Pancreatic Adenocarcinoma: What`s hot

Eva Karamitopoulou-Diamantis
Institute of Pathology
University of Bern

11.09.2018, 30th ECP, Bilbao

Pancreatic Cancer and the Microbiome

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CANCER DISCOVERY

The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression

Smruti Pushalkar, Mautin Hundeyin, Donnele Daley, et al.

DOI: 10.1158/2159-8290.CD-17-1134 Published April 2018

Pancreatic Cancer and the Microbiome

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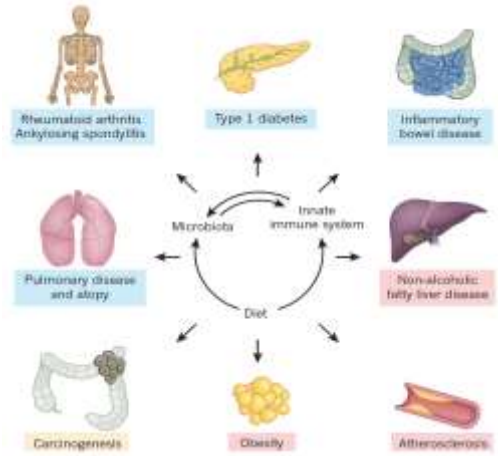
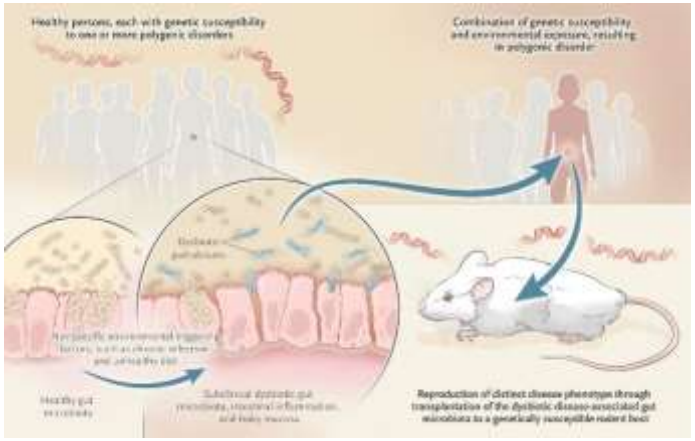
- When administered to wild-type mice, bacteria migrated into the pancreas, suggesting that intestinal bacteria may affect the pancreatic microenvironment
  - In both mice and humans, tumorous tissue had an increased bacterial abundance compared with normal pancreas
  - In a mouse model of pancreatic cancer, mice grown in germ-free conditions exhibited reduced disease progression
  - Treatment with antibiotics reduced tumor burden while repopulation with select bacterial species from untreated tumor-bearing mice accelerated tumorigenesis





Pushalkar S et al, Cancer Discov 2018, Lynch SV and Pedersen O, N Engl J Med 2016

Pancreatic Cancer and the Microbiome

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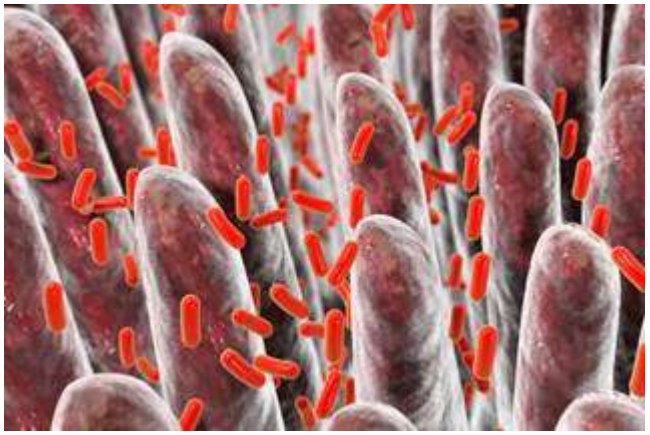
- Ablation of the microbiome protects against pre-invasive lesions and invasive cancer
- Ablation was associated with immunogenic reprogramming of the tumor microenvironment including:
  - reduction in myeloid-derived suppressor cells
  - increase in M1 macrophage differentiation,
  - promoting TH1 differentiation of CD4+ T cells and CD8+ T-cell activation
- Bacterial ablation also enabled efficacy for checkpoint-targeted immunotherapy by upregulating PD-1 expression



Pushalkar S et al, Cancer Discov 2018

Long Term Survivors in 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]§

Long Term Survivors (LTS) in Pancreatic Cancer

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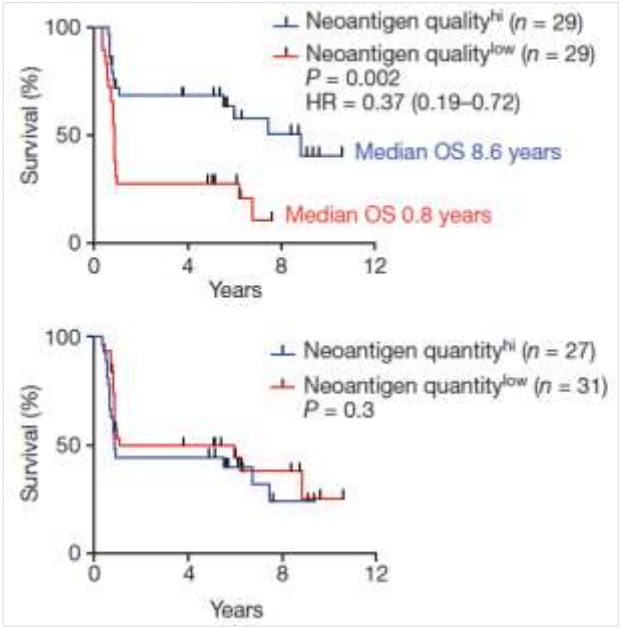
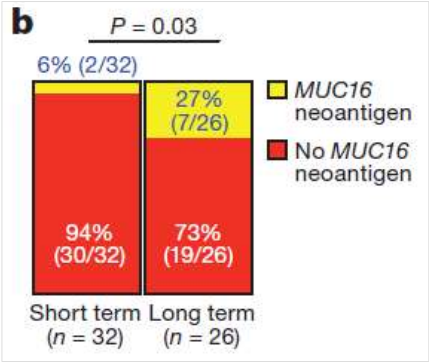
- Authors used genetic, immuno-histochemical and transcriptional profiling, computational biophysics, and functional assays to identify T-cell antigens in LTS of pancreatic cancer
- Using whole exome sequencing and *in silico* neoantigen prediction, found that both the highest neoantigen number and the most abundant CD8+ T-cell infiltrates, but neither alone, identified LTS
- Investigating the specific neoantigen qualities promoting T-cell activation in LTS, discovered enrichment in neoantigens in the tumor antigen MUC16 (CA125)





Balachandran VP et al, Nature 2017

Long Term Survivors (LTS) in Pancreatic Cancer

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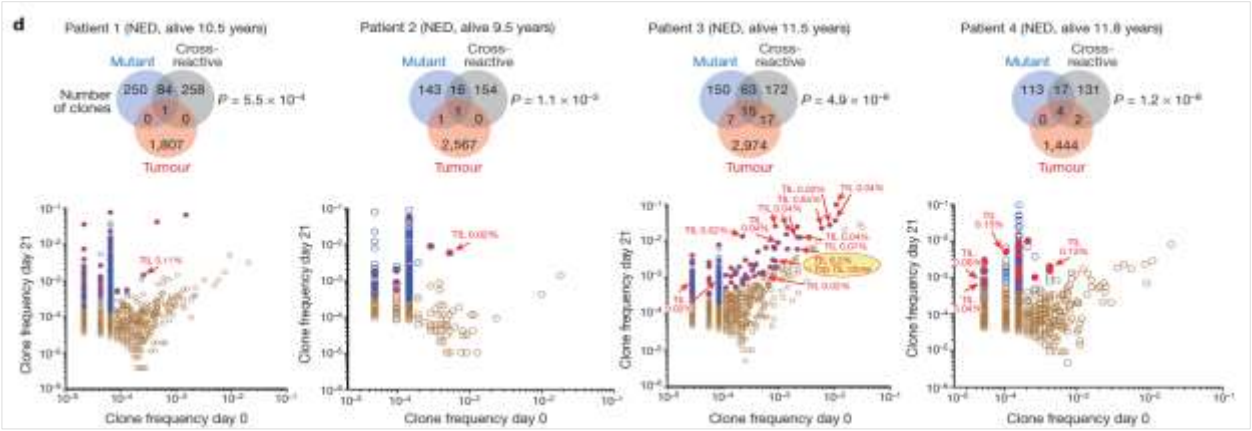
- Detected intratumoral and lasting circulating T-cell reactivity to MUC16 neoantigens in LTS
- Including clones that predicted crossreactive microbial epitopes, consistent with neoantigen molecular mimicry
- Selective loss of high-quality and MUC16 neoantigenic clones on metastatic progression, suggesting neoantigen immunoediting
- Identified neoantigen quality as a biomarker for immunogenic tumors that may guide the application of immunotherapy



Role of KRAS in Pancreatic Cancer

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ARTICLE

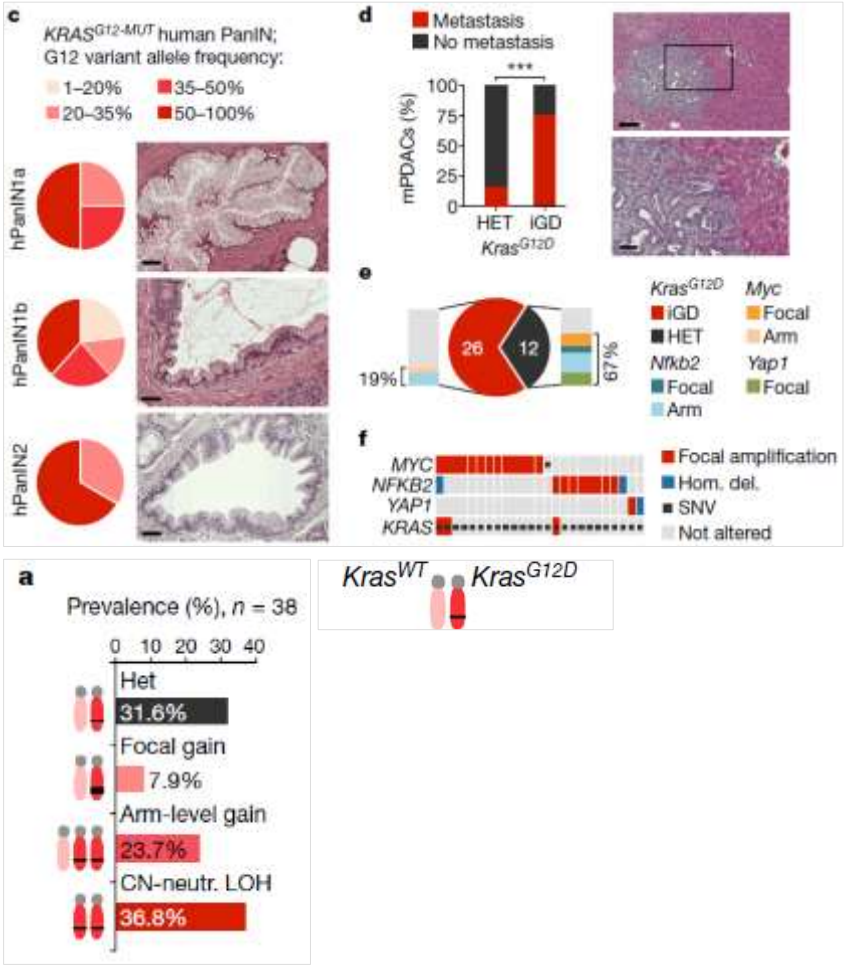
doi:10.1038/nature25459

Evolutionary routes and *KRAS* dosage define pancreatic cancer phenotypes

Sebastian Mueller[1,2*], Thomas Engleitner[1,2,3*], Roman Maresch[1,2,3*], Magdalena Zukowska[1,2], Sebastian Lange[1,2], Thorsten Kaltenbacher[1,2,3], Björn Konukiewitz[4], Rupert Öllinger[1,2], Maximilian Zwiebel[2], Alex Strong[5], Hsi-Yu Yen[3,6], Ruby Banerjee[5], Sandra Louzada[5], Beiyuan Fu[5], Barbara Seidler[1,2], Juliana Götzfried[2], Kathleen Schuck[2], Zonera Hassan[2], Andreas Arbeiter[2], Nina Schönhuber[1,2], Sabine Klein[1,2], Christian Veltkamp[1,2], Mathias Friedrich[5], Lena Rad[2], Maxim Barenboim[2,3], Christoph Ziegenhain[7], Julia Hess[8], Oliver M. Dovey[5], Stefan Eser[2], Swati Parekh[7], Fernando Constantino-Casas[9], Jorge de la Rosa[5,10,11], Marta I. Sierra[12], Mario Fraga[12,13], Julia Mayerle[14], Günter Klöppel[4], Juan Cadiñanos[5,10], Pentao Liu[5], George Vassiliou[5], Wilko Weichert[3,4], Katja Steiger[4,6], Wolfgang Enard[7], Roland M. Schmid[2,3], Fengtang Yang[5], Kristian Unger[8], Günter Schneider[2,3], Ignacio Varela[15], Allan Bradley[5], Dieter Saur[1,2,3]§ & Roland Rad[1,2,3]§

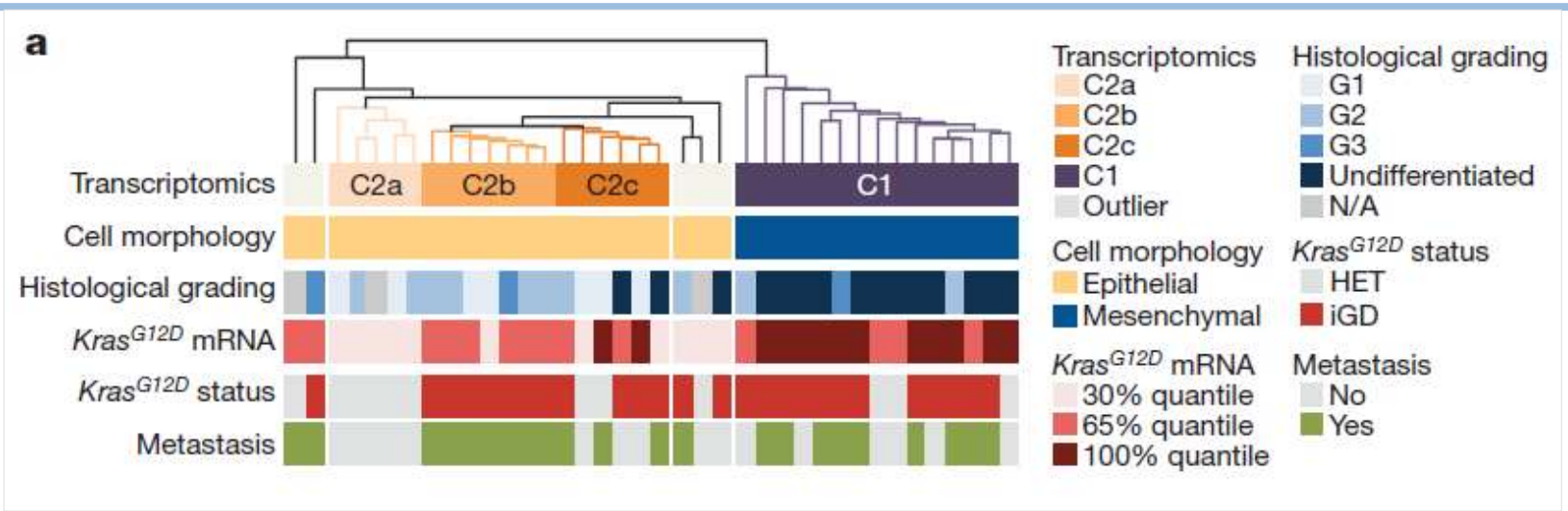
Role of KRAS in Pancreatic Cancer

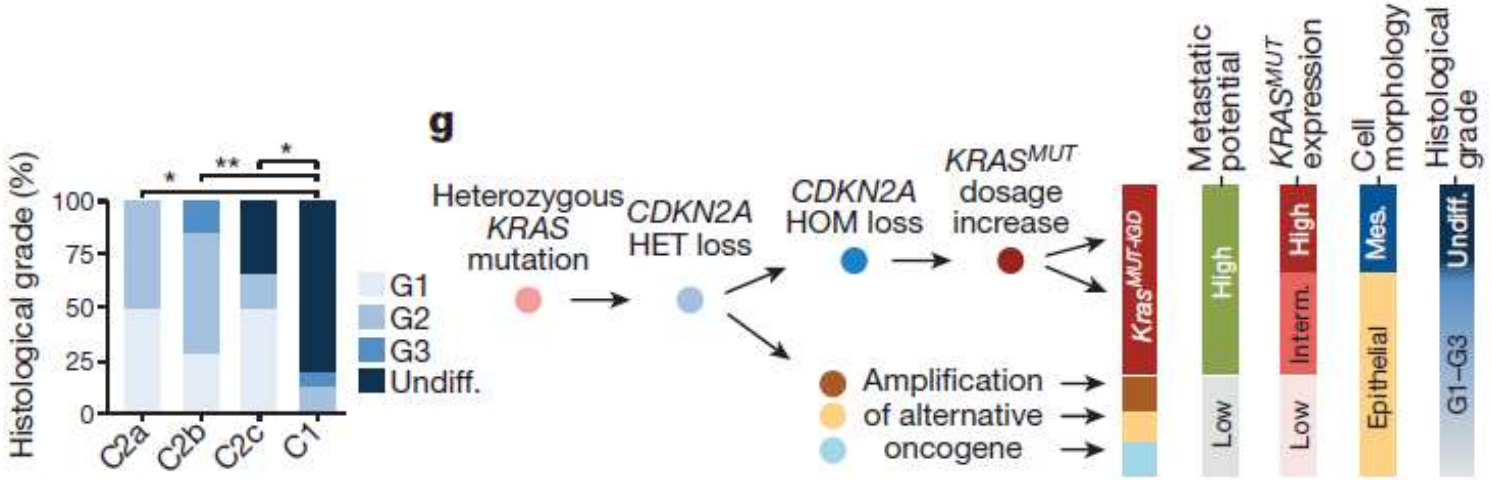
- Increase in gene dosage of mutant KRAS in hPDAC precursors, which drives both early tumorigenesis and metastasis
- Highest $Kras^{MUT}$ levels found in aggressive undifferentiated phenotypes
- Alternative oncogenic gains (Myc, Yap1 or Nfkb2) collaborated with heterozygous $Kras^{MUT}$ in driving tumorigenesis, but had lower metastatic potential



Mueller S et al, Nature 2018

Role of KRAS in Pancreatic Cancer





Association of Alterations in Main Driver Genes With Outcomes in Pancreatic Cancer

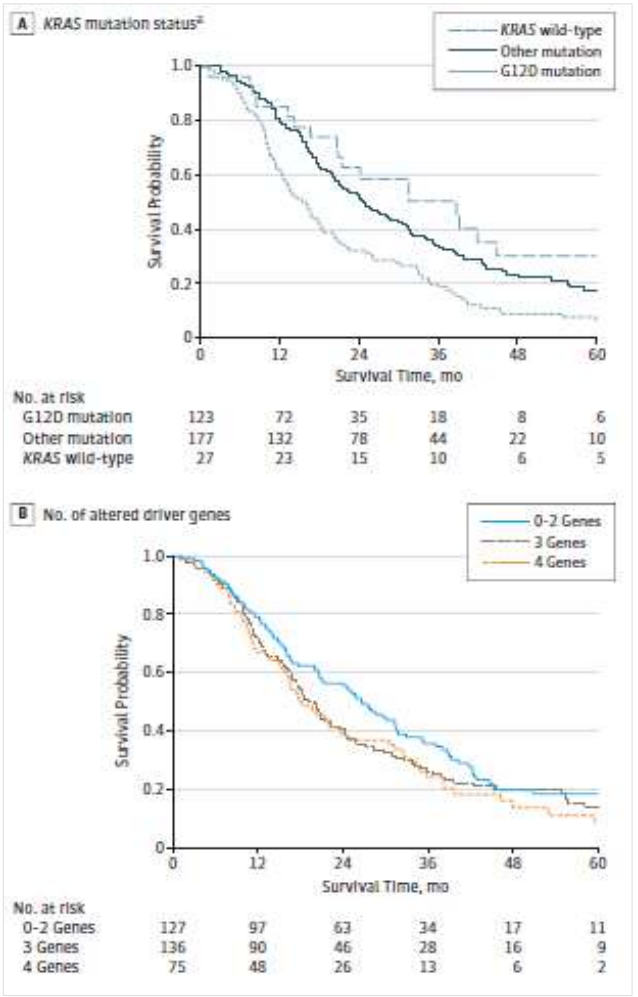
JAMA Oncology | Brief Report

Association of Alterations in Main Driver Genes With Outcomes of Patients With Resected Pancreatic Ductal Adenocarcinoma

Zhi Rong Qian, MD, PhD; Douglas A. Rubinson, MD, PhD; Jonathan A. Nowak, MD, PhD; Vicente Morales-Oyarvide, MD, MPH; Richard F. Dunne, MD; Margaret M. Kozak, MD; Marisa W. Welch, BA; Lauren K. Brais, MPH; Annacarolina Da Silva, MD; Tingting Li, MD, PhD; Wanwan Li, MD; Atsuhiro Masuda, MD, PhD; Juhong Yang, MD, PhD; Yan Shi, MD, PhD; Mancang Gu, PhD; Yohei Masugi, MD, PhD; Justin Bui, BS; Caitlin L. Zellers, BA; Chen Yuan, MS; Ana Babic, PhD; Natalia Khalaf, MD; Andrew Aguirre, MD, PhD; Kimmie Ng, MD, MPH; Rebecca A. Miksad, MD, MPH; Andrea J. Bullock, MD; Daniel T. Chang, MD; Jennifer F. Tseng, MD, MPH; Thomas E. Clancy, MD; David C. Linehan, MD; Jennifer J. Findeis-Hosey, MD; Leona A. Doyle, MD; Aaron R. Thorner, PhD; Matthew Ducar, MS; Bruce Wollison; Angelica Laing, BA; William C. Hahn, MD, PhD; Matthew Meyerson, MD, PhD; Charles S. Fuchs, MD, MPH; Shuji Ogino, MD, PhD, MS; Jason L. Hornick, MD, PhD; Aram F. Hezel, MD; Albert C. Koong, MD, PhD; Brian M. Wolpin, MD, MPH

Association of Alterations in Main Driver Genes With Outcomes in Pancreatic Cancer

- 356 patients with resected PDAC
- Immunohistochemistry and next-generation DNA sequencing of formalin-fixed, paraffin-embedded resection specimens
- Identified alterations in the 4 main driver *genes (KRAS, CDKN2A, SMAD4*, and *TP53)*
- Disease-free survival and overall survival were associated with the presence and pattern of alterations in these 4 genes independent of previously identified prognostic factors



Qian ZR et al, JAMA Oncol 2017

Association of Alterations in Main Driver Genes With Outcomes in Pancreatic Cancer

Table 1. Disease-Free Survival and Overall Survival by *KRAS*, *CDKN2A*, *SMAD4*, and *TP53* Tumor Status

	Disease-Free Survival (n = 335)						Overall Survival (n = 338)					
			Rate						Rate			
Driver Gene	Patients, No. (%)	Median (IQR), mo	2-y Survival, %	5-y Survival, %	HR (95% CI)[a]	*P* Value[b]	Patients, No. (%)	Median (IQR), mo	2-y Survival, %	5-y Survival, %	HR (95% CI)[a]	*P* Value[b]
KRAS												
Wild-type	27 (8.1)	16.2 (8.9-30.5)	30.2	20.2	1 [Reference]		27 (8.0)	38.6 (16.6-63.1)	63.0	30.2	1 [Reference]	
Mutant	308 (91.9)	12.3 (6.7-27.2)	27.5	12.4	1.72 (1.04-2.84)	.03	311 (92.0)	20.3 (11.3-38.3)	44.5	13.0	1.55 (0.96-2.51)	.08
CDKN2A												
Intact	111 (33.1)	14.8 (8.2-30.5)	31.2	16.9	1 [Reference]		112 (33.1)	24.6 (14.1-44.6)	53.8	19.5	1 [Reference]	
Lost	224 (66.9)	11.5 (6.2-24.5)	26.0	11.5	1.62 (1.19-2.20)	.002	226 (66.9)	19.7 (10.9-37.1)	42.3	11.9	1.44 (1.08-1.91)	.01
SMAD4												
Intact	172 (51.3)	11.5 (6.6-30.1)	27.1	14.4	1 [Reference]		173 (51.2)	21.3 (18.2-26.7)	49.1	15.8	1 [Reference]	
Lost	163 (48.7)	13.6 (7.4-27.0)	28.4	12.3	1.18 (0.90-1.55)	.25	165 (48.8)	20.5 (11.3–39.3)	43.0	12.9	1.07 (0.83-1.38)	.62
TP53												
Wild-type	118 (35.2)	14.8 (8.1-30.5)	31.4	13.9	1 [Reference]		119 (35.2)	24.6 (13.5-44.6)	50.7	18.7	1 [Reference]	
Altered	217 (64.8)	10.8 (6.2-24.5)	25.7	12.6	1.33 (1.02-1.75)	.04	219 (64.8)	20.3 (11.1-37.8)	43.5	12.3	1.18 (0.91-1.53)	.23

Qian ZR et al, JAMA Oncol 2017

Association of Alterations in Main Driver Genes With Outcomes in Pancreatic Cancer

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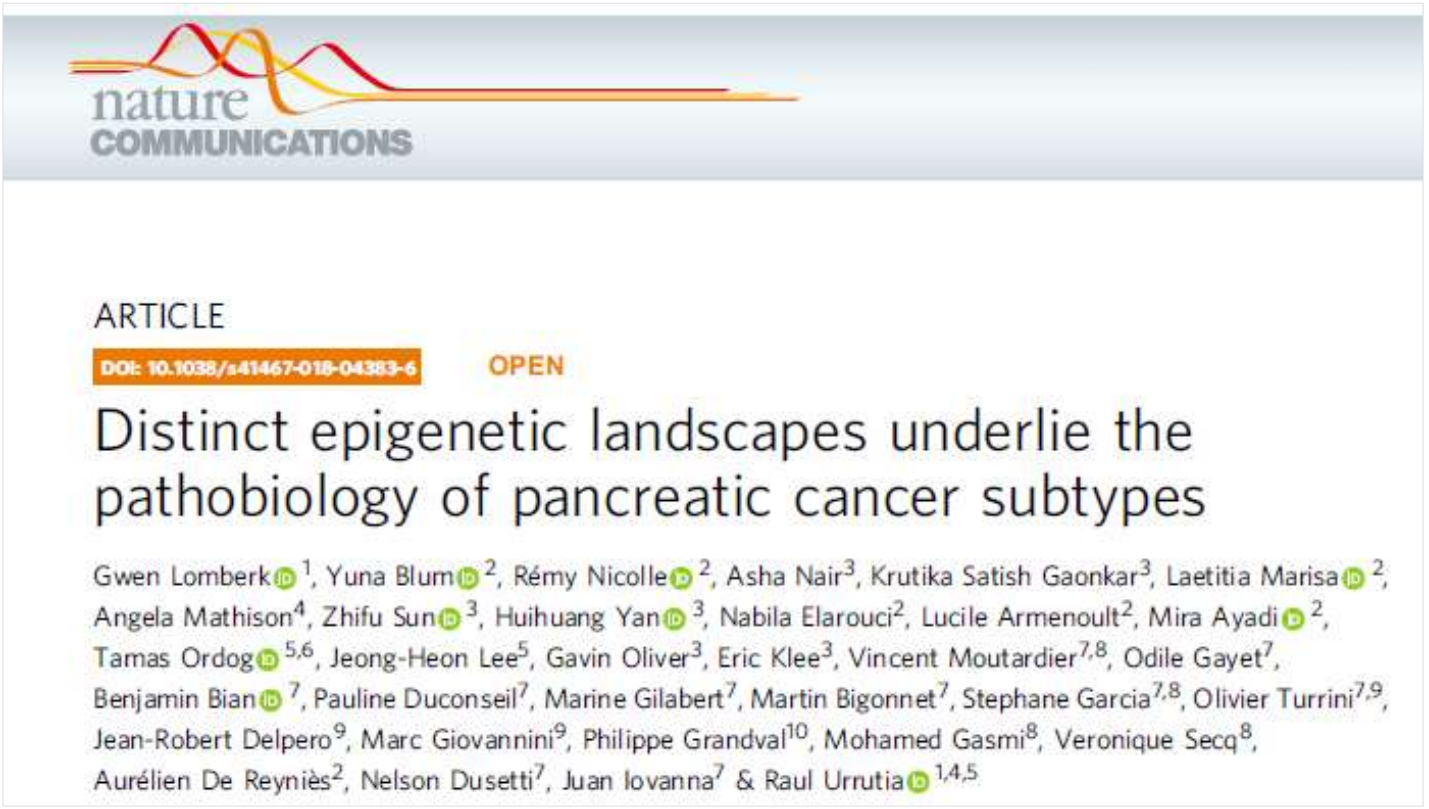
Table 2. Disease-Free Survival and Overall Survival by *KRAS* Codon Mutation and Combined *KRAS*, *CDKN2A*, *SMAD4*, and *TP53* Gene Alterations

Driver Gene Alteration	Disease-Free Survival (n = 335)			Overall Survival (n = 338)		
	Patients, No. (%)	HR (95% CI)[a]	*P* Value[b]	Patients, No. (%)	HR (95% CI)[a]	*P* Value[b]
KRAS mutation[c]						
G12D	122 (36.4)	1 [Reference]		123 (36.4)	1 [Reference]	
G12V	104 (31.0)	0.57 (0.41-0.79)	<.001	105 (31.1)	0.63 (0.46-0.87)	.005
G12R	44 (13.1)	0.67 (0.43-1.05)	.08	45 (13.3)	0.82 (0.54-1.25)	.35
Other codon	25 (7.5)	0.63 (0.37-1.10)	.10	25 (7.4)	0.83 (0.50-1.39)	.48
2 Codon mutations	11 (3.3)	0.27 (0.11-0.69)	.006	11 (3.3)	0.55 (0.26-1.15)	.11
Wild-type	27 (8.1)	0.38 (0.22-0.65)	<.001	27 (8.0)	0.50 (0.30-0.83)	.008
No. of altered genes						
0-2 Genes	126 (37.6)	1 [Reference]		127 (37.6)	1 [Reference]	
3 Genes	135 (40.3)	1.37 (1.01-1.86)	.05	136 (40.2)	1.22 (0.91-1.64)	.18
4 Genes	74 (22.1)	1.79 (1.24-2.59)	.002	75 (22.2)	1.38 (0.98-1.94)	.06
Gene combinations[d]						
0-2 Genes	126 (37.6)	1 [Reference]		127 (37.6)	1 [Reference]	
3 Genes						
KRAS, *SMAD4*, *TP53*	35 (10.4)	1.16 (0.74-1.82)	.53	35 (10.4)	1.08 (0.69-1.69)	.75
KRAS, *CDKN2A*, *TP53*	64 (19.1)	1.51 (1.04-2.20)	.03	64 (18.9)	1.38 (0.96-1.98)	.08
KRAS, *CDKN2A*, *SMAD4*	34 (10.1)	1.27 (0.79-2.05)	.32	35 (10.4)	1.28 (0.80-2.06)	.30

Epigenetic Alterations in Pancreatic Cancer



nature COMMUNICATIONS

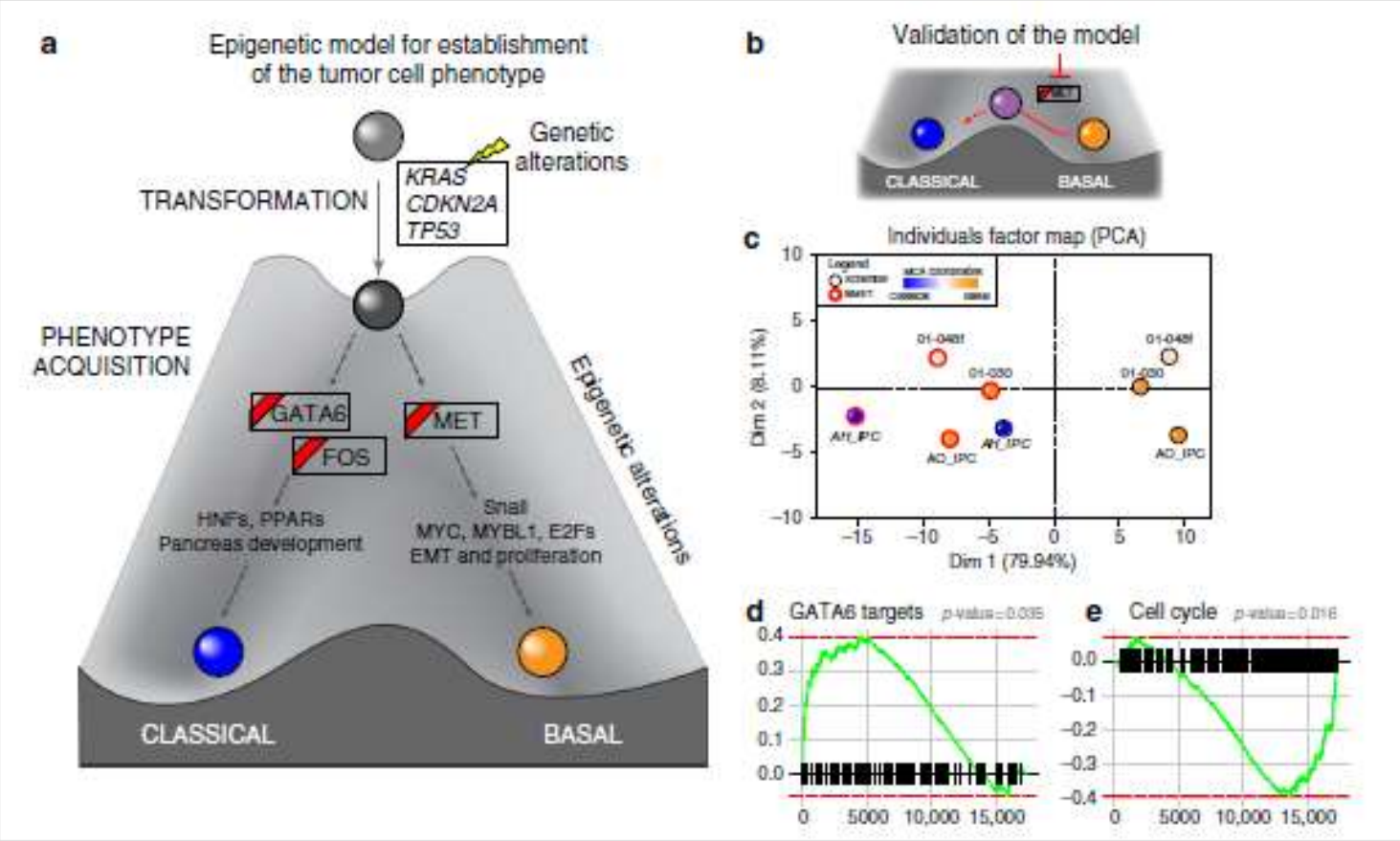
ARTICLE

DOI: 10.1038/s41467-018-04383-6 OPEN

Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes

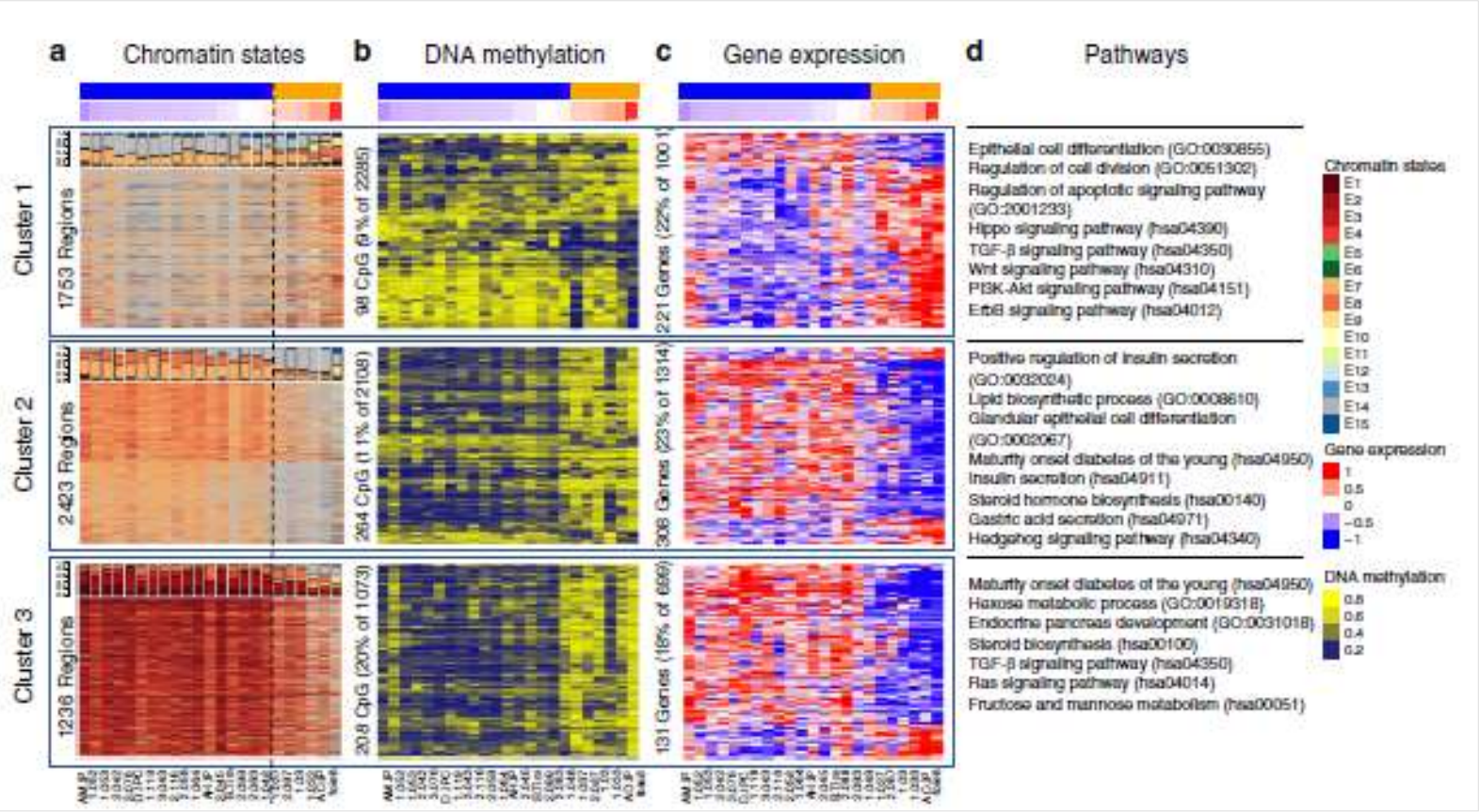
Gwen Lomberk[1], Yuna Blum[2], Rémy Nicolle[2], Asha Nair[3], Krutika Satish Gaonkar[3], Laetitia Marisa[2], Angela Mathison[4], Zhifu Sun[3], Huihuang Yan[3], Nabila Elarouci[2], Lucile Armenoult[2], Mira Ayadi[2], Tamas Ordog[5,6], Jeong-Heon Lee[5], Gavin Oliver[3], Eric Klee[3], Vincent Moutardier[7,8], Odile Gayet[7], Benjamin Bian[7], Pauline Duconseil[7], Marine Gilabert[7], Martin Bigonnet[7], Stephane Garcia[7,8], Olivier Turrini[7,9], Jean-Robert Delpero[9], Marc Giovannini[9], Philippe Grandval[10], Mohamed Gasmi[8], Veronique Secq[8], Aurélien De Reyniès[2], Nelson Dusetti[7], Juan Iovanna[7] & Raul Urrutia[1,4,5]

Epigenetic Alterations in Pancreatic Cancer



Lomberk G et al, Nat Com 2018

Epigenetic Alterations in Pancreatic Cancer



Lomberk G et al, Nat Com 2018

Organoids in Pancreatic Cancer

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CANCER DISCOVERY

Organoid profiling identifies common responders to chemotherapy in pancreatic cancer.

Tiriac H, Belleau P, Engle DD, et al.

Cancer Discov. 2018 May 31. pii: CD-18-0349. doi: 10.1158/2159-8290.CD-18-0349. [Epub ahead of print]

Organoids in Pancreatic Cancer

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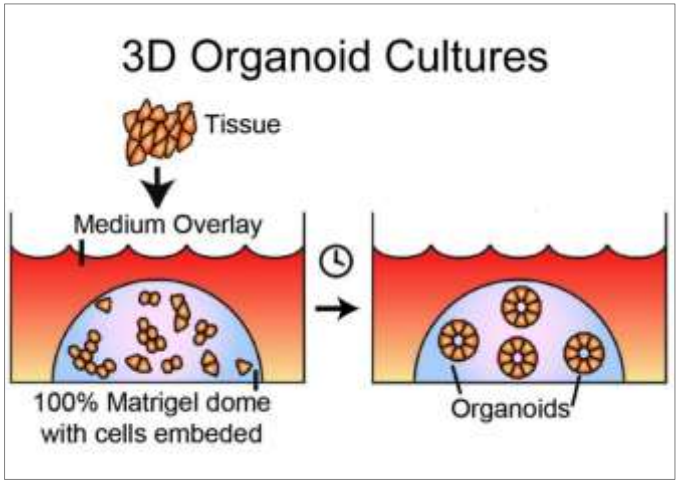
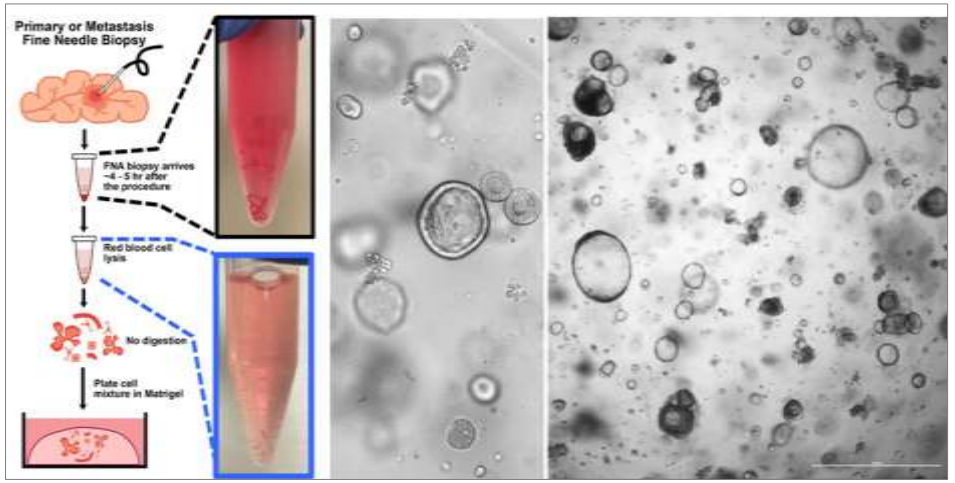
- PDOs exhibited heterogeneous responses to standard-of-care chemotherapeutics and investigational agents
- PDO therapeutic profiles paralleled patient outcomes
- PDOs enable longitudinal assessment of chemo-sensitivity and evaluation of synchronous metastases





Organoids in Pancreatic Cancer

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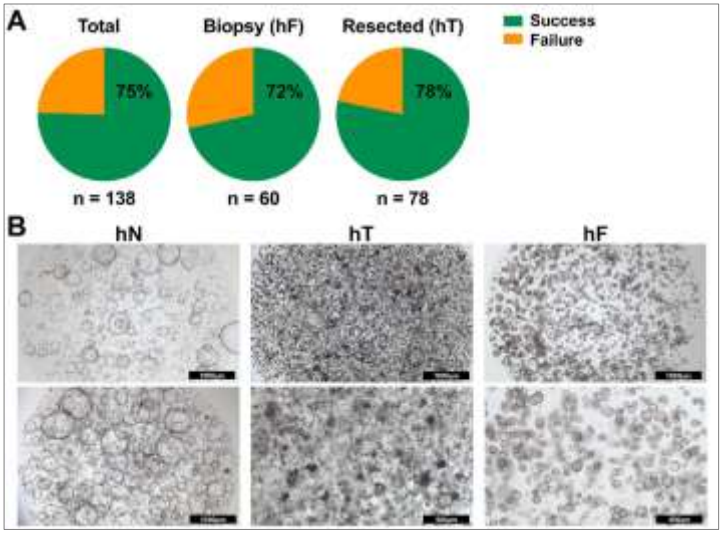
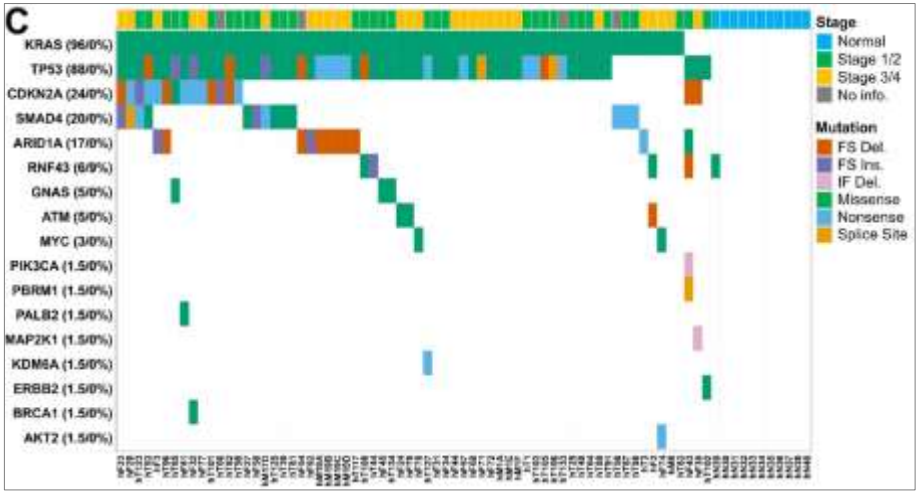
- Organoid-based gene expression signatures of chemo-sensitivity predicted improved responses for many patients to chemotherapy in both the adjuvant and advanced disease settings
- Nominated alternative treatment strategies for chemorefractory PDOs using targeted agent therapeutic profiling
- Combined molecular and therapeutic profiling of PDOs may predict clinical response and enable prospective therapeutic selection





Tiriac H et al, Cancer Discov 2018

Liquid Biopsy in Pancreatic Cancer

JOURNAL OF CLINICAL ONCOLOGY | BIOLOGY OF NEOPLASIA

Serum Biomarker Signature-Based Liquid Biopsy for Diagnosis of Early-Stage Pancreatic Cancer

Linda D. Mellby, Andreas P. Nyberg, Julia S. Johansen, Christer Wingren, Børge G. Nordestgaard, Stig E. Bojesen, Breeana L. Mitchell, Brett C. Sheppard, Rosalie C. Sears, and Carl A.K. Borrebaeck

Liquid Biopsy in Pancreatic Cancer

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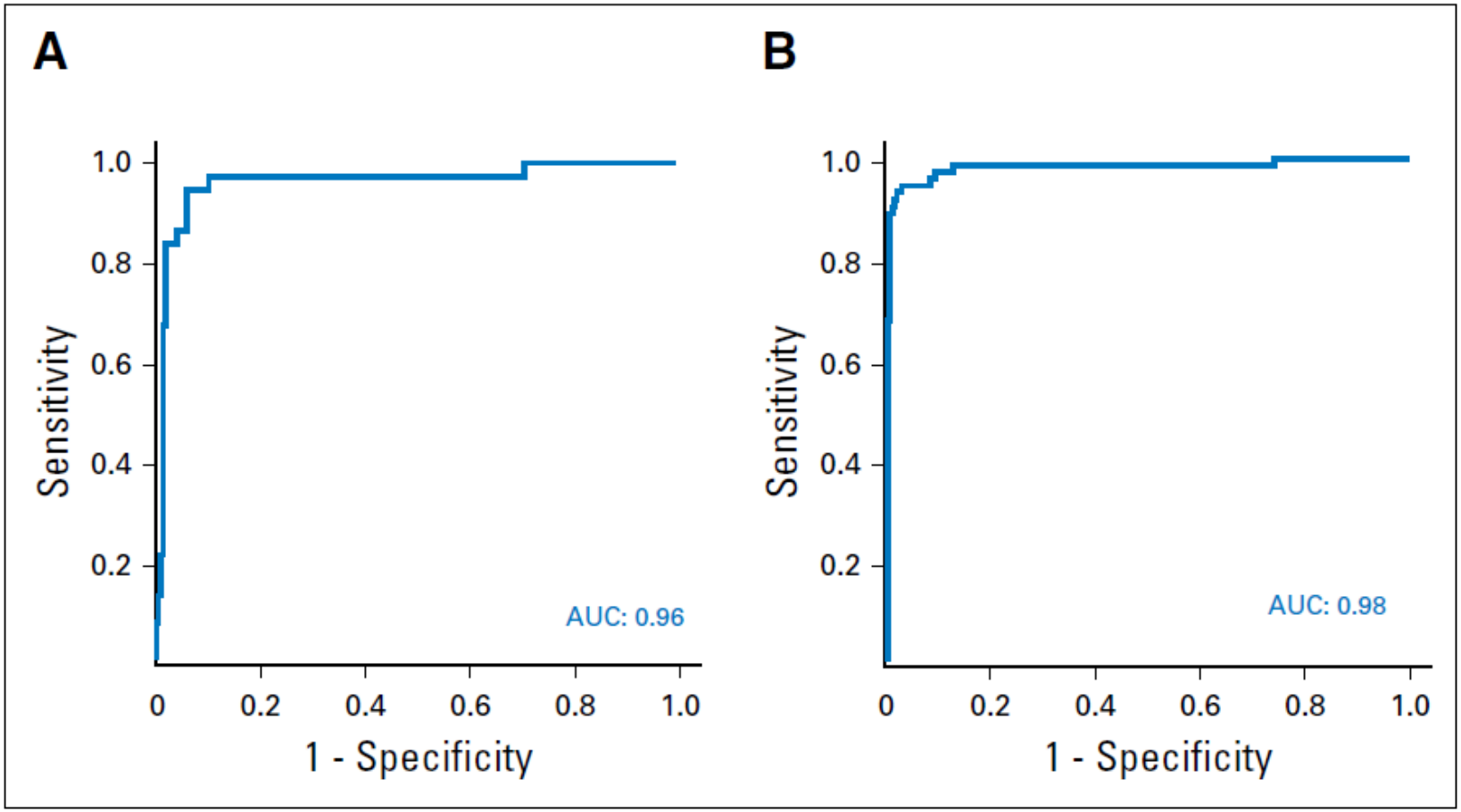
Table 3. Consensus Signature

Apolipoprotein A1
Aprataxin and PNK-like factor
Calcineurin B homologous protein 1
Calcium/calmodulin-dependent protein kinase type IV
Complement C3
Complement C4
Complement C5
Cyclin-dependent kinase 2
Disks large homolog 1
GTP-binding protein GEM
HADH2 protein
Intercellular adhesion molecule 1
Interferon gamma
Interleukin-13
Interleukin-4
Interleukin-6
Lewis x
Lymphotoxin-alpha
Membrane-associated guanylate kinase, WW and PDZ domain-containing protein 1
Myomesin-2
Plasma protease C1 inhibitor
PR domain zinc finger protein 8
Properdin
Protein kinase C zeta type
Protein-tyrosine kinase 6
Serine/threonine-protein kinase MARK1
Sialyl Lewis x
Vascular endothelial growth factor
Visual system homeobox 2

Mellby LD, Nyberg AP, Johansen JS, et al. J Clin Oncol. 2018 Aug 14

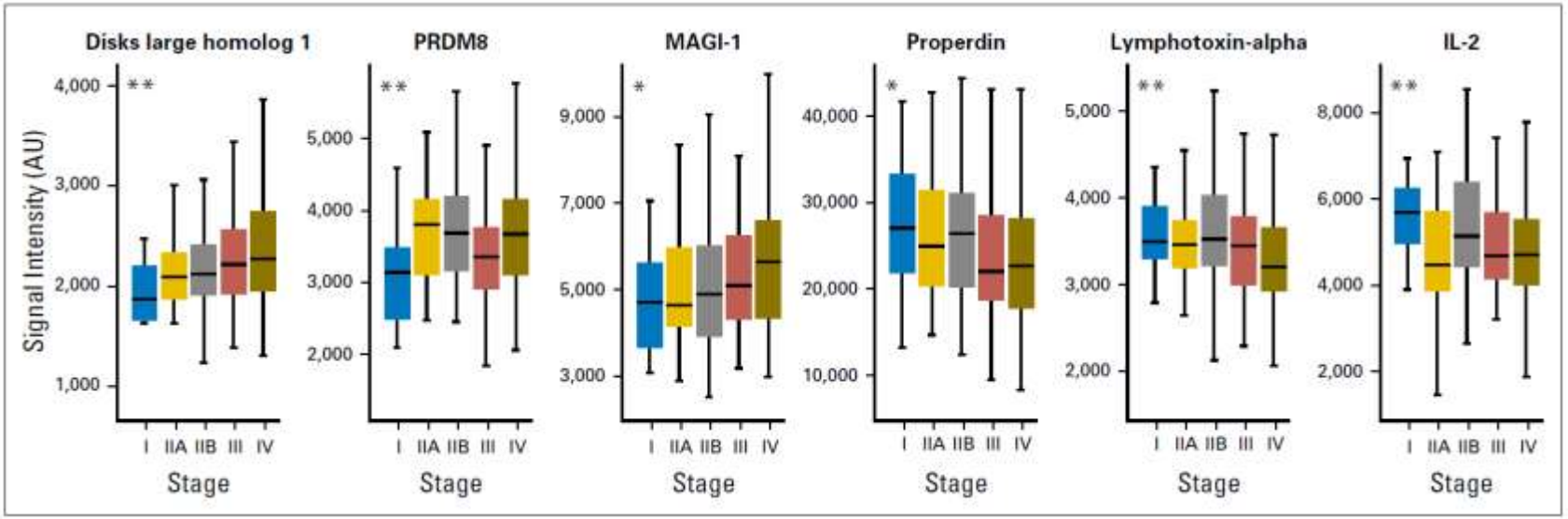
Liquid Biopsy in Pancreatic Cancer



Classification of (A) normal control (NC) samples from pancreatic ductal adenocarcinoma (PDAC) stage I and II, and (B) PDAC stage III and IV

Mellby LD, Nyberg AP, Johansen JS, et al. J Clin Oncol. 2018 Aug 14

Liquid Biopsy in Pancreatic Cancer



Thank you!

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Pancreas Cleanse Juice

5 carrots
1/2 beet
1 apple
3 stalks of celery
4 stalks of kale
OR 4 stalks of asparagus
1 Lemon

This juice tastes amazing! :)