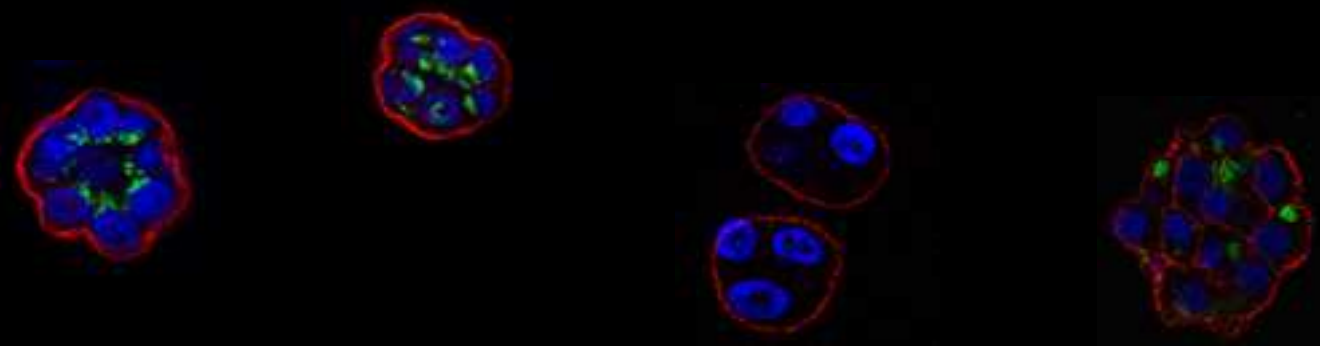


Linking Tissue Microarchitectures to Rationalized Molecular Diagnostics in Glandular Cancers

Kelvin K. Tsai , M.D., Ph.D.

Laboratory for Tumor Epigenetics and Stemness (TES Lab)

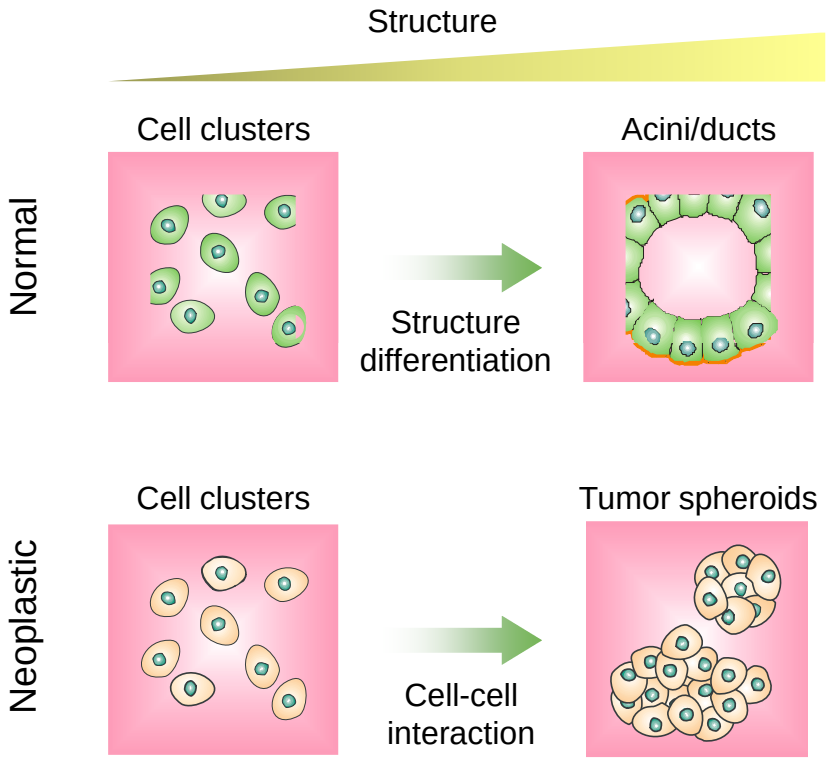
NATIONAL INSTITUTE OF CANCER RESEARCH

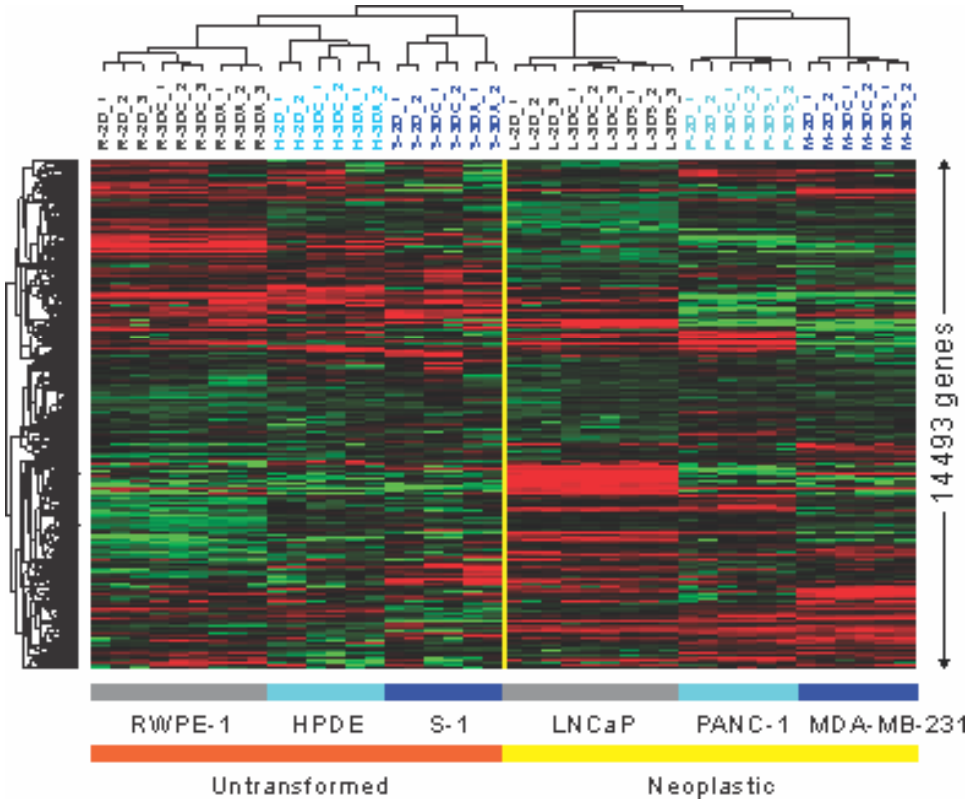
NATIONAL HEALTH RESEARCH INSTITUTES (NHRI), TAIWAN

Problems with current molecular diagnostics

- Onco*type* DX®: Knowledge-based but biased toward preselected markers
- MammaPrint® or PAM50: Computation-derived; not directly linked to tumor biology or pathways (cancer stemness, differentiation, *etc*.)
- None of them can guide the use of targeted therapeutics.

Modeling stem cells differentiation into tissue microarchitectures



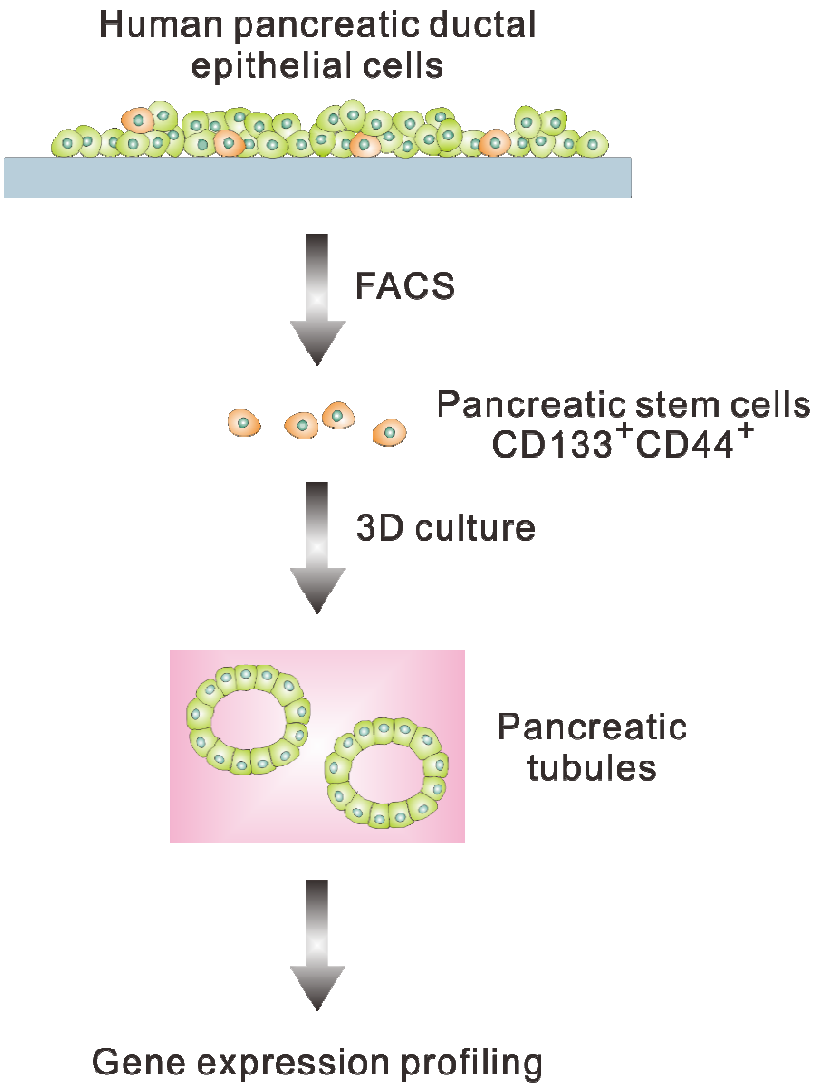


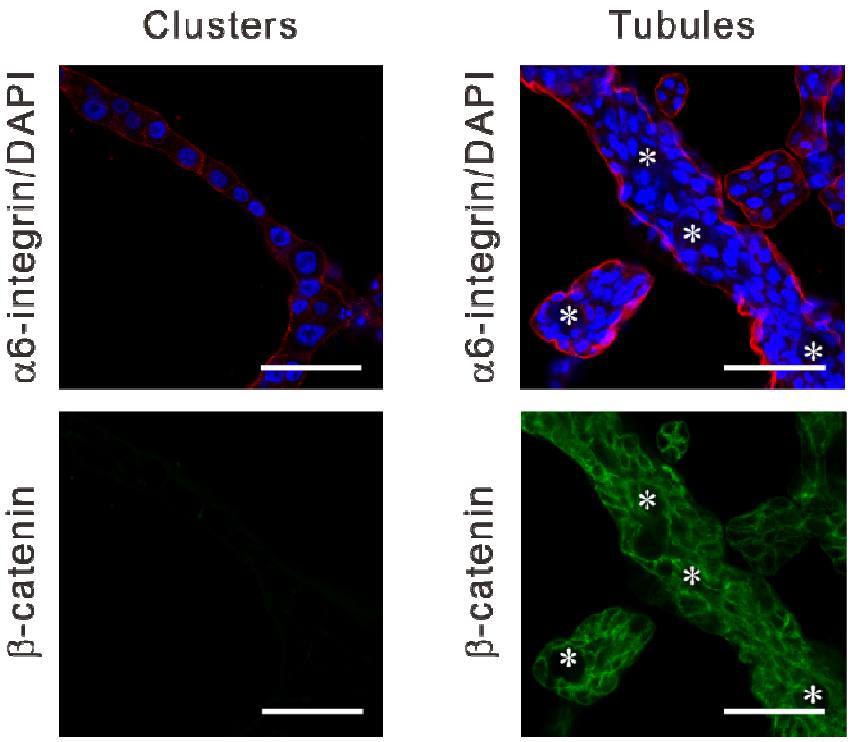
HPDE (pancreatic ductal)
RWPE-1 (prostatic glands)
S-1 (mammary glands)

PANC-1 (pancreatic cancer)
LNCaP (prostate cancer)
MDA-MB-231 (breast cancer)

The TES Lab, National Health Research Institutes

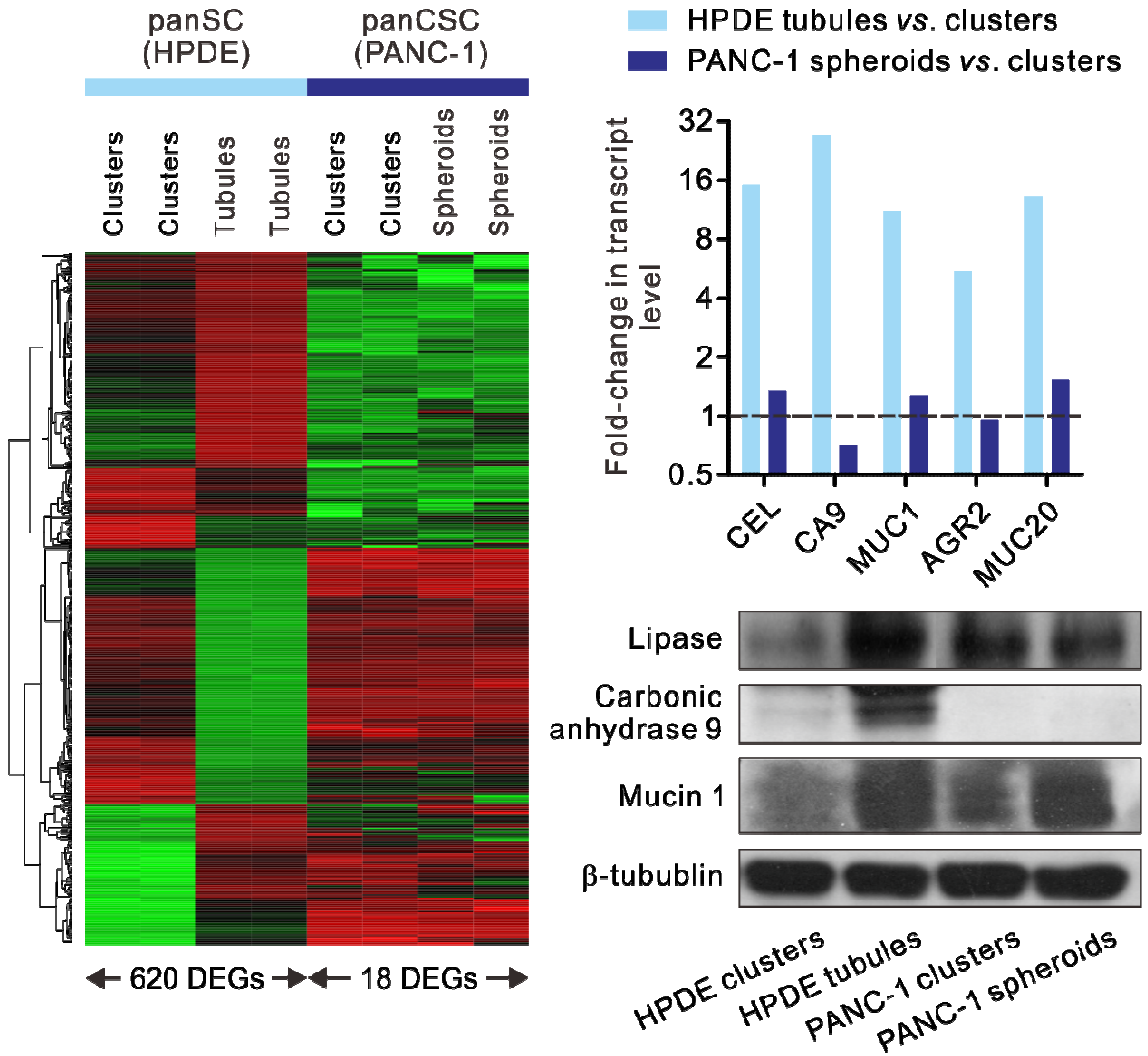
Recapitulating tubular differentiation of pancreatic stem cells





Gastroenterology 2013;145:1110

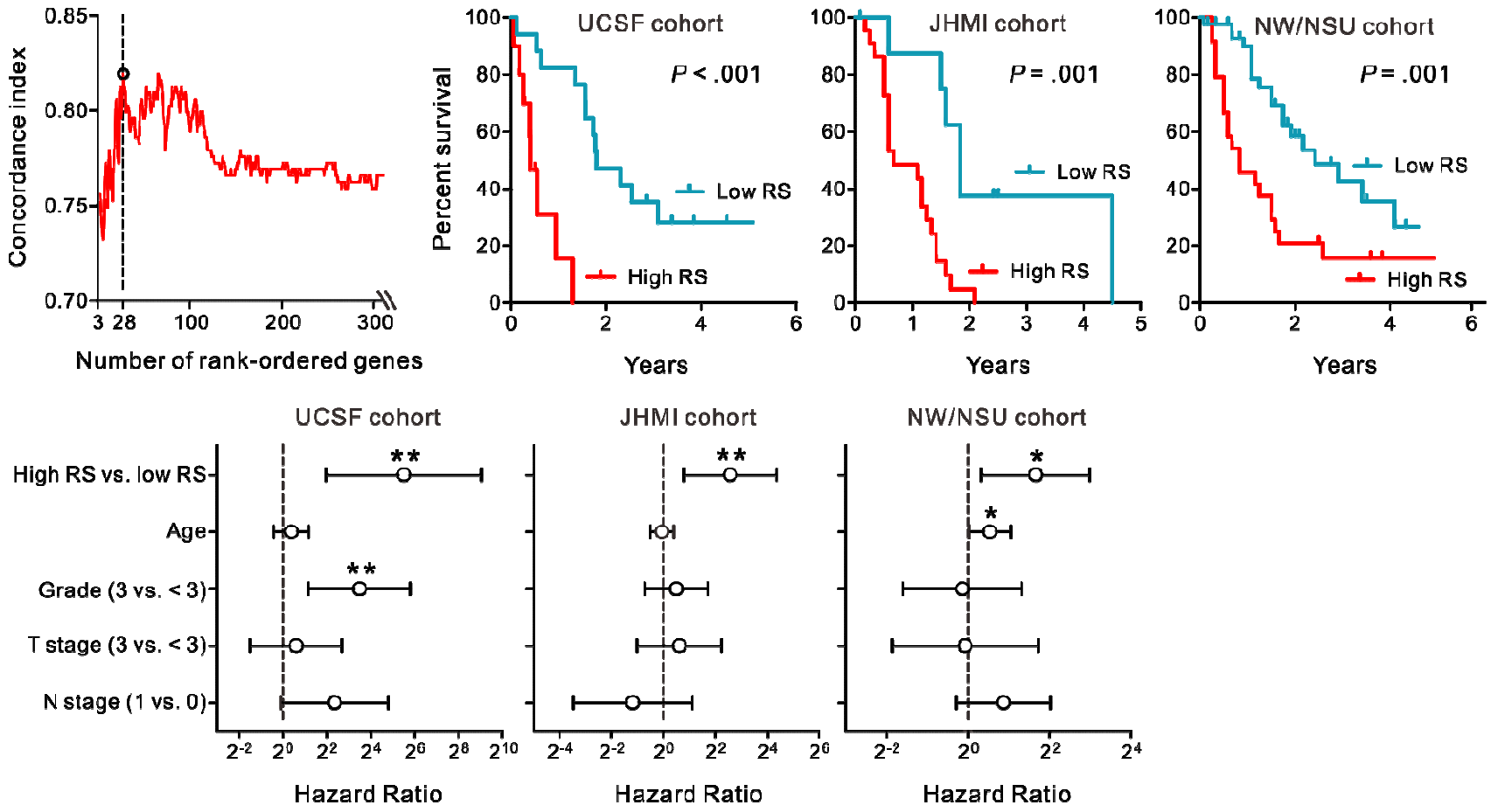
Molecular profiling of pancreatic tubular differentiation



*panSC: pancreatic stem cells; panCSCs: pancreatic cancer stem cells
*HPDE, human pancreatic ductal epithelial cells; *DEG, differentially expressed genes

Gastroenterology 2013;145:1110

A tubulogenesis-specific prognostic signatur in pancreatic cancer



*PDAC, pancreatic ductal adenocarcinoma
*RS, Risk Score for poor survival

Gastroenterology 2013;145:1110

The Pan*GUIDE* genes

Cancer stemness
ASPM
Undisclosed stem cell marker

Differentiation
ATP9A
ACOX3
CDC45L
SLC40A1
AGR2

Reference
RPL13A
GAPDH
To be chosen by data set testing

USPTO No. 61/824,679; PCT/US2014/38504

Survival prediction by the Pan*GUIDE* assay

	Patient 1	Patient 2	Patient 3	Patient 4
Risk Score	-2.900	-0.774	-0.042	5.177
Expected survival (year)	3.086	1.730	1.347	0.263
Observed survival (year)	3.841	1.730	1.292	0.178
Likelihood of survival beyond 1 year	90.4%	70.8%	59.0%	< 0.1%
Survival beyond 1 year	Yes	Yes	Yes	No

*Overall survival and one-year survival rate of selected patients in the UCSF cohort as predicted by the Pan*GUIDE*.

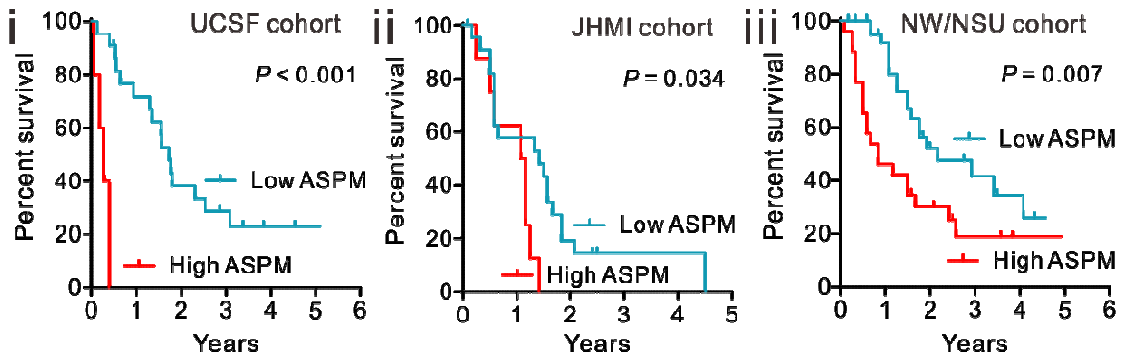
USPTO No. 61/824,679; PCT/US2014/38504

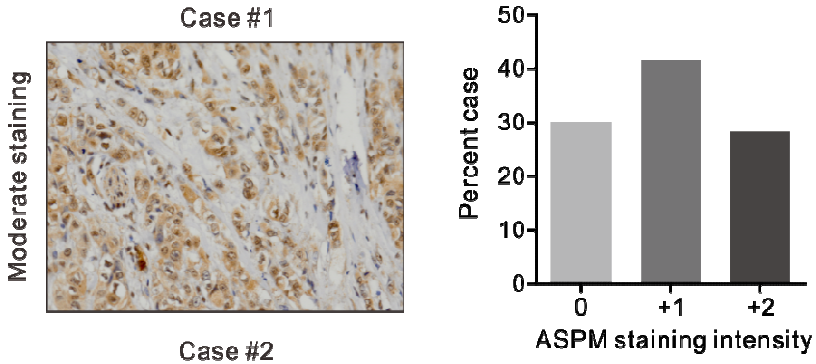
Prognostic accuracy of the Pan*GUIDE*

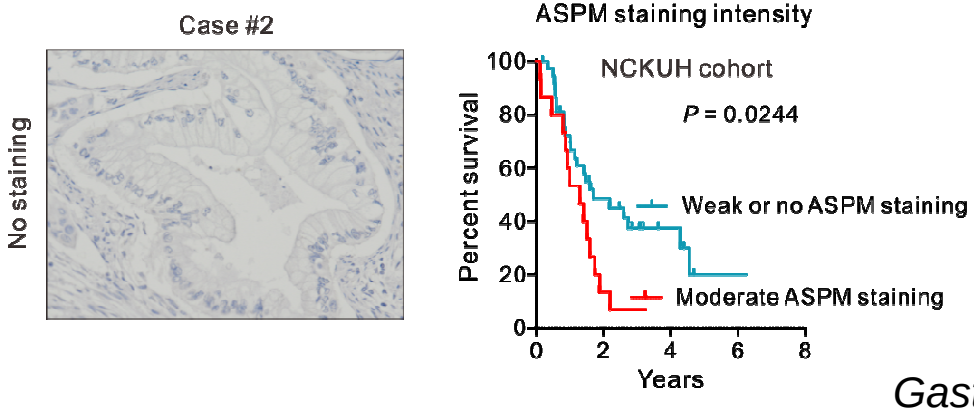
	Accuracy	95% CI	*P* value
University of California, San Francisco cohort			
Clinico-pathological criteria	80.2%	72.0%-88.4%	
Pan*GUIDE*	95.0%	89.6%-100.0%	0.001
62-gene PDAssigner	80.5%	69.2%-91.9%	0.477
6-gene metastasis signature	57.3%	40.2%-74.4%	0.993
Johns Hopkins Medical Institutions cohort			
Clinico-pathological criteria	57.4%	49.1%-65.6%	
Pan*GUIDE*	83.3%	66.3%-100.0%	0.002
62-gene PDAssigner	58.6%	44.8%-72.4%	0.431
6-gene metastasis signature	68.4%	56.9%-79.8%	0.084
Northwestern Memorial Hospital cohort			
Clinico-pathological criteria	67.2%	57.4%-77.1%	
Pan*GUIDE*	81.2%	67.8%-94.6%	0.032
62-gene PDAssigner	68.6%	58.8%-78.4%	0.410
6-gene metastasis signature	64.0%	53.8%-74.3%	0.678

Gastroenterology 2013; *Nat Med* 2011; *PLoS Med* 2010

ASPM as a poor prognostic marker in PDAC

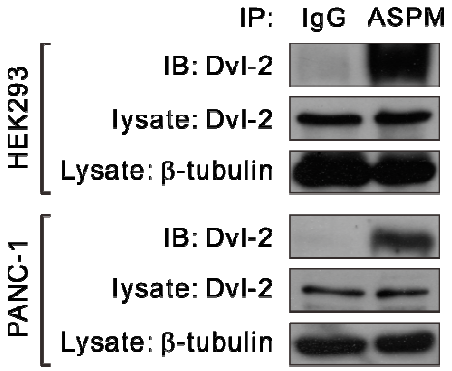


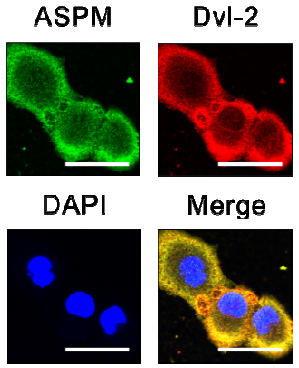


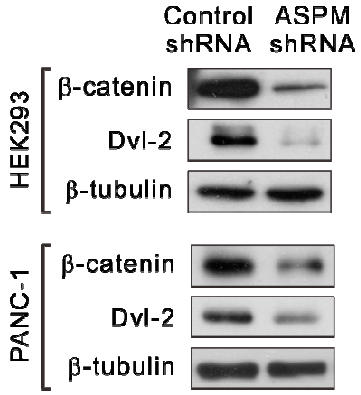


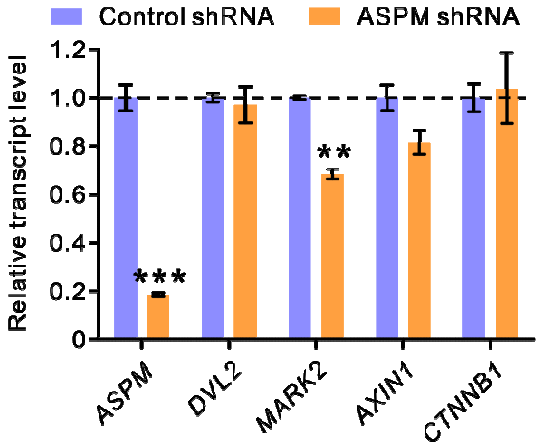
Gastroenterology 2013;145:1110

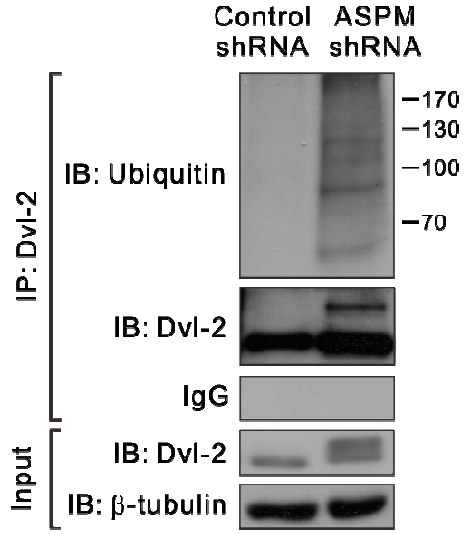
ASPM bolsters Wnt activity by stabilizing the dishevelled proteins

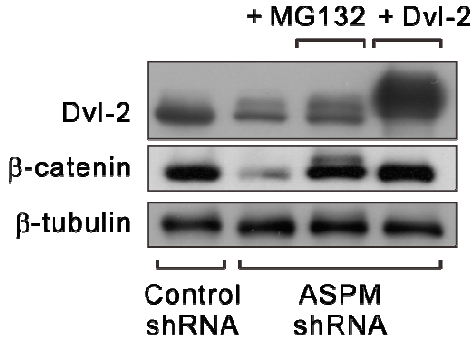






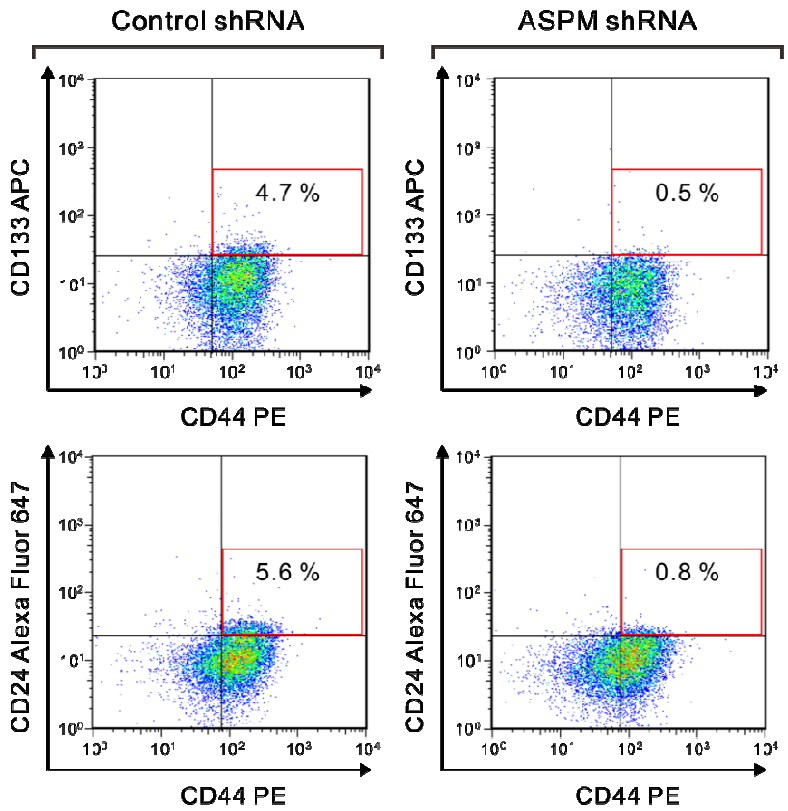


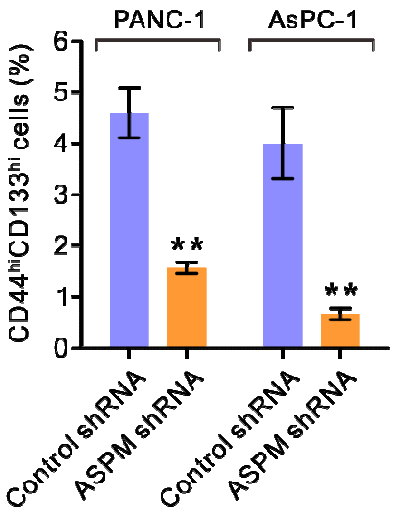


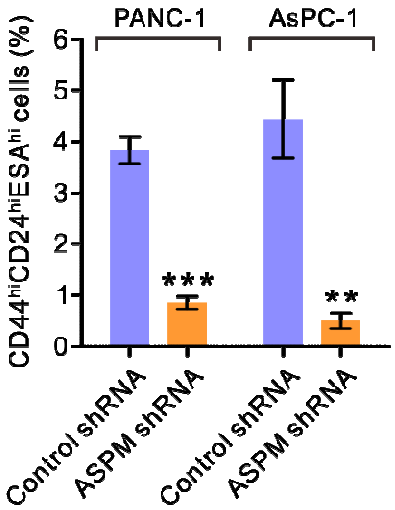


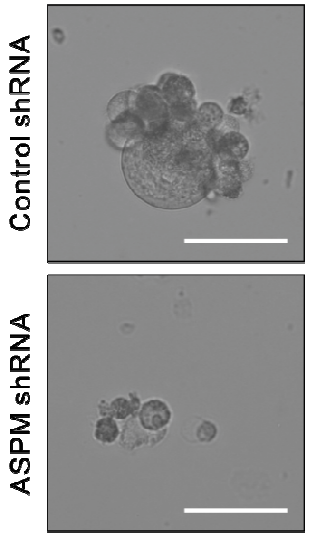
Gastroenterology 2013;145:1110

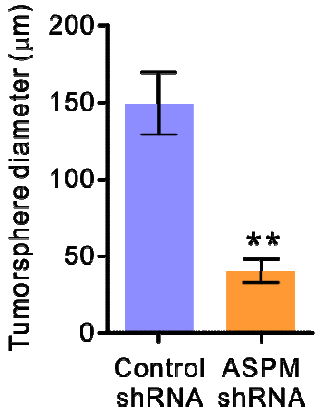
ASPM maintains pancreatic cancer stemness





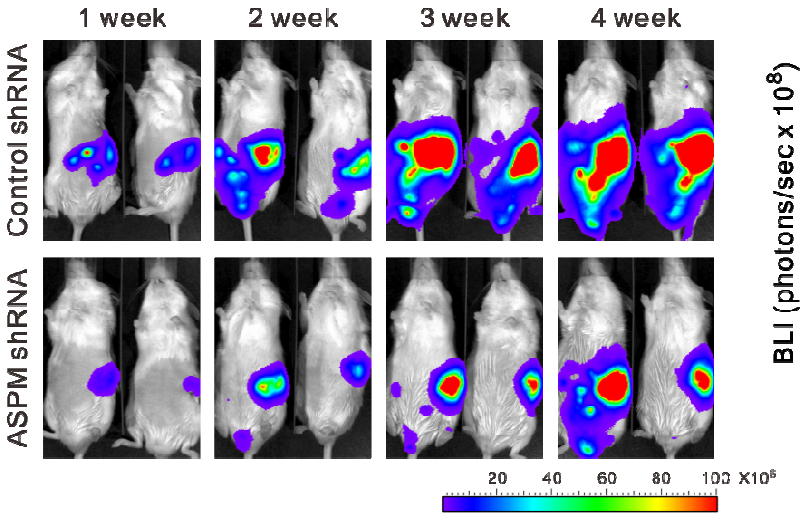


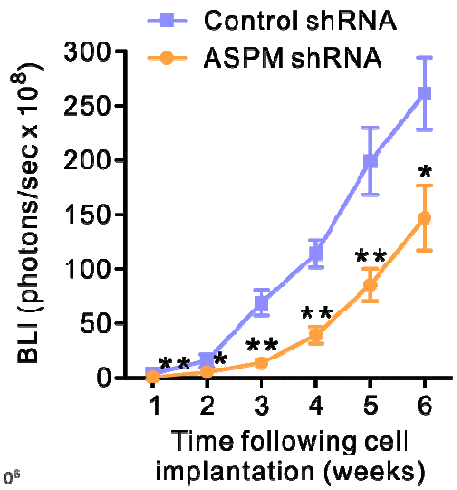


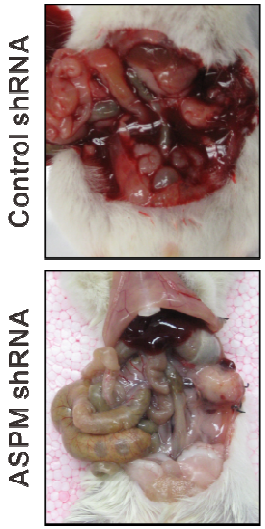


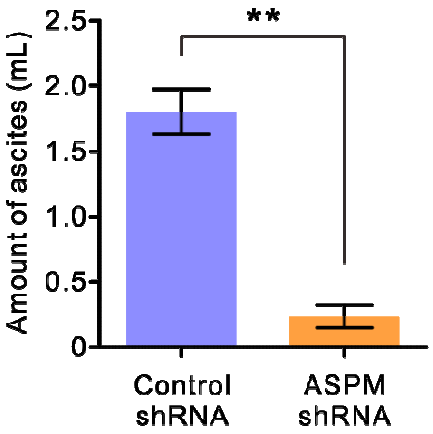
Gastroenterology 2013;145:1110

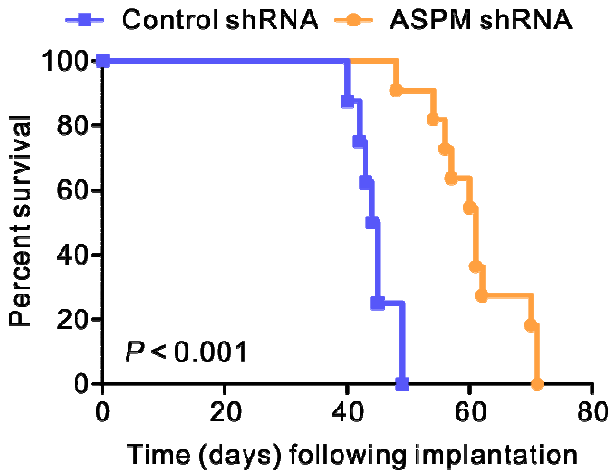
ASPM contributes to pancreatic cancer aggressiveness









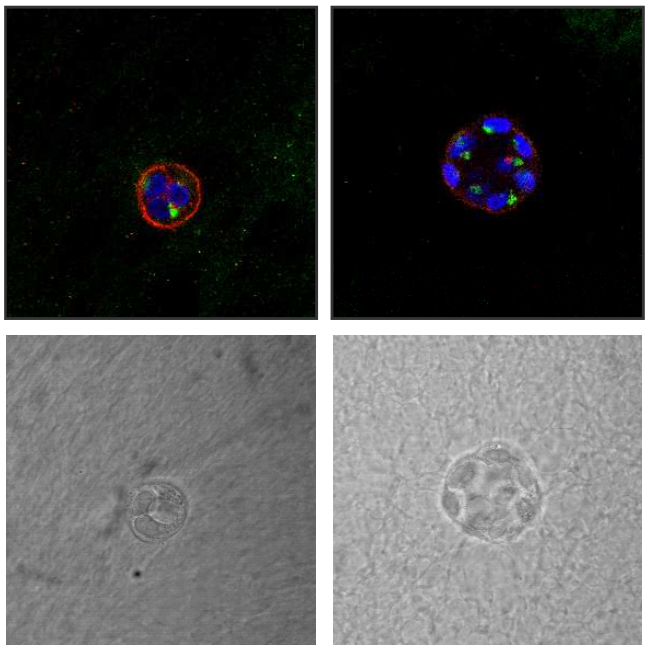


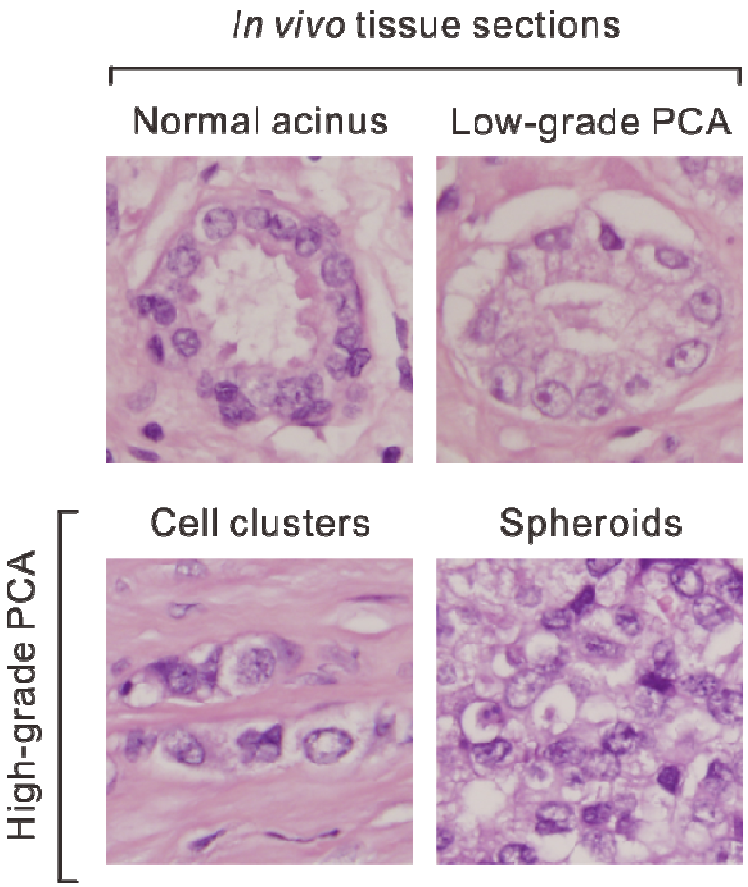
Gastroenterology 2013;145:1110

Summary of the Pan*GUIDE* assay

- A 7-gene prognostic signature the Pan*GUIDE* in pancreatic cancer.
- Stemness- and differentiation-associated; highly accurate
- Applicable to patients with localized or metastatic pancreatic cancer due to shared tumor biology.
- Detected on fresh frozen or FFPE samples.
- Multiplex qPCR, RNA-seq or NanoString
- Outputs:
  1. Standardized Risk Score
  2. Overall survival
  3. Yearly survival rate

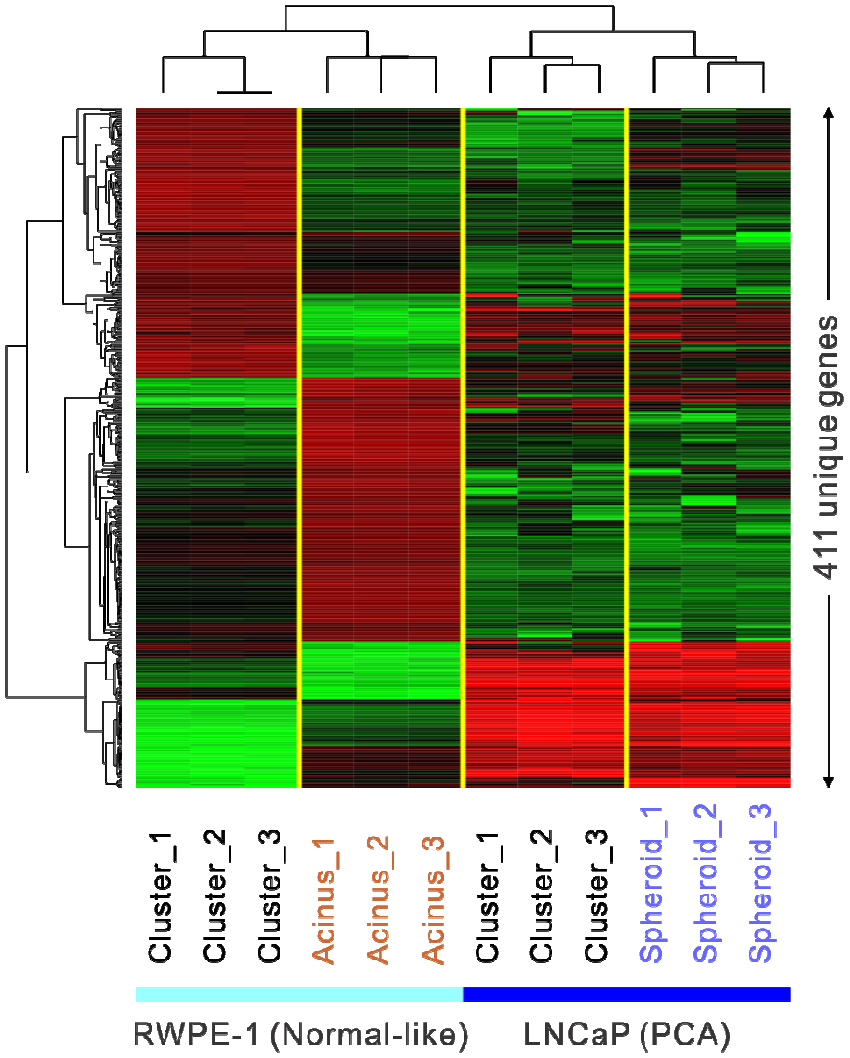
Structural and functional differentiation of prostatic glands *ex vivo*

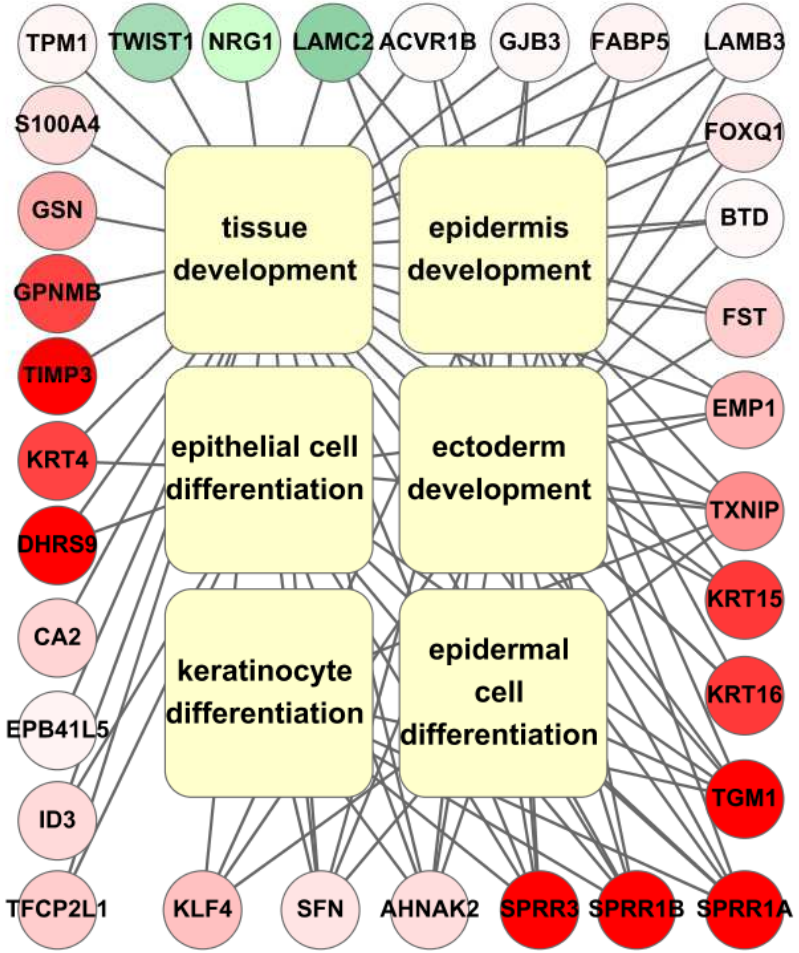




Am J Pathol 2013;182:363

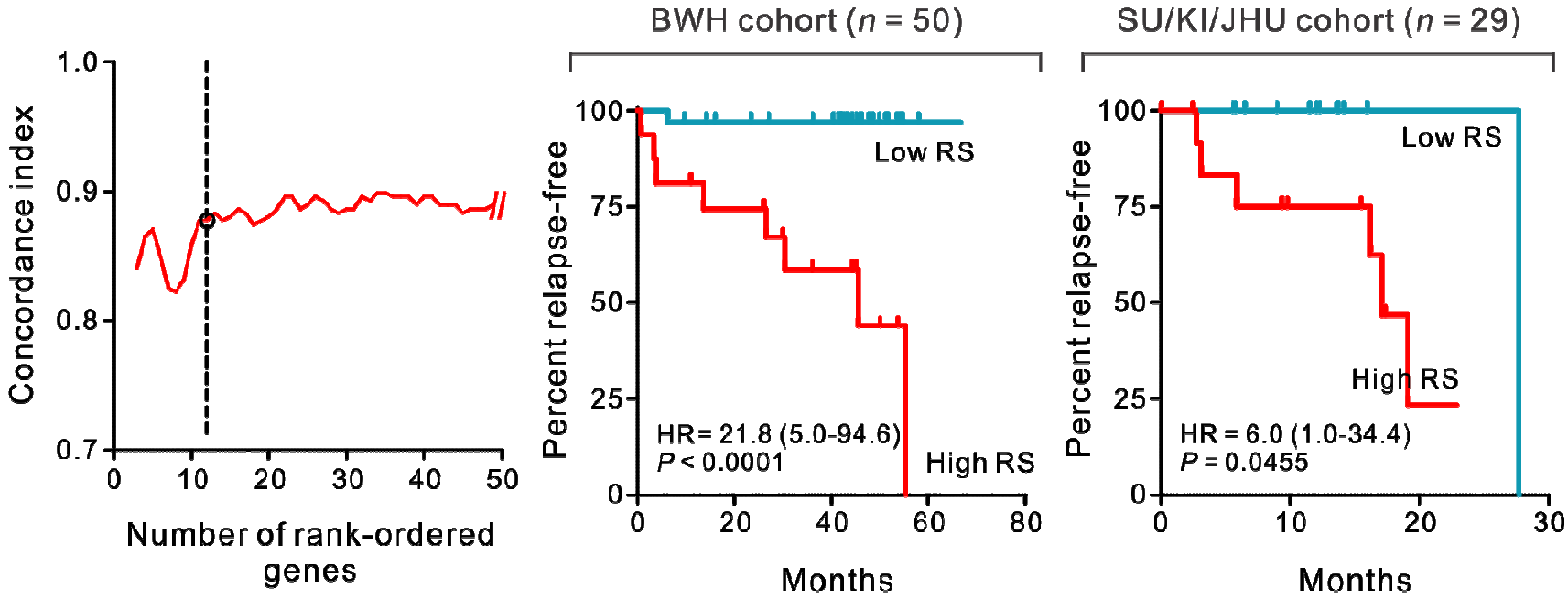
Transcriptional alterations specific to prostate acinar differentiation





Am J Pathol 2013;182:363

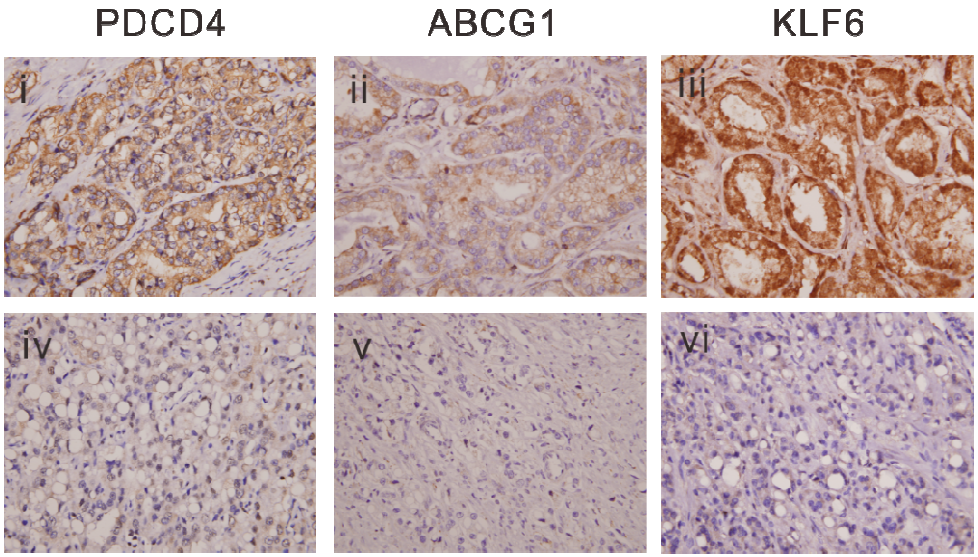
A tissue microarchitecture-specific prognosti signature of prostate cancer

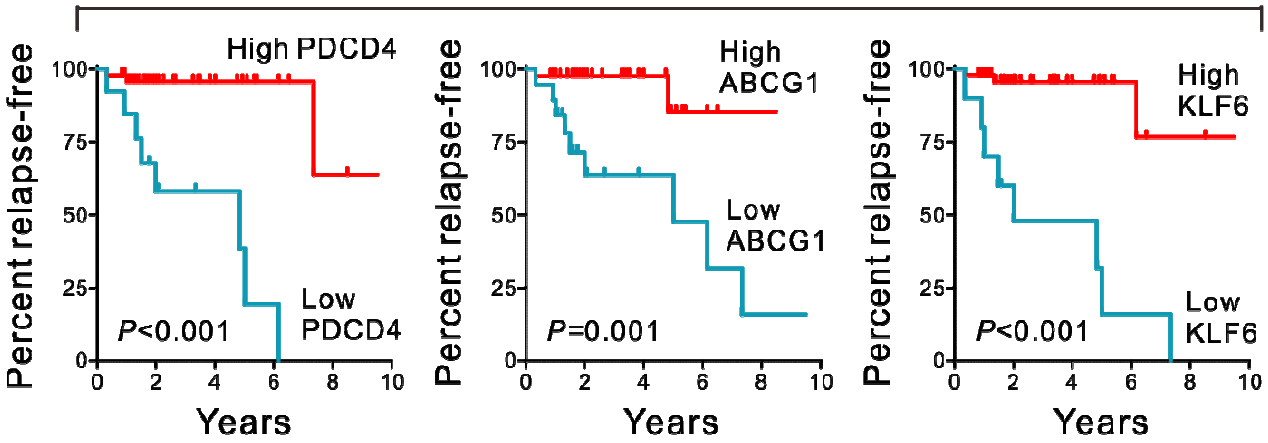


RS: relapse score
HR: hazard ratio for post-OP relapse
BWH: Brigham and Woman's Hospital
SU: Stanford University
KI: Karolinska Institute
JHU: Johns Hopkins University

Am J Pathol 2013;182:363

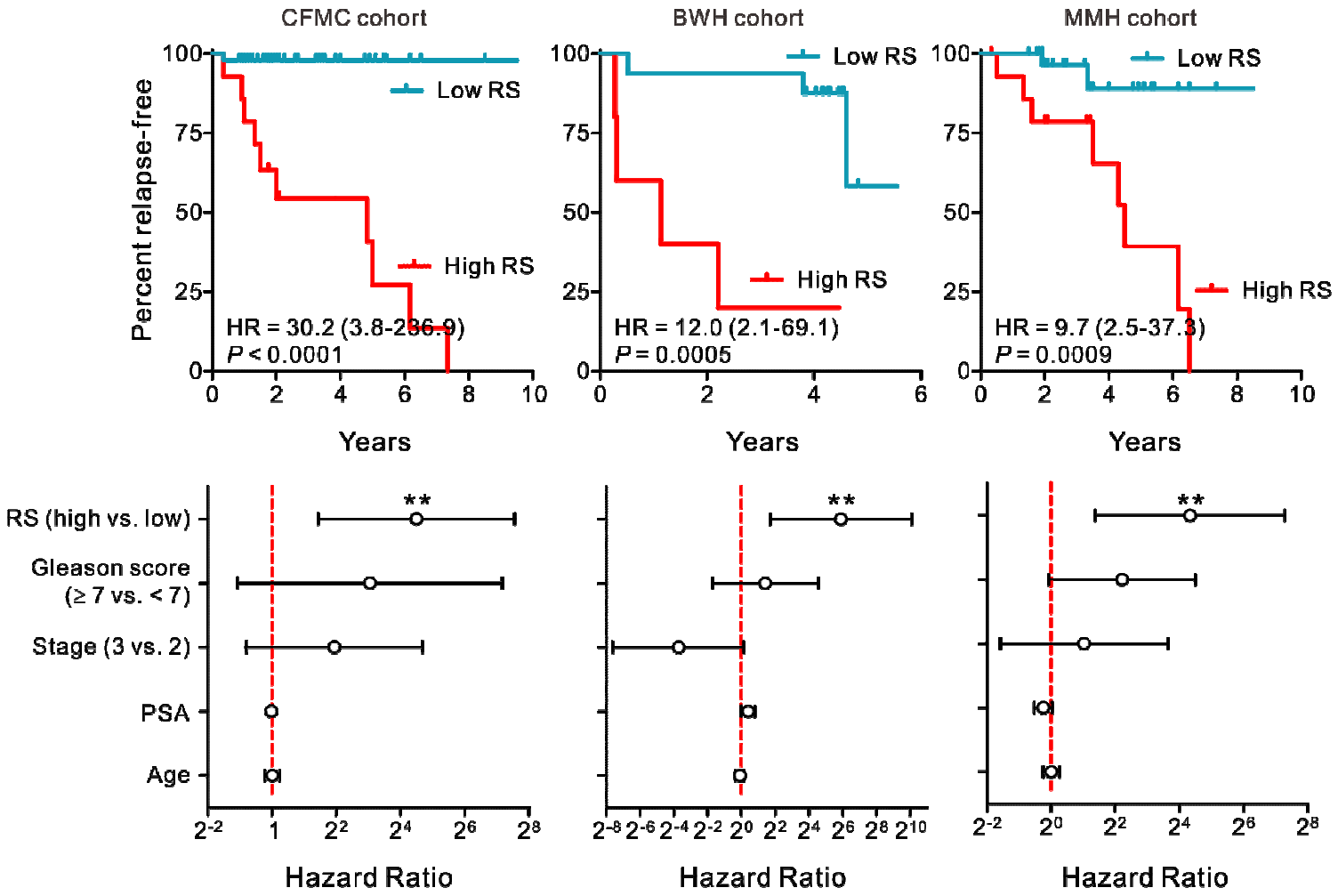
PDCD4, *KLF6* and *ABCG1* as differentiation-specific prognostic markers in prostate cancer





Am J Pathol 2013;182:363

ProsGUIDE: a 3-gene prognostic signature in prostate cancer



Am J Pathol 2013;182:363

Prediction accuracy of the Pros*GUIDE*

	Accuracy	95% CI	*P* value for C-index	*P* value vs. clinical
The Brigham and Women's Hospital cohort				
Clinico-pathologic criteria*	61.7%	42.8-80.6%	0.113	
Pros*GUIDE*	93.9%	86.2-100.0%	< 0.001	0.002
The Chimei Foundational Medical Center cohort				
Clinico-pathologic criteria*	69.5%	53.7-85.4%	0.0079	
Pros*GUIDE*	95.1%	85.9-100.0%	< 0.0001	0.001

*Includes age, stage, PSA, and Gleason score.

Am J Pathol 2013;182:363

Survival prediction by the Pros*GUIDE* assay

	Patient 1	Patient 2	Patient 3	Patient 4
Recurrence score by Pros*GUIDE*	4.645	3.546	-1.132	-2.216
Predicted recurrence-free survival (years)	0.31	0.52	> 4.61	> 4.61
Observed recurrence-free survival (years)	0.31	1.13	3.85	5.55
Predicted 3-year recurrence rate	96.6%	80.2%	6.8%	3.3%
Observed recurrence before 3 years	Yes	Yes	No	No

Three-year recurrence rates and recurrence-free survival of selected patients in the Brigham and Women's Hospital cohort as predicted by Pros*GUIDE*.

US 13/853,548; PCT/US13/34411

Summary of the Pros*GUIDE* assay

- A 3-gene prognostic signature for prostate cancer
- Differentiation-specific; highly accurate
- Applicable to patients with localized or metastatic prostate cancer due to shared tumor biology.
- Fresh frozen or FFPE samples
- Multiplex qPCR, RNA-seq, NanoString or IHC
- Output:
  1. Standardized Risk Score
  2. Recurrence-free survival
  3. Yearly recurrence rate

Clinical utility of Pan*GUIDE* and Pros*GUIDE*

- Provides an individualized and accurate risk assessments that supersede clinico-pathologic criteria.
- Selects patients with early disease relapse or mortality for more aggressive neoadjuvant or adjuvant therapy.
- Guides clinical decision-making and patient-tailored treatment plans.
- Potentially improves the treatment outcome and/or the successful rate of clinical trials.

Acknowledgement

The TES Lab, NHRI



Prof. Valerie M. Weaver
Center for bioengineering and tissue regeneration, UCSF
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Dr. Yan-Shen Shan, NCKUH
(pancreatic cancer specimen and clinical data), Prof. Chi-Rong Li, Chung Shan Medical U
(bioinformatics, statistics)

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