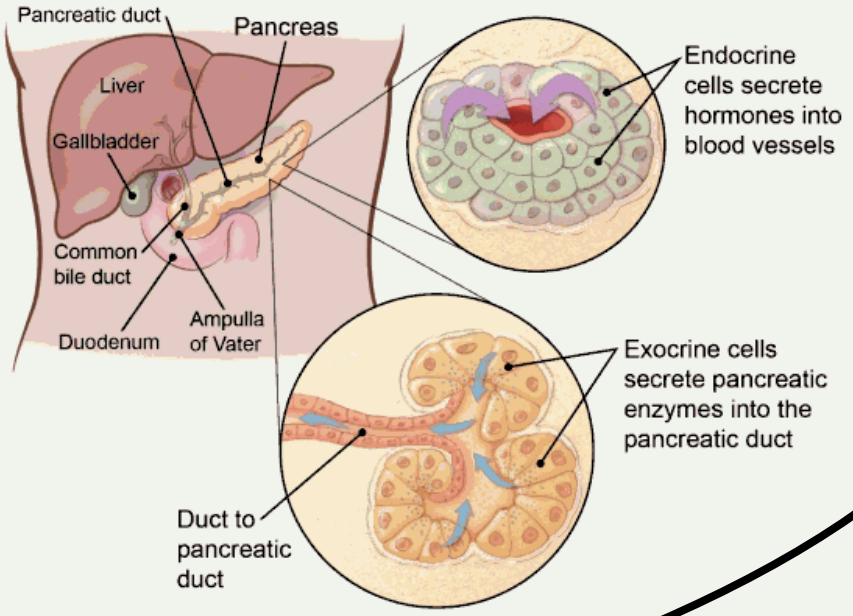
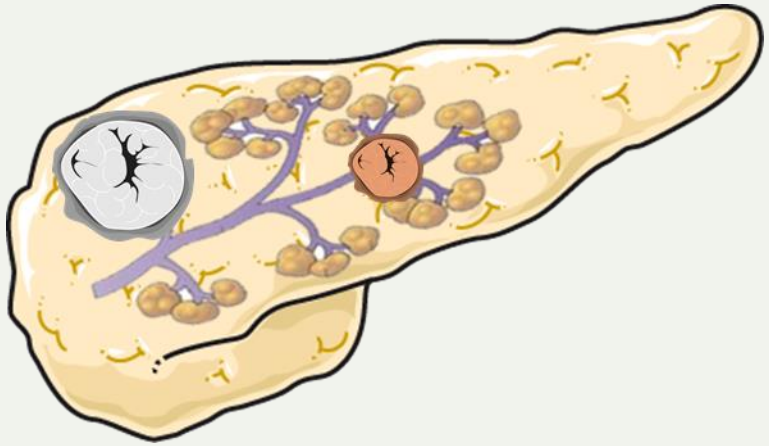
Molecular basis of pancreatic cancer chemoresistance:

Emerging role of microRNAs and metabolism

Pancreatic Cancer





Pancreatic Ductal AdenoCarcinoma (PDAC)

Exocrine cells

93 %

7 %

NeuroEndocrine Tumor (NETs)

Endocrine cells

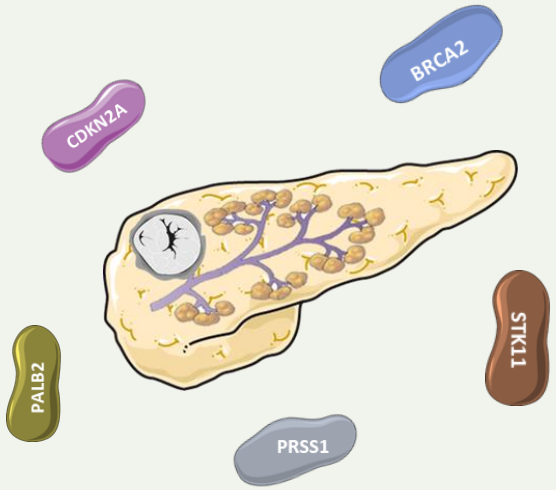
Risk factors

Modificable Risk Factors

- *Smoking*
- *Alcohol*
- *Obesity*
- *Dietary factor*
- *Occupational exposures*
- *Diabetes*

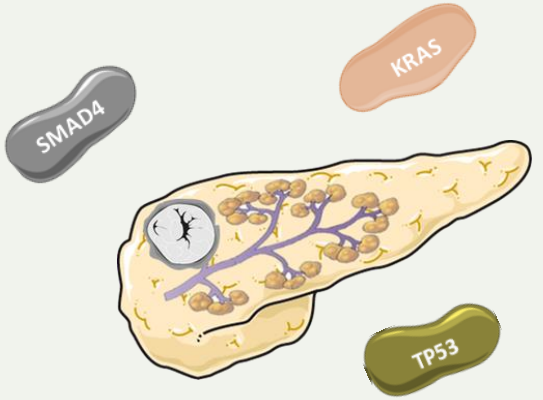
Genetic Factors

Germ-line mutations



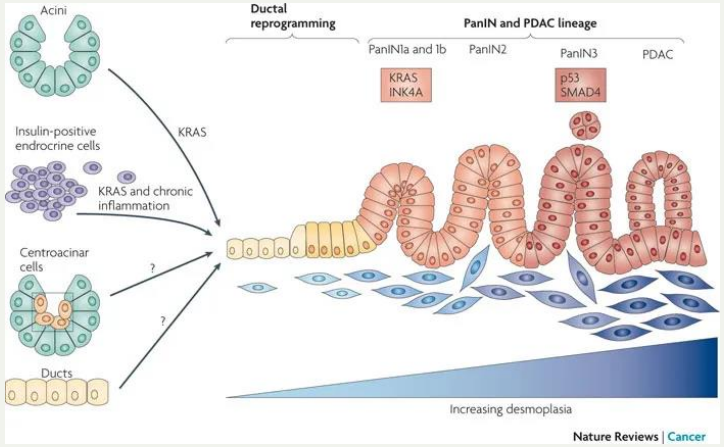
BRCA2
CDKN2A
STK11
PALB2
PRSS1

Somatic mutations



KRAS
TP53
SMAD4
p16

Approximately **10**% of **PDAC** have a familial **inheritance**



Let's talk numbers…

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%**

Cancer Statistics, 2019
CA CANCER J CLIN 2019;69:7–34

Median Age at Diagnosis

70

Survival Statistics

Based on data from SEER 18 2009-2015. Gray figures represent those who have died from pancreatic cancer. Blue figures represent those who have survived 5 years or more.

Lack of appropriate diagnosis

Chemoresistance

Treatment

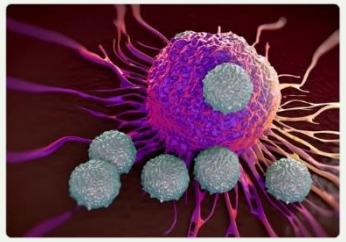
10–20%: Resectable PDAC
50%: metastatic PDAC
35% locally advanced PDAC

Surgical Resection

Chemotherapy

- *Gemcitabine*
- *FOLFIRINOX*
- ABRAXANE (nab-Paclitaxel)

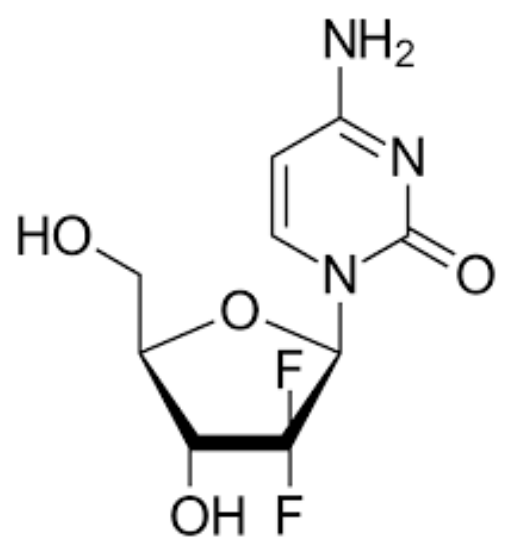
Radiotherapy

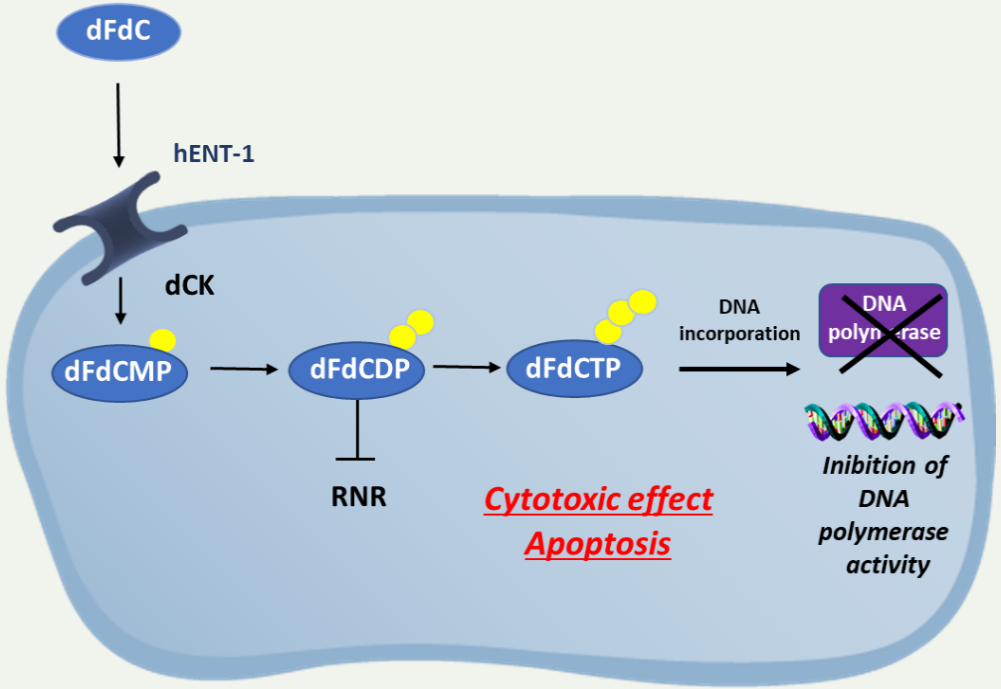


Immunotherapy

ChemoTherapy

Gemcitabine

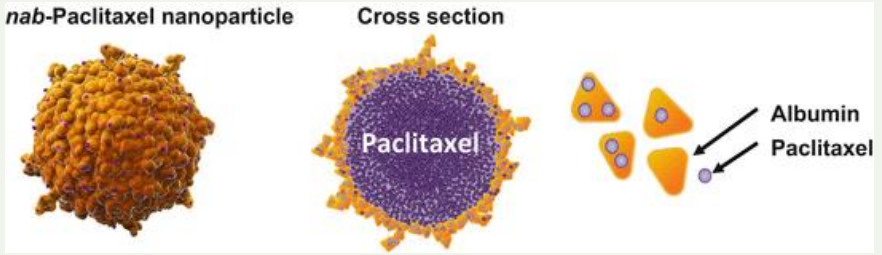


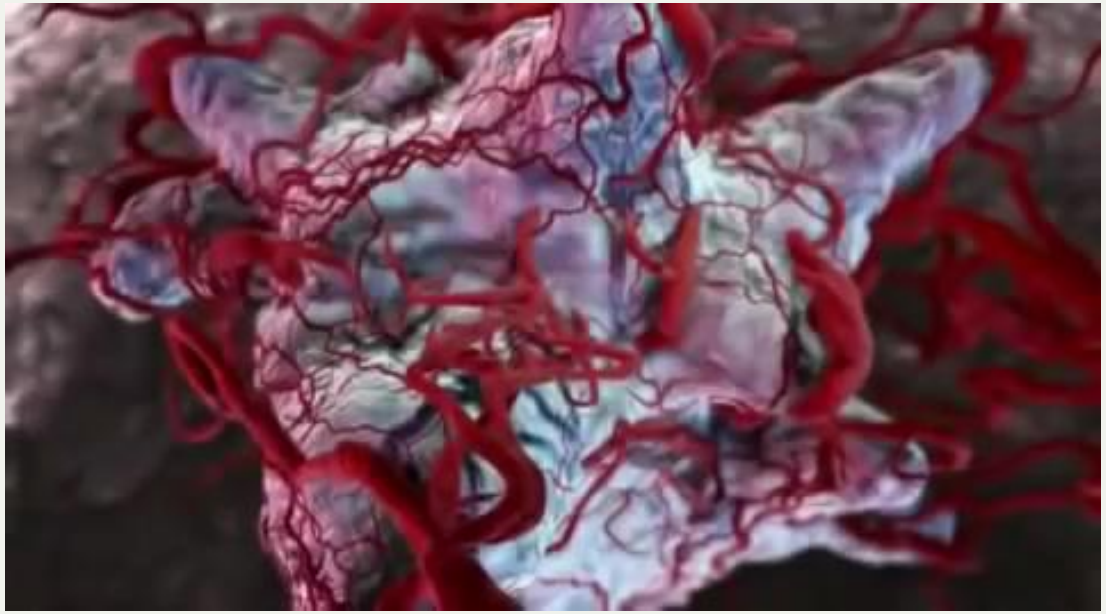


Toxicity: Gemcitabine has a good toxicity profile, with myelosuppression being the most common side effect, while non-hematological events are relatively uncommon.

ChemoTherapy

Gem + ABRAXANE





Toxicity: Neutropenia (23%)
Leukopenia (20%)
Thrombocytopenia (5%)
Anemia (4%)

ChemoTherapy

FOLFIRINOX

- ***FOL – folinic acid (leucovorin)***
- ***F – fluorouracil (5-FU)***
- ***IRIN – irinotecan (Camptosar)***
- ***OX – oxaliplatin (Eloxatin)***

Phase III clinical trial PRODIGE-4/ACCORD-11

FOLFIRINOX: *Standard treatment in metastatic PDAC*

Significant improvement in survival

Toxicity:
Neutropenia (45.7%)
Febrile Neutropenia (5.4%)
Thrombocytopenia (9.1%)
Vomiting (14.5%)
Diarrhea (12.7%)

Mechanisms of acquired chemoresistance

- *Membrane transporters*
- *Nucleoside enzymes*
- *Epithelial-mesenchymal transition (EMT)*
- *Cancer Stem cells*
- *Microenvironmental factors*

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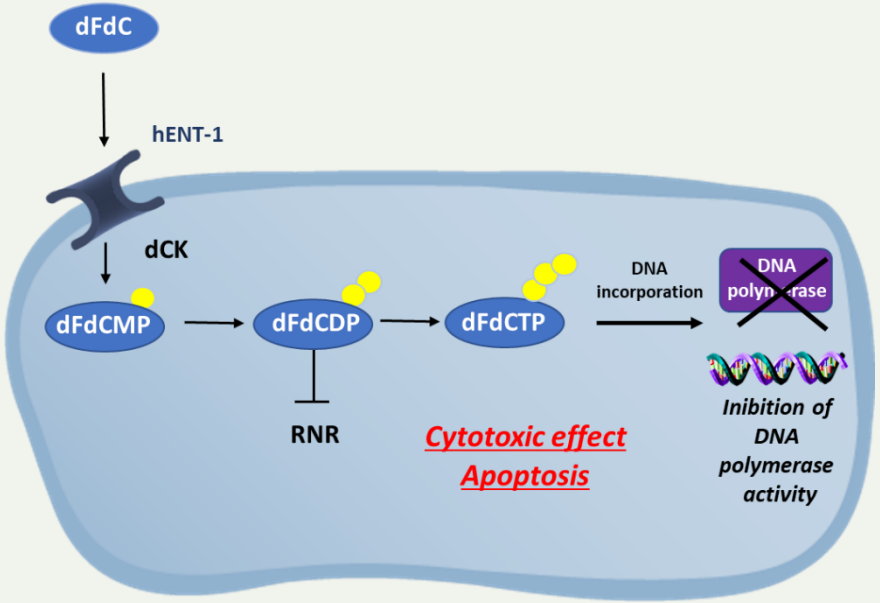

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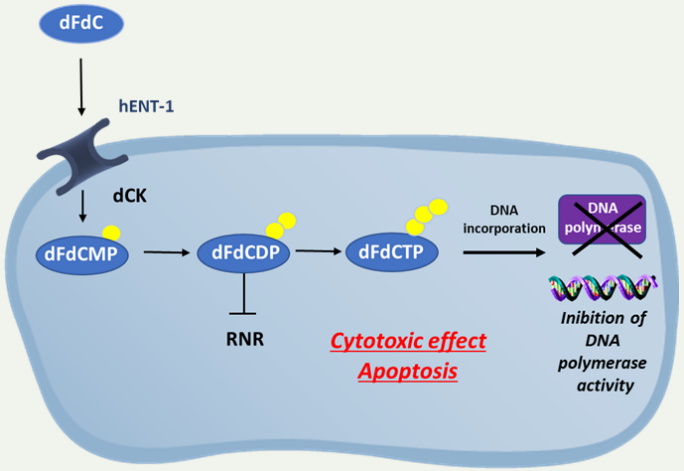

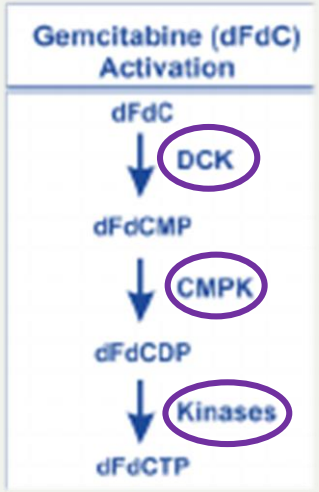

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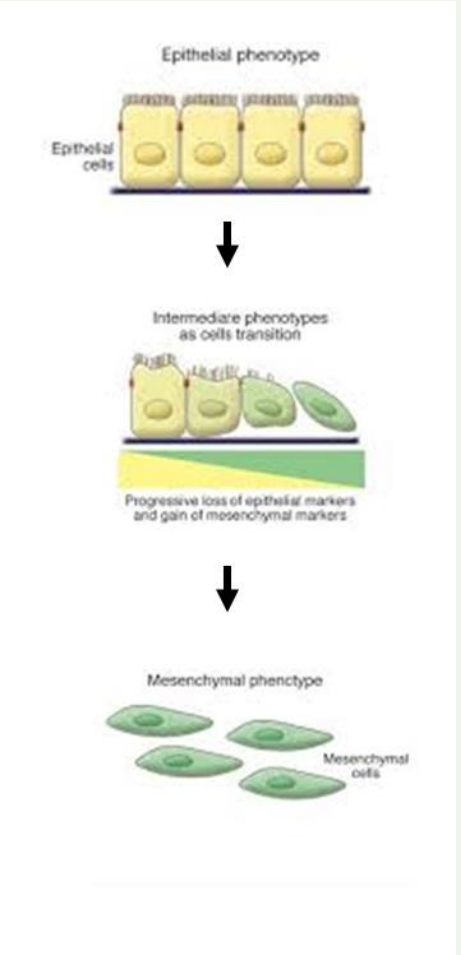

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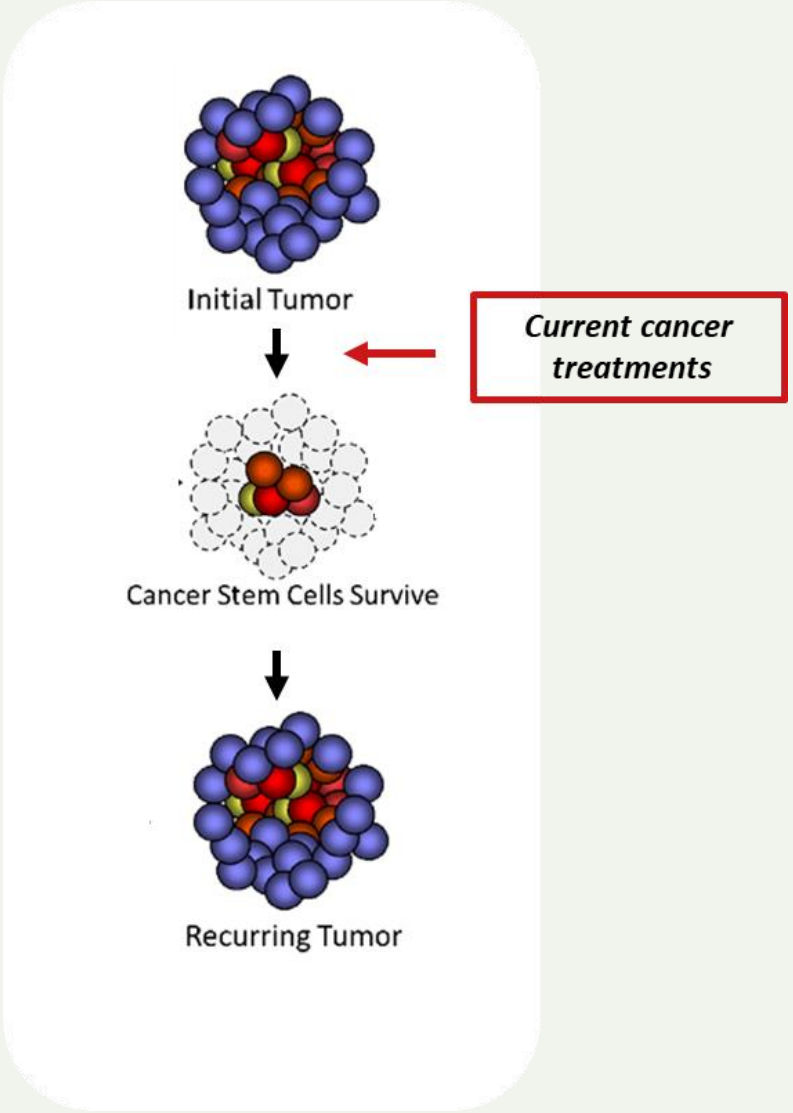

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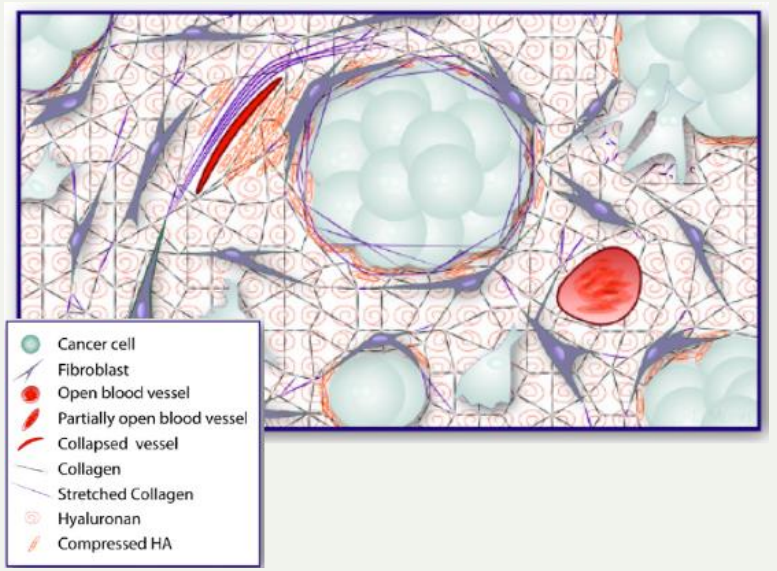
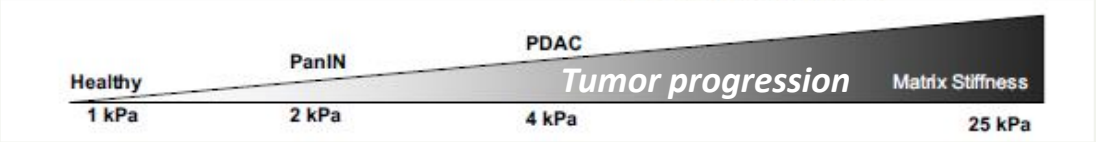


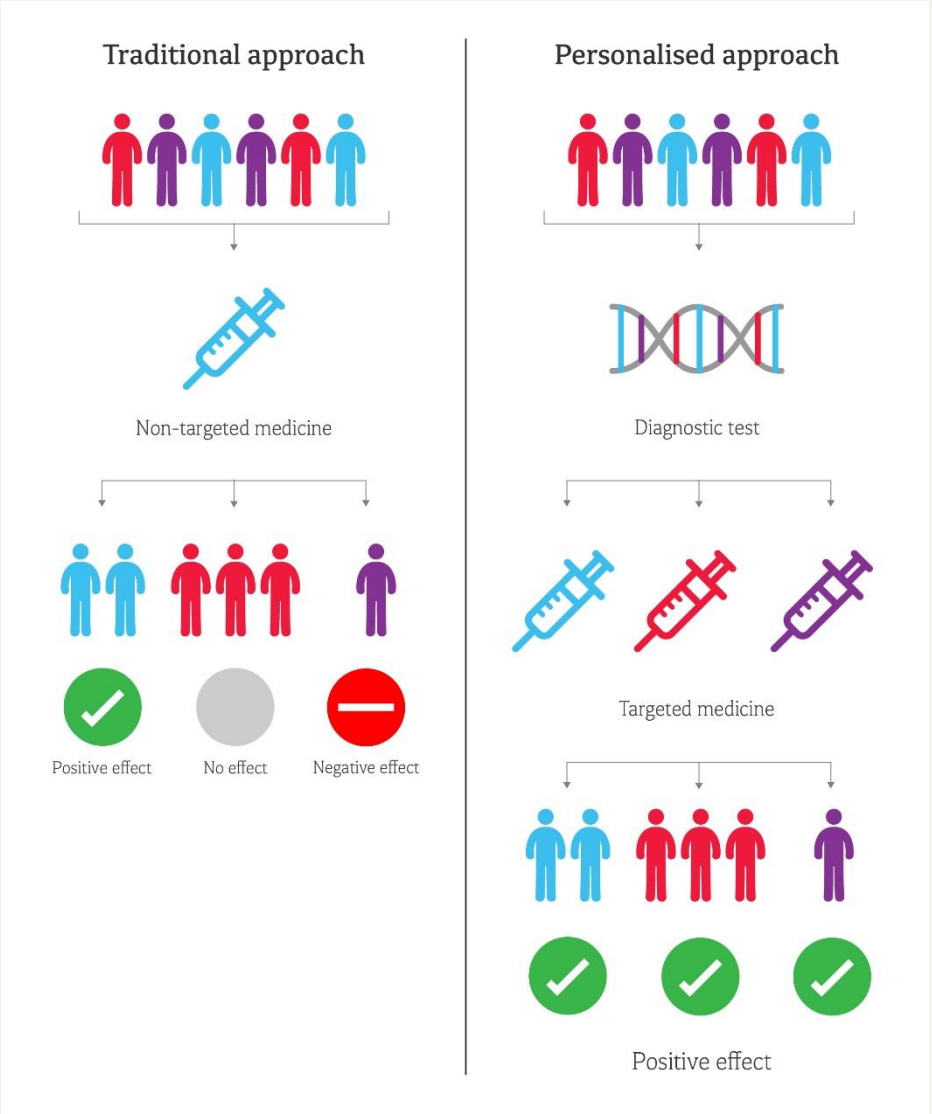


Tissue stiffness

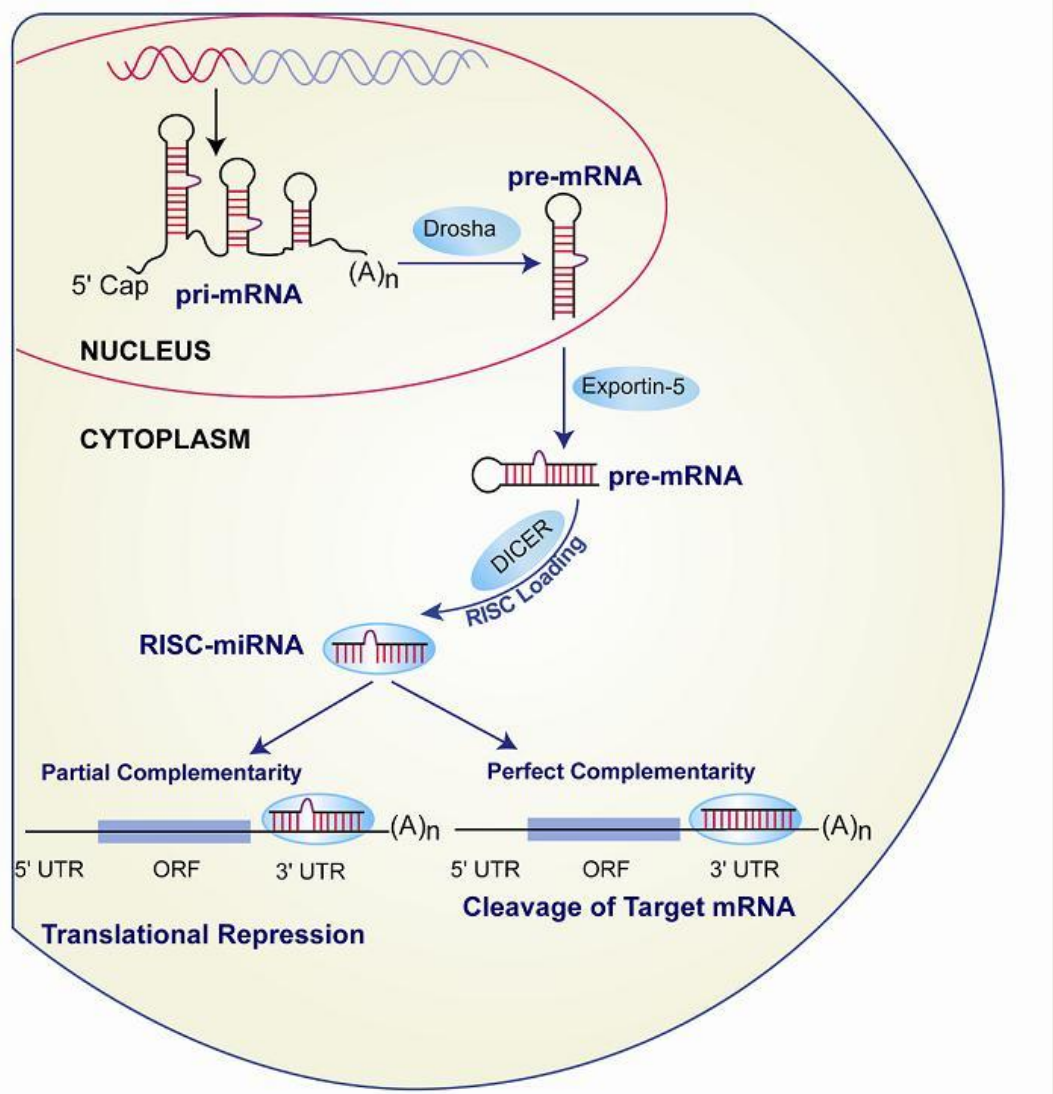
ECM proteins

New tools to overcome PDAC resistance

Personalised medicine



MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy



New tools to overcome PDAC resistance

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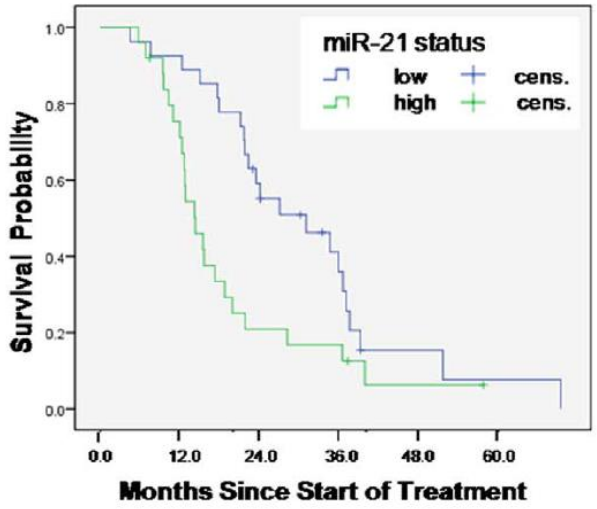
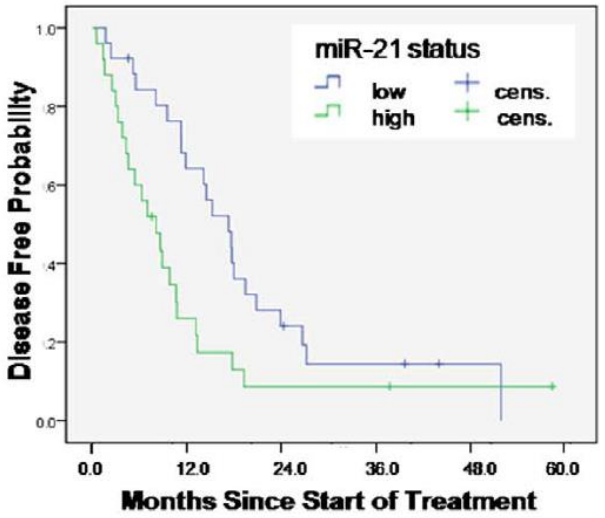
miR-21 – Gemcitabine+5FU

Identification of MicroRNA-21 as a Biomarker for Chemoresistance and Clinical Outcome Following Adjuvant Therapy in Resectable Pancreatic Cancer

Jin-Hyeok Hwang[1,2,3], Johannes Voortman[1,4], Elisa Giovannetti[4,5], Seth M. Steinberg[6], Leticia G. Leon[4], Yong-Tae Kim[3], Niccola Funel[7], Joo Kyung Park[3], Min A. Kim[8], Gyeong Hoon Kang[8], Sun-Whe Kim[9], Marco Del Chiaro[7], Godefridus J. Peters[4], Giuseppe Giaccone[1]*

Adjuvant treated patients





⬆ *miR-21*

⬆ *Chemoresistance*

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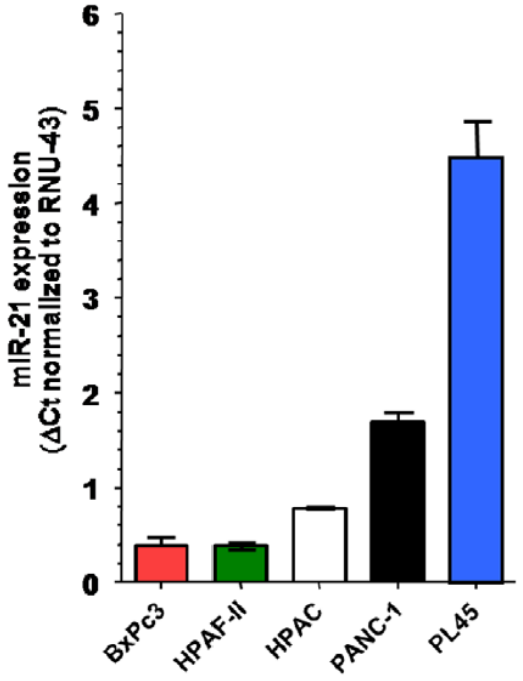

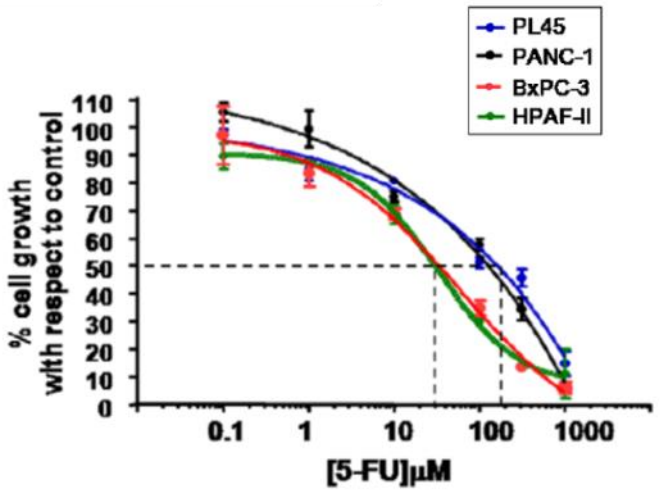

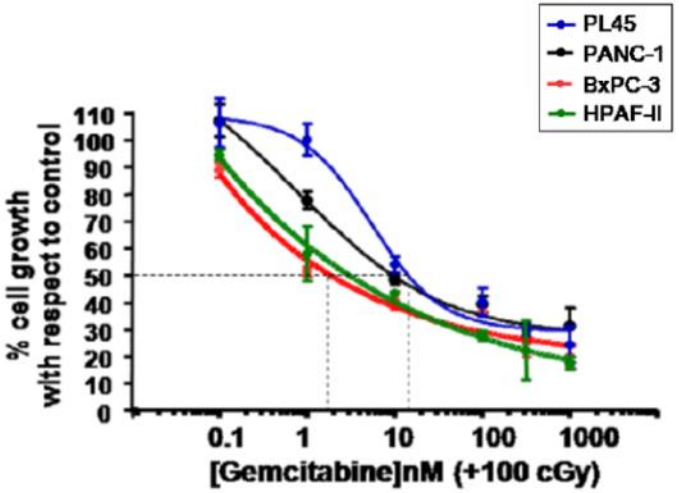

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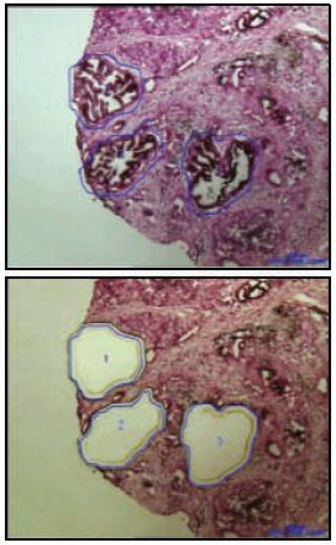
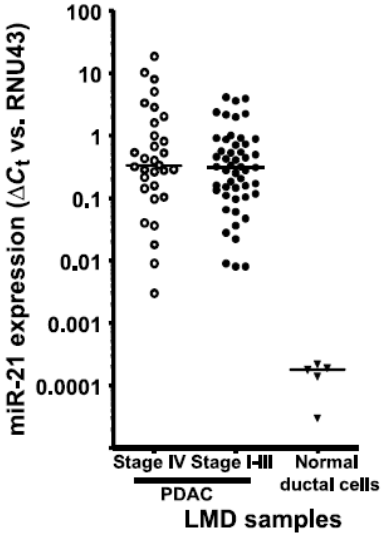


Example of extracted tumor epithelium and stroma before and after LMD



Therapeutics, Targets, and Chemical Biology

Cancer Research

MicroRNA-21 in Pancreatic Cancer: Correlation with Clinical Outcome and Pharmacologic Aspects Underlying Its Role in the Modulation of Gemcitabine Activity

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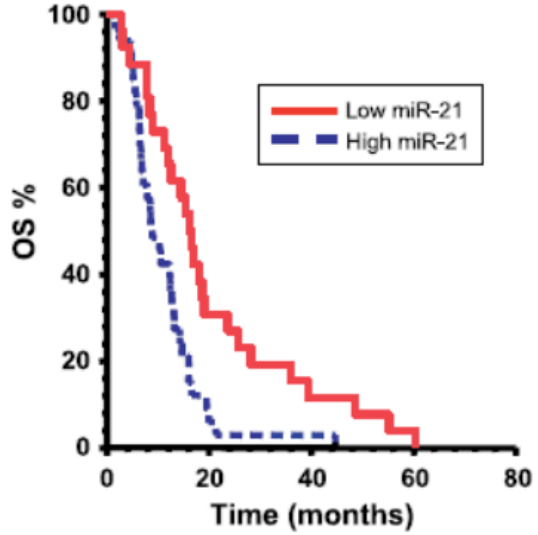
Adjuvant and metastatic setting



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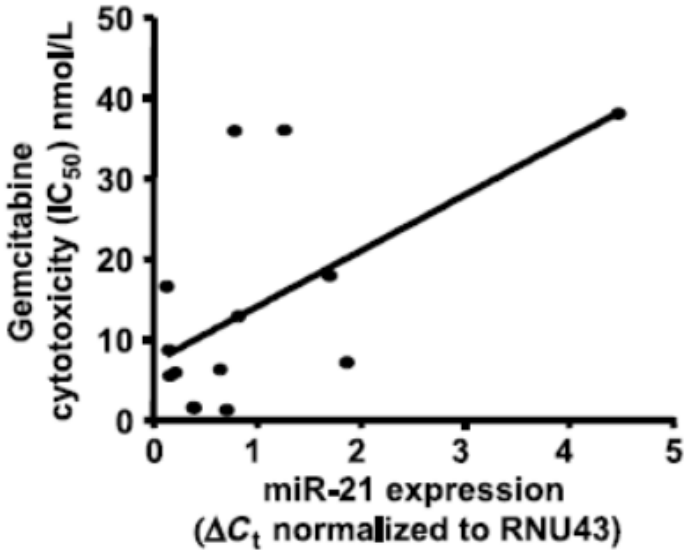

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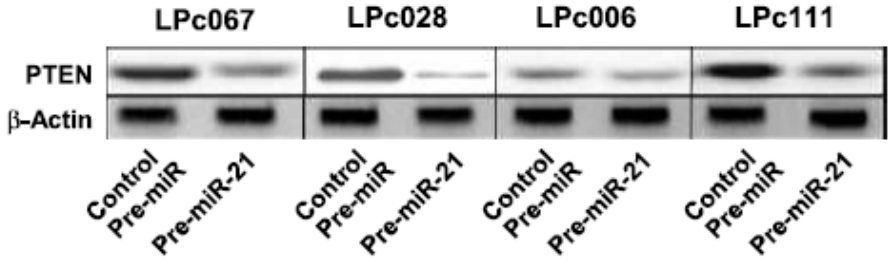
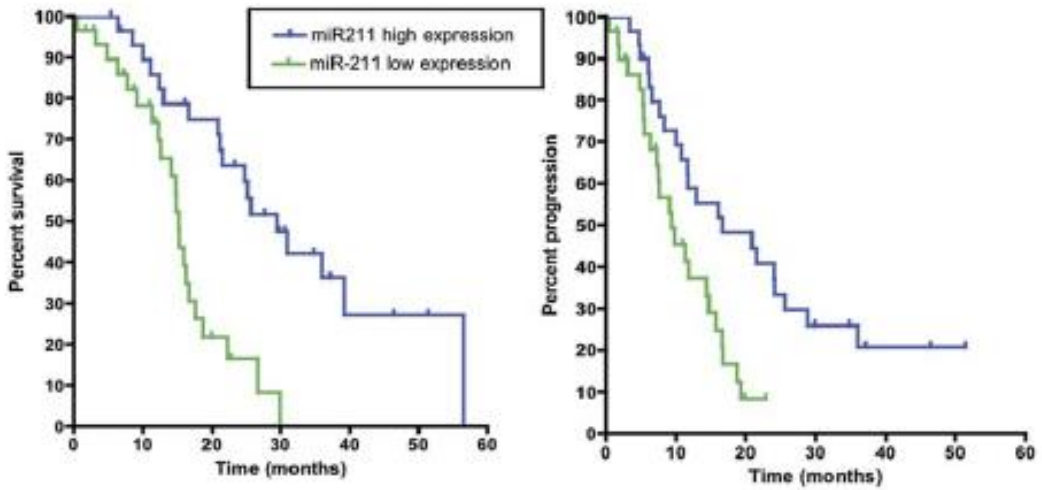


⬇ PTEN ⬇ Apoptosis

New tools to overcome PDAC resistance

MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy

miR-211 – Gemcitabine



⬇ *miR-211* ⬆ *Chemoresistance*

OPEN ACCESS Freely available online PLOS ONE

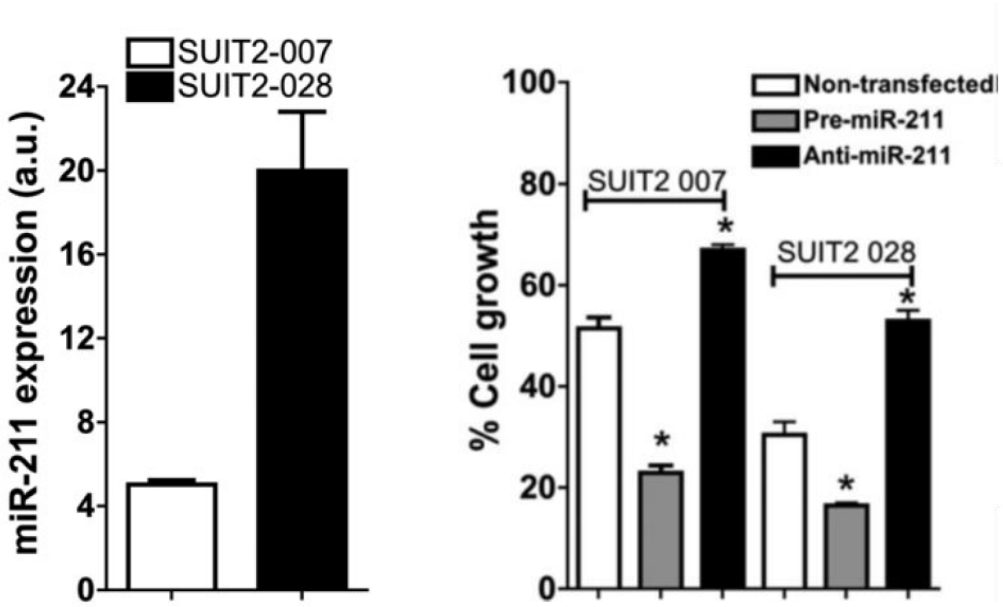
High-Throughput MicroRNA (miRNAs) Arrays Unravel the Prognostic Role of MiR-211 in Pancreatic Cancer

Elisa Giovannetti[1]*, Arjan van der Velde[2], Niccola Funel[3], Enrico Vasile[4], Vittorio Perrone[5], Leticia G. Leon[2], Nelide De Lio[5], Amir Avan[1], Sara Caponi[4], Luca E. Pollina[3], Valentina Gallá[1], Hiroko Sudo[6], Alfredo Falcone[4], Daniela Campani[3], Ugo Boggi[5], Godefridus J. Peters[1]

Nucleosides Nucleotides Nucleic Acids. 2014;33(4-6):384-93. doi: 10.1080/15257770.2014.891741.

miR-211 modulates gemcitabine activity through downregulation of ribonucleotide reductase and inhibits the invasive behavior of pancreatic cancer cells.

Maftouh M[1], Avan A, Funel N, Frampton AE, Fiuji H, Pelliccioni S, Castellano L, Galla V, Peters GJ, Giovannetti E.



New tools to overcome PDAC resistance

MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy

miR-142-5p – Gemcitabine

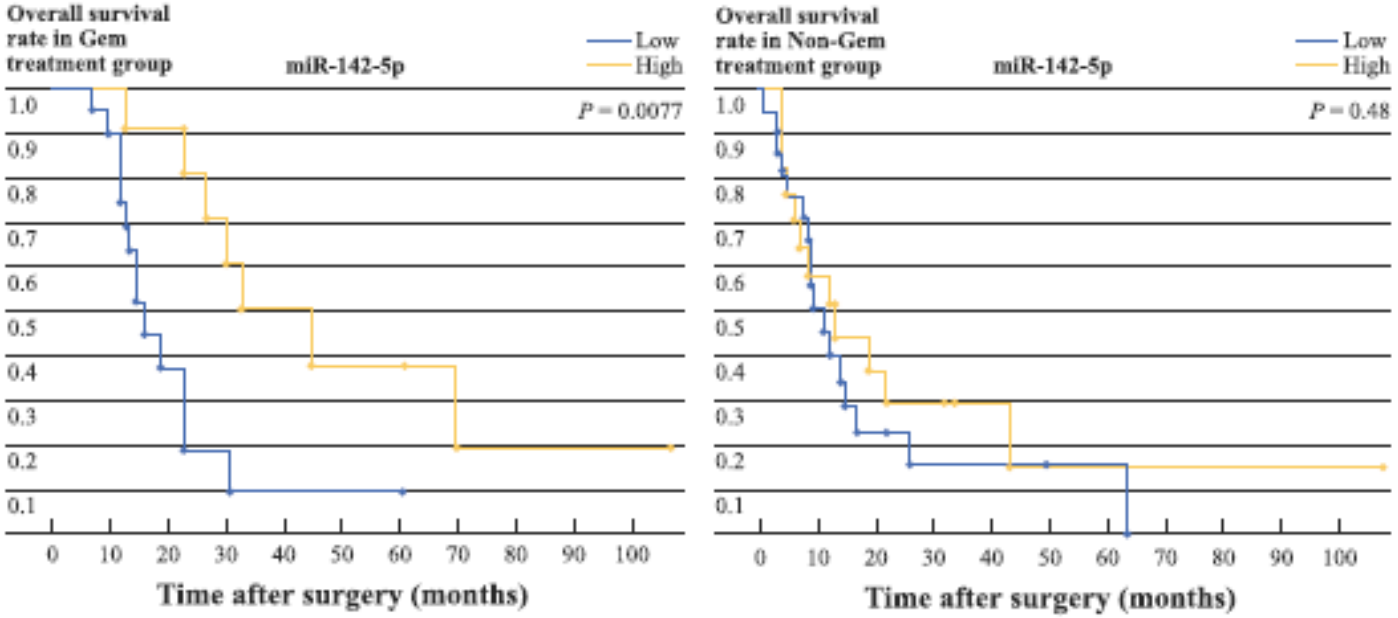
Ann Surg Oncol (2011) 18:2381–2387
DOI 10.1245/s10434-011-1602-x

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

MicroRNA Expression as a Predictive Marker for Gemcitabine Response after Surgical Resection of Pancreatic Cancer

Kenoki Ohuchida, PhD[1,2], Kazuhiro Mizumoto, PhD[1,3], Tadashi Kayashima, MD[1], Hayato Fujita, PhD[1], Taiki Moriyama, PhD[1], Takao Ohtsuka, PhD[1], Junji Ueda, PhD[1], Eishi Nagai, PhD[1], Makoto Hashizume, PhD[2], and Masao Tanaka, PhD[1]



⬇ *miR-142-5p*

⬆ *Chemoresistance*

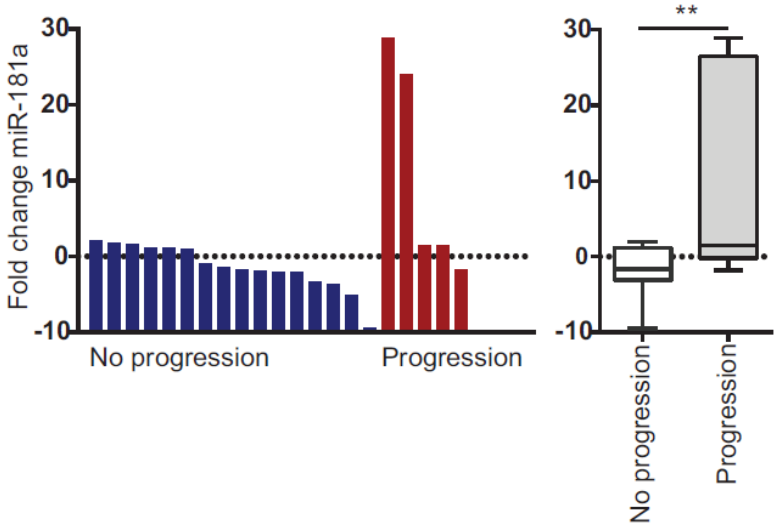
New tools to overcome PDAC resistance

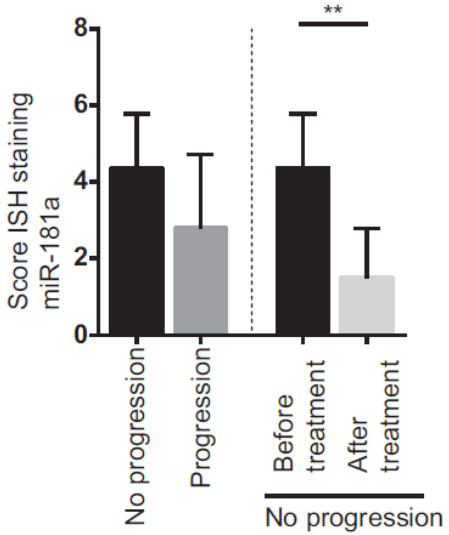
MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy

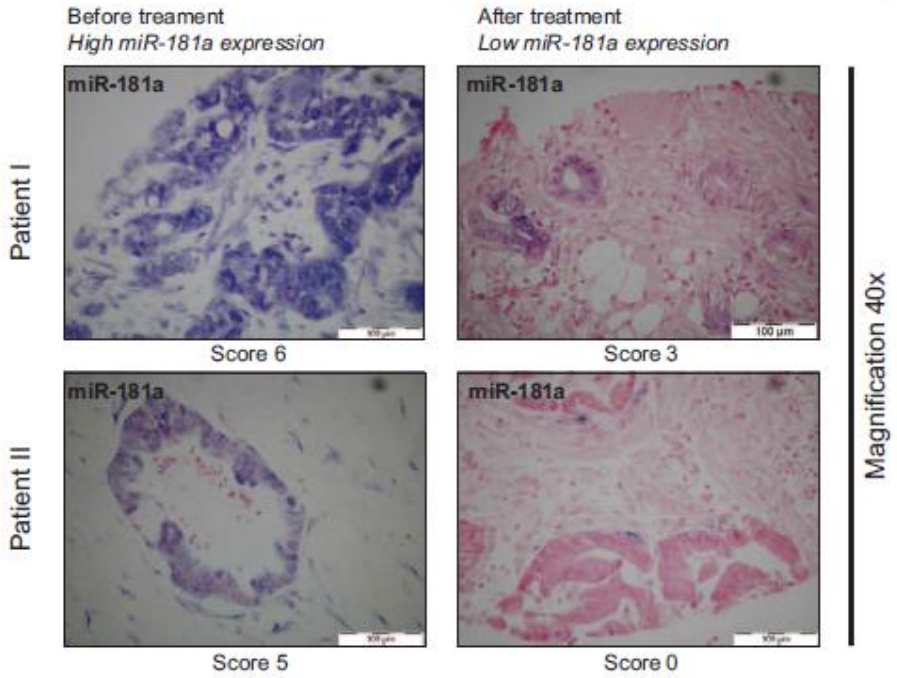
miR-181a-5p – FOLFIRINOX

Plasma miR-181a-5p Downregulation Predicts Response and Improved Survival After FOLFIRINOX in Pancreatic Ductal Adenocarcinoma

Laura L. Meijer, MD, Ingrid Garajová, MD, PhD,†‡ Chiara Caparello, MD,§ Tessa Y. S. Le Large, MD,*†¶ Adam E. Frampton, PhD, FRCS, FRSB, FESSR,# Enrico Vasile, MD, PhD,§ Niccola Funel, PhD,** Geert Kazemier, MD, PhD, FEBS,* and Elisa Giovannetti, MD, PhD†***







New tools to overcome PDAC resistance

MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy

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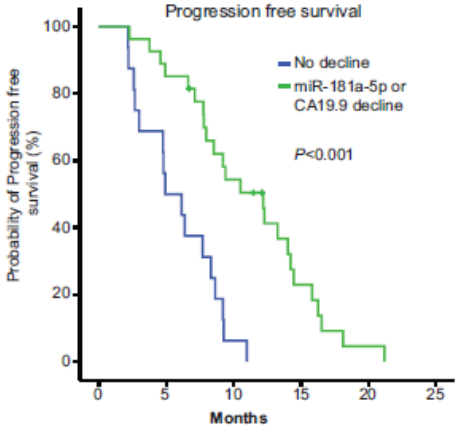
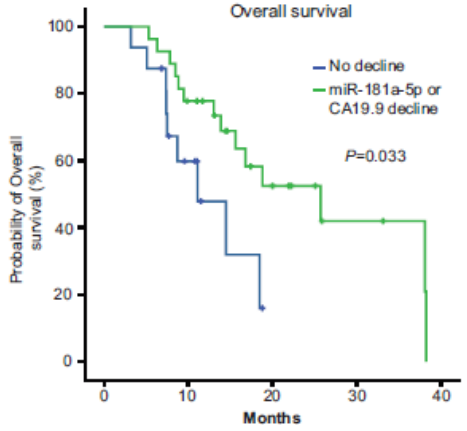
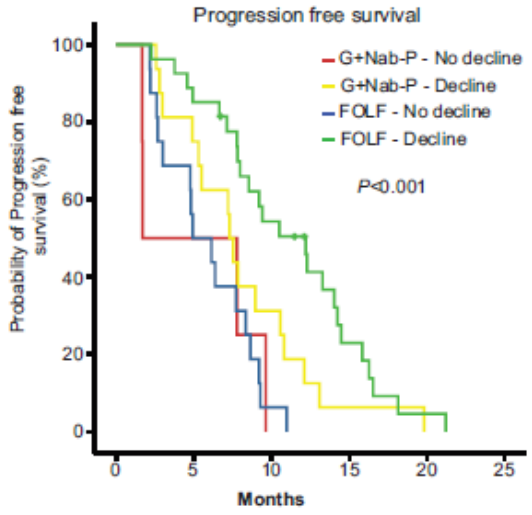
FOLFIRINOX POPULATION

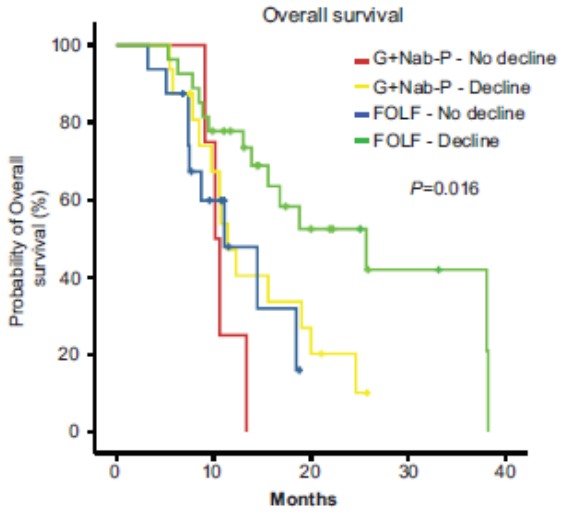




⬇ *miR-181a-5p* ⬇ *Chemoresistance*

BOTH COHORTS

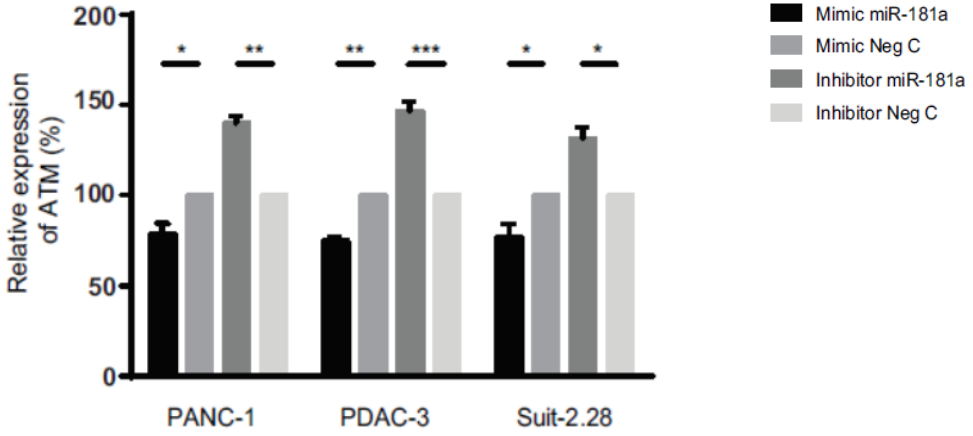




New tools to overcome PDAC resistance

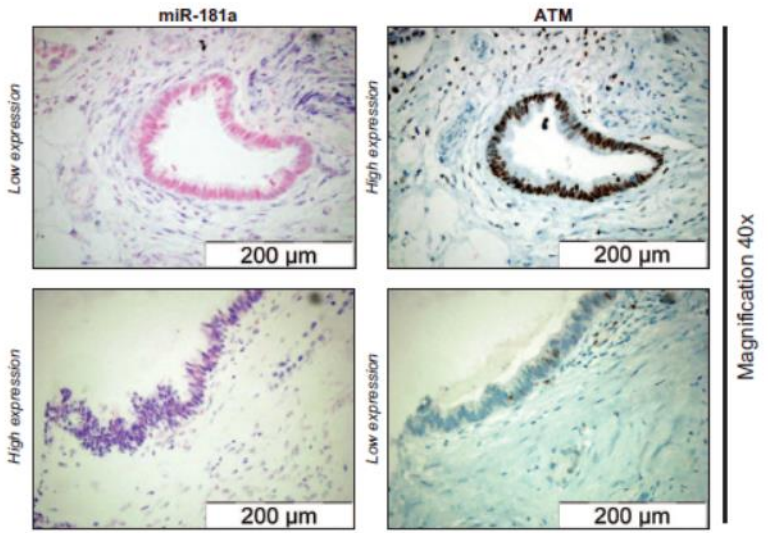
MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy

miR-181a-5p – FOLFIRINOX



Plasma miR-181a-5p Downregulation Predicts Response and Improved Survival After FOLFIRINOX in Pancreatic Ductal Adenocarcinoma

Laura L. Meijer, MD, Ingrid Garajová, MD, PhD,†‡ Chiara Caparello, MD,§ Tessa Y. S. Le Large, MD,*†¶ Adam E. Frampton, PhD, FRCS, FRSB, FESSR,# Enrico Vasile, MD, PhD,§ Niccola Funel, PhD,** Geert Kazemier, MD, PhD, FEBS,* and Elisa Giovannetti, MD, PhD†***



⬆ *miR-181a-5p* ⬇ *ATM*

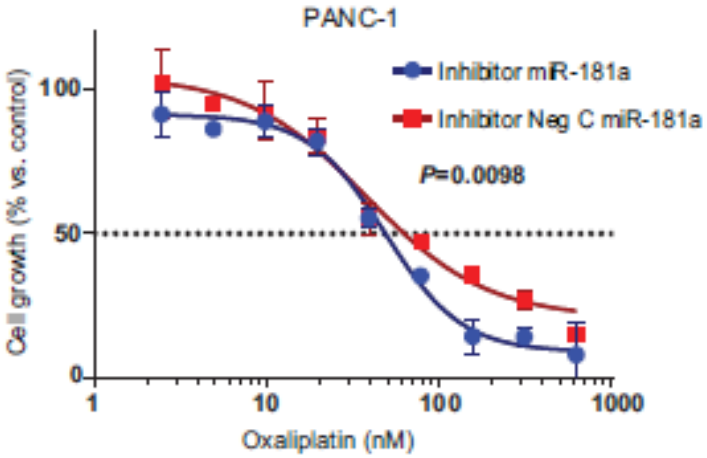
New tools to overcome PDAC resistance

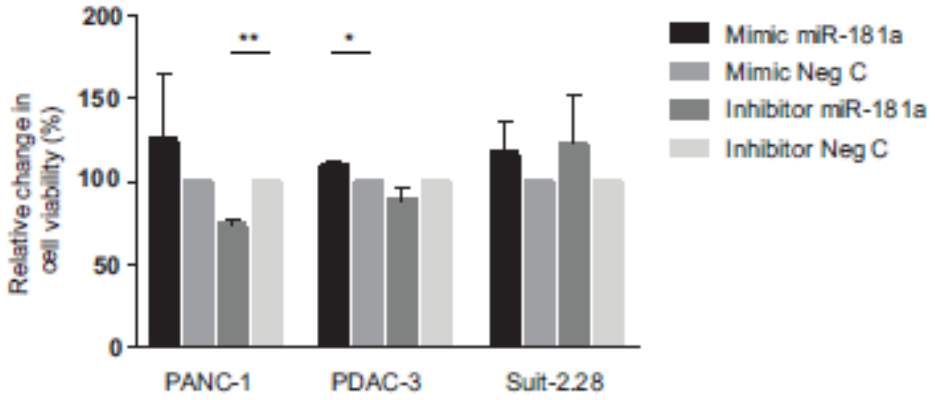
MicroRNAs to predict the sensitivity/resistance to conventional chemotherapy

miR-181a-5p – FOLFIRINOX

Plasma miR-181a-5p Downregulation Predicts Response and Improved Survival After FOLFIRINOX in Pancreatic Ductal Adenocarcinoma

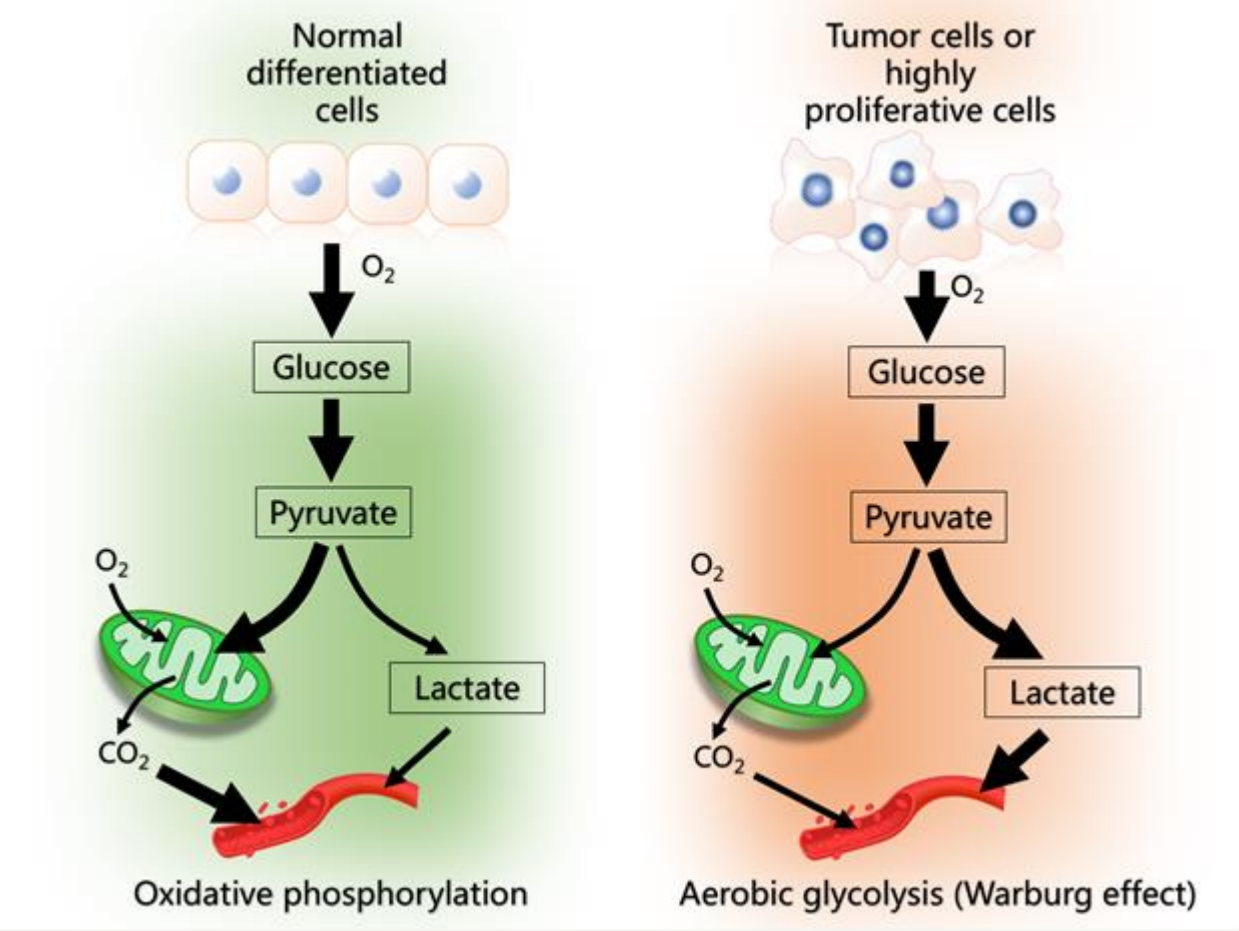
Laura L. Meijer, MD, Ingrid Garajová, MD, PhD,†‡ Chiara Caparello, MD,§ Tessa Y. S. Le Large, MD,*†¶ Adam E. Frampton, PhD, FRCS, FRSB, FESSR,# Enrico Vasile, MD, PhD,§ Niccola Funel, PhD,** Geert Kazemier, MD, PhD, FEBS,* and Elisa Giovannetti, MD, PhD†***





New tools to overcome PDAC resistance

Metabolic reprogramming in primary tumor and cancer metastasis

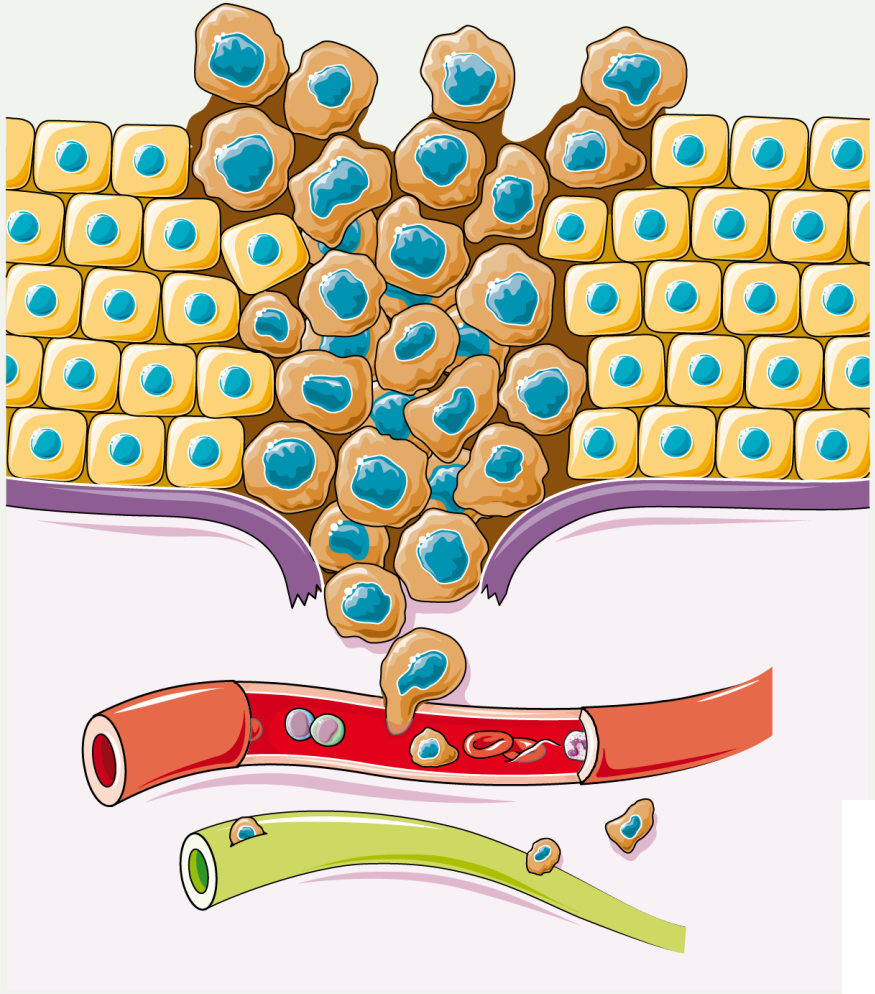


WARBURG EFFECT

Despite the presence of oxygen, cancer cells switch from oxidative phosphorylation (OXPHOS) to aerobic glycolysis, resulting in high rate glycolysis followed by acid fermentation

New tools to overcome PDAC resistance

Metabolic reprogramming in primary tumor and cancer metastasis



Once cancer cells begin to spread from the original tumor to other organs or tissue of the body, their energy requirements change

Metabolic flexibility → *Efficient colonization of distant sites*

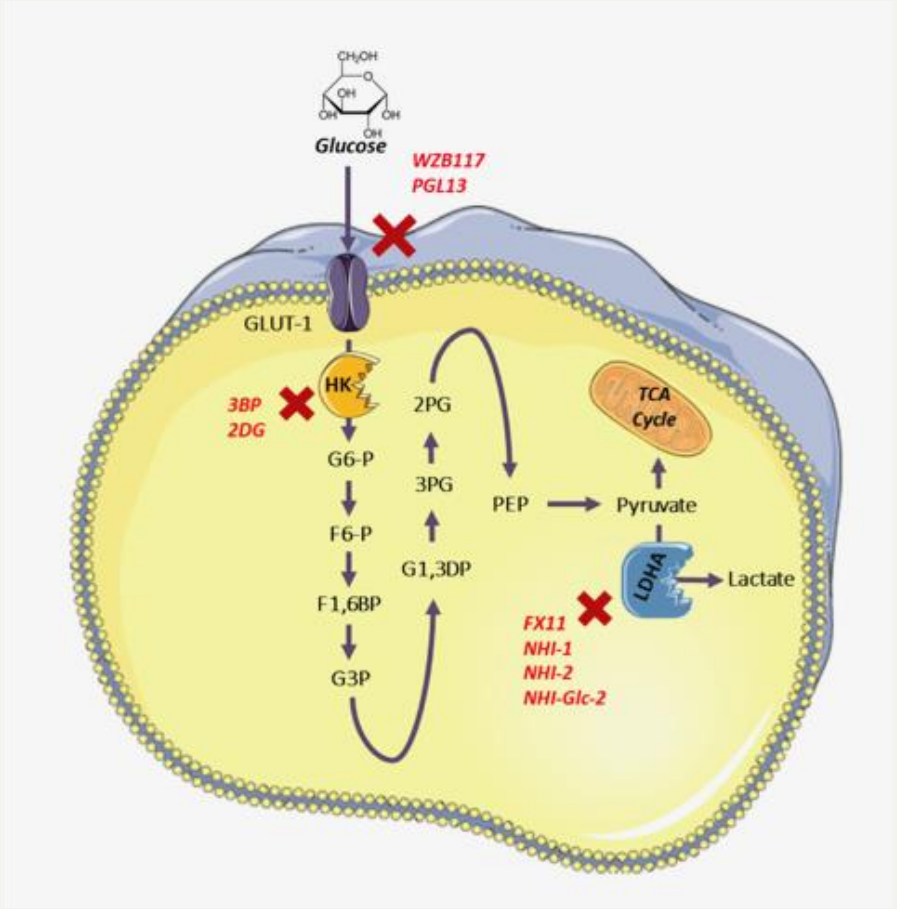
OXPHOS →

PDK1-Dependent Metabolic Reprogramming Dictates Metastatic Potential in Breast Cancer

Fanny Dupuy,[1,2] Sébastien Tabariès,[1,3] Sylvia Andrzejewski,[1,2] Zhifeng Dong,[1,3] Julianna Blagih,[1,4] Matthew G. Annis,[1,3] Atilla Omeroglu,[5] Dongxia Gao,[6] Samuel Leung,[6] Eitan Amir,[7] Mark Clemons,[8] Adriana Aguilar-Mahecha,[9] Mark Basik,[9] Emma E. Vincent,[1,4] Julie St.-Pierre,[1,2] Russell G. Jones,[1,4,*] and Peter M. Siegel[1,2,3,*]

New tools to overcome PDAC resistance

Anti-cancer agents targeting the Warburg effect



- *Glucose uptake* **GLUT-1**
- *Glucose retention* **HK**
- *Lactate production* **LDH-A**

New tools to overcome PDAC resistance

Anti-cancer agents targeting the Warburg effect

Glucose transporter GLUT1 expression and clinical outcome in solid tumors: a systematic review and meta-analysis

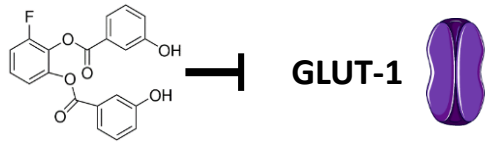
Ji Wang[1,2,*], Chenyang Ye[3,*], Cong Chen[1,2], Hanchu Xiong[1,2], Binbin Xie[1,2], Jichun Zhou[1,2], Yongxia Chen[1,2], Shu Zheng[3,4], Linbo Wang[1,2]

Overexpression of GLUT-1 has been found in various tumour types

Glucose metabolism is even more active in cancer stem cells (CSCs)

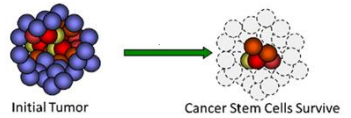
Targeting the facilitative glucose transporter GLUT1 inhibits the self-renewal and tumor-initiating capacity of cancer stem cells

Keita Shibuya[1,2,3,*], Masashi Okada[1,*], Shuhei Suzuki[1,4], Manabu Seino[1,5], Shizuka Seino[1,2,3,6], Hiroyuki Takeda[1,4] and Chifumi Kitanaka[1,2,3,6]



WZB117

GLUT-1



WZB117 inhibit the self-renewal and tumor-initiating capacity of the CSCs

New tools to overcome PDAC resistance

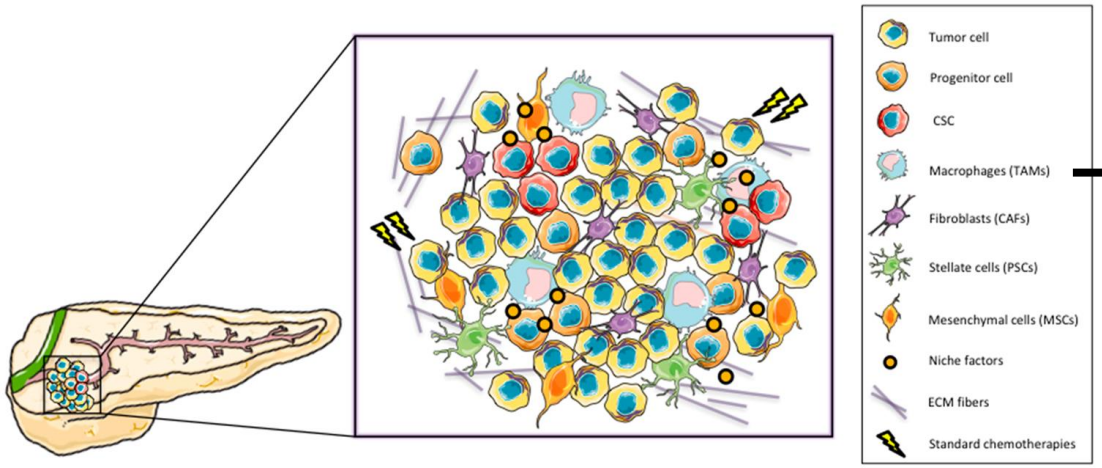
Anti-cancer agents targeting the Warburg effect

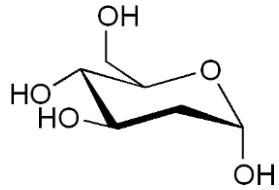
Glucose

G6-P

Warburg metabolism in tumor-conditioned macrophages promotes metastasis in human pancreatic ductal adenocarcinoma

Hweixian Leong Penny[a], Je Lin Sieow[a], Giulia Adriani[b], Wei Hseun Yeap[a], Peter See Chi Ee[a], Boris San Luis[a], Bernett Lee[a], Terence Lee[c], Shi Ya Mak[d], Ying Swan Ho[d], Kong Peng Lam[d], Choon Kiat Ong[e], Ruby Y. J. Huang[f], Florent Ginhoux[a], Olaf Rotzschke[a], Roger D. Kamm[b,g], and Siew Cheng Wong[a]





2DG – *2-deoxyglucose*

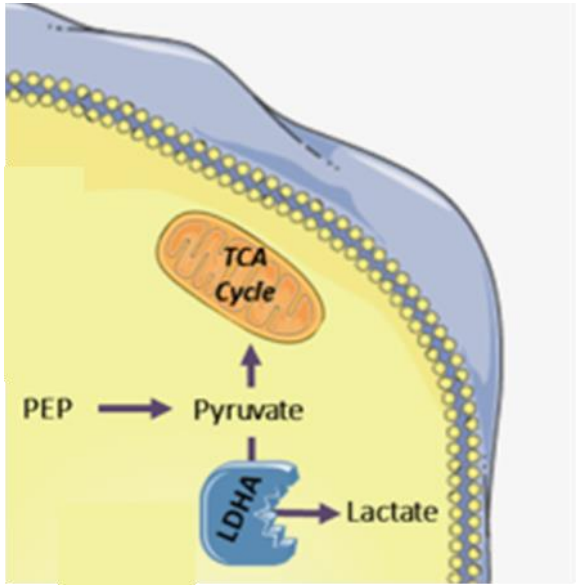
Warburg Metabolism

Promoting tumour growth and dissemination

Phase I dose-escalation trial : **Combination of 2-DG and Docetaxel**

New tools to overcome PDAC resistance

Anti-cancer agents targeting the Warburg effect



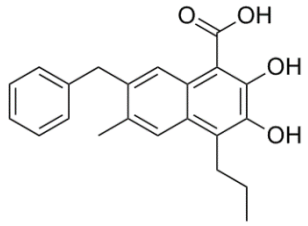
Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression

Anne Le[a], Charles R. Cooper[a], Arvin M. Gouw[b], Ramani Dinavahi[a], Anirban Maitra[b,c], Lorraine M. Deck[d], Robert E. R
David L. Vander Jagt[e], Gregg L. Semenza[c,f,g,h,1] and Chi V. Dang[a,b,c,i,j,k,2]

Therapeutic targeting of the Warburg effect in pancreatic cancer relies on an absence of p53 function

N.V. Rajeshkumar[1,¥,$], Prasanta Dutta[2,$], Shinichi Yabuuchi[1], Roeland F. de Wilde[1], Gary V. Matrinez[2], Anne Le[1], Jurre J. Kamphorst[3], Josh D. Rabinowitz[3], Sanjay K. Jain[4], Manuel Hidalgo[5], Chi V. Dang[6,*], Robert J. Gillies[2], and Anirban Maitra[7,*]

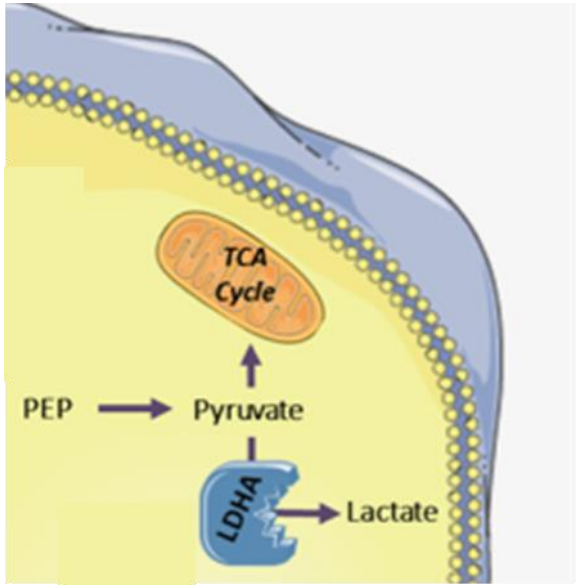
FX11



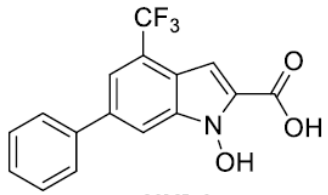
Reduction of LDH-A expression reduced ATP levels and induced significant oxidative stress and cell death

New tools to overcome PDAC resistance

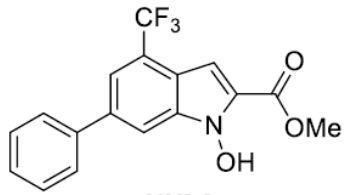
Anti-cancer agents targeting the Warburg effect



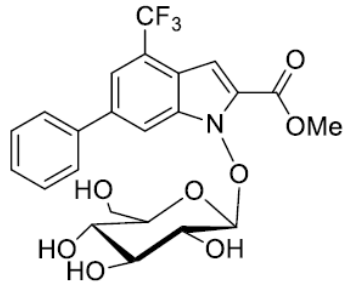
N-hydroxyindole-based compounds



NHI-1



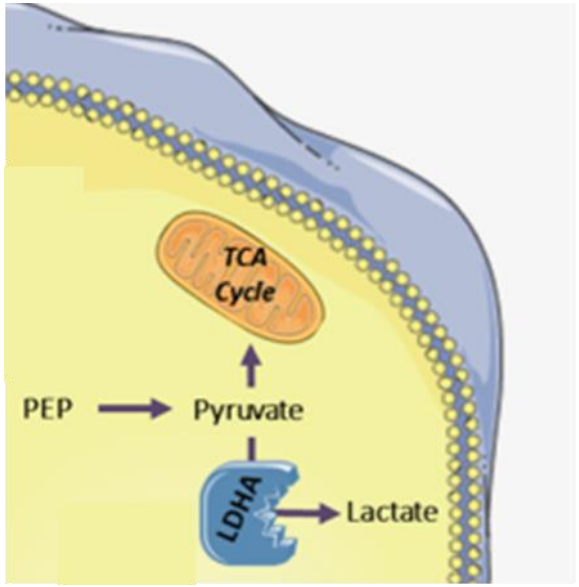
NHI-2

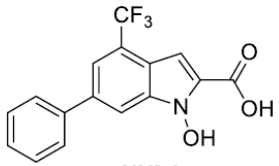


NHI-Glc-2

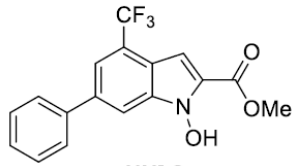
New tools to overcome PDAC resistance

Anti-cancer agents targeting the Warburg effect

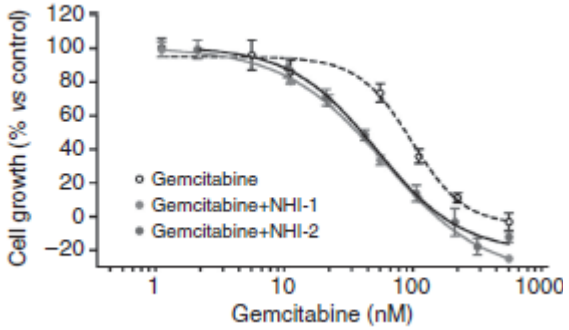




NHI-1

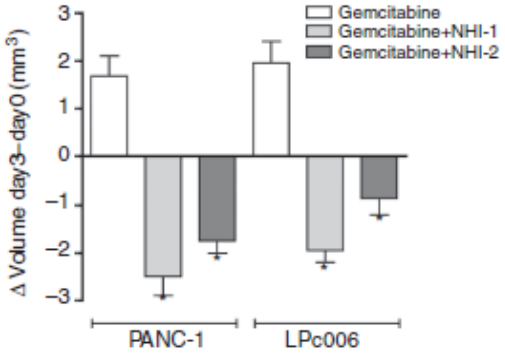


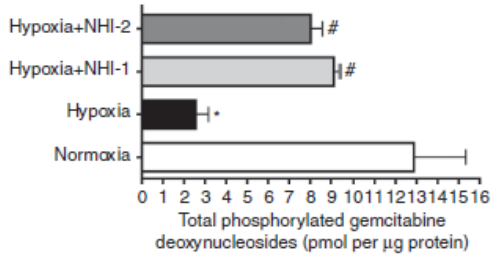
NHI-2



Synergistic interaction of novel lactate dehydrogenase inhibitors with gemcitabine against pancreatic cancer cells in hypoxia

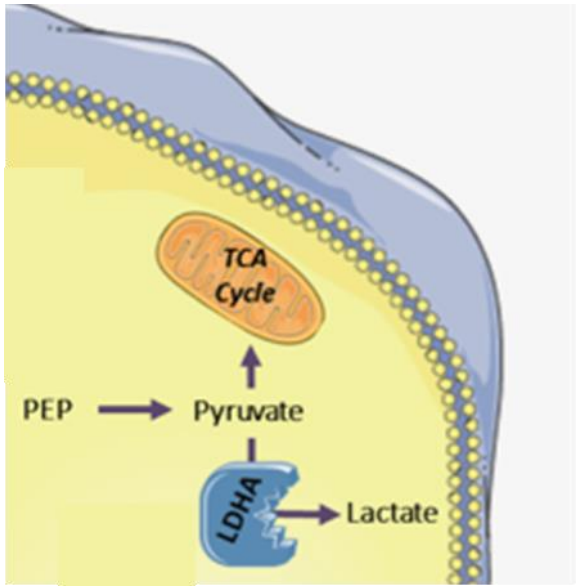
M Maftouh[1,5], A Avan[1,5], R Sciarrillo[1], C Granchi[2], L G Leon[3], R Rani[2], N Funel[4], K Smid[1], R Honeywell[1], U Boggi[4], F Minutolo[2], G J Peters[1] and E Giovannetti[*,1]

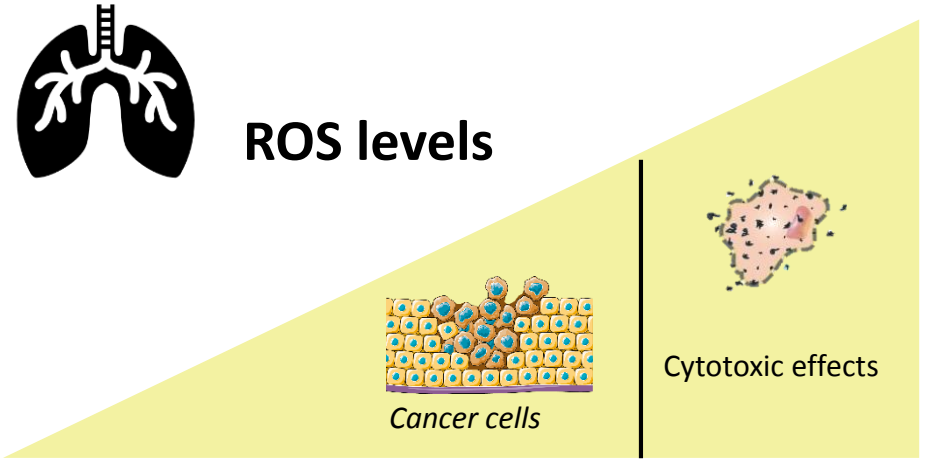


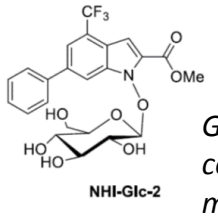


New tools to overcome PDAC resistance

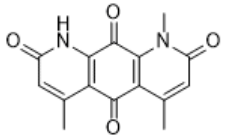
Anti-cancer agents targeting the Warburg effect







Glucose-conjugated methyl ester → Superoxide

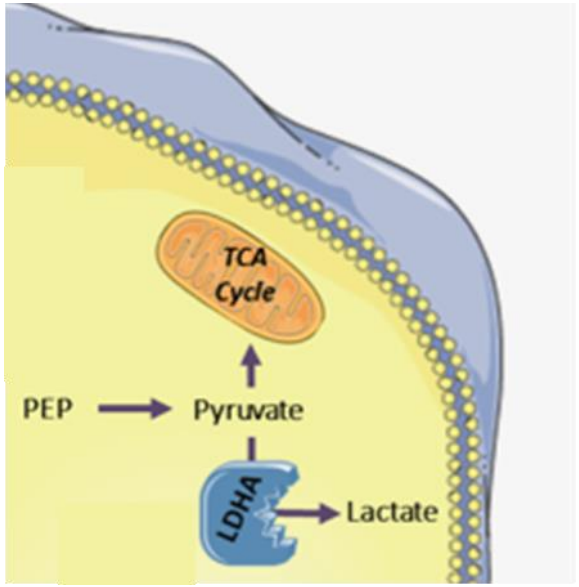


DNQ → Hydrogen peroxide

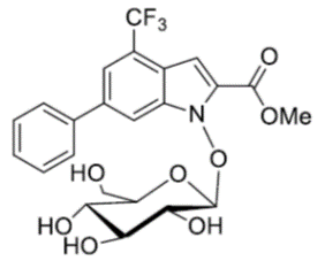
The selective generation of superoxide in cancer cells synergizes with drug-generated hydrogen peroxide, resulting in potent and selective cancer cell death

New tools to overcome PDAC resistance

Anti-cancer agents targeting the Warburg effect



Glucose-conjugated methyl ester

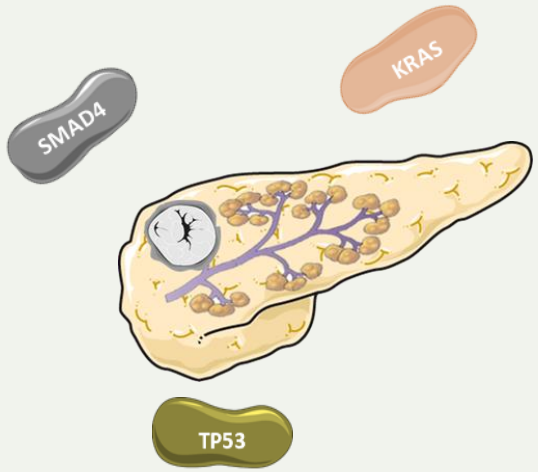


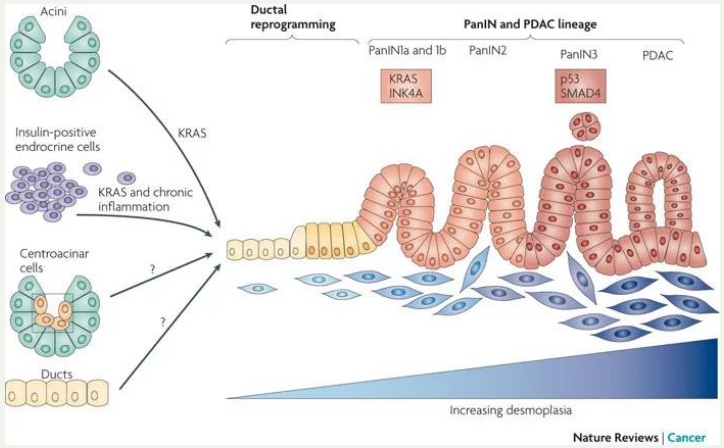
NHI-Glc-2

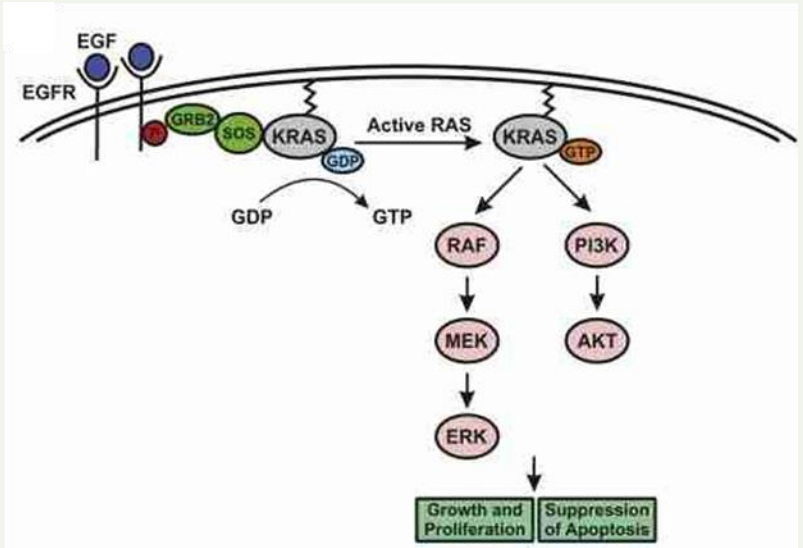
Preliminary *in vitro* and *in vivo* studies showed a potential synergist interaction between **NHII-Glc-2** and **gemcitabine** in PDAC models

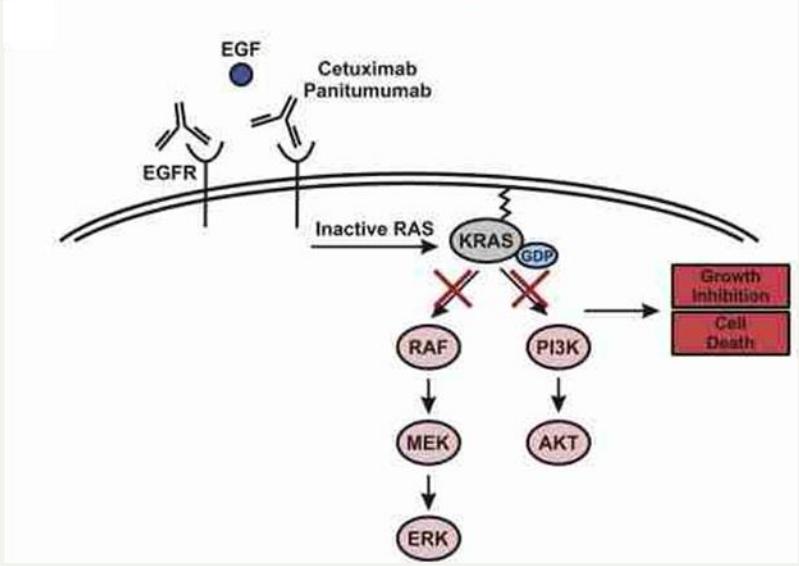
Oncogenic KRAS mutation

Somatic mutations

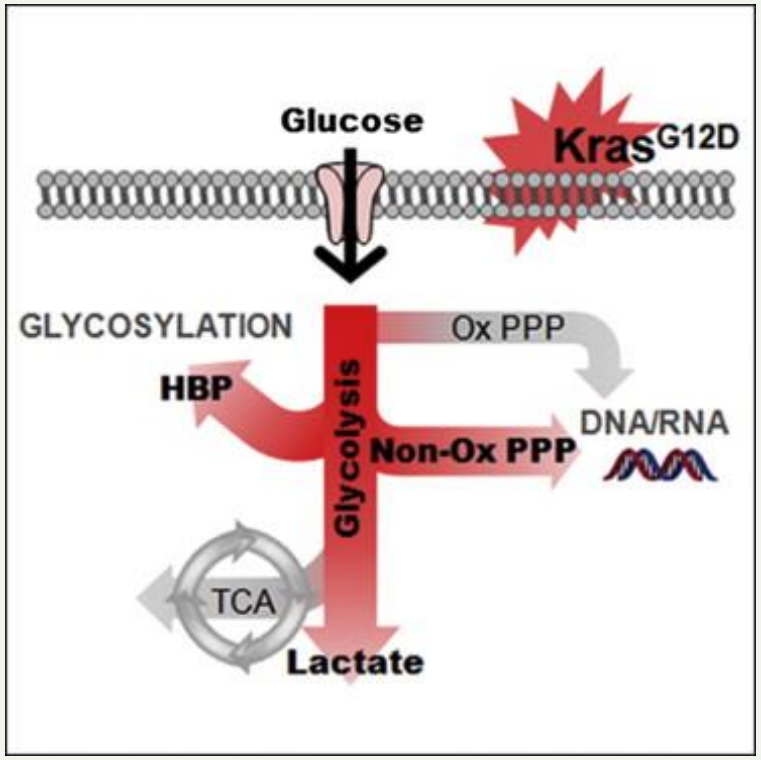








Role of KRAS in controlling cancer metabolism



Mutated KRAS enhances the expression of GLUT1 and several rate limiting glycolytic enzyme, including HK and LDH-A.

Metabolic targeting strategies could represent a valid method to effectively target tumors driven by KRAS

Summary

We summarized the main therapeutic option for PDAC

Personalized medicine: use of microRNAs as novel potential biomarkers to predict drug activity.

Anti-cancer agents targeting the Warburg Effect: new experimental compounds that target glycolytic metabolism and their potential use to improve current therapies against PDAC

Any questions?