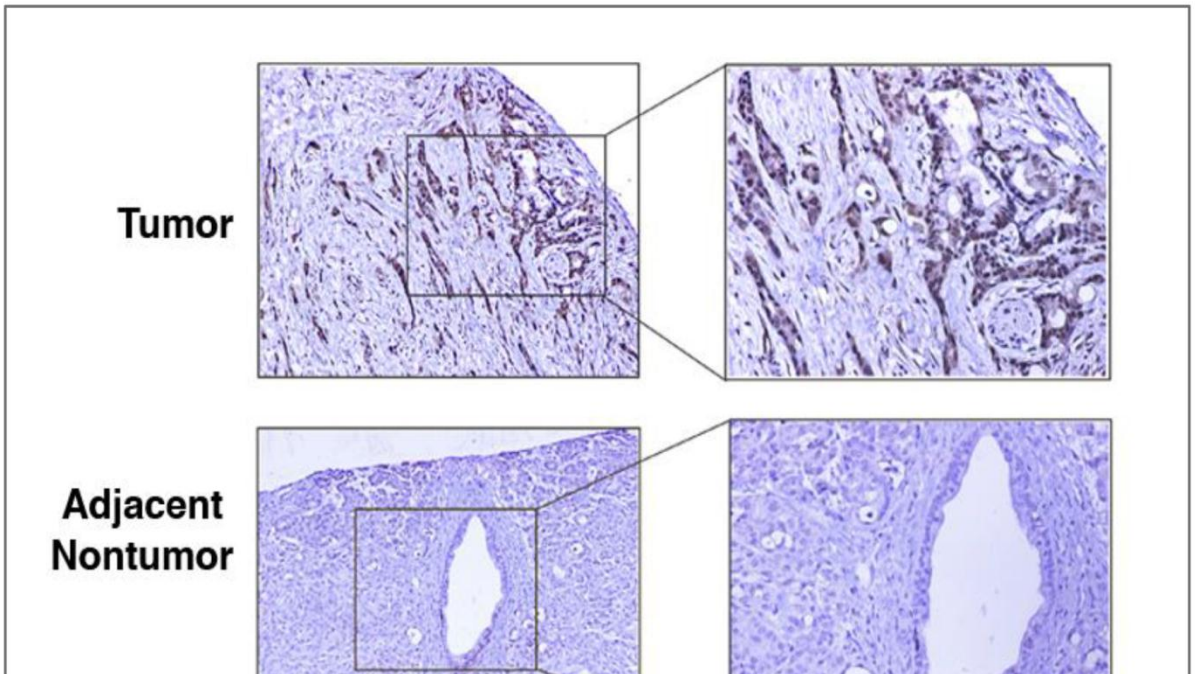
Perspective

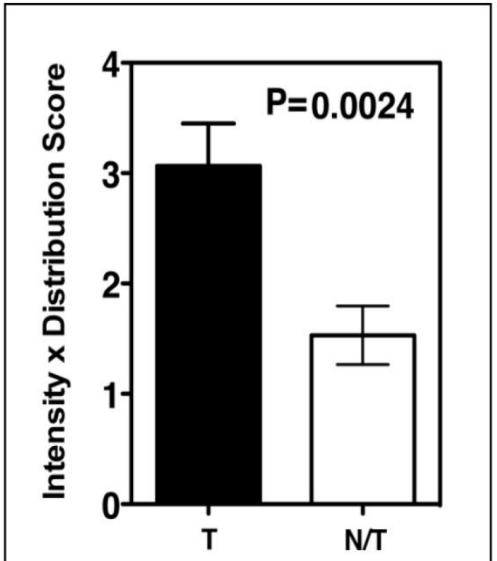
Cell PRESS

Macrophage Migration Inhibitory Factor:

Increased Expression of MIF in Tumors from Pancreatic Carcinoma Cases

Increased Expression of MIF in Tumors from Pancreatic Carcinoma Cases





A Higher Expression of MIF is Associated with Poor Survival in Human Pancreatic Carcinoma Cases

A Higher Expression of MIF is Associated with Poor Survival in Human Pancreatic Carcinoma Cases

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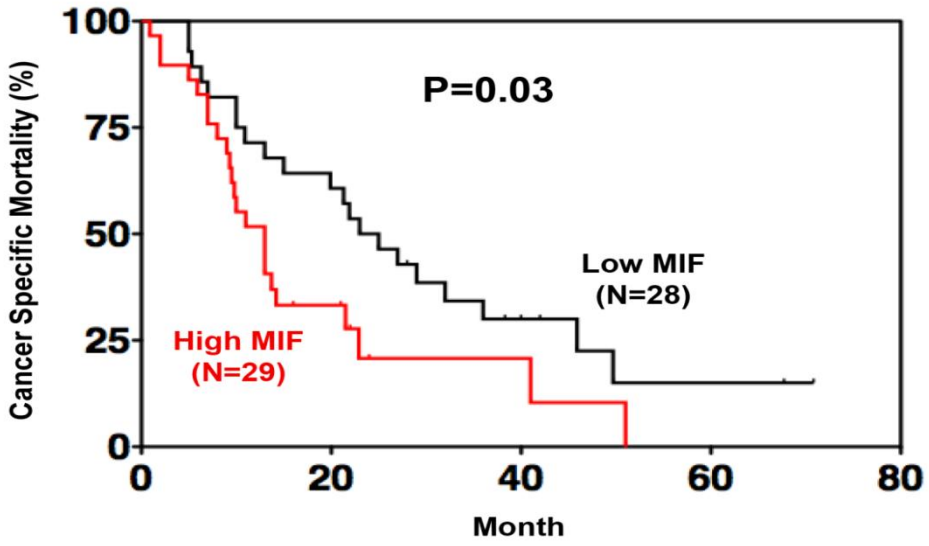
Human Pancreatic Carcinoma Cases



Variables (comparison/referent)	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
MIF (High/Low)	2.21 (1.16-4.22)	0.016	2.26 (1.17-4.37)	0.015
Grading (G3-4/G1-2)	1.86 (1.01-3.45)	0.048	1.90 (1.02-3.54)	0.044
Resection margin (R1/R0)	1.53 (0.82-2.83)	0.178		
Stage (IIB-III/I-IIA)	1.62 (0.79-3.36)	0.191		

Funamizu, N.....Hussain, S.P., Int. J. Cancer, 132, 2012

A higher expression of MIF is associated with poor survival in human pancreatic carcinoma cases

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A Higher Expression of MIF is Associated with Poor Survival in Human Pancreatic Carcinoma Cases

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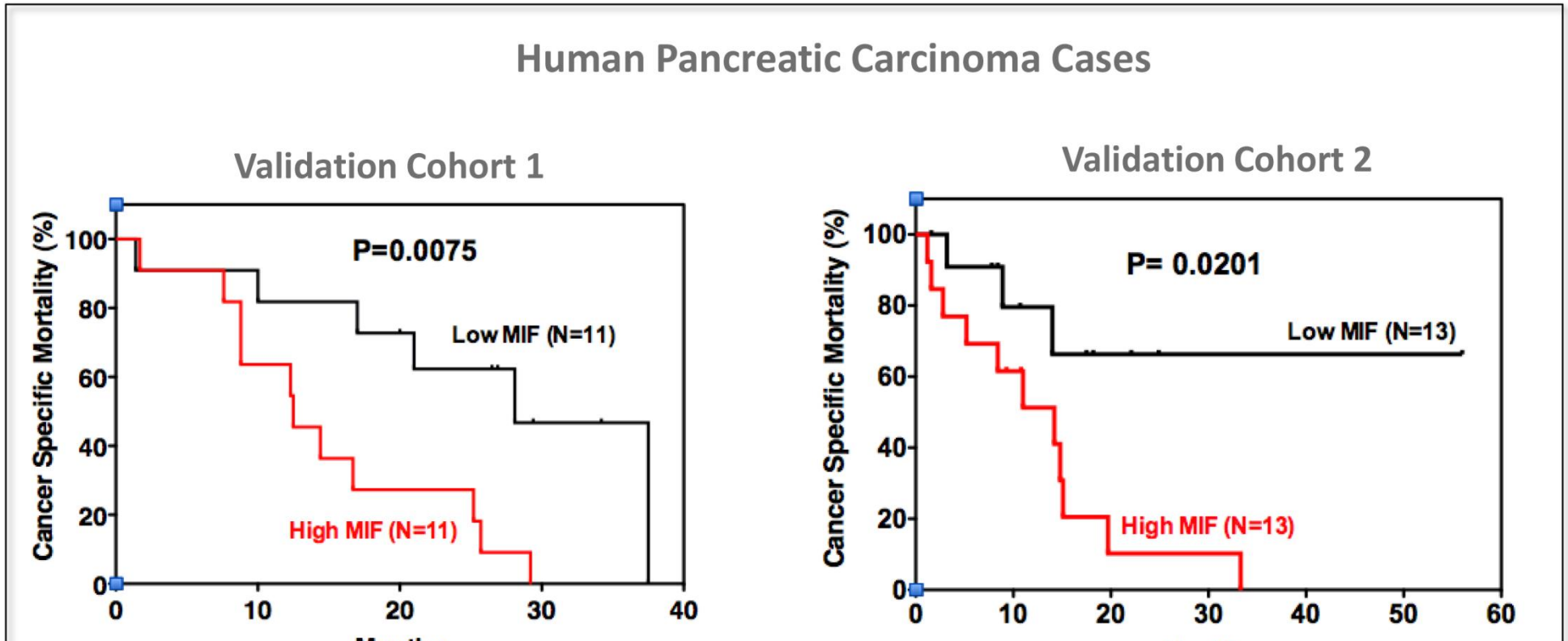
Validation in Independent Cohorts



EMT Enhances Malignant Progression

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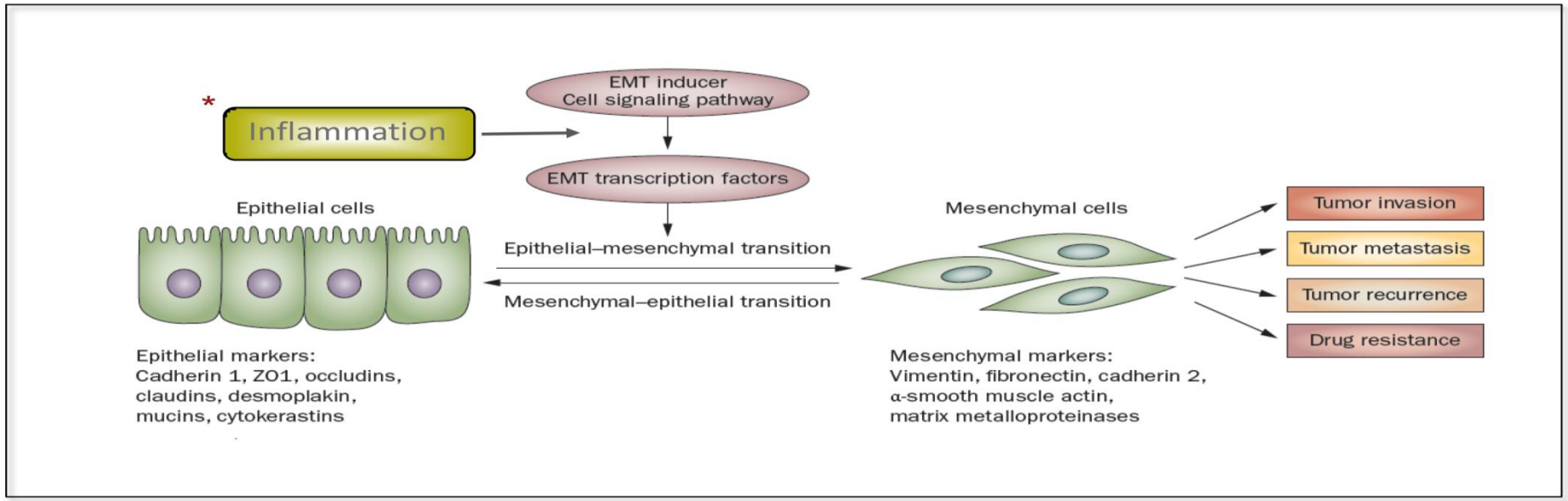
EMT Enhances Malignant Progression in Pancreatic cancer



Wang et. al., Nat. Rev. Gastroenterology & Hepatol., 2011

* Rhim et. al., Cell, 2012.

MIF Induces EMT

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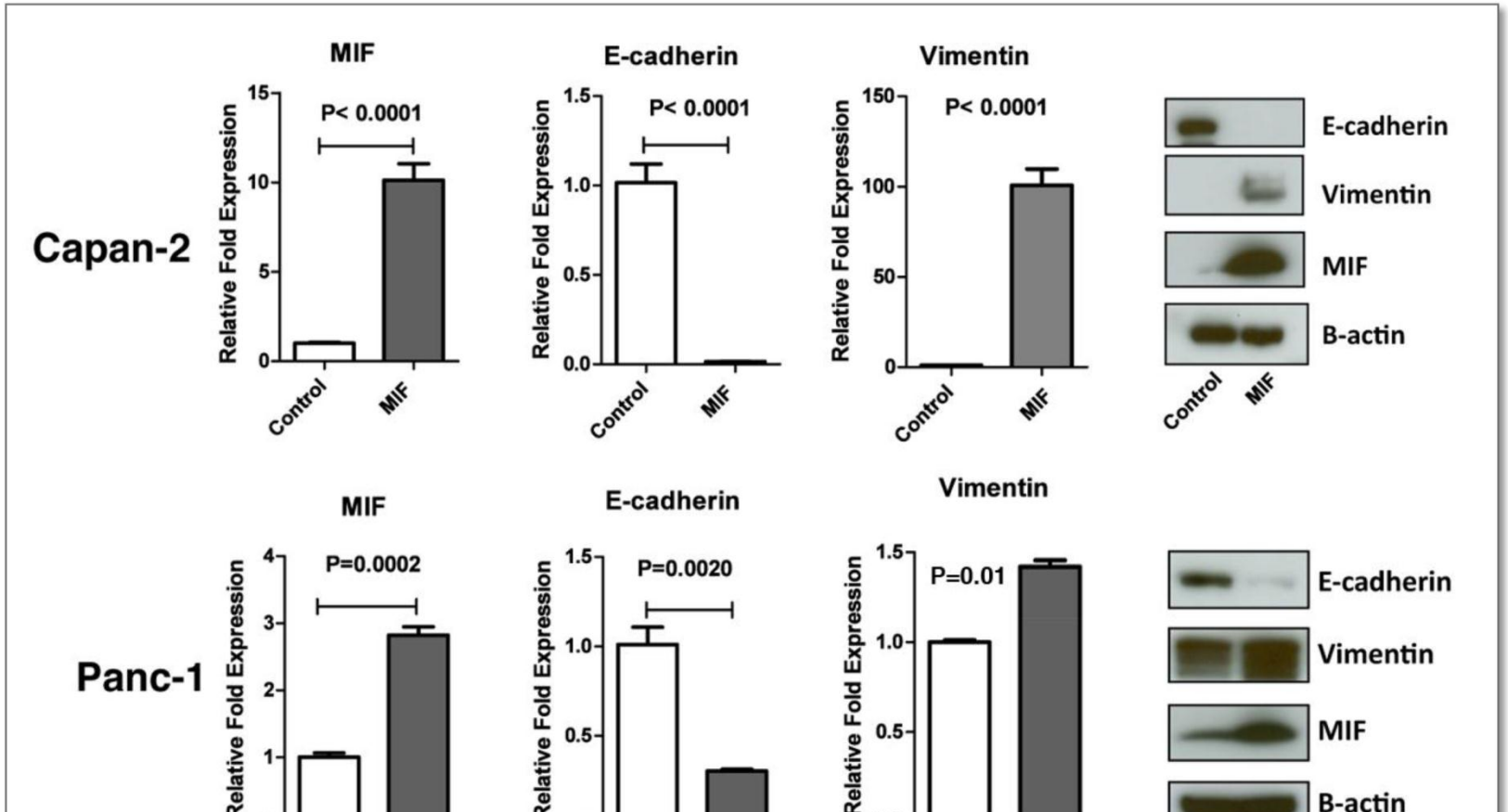
MIF induces EMT in Pancreatic Cancer Cells



MIF Induces EMT in Pancreatic Cancer Cells

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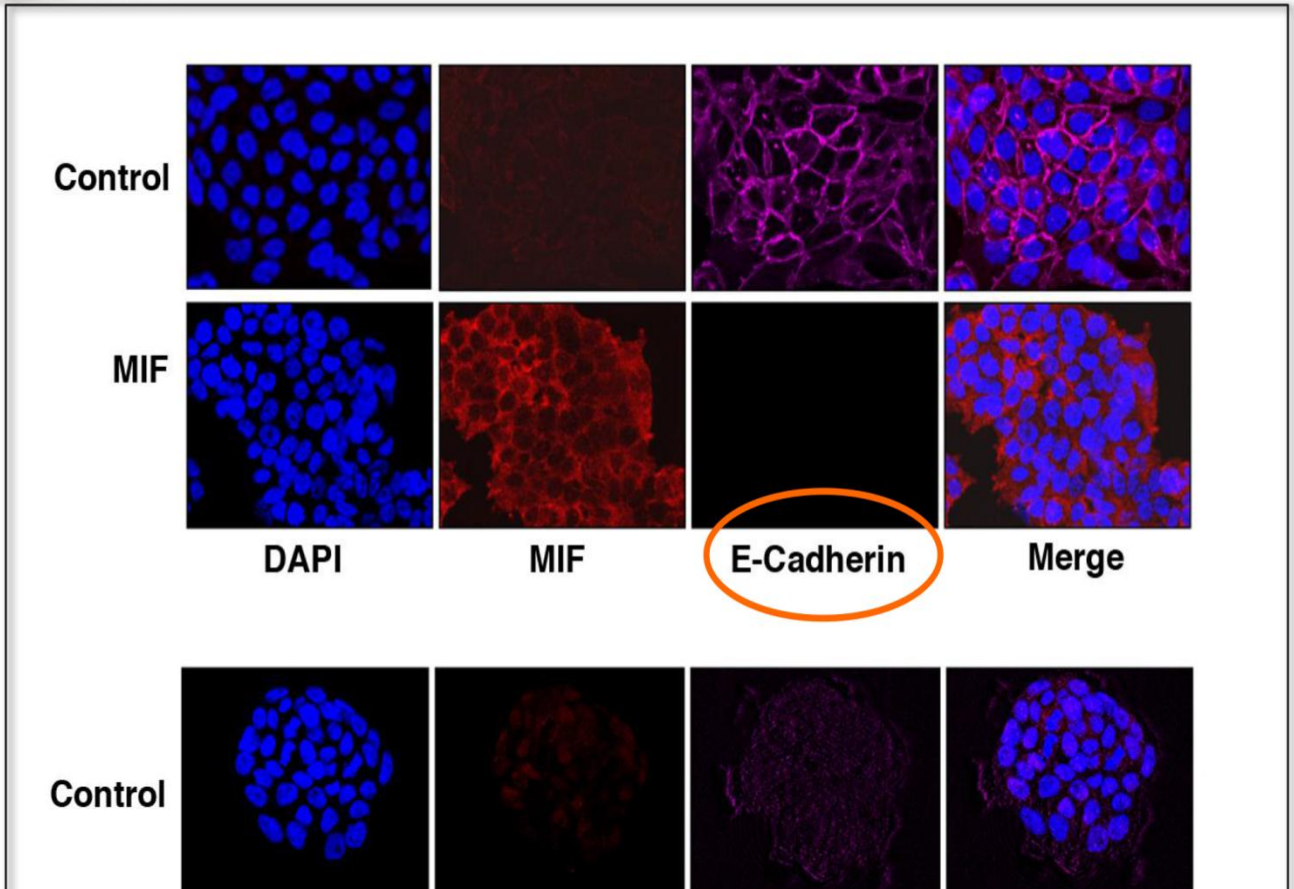
MIF Induces EMT in Pancreatic Cancer Cells



MIF accelerates tumor growth

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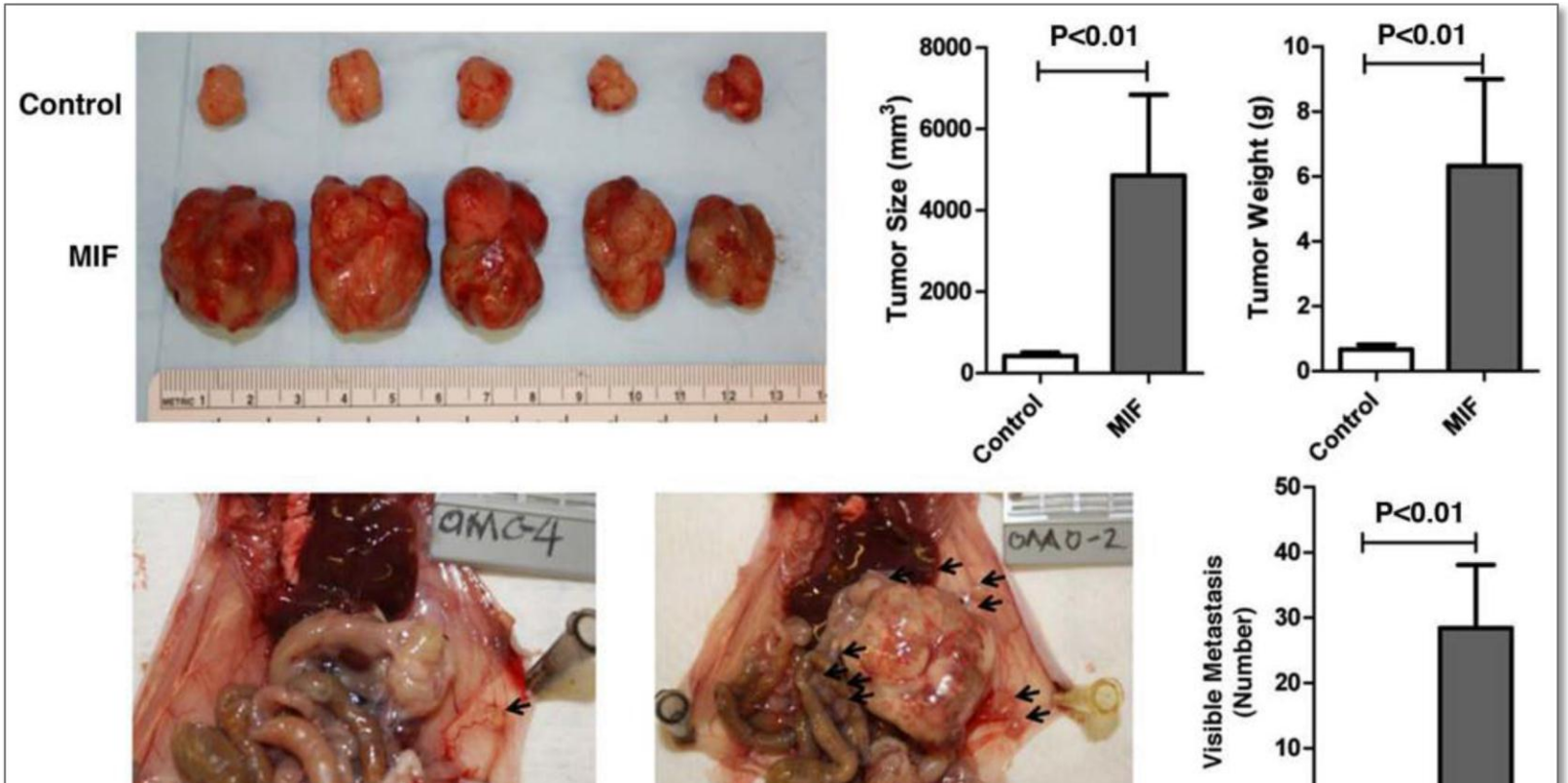
MIF Accelerates Tumor Growth and Metastasis in Orthotopic Xenografts in Mice



MIF alters Global Gene Expression Profile

MIF Induces a Marked Change in Global Gene Expression Profile including EMT-related Genes in Orthotopic Tumors

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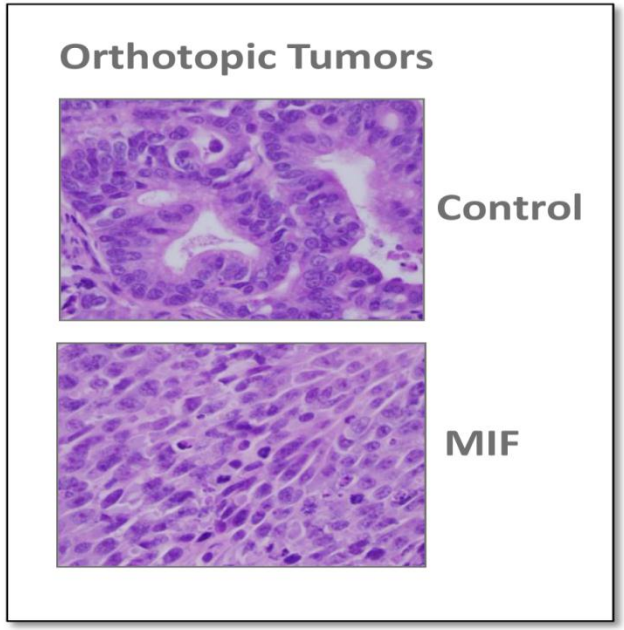
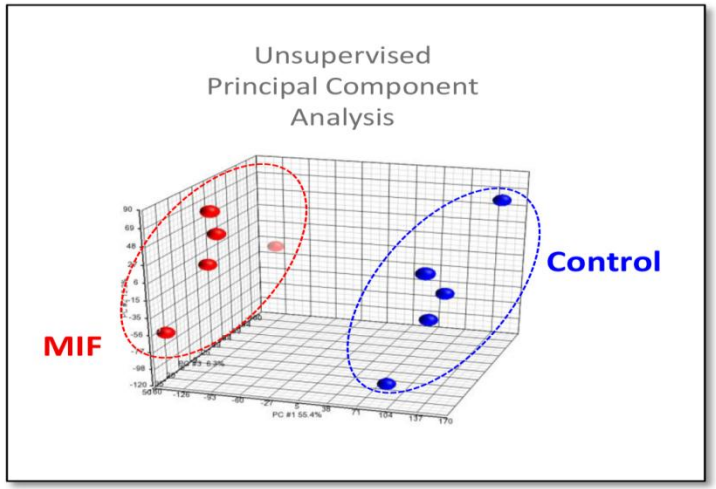
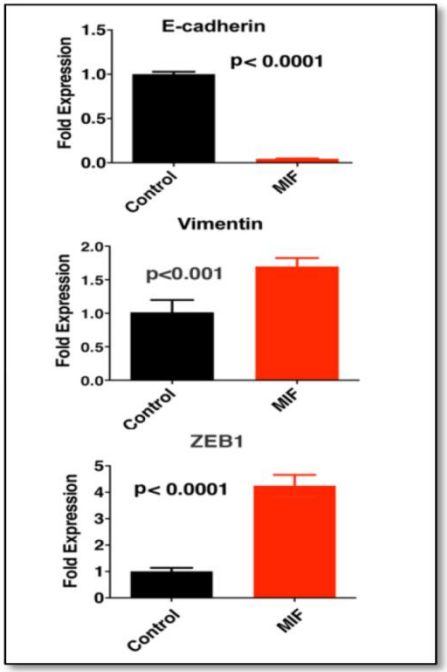






- MIF over-expressing tumors are poorly differentiated.
- MIF induces a change in global gene expression profile.
- MIF over-expressing tumors showed expression of EMT-related genes.

MIF Enhances Cancer Progression

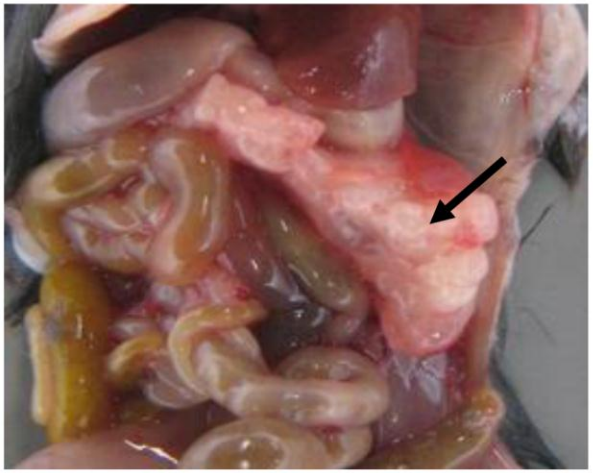
Ongoing Study

HYPOTHESIS: MIF Enhances Pancreatic Cancer Progression

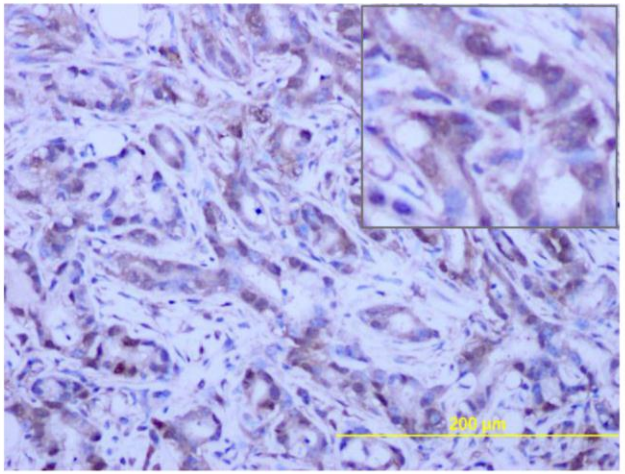
Pancreatic Tumors in KPC Mice Express a High Level of MIF

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

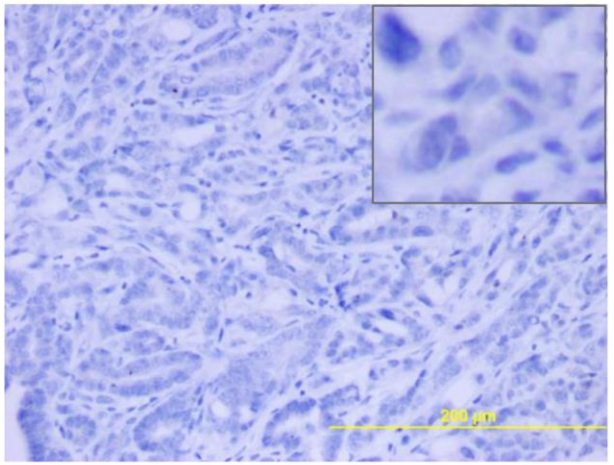
MIF Immunostaining



KPC



KPC



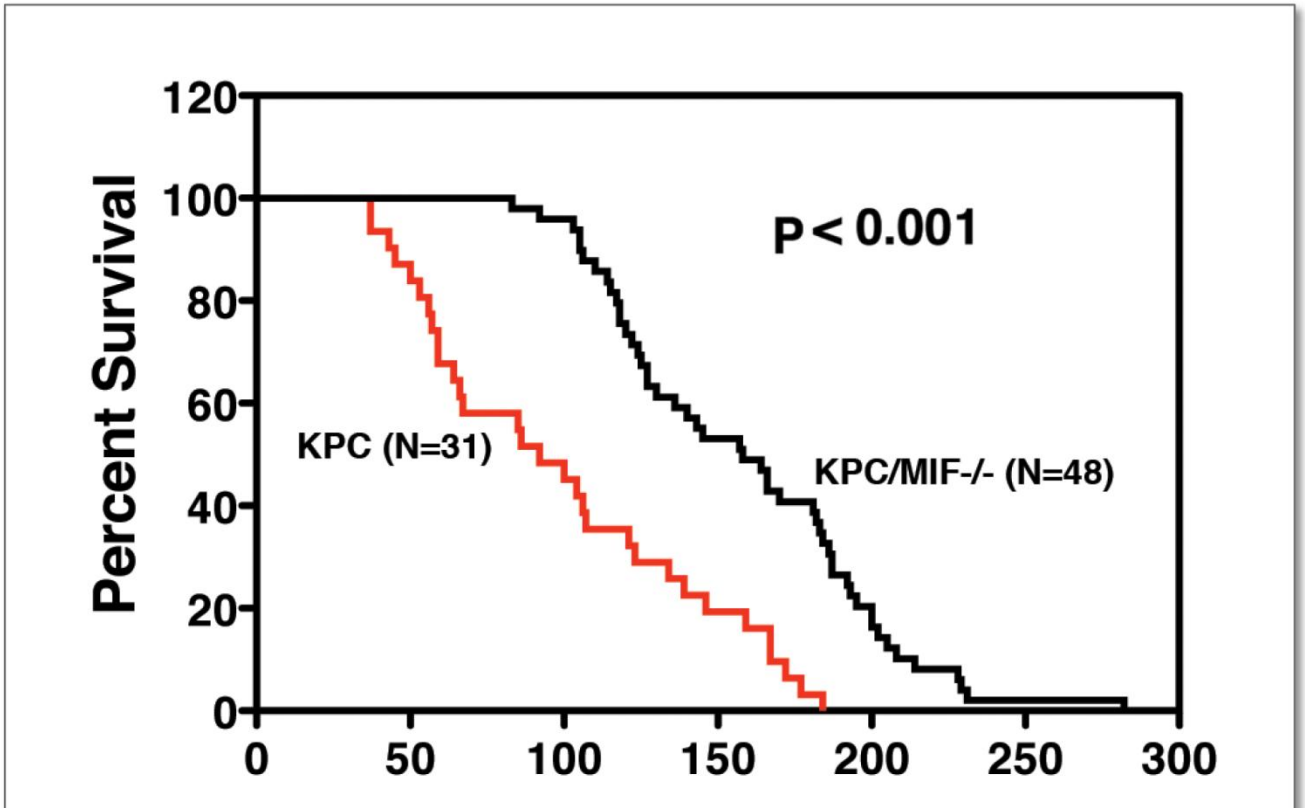
KPC/$MIF^{-/-}$

MIF and cancer progression

Ongoing Study

HYPOTHESIS: MIF Enhances Pancreatic Cancer Progression

MIF-Deficient KPC Mice Show Longer Survival



SUMMARY

SUMMARY

- A higher MIF expression is associated with poor outcome in PDAC patients.
- MIF induces EMT in pancreatic cancer cell lines.
- MIF enhances growth and metastasis of tumor xenografts in mice.
- MIF-deficiency increases survival in KPC mice with lethal PDAC.
- MIF may be a candidate target for designing improved treatment.

Pancreatic Tumor Biology

Understanding Pancreatic Tumor Biology is Key to Improving Disease Outcome