Paper de l'estroma en càncer de pàncrees

Controvèrsies i noves teràpies

Dra. **Berta Laquente**, MD, PhD
Servei Oncologia Mèdica, Institut Català d'Oncologia

Dr. **David G. Molleví**, PhD
Programa Contra la Resistència Terapèutica del Càncer
Institut Català d'Oncologia

XXV Congrés Societat Catalana Digestologia
Reus, 28 Gener 2016

International Agency for Research on Cancer
World Health Organization

Estimated age-standardised incidence rate per 100,000
Pancreas: both sexes, all ages

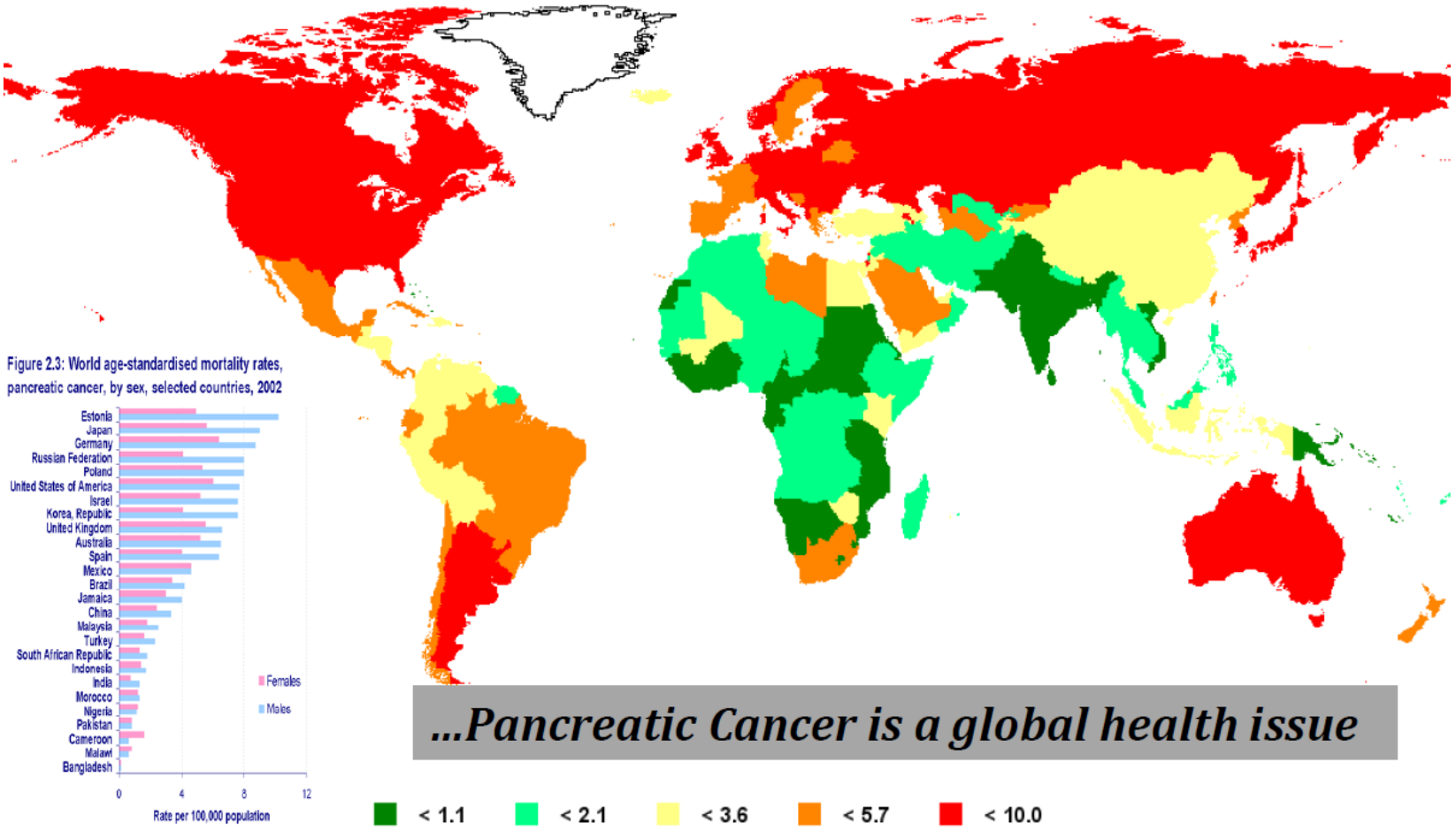


Figure 2.3: World age-standardised mortality rates, pancreatic cancer, by sex, selected countries, 2002

...Pancreatic Cancer is a global health issue

GLOBOCAN 2008 (IARC) - 24.1.2011

Cáncer de páncreas en cifras

- Es el 7º cáncer más prevalente en Europa y supone el 2.8% de los tumores en varones y el 3.4 % en mujeres.

- Es el 4º que mayor mortalidad ocasiona, más del 95 % de los pacientes diagnosticados, fallecen por la enfermedad.

- Según el European Cancer Observatory hay 103,773 personas viviendo actualmente con cáncer de páncreas en Europa.

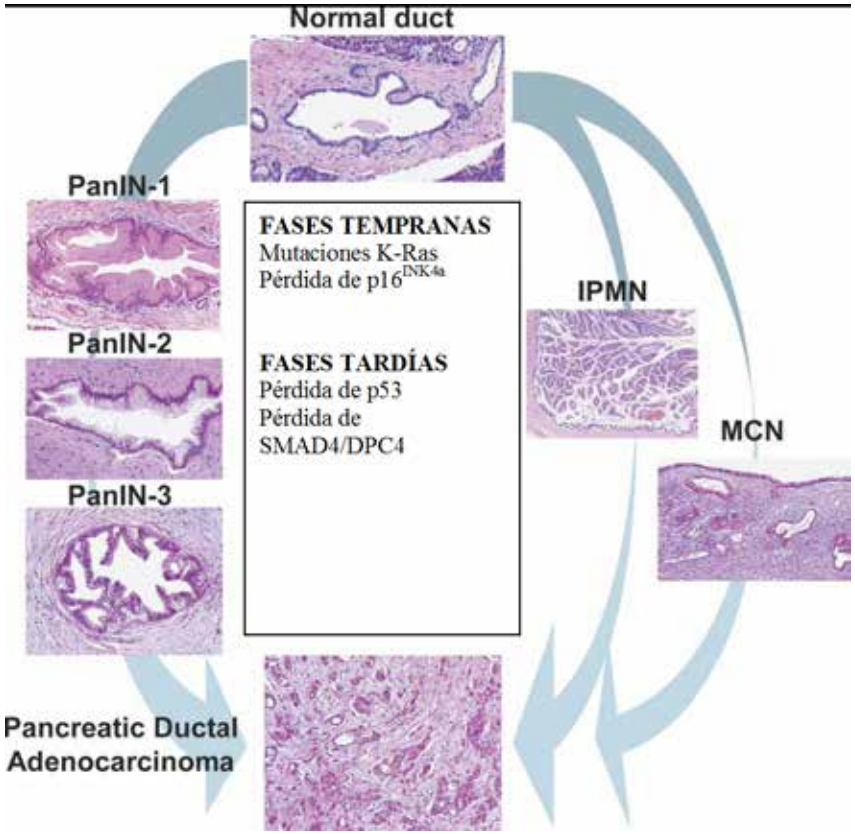
- Según el estudio Eurocare , la tasa de supervivencia al año en Europa es del 11.5 % al 28.3%.

- Solamente un 5.7% de los pacientes diagnosticados de CP en Europa están vivos a los 5 años del diagnóstico. Esto significa que de cada 20 personas diagnosticadas, sólo una estará viva cinco años más tarde.

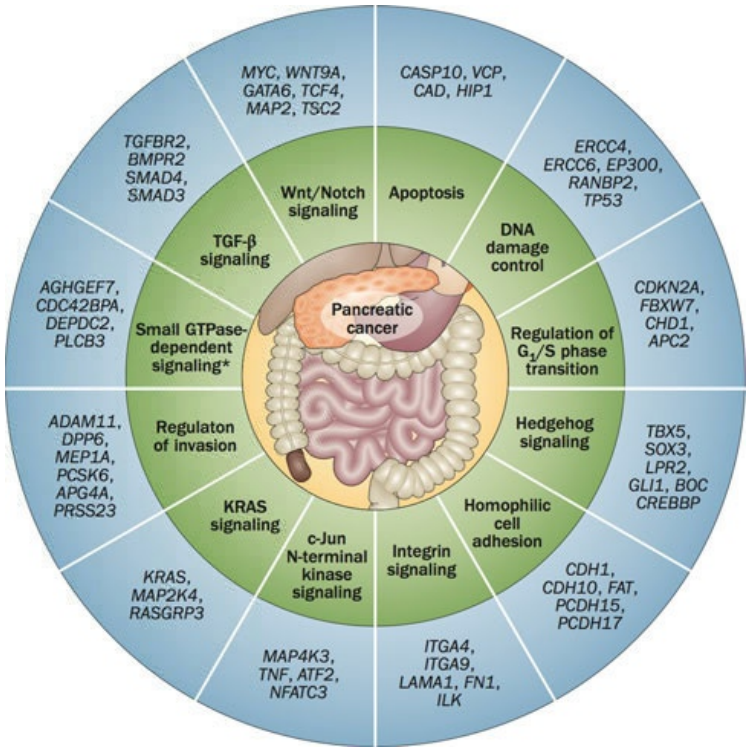
The Biology of Pancreas Cancer

- **Accumulation of gene mutations:**

1. Activation of *KRAS* oncogene (90%)
2. Inactivation of tumor-suppressor gene *CDKN2A* (95%)
3. Inactivation of tumor-suppressor gene *TP53* (50-70%)
4. Deleted in pancreatic cancer 4 (*DPC4*) (50%)



Core signaling pathways in PDAC



Cellular/Signalling Pathway Alterations

Pathway	% tumors with ≥1 genetic alteration	Pathway	% tumors with ≥1 genetic alteration
Apoptosis	100	JNK signalling	96
DNA damage control	83	KRAS signalling	100
Regulation of G_1/S phase transition	100	Regulation of invasion	92
Hedgehog signalling	100	Small GTPase-dep signalling	79
Homophilic cell adhesion	79	TGF-β	100
Integrin signalling	67	Wnt/Notch	100

Genetic alterations associated with 12 cellular signalling pathways can contribute to the development of pancreatic cancer

Jones et al Science 321, 1801 (2008); J Hepatobiliary Pancreat Sci 2013.

J Hepatobiliary Pancreat Sci 2013. *Word cloud* made in wordle.net

Cáncer de páncreas: importancia clínica

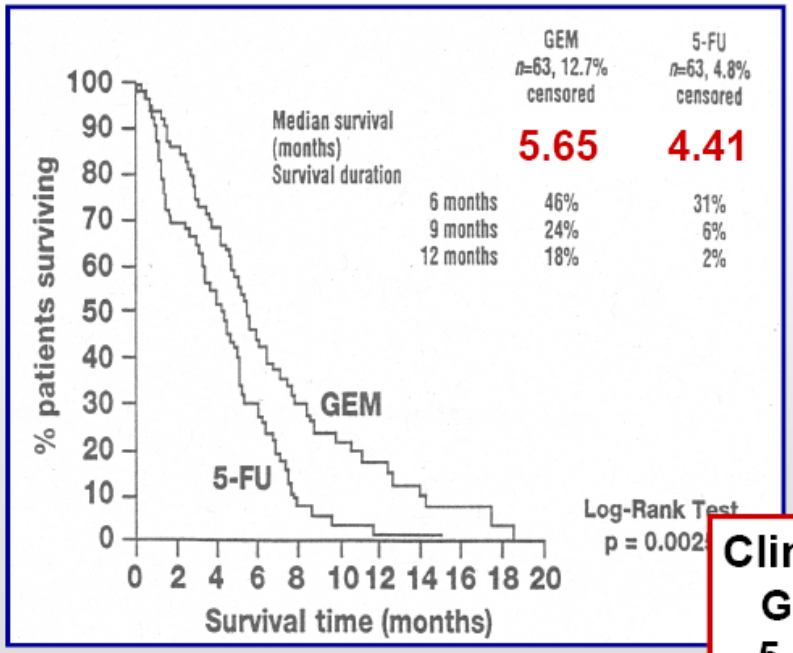
Aún los localizados con posibilidades de resección (aprox 15% de los casos) tienen una SV inferior al 20% a los 5 años.

Estadio enfermedad	Porcentaje pacientes al diagnóstico	Supervivencia mediana (meses)
Metastático	60	8.5-11
Localmente avanzado	25	10-12
Resecable	15	20-23

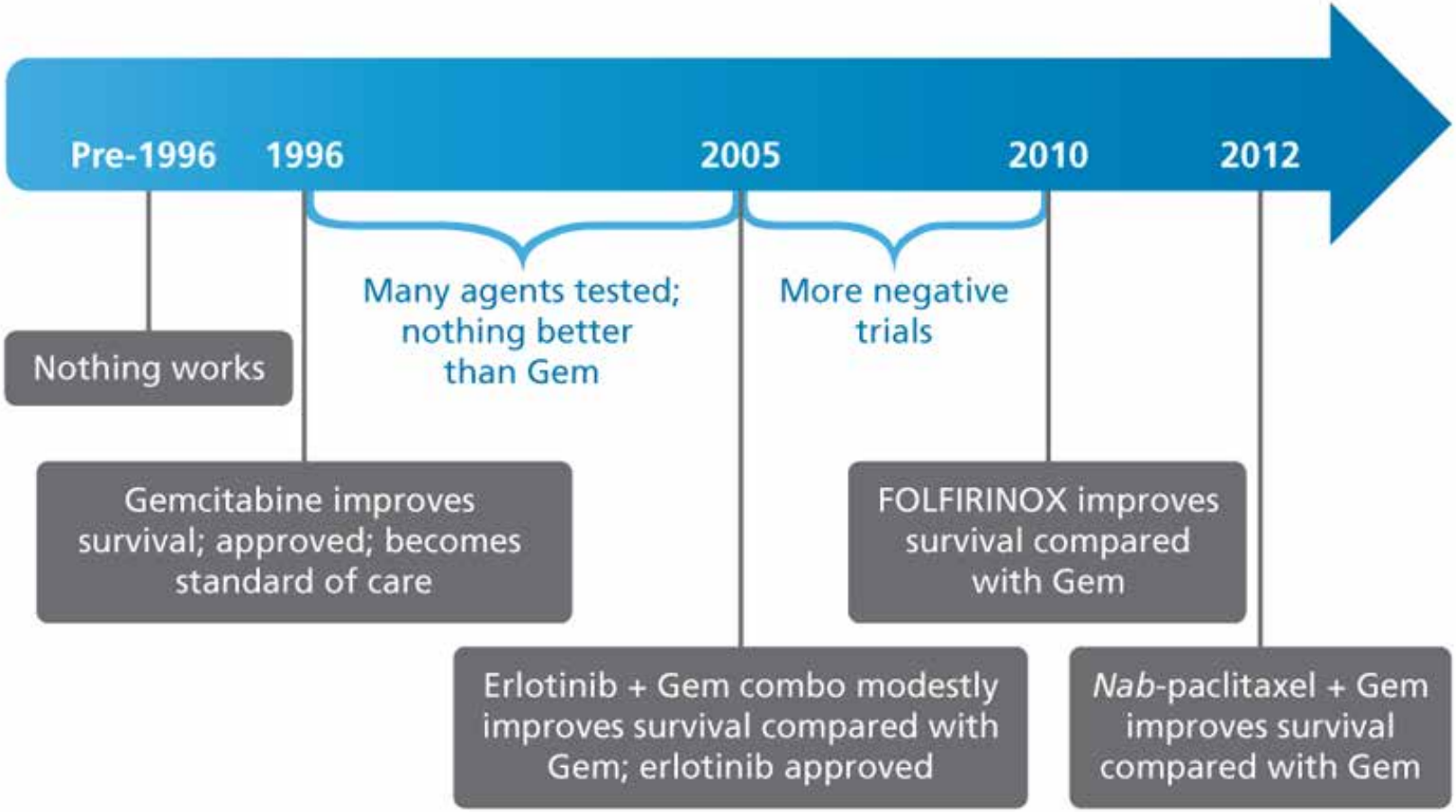
1. Geer RJ, Brennan MF. Am J Surg 1993; 165:68-72.
2. Willett CG, et al. J Clin Oncol. 2005;23:4538-4544.

Tratamiento cáncer de páncreas metastásico

TRATAMIENTO ESTÁNDAR DESDE 1997



Pancreatic Cancer: Many Agents Tested, Little to No Activity Until Recently

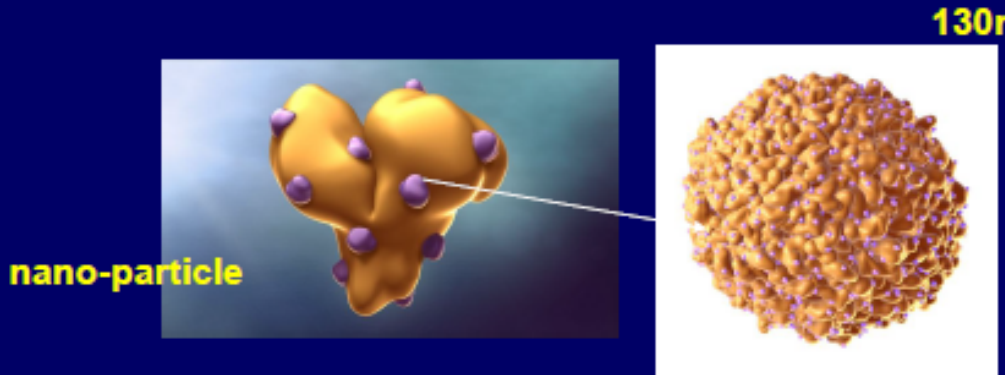


GEM+ Nab-PACLITAXEL trial: MPACT TRIAL

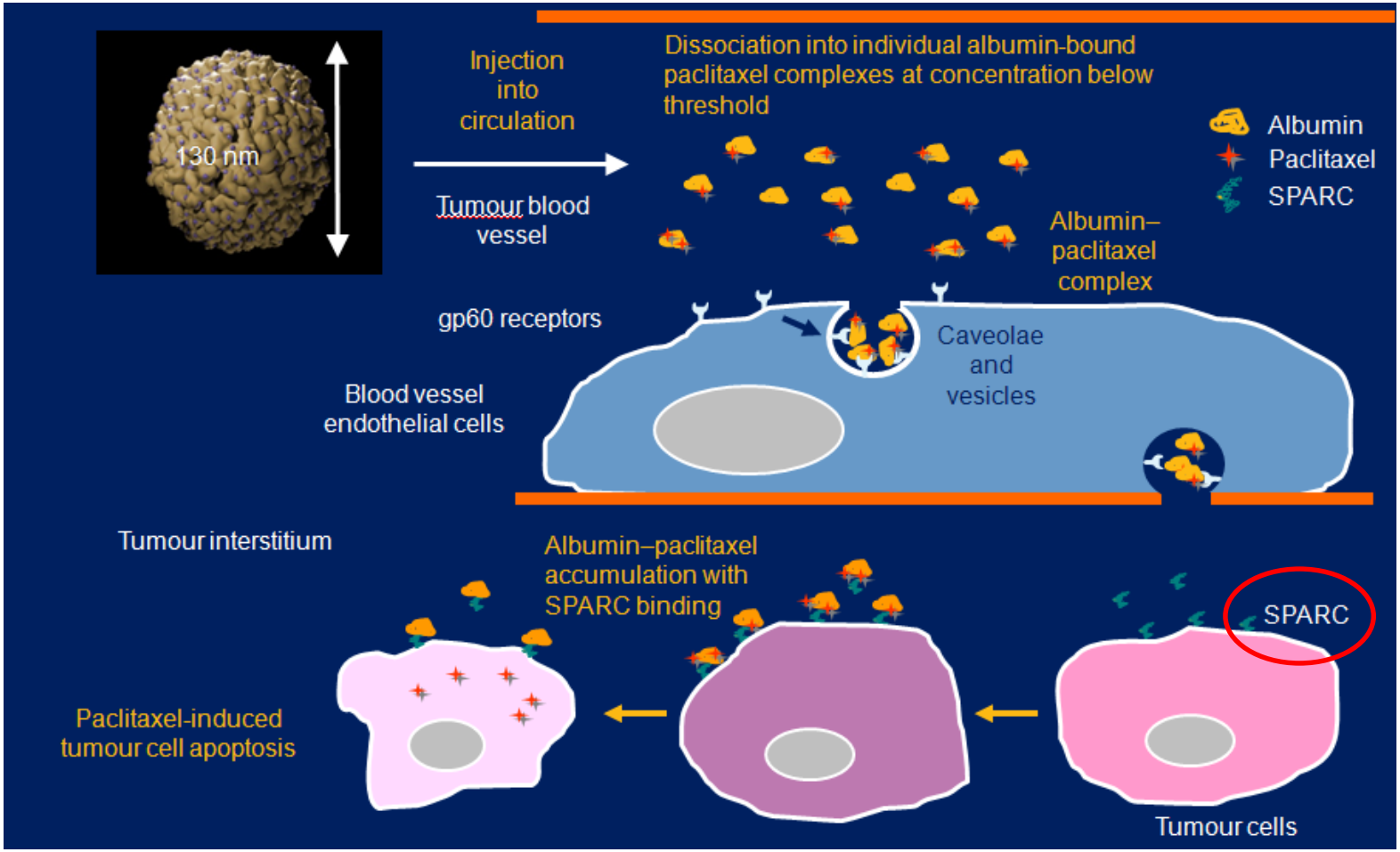
nab-Paclitaxel:

nanoparticle albumin-bound paclitaxel

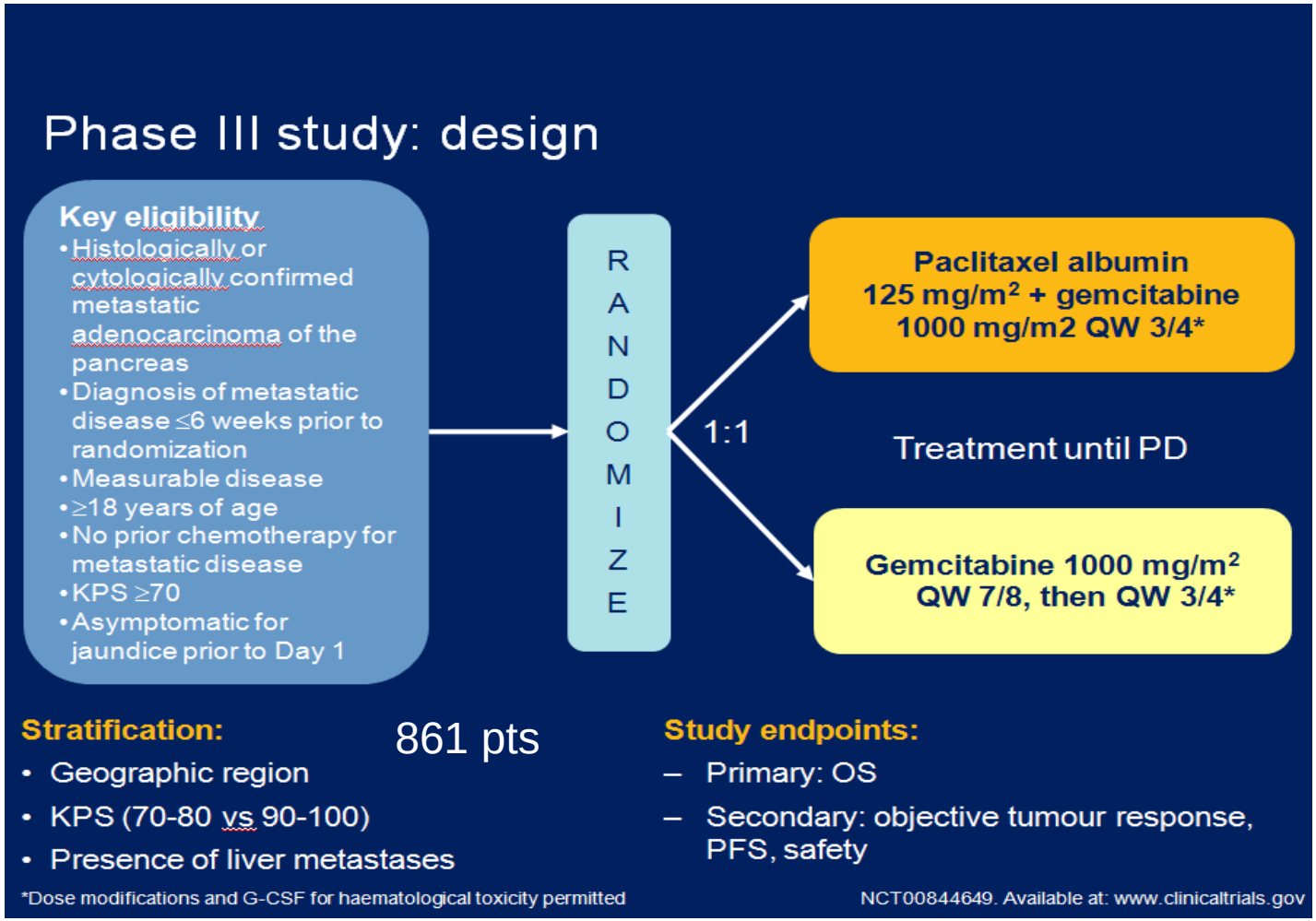
- ***nab-Paclitaxel:*** **colloidal suspension of paclitaxel and human serum albumin**
- **this creates a new delivery system**
- **binding of albumin to SPARC mechanism of action**



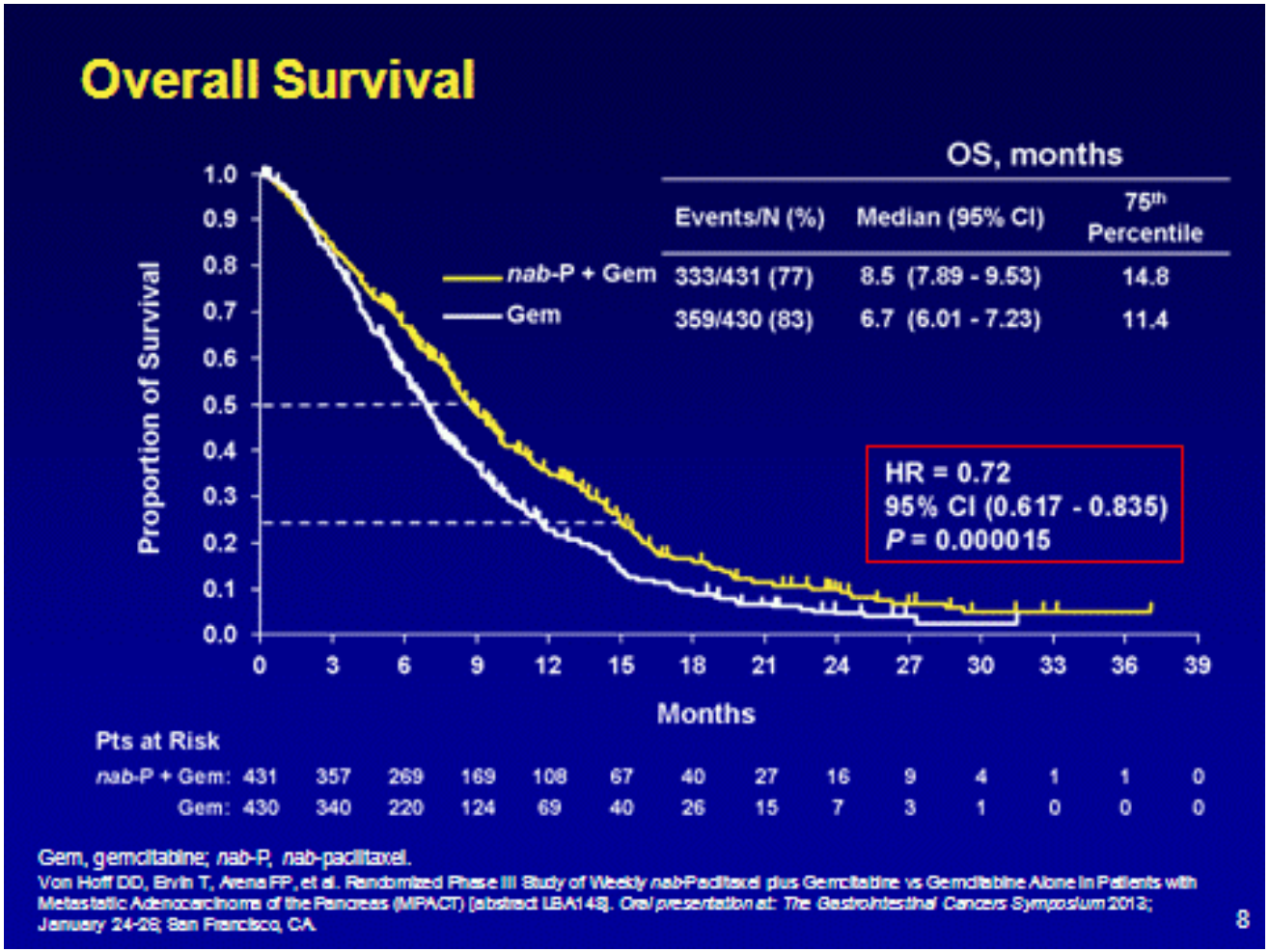
Transport across endothelial cells and albumin-binding proteins



MPACT trial


Phase III study: design
Key eligibility
• Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas
• Diagnosis of metastatic disease ≤6 weeks prior to randomization
• Measurable disease
• ≥18 years of age
• No prior chemotherapy for metastatic disease
• KPS ≥70
• Asymptomatic for jaundice prior to Day 1
RANDOMIZE
1:1
Paclitaxel albumin 125 mg/m² + gemcitabine 1000 mg/m2 QW 3/4*
Treatment until PD
Gemcitabine 1000 mg/m² QW 7/8, then QW 3/4*
861 pts
Stratification:
• Geographic region
• KPS (70-80 vs 90-100)
• Presence of liver metastases
Study endpoints:
– Primary: OS
– Secondary: objective tumour response, PFS, safety
*Dose modifications and G-CSF for haematological toxicity permitted
NCT00844649. Available at: www.clinicaltrials.gov

Overall Survival

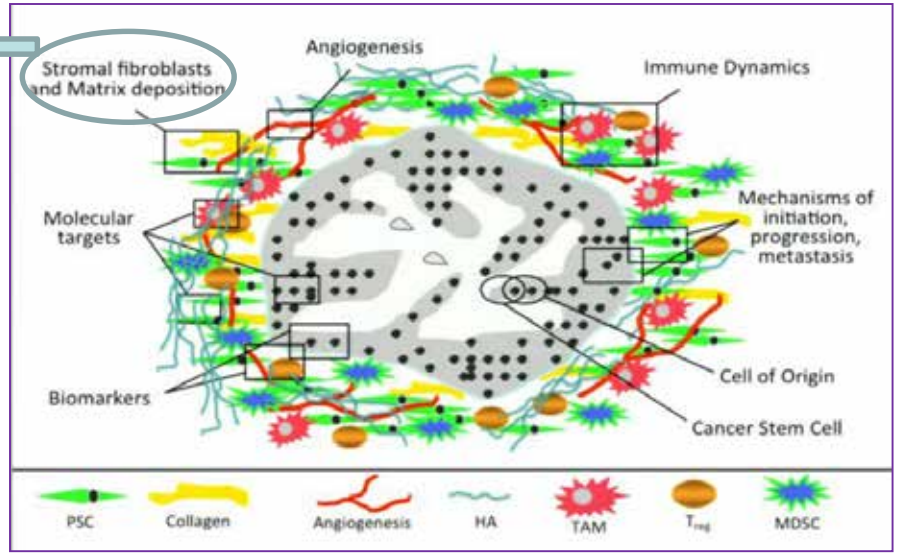


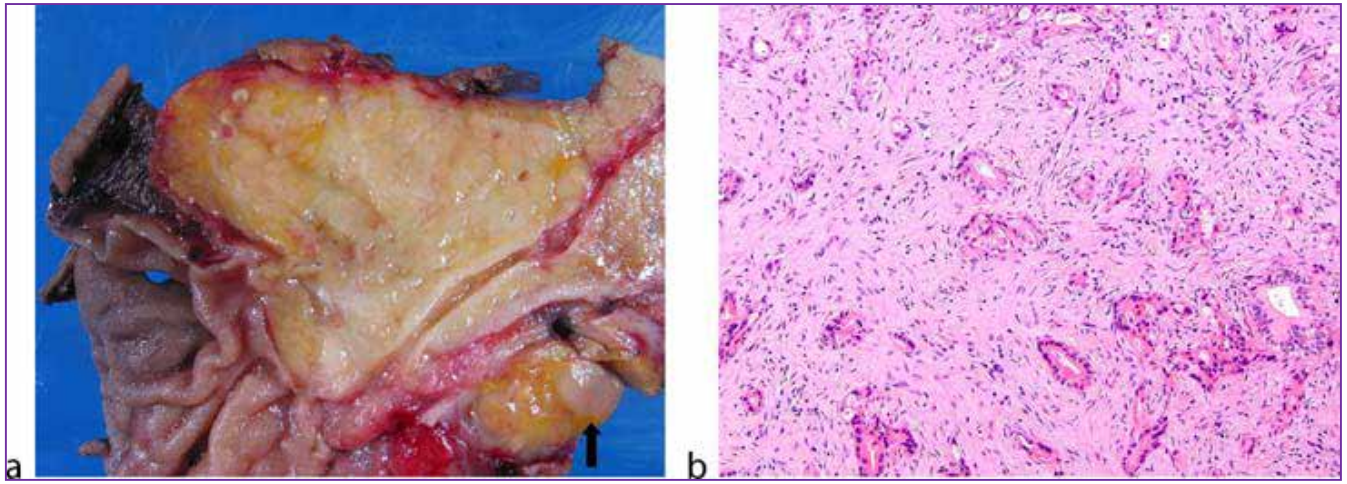
Gem, gemcitabine; *nab*-P, *nab*-paclitaxel

Von Hoff DD, Ervin T, Arena FP, et al. Randomized Phase III Study of Weekly *nab*-Paclitaxel plus Gemcitabine vs Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas (MPACT) [abstract LBA148]. *Oral presentation at: The Gastrointestinal Cancers Symposium* 2013; January 24-26; San Francisco, CA.

Stromal complexity, desmoplasia: major challenge for genomic research and clinical diagnostics

Alfa-SMA positivos





Targeting stromal response

- Enzimatic targeting of the stroma:

  PEGH: PEGPH20: PEGylated Recombinant Human Hyaluronidase. Phase 2 results.

  VCN-01 is a tumor-selective replication-competent adenovirus expressing PH20 hyaluronidase. Phase 1 ongoing.

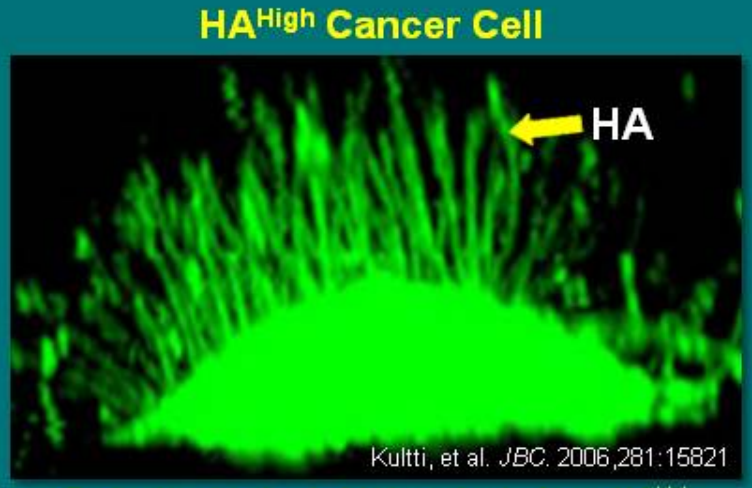
- Embryonic signaling pathways:

  Hedhegog Pathway: Negative Phase 2

  Notch Pathway: Demcizumab (Ac against Delta 4 Notch receptor). Phase 2 ongoing.

Hyaluronan (HA): A Barrier to Therapeutic Access

- **Highly hydrophilic, megadalton glycosaminoglycan (GAG) that can generate large immobile fluid phase**
- **Compromises Access to the Tumor**
  - Increased tumor interstitial fluid pressure [1,2]
  - Compresses vasculature [2-4]
  - HA-rich tumor cell "coat" can hinder host immune cell access
- **HA also signals through surface receptors**



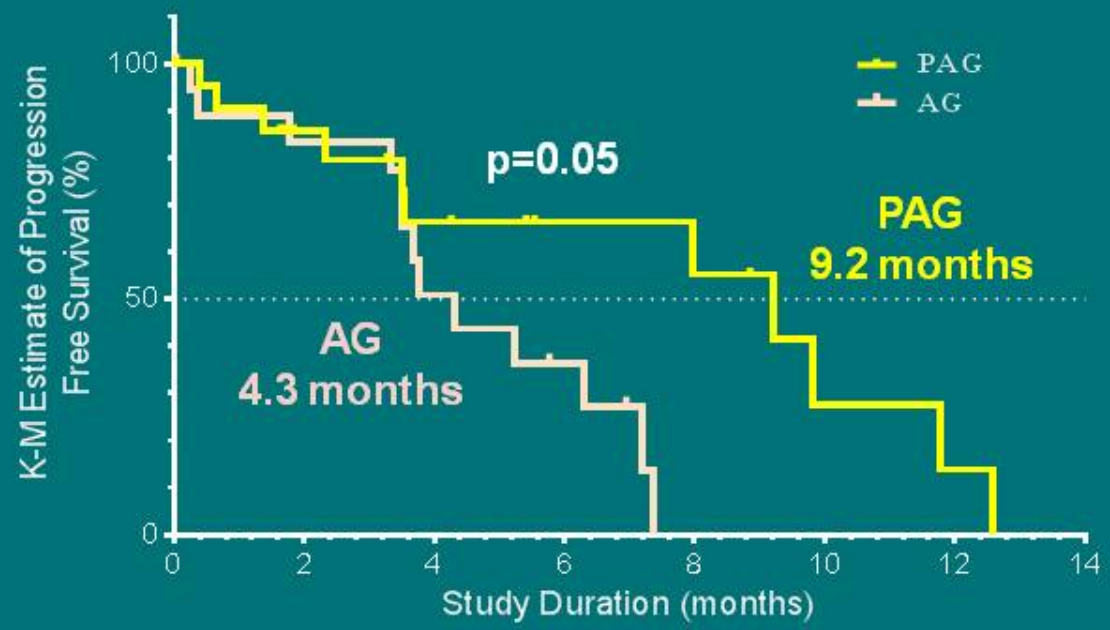
Protective 'spikes' of HA protrude from HA^{high} tumor cell in culture

1. Brekken, et al. *Anticancer Res.* 2000,20:3503. 2. Provenzano and Hingorani, *Br. J. Cancer.* 2013,108:1.
3. Thompson, et al. *Mol Cancer Ther.* 2010,9:3052. 4. Stylianopoulos, et al. *PNAS. 2013*,110:18632.

Presented By Sunil Hingorani at 2015 ASCO Annual Meeting

PEGH: PEGPH20: PEGylated Recombinant Human Hyaluronidase + Gemcitabine+ Nab-Paclitaxel.

PFS in HA-High Patients



At Risk									
	PAG	23	14	10	6	5	2	1	0
	AG	21	14	7	4	0	0	0	0

HR
0.39 (0.15, 1.04)

Targeting stromal response:
Embryonic signaling pathways

Hedgehog Pathway

NEGATIVE Phase 2 studies
Vismodegib
Saridegib

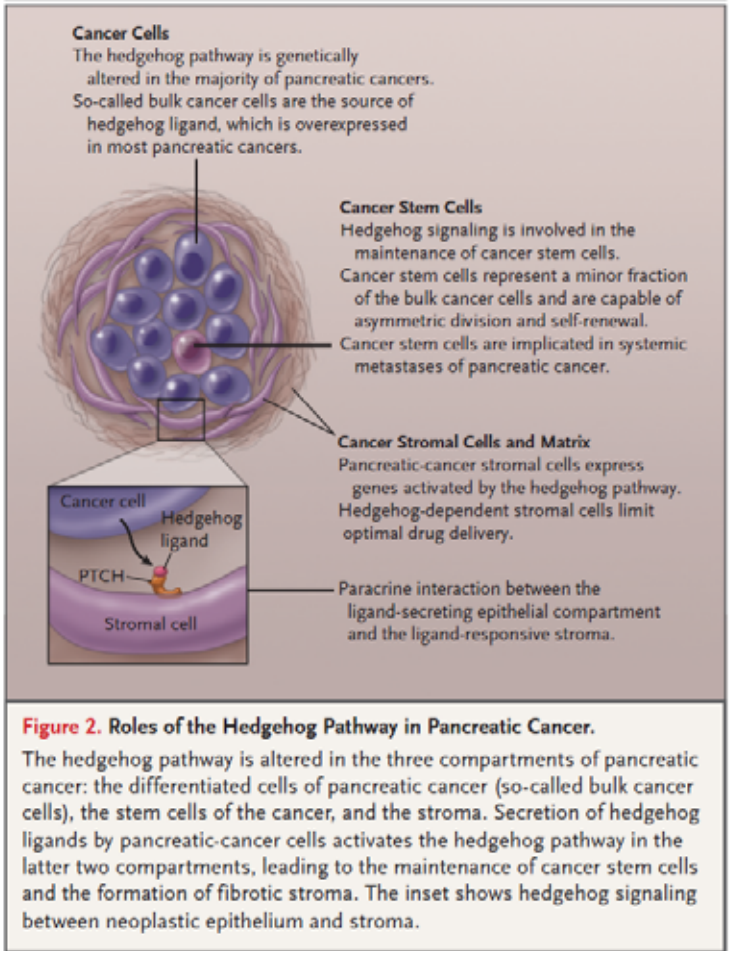
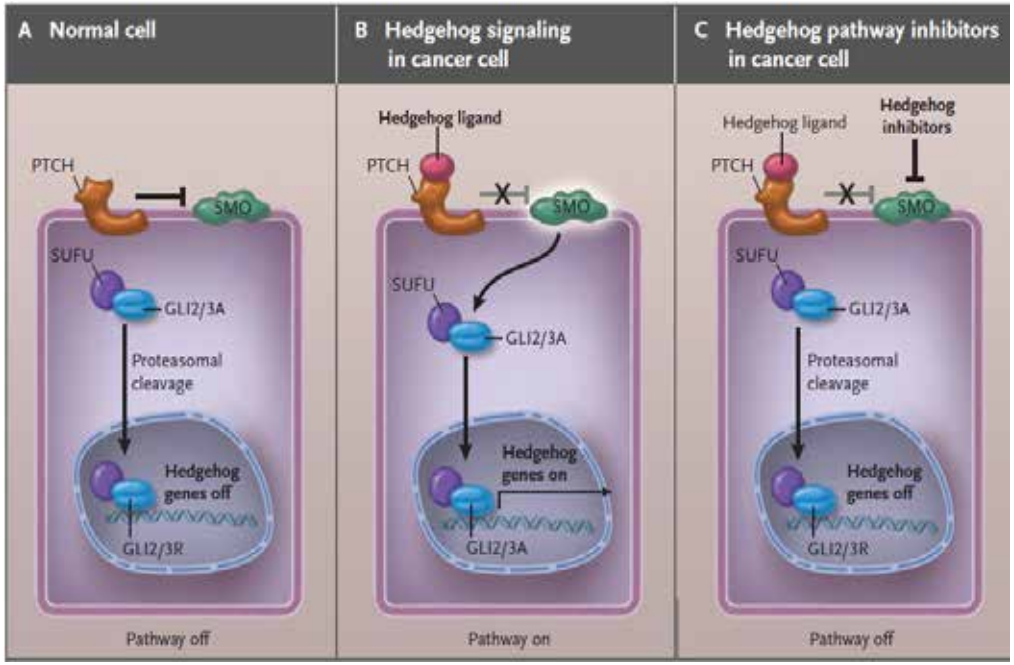


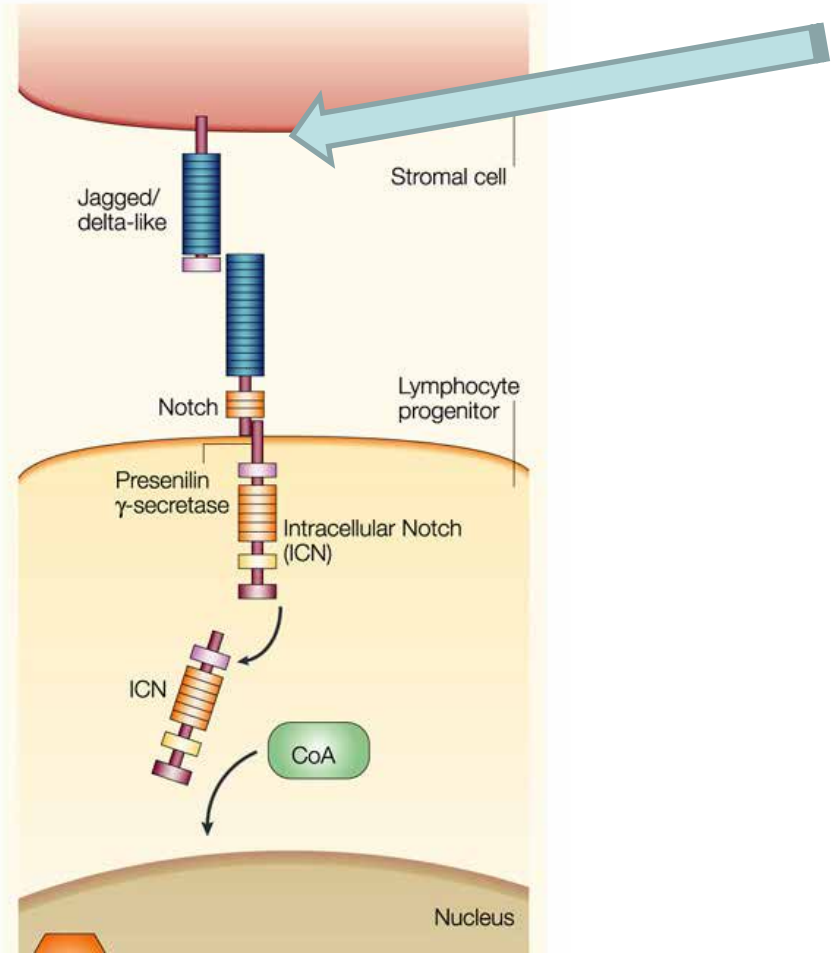
Figure 2. Roles of the Hedgehog Pathway in Pancreatic Cancer.
The hedgehog pathway is altered in the three compartments of pancreatic cancer: the differentiated cells of pancreatic cancer (so-called bulk cancer cells), the stem cells of the cancer, and the stroma. Secretion of hedgehog ligands by pancreatic-cancer cells activates the hedgehog pathway in the latter two compartments, leading to the maintenance of cancer stem cells and the formation of fibrotic stroma. The inset shows hedgehog signaling between neoplastic epithelium and stroma.



Targeting stromal response:

Embryonic signaling pathways

Notch pathway



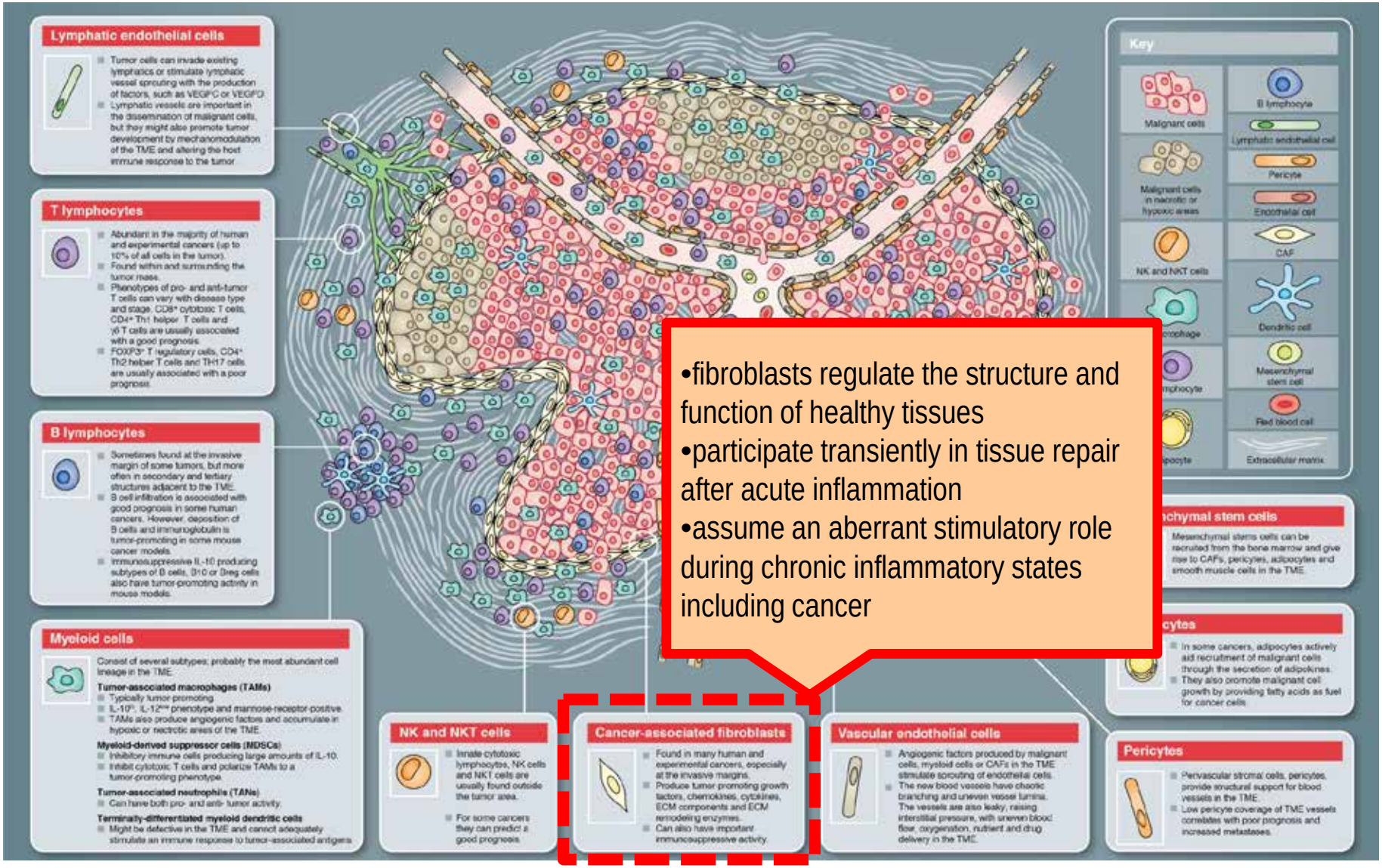
Demcizumab Phase 1b in PC.

47 pts plus gemcitabine+ Nab-paclitaxel.

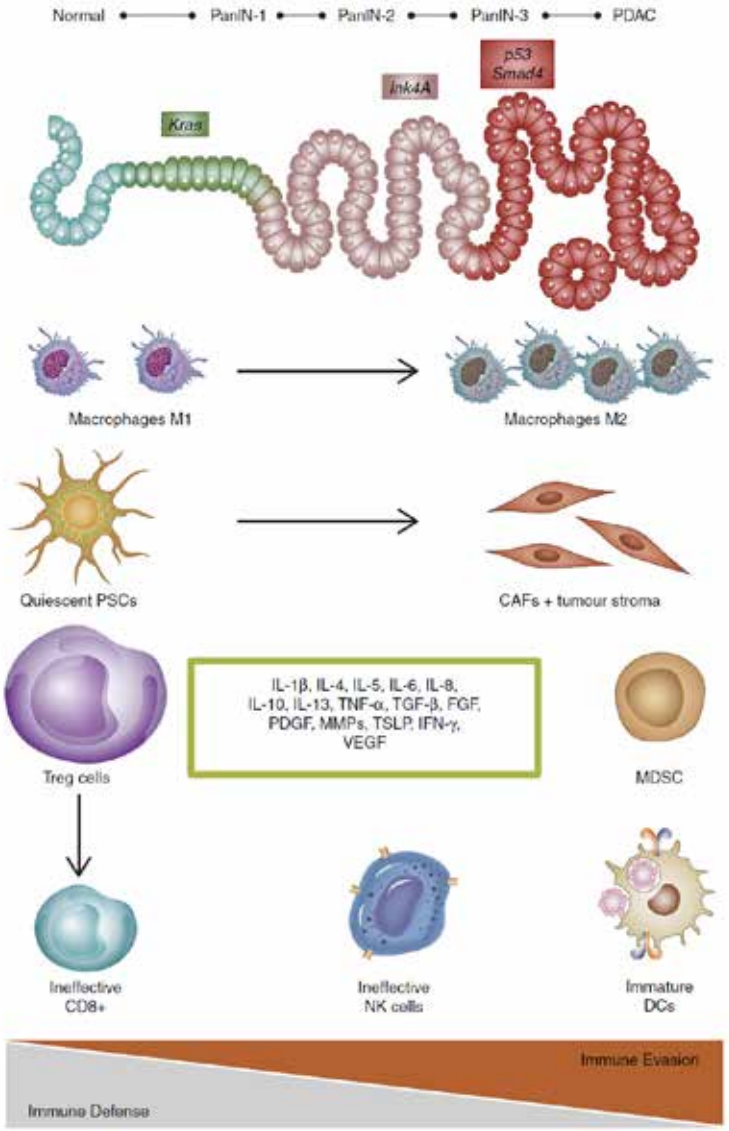
22 evaluable pts

41% PR and 10 SD

Microambient tumoral



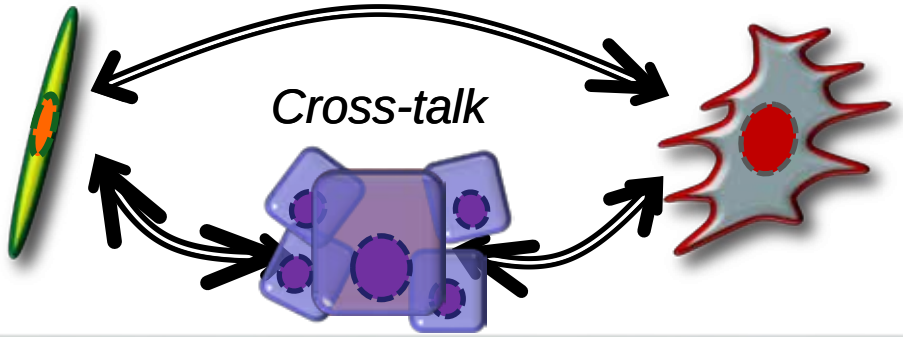
Microambient tumoral



Heterotypic interactions keep the homeostatic balance

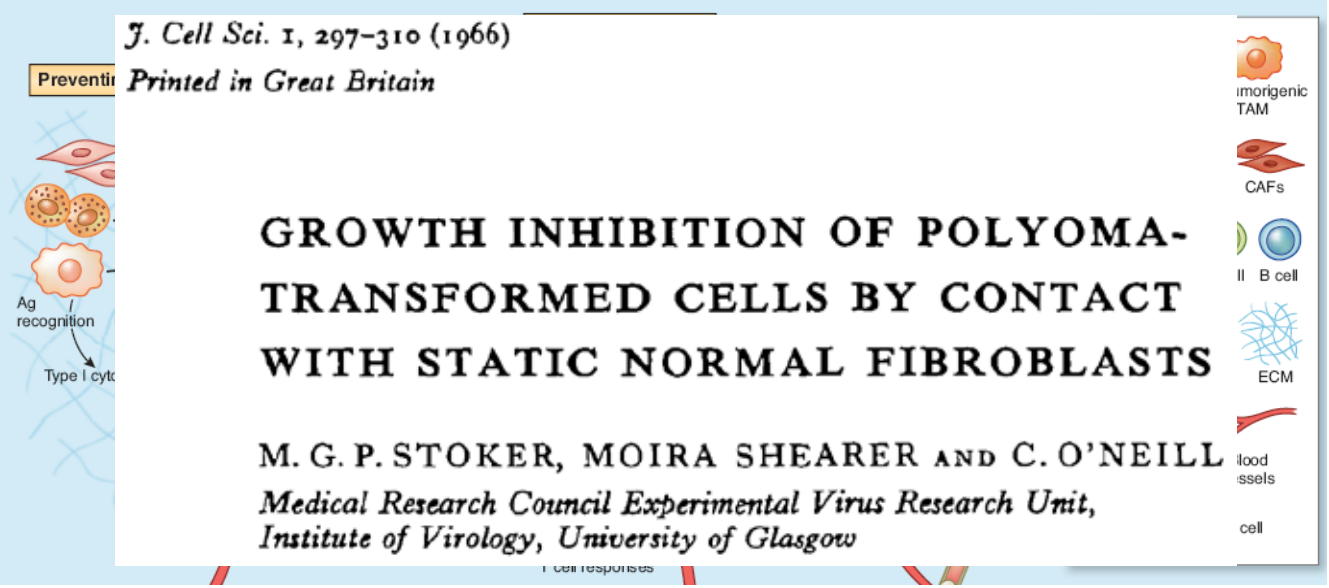
ECOSYSTEM

Physiologic conditions:
- Organ development
- Maintenance of shape and size of organs
- Remodelling after wound healing
- etc



Tumour evolves to give support to changes as a result of selective preassures imposed by the microenvironment.

Each change imposed by an oncogenic stress has repercussion both in the cell suffering the change and in its surroundings.

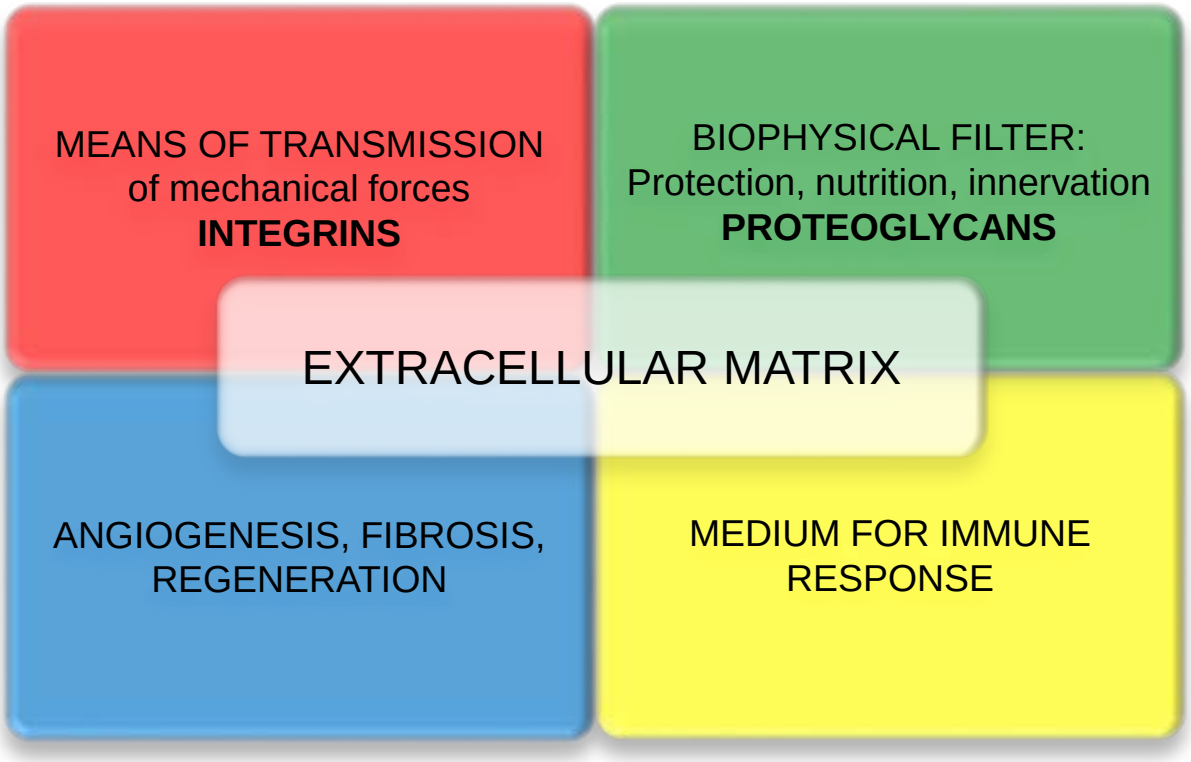


J. Cell Sci. 1, 297–310 (1966)
Printed in Great Britain

GROWTH INHIBITION OF POLYOMA-TRANSFORMED CELLS BY CONTACT WITH STATIC NORMAL FIBROBLASTS

M. G. P. STOKER, MOIRA SHEARER AND C. O'NEILL
Medical Research Council Experimental Virus Research Unit, Institute of Virology, University of Glasgow

ECM: extracellular matrix-3D network



Homeostasis-providing context

ECM: extracellular matrix components-Cancer

Cancer = Homeostatic balance X

ALTERATION IN MECHANOTRANSDUCTION

LOSS OF THE BIOPHYSICAL FILTERING FUNCTION

ALTERATION OF THE EXTRACELLULAR MATRIX

DEREGULATION OF ANGIOGENESIS AND FIBROSIS

LOSS OF SUBSTRATE FOR A PROPER IMMUNE RESPONSE

Estroma en el adenocarcinoma pancreàtic amic o enemic?

Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival

Stromal Elements Act to Restrain, Rather Than Support, Pancreatic Ductal Adenocarcinoma

Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti–PD-L1 immunotherapy in pancreatic cancer

Stromal response to Hedgehog signaling restrains pancreatic cancer progression

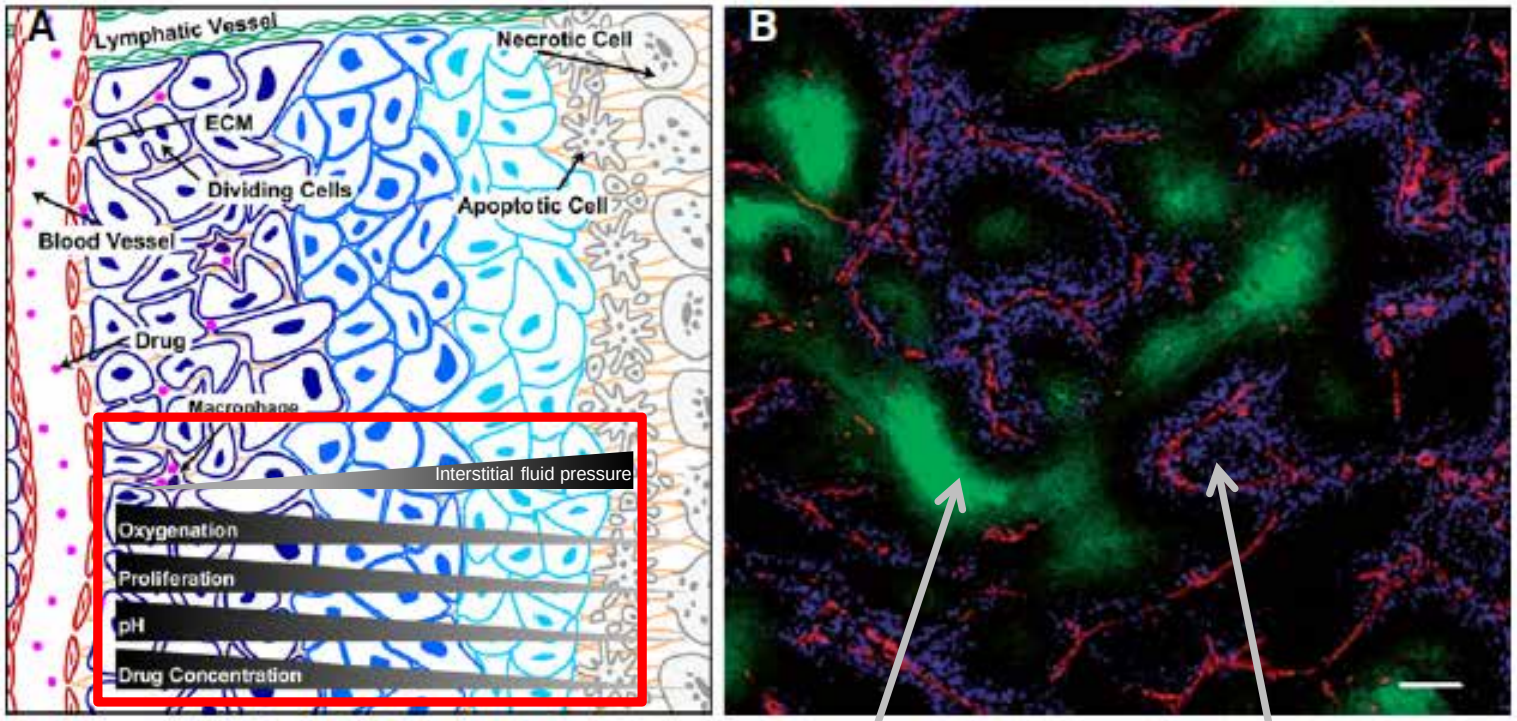
Stromal biology and therapy in pancreatic cancer: a changing paradigm

Enzymatic Targeting of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma

Vitamin D Receptor-Mediated Stromal Reprogramming Suppresses Pancreatitis and Enhances Pancreatic Cancer Therapy

La arquitectura tissular condiciona l'eficàcia de la quimioterapia

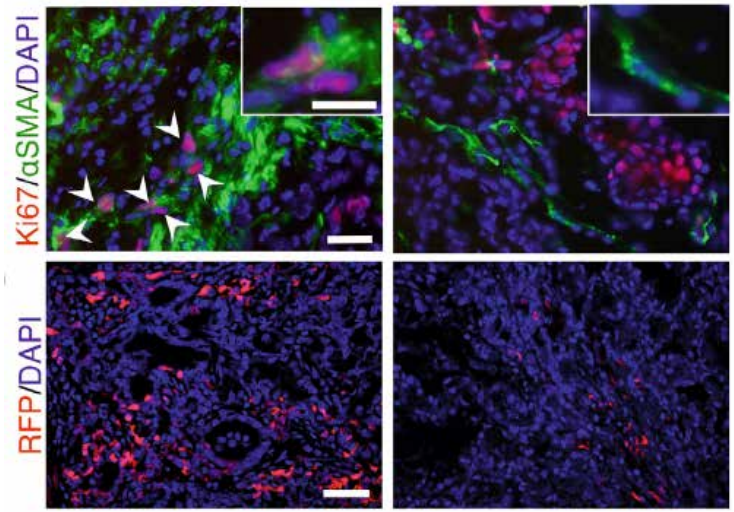
The composition and organization of the <u>ECM</u> *and stromal components contribute to marked gradients in drug concentration, increased interstitial fluid pressure and metabolic changes, all of which can strongly enhance the resistance of tumor cells to drug agents*



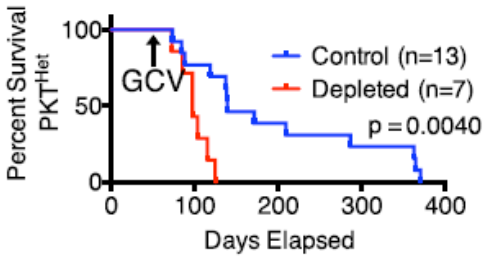
Estratègies de tractament en càncer pancreàtic basades en l'estroma

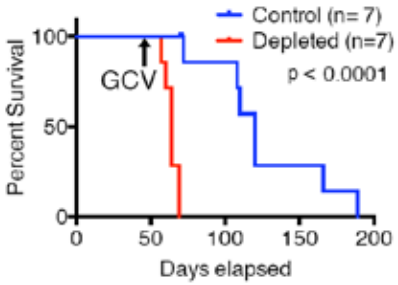
- Depleció de fibroblasts associats a carcinoma
- Degradació/Digestió matriu extracel·lular
- Interrupció del crosstalk entre estroma i epiteli
- Reprogramació de fibroblasts

Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival



PKT^{het} mice

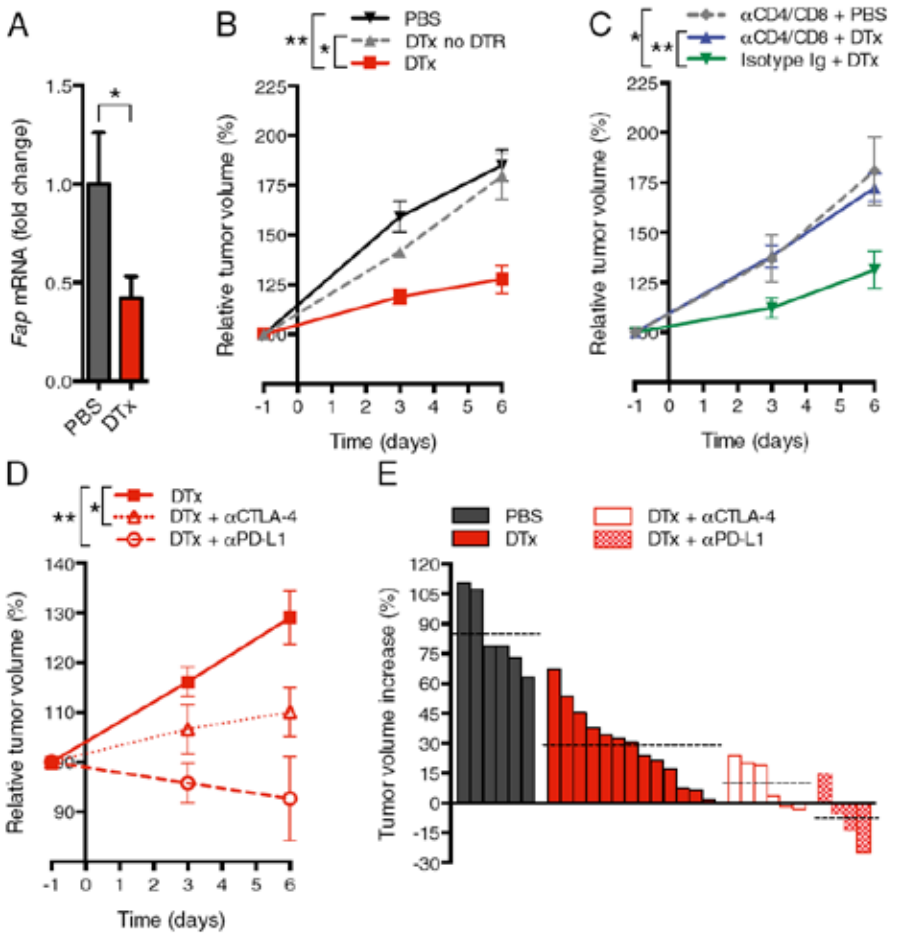




KPC mice (Kras/TP53)

Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti–PD-L1 immunotherapy in pancreatic cancer

FAP-DTR mice (diphteria toxin receptor)

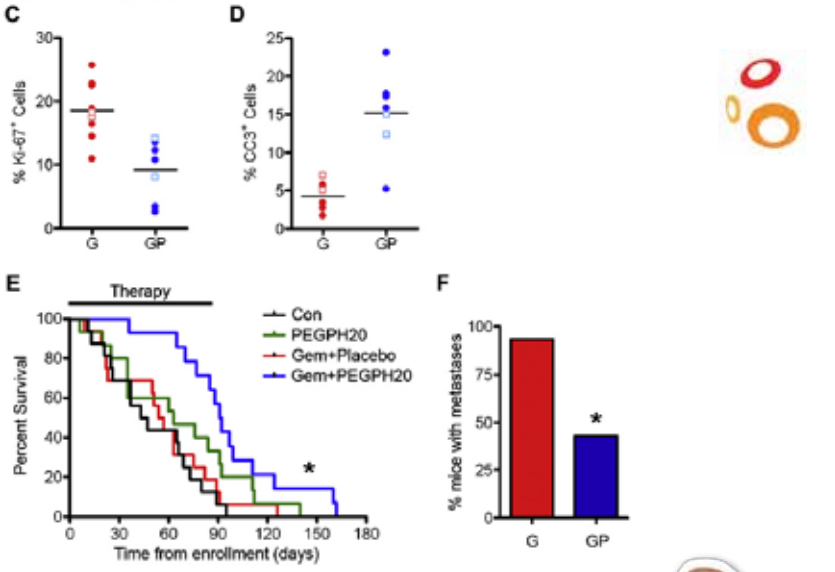


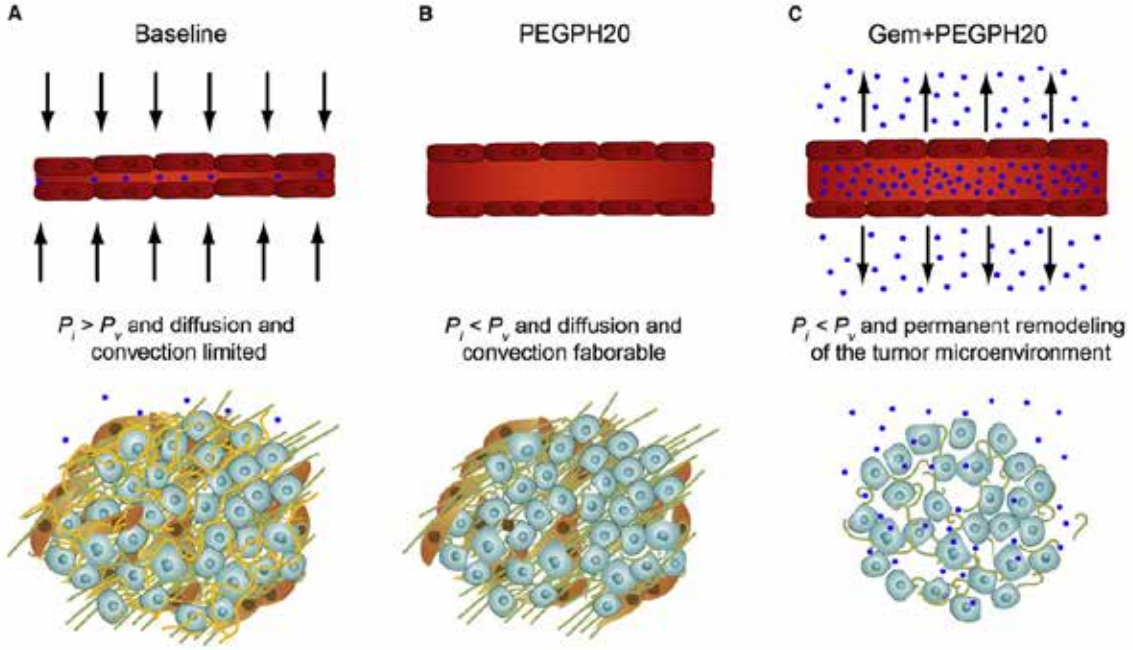
Cancer Cell
Article

Enzymatic Targeting of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma

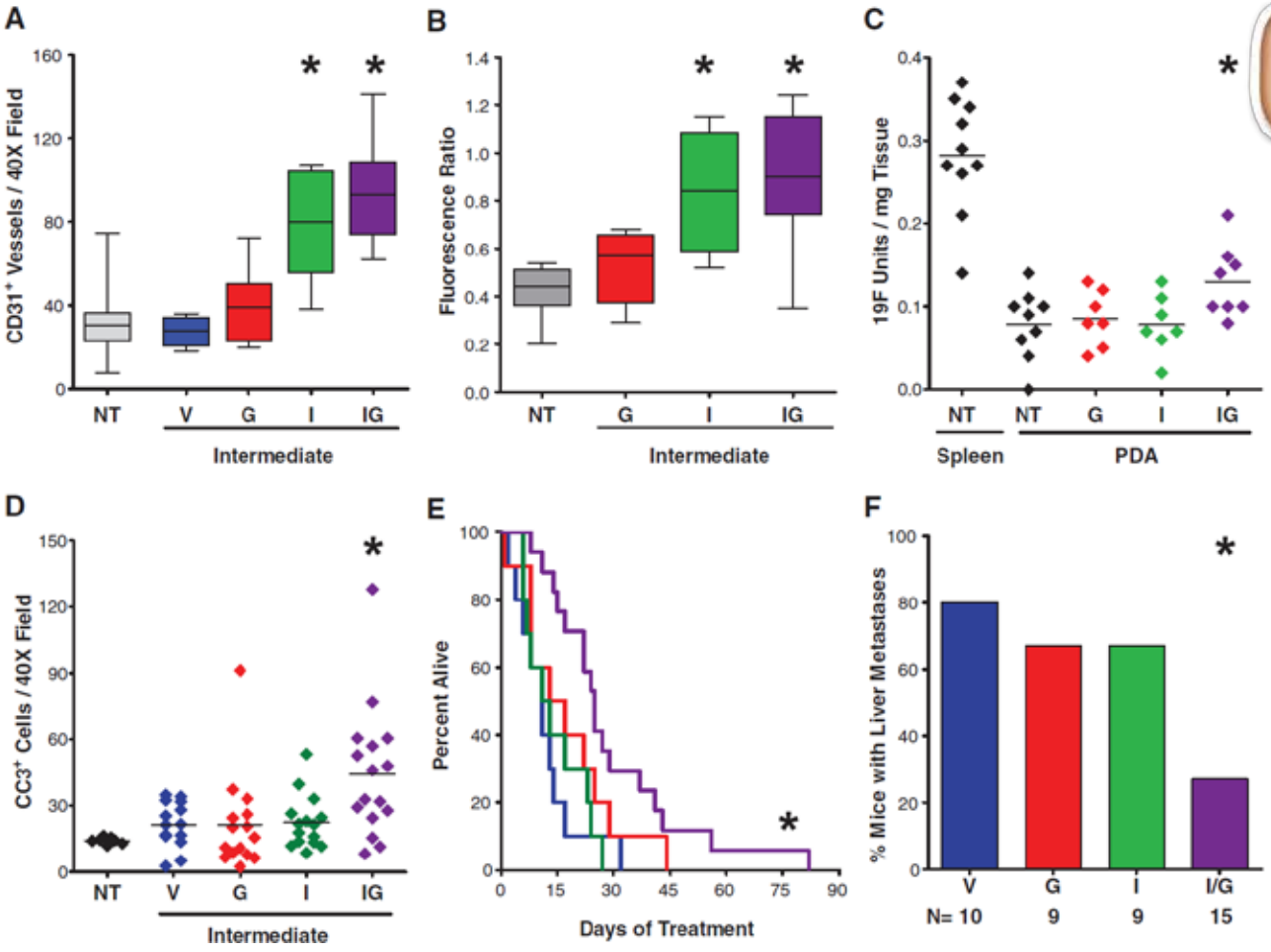
PEGPH20: hyaluronidase

Targeting the tumor architecture



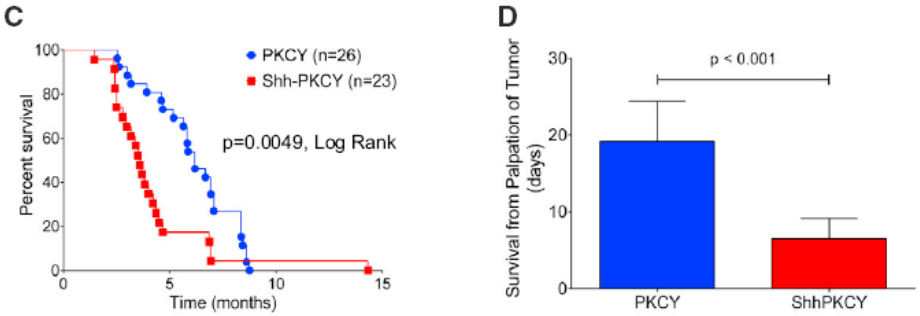


Inhibition of Hedgehog Signaling Enhances Delivery of Chemotherapy in a Mouse Model of Pancreatic Cancer



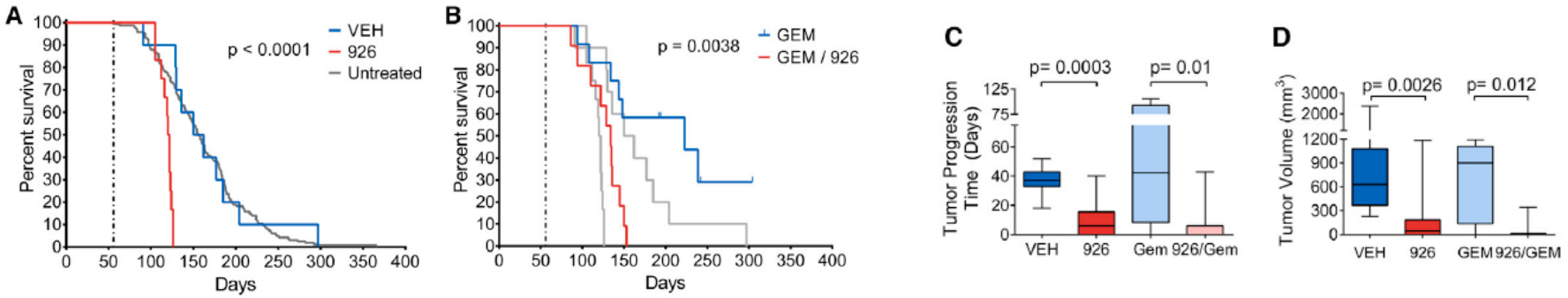
Stromal Elements Act to Restrain, Rather Than Support, Pancreatic Ductal Adenocarcinoma

Shh$^{-/-}$ tumor cells → Paracrine signaling

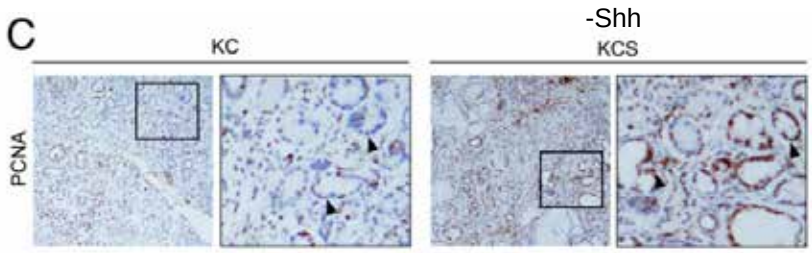


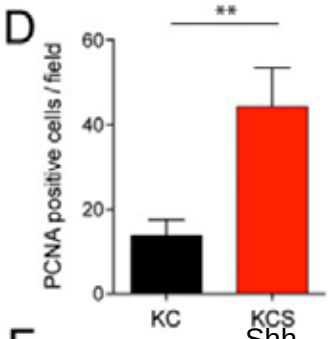
Shh pharmacologic inhibition

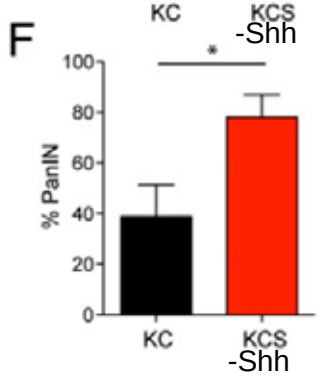
KPC mice

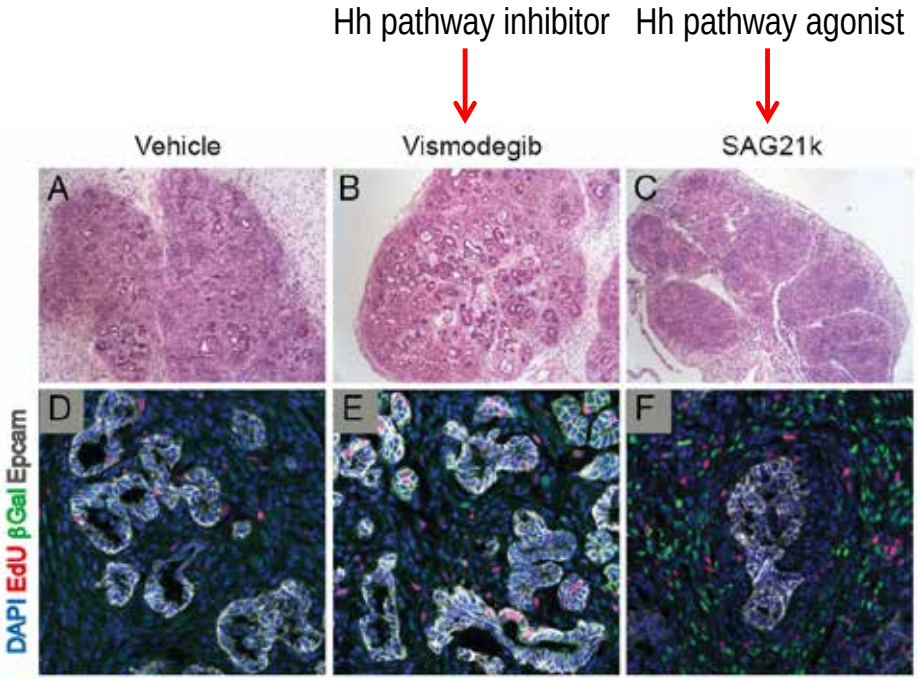


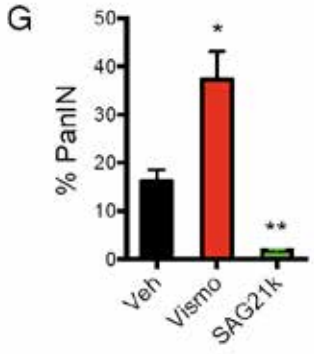
Stromal response to Hedgehog signaling restrains pancreatic cancer progression

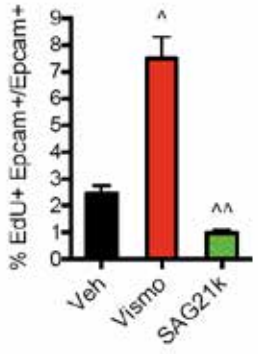




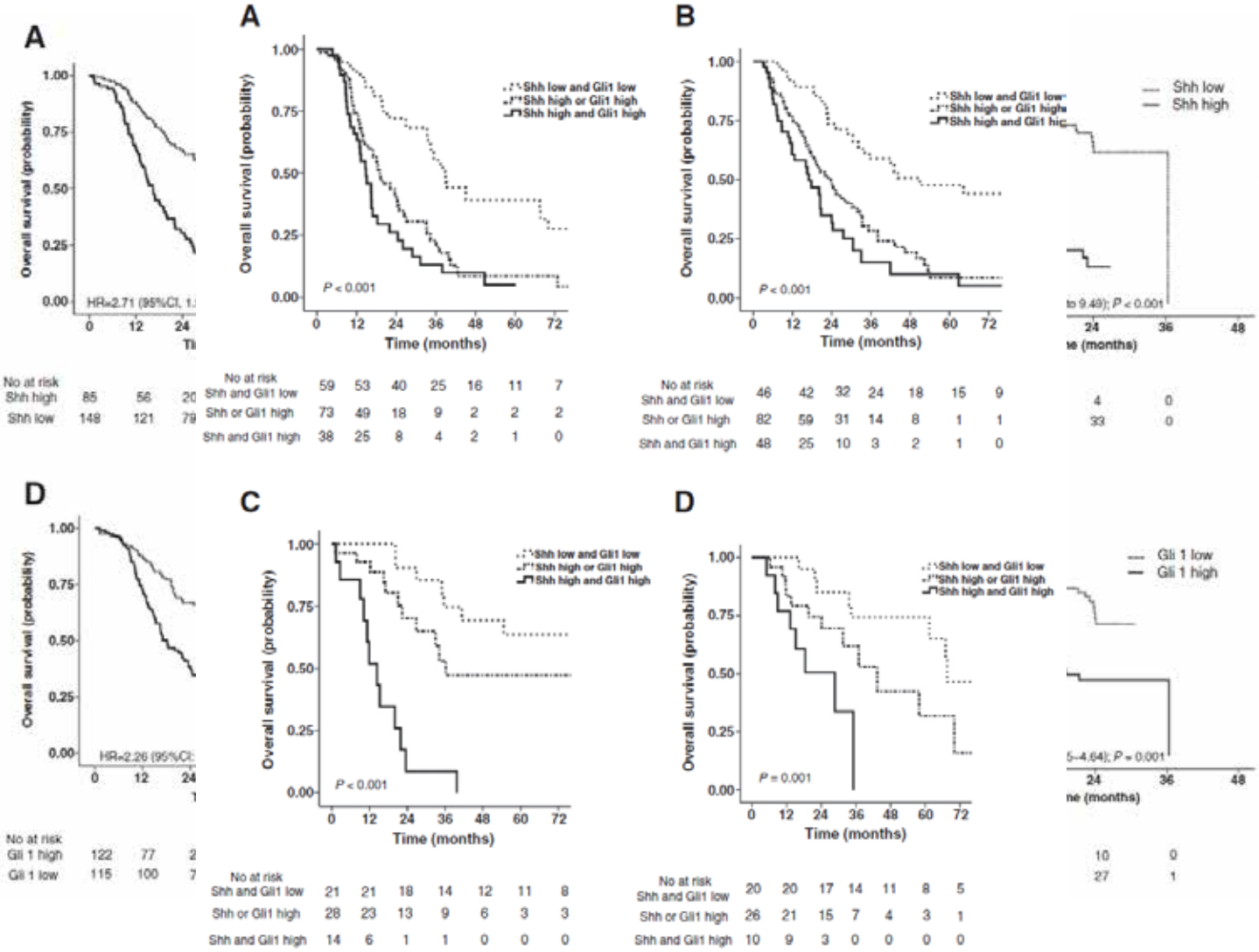




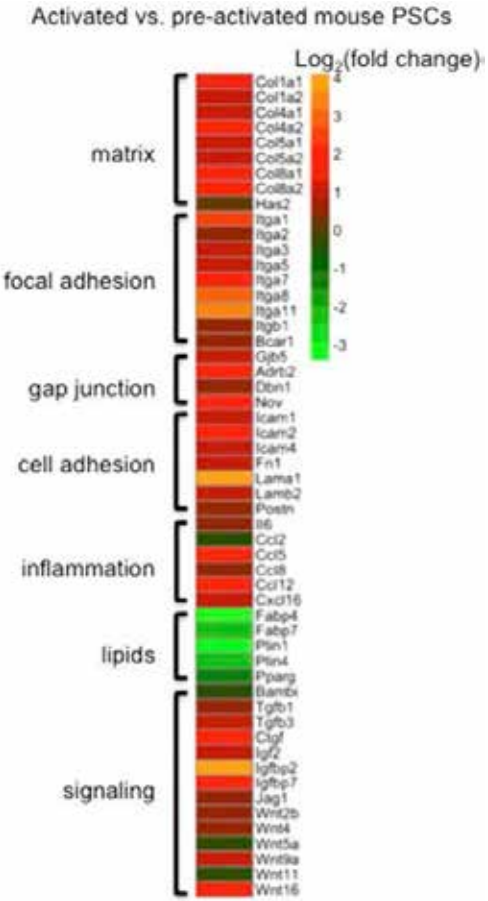


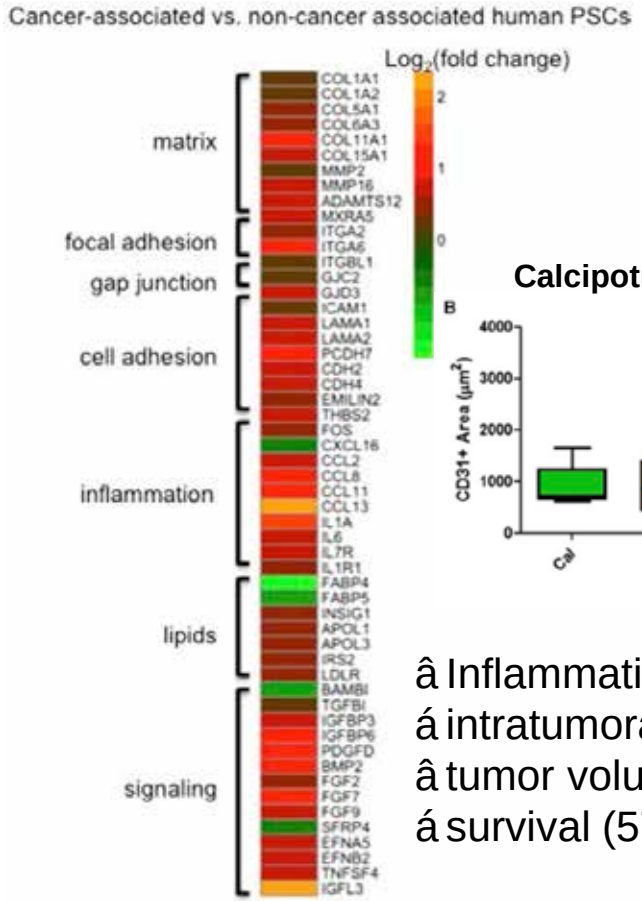


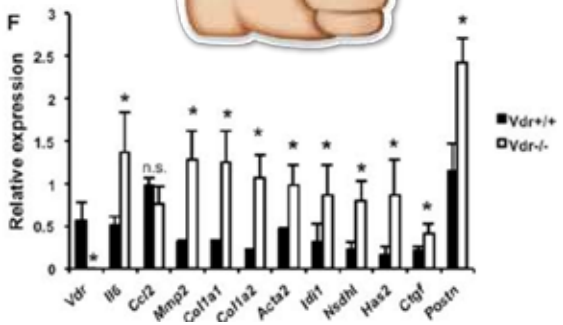
Sonic Hedgehog and Gli1 Expression Predict Outcome in Resected Pancreatic Adenocarcinoma



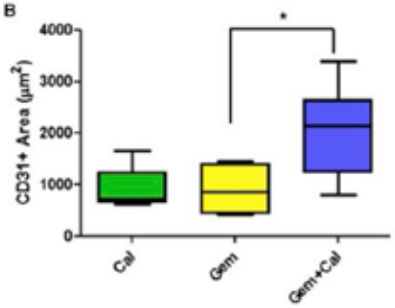
Vitamin D Receptor-Mediated Stromal Reprogramming Suppresses Pancreatitis and Enhances Pancreatic Cancer Therapy

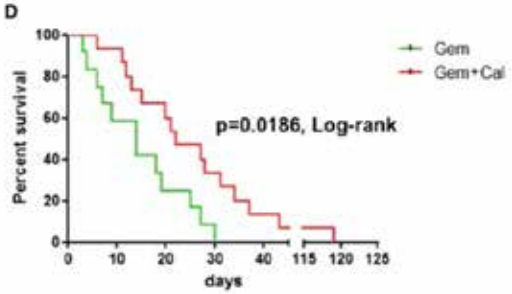




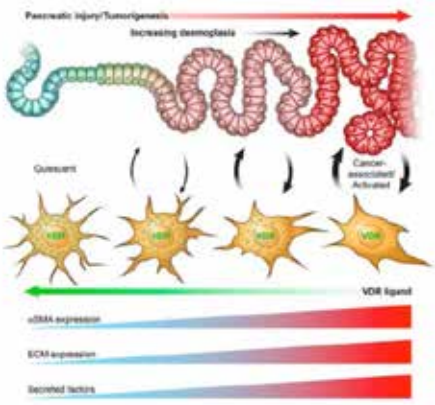


Calcipotriol treatment





â Inflammation, fibrosis
á intratumoral Gemcitabine
â tumor volume
á survival (57%)



Thanks a lot!!!