What's Next for Cancer Immunotherapy:
Is the tumor microenvironment telling us something? How can we listen better?

Sandip Pravin Patel MD

Associate Professor, UCSD

Co-Leader, Experimental Therapeutics

Deputy Director, San Diego Center for Precision Immunotherapy

Director, Clinical Trials Office

Email: patel@ucsd.edu

Twitter: @PatelOncology

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Overview

- Immunobiology primer
- Biomarker development
- Next generation immunotherapy biomarkers
- A path forward

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Immunobiology Overview

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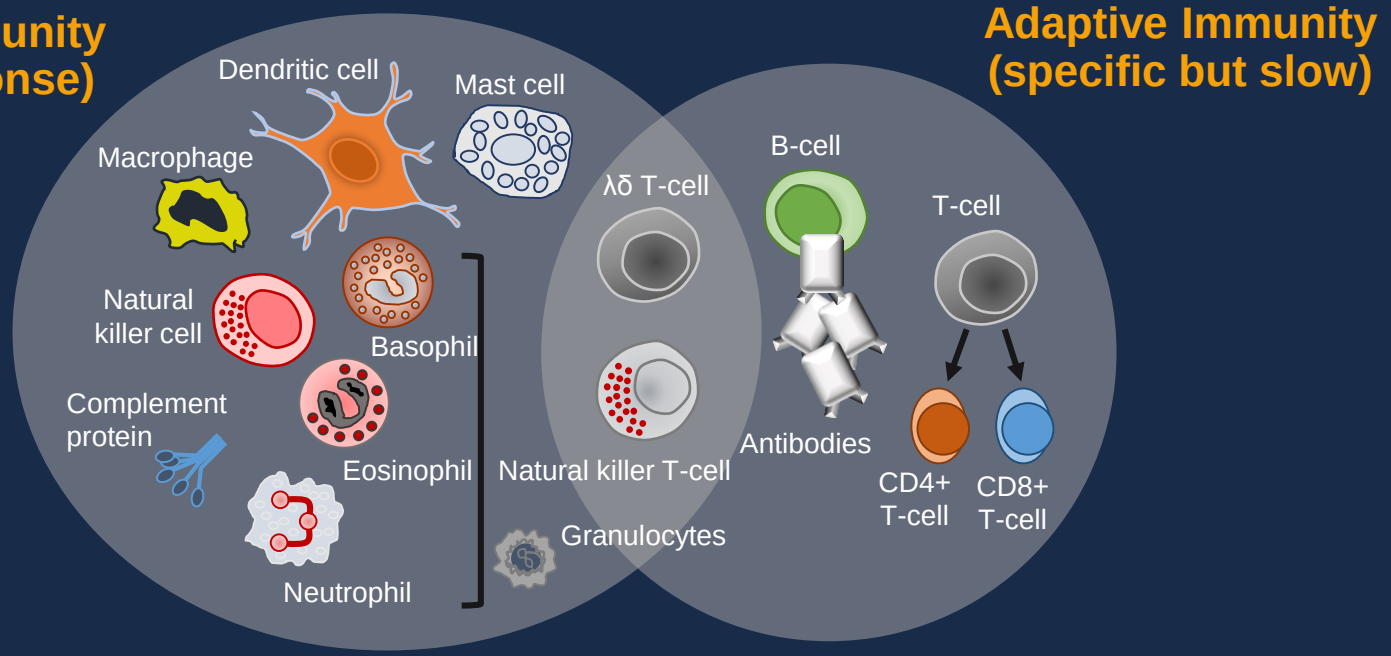
Immune System Function and Immune Response



Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

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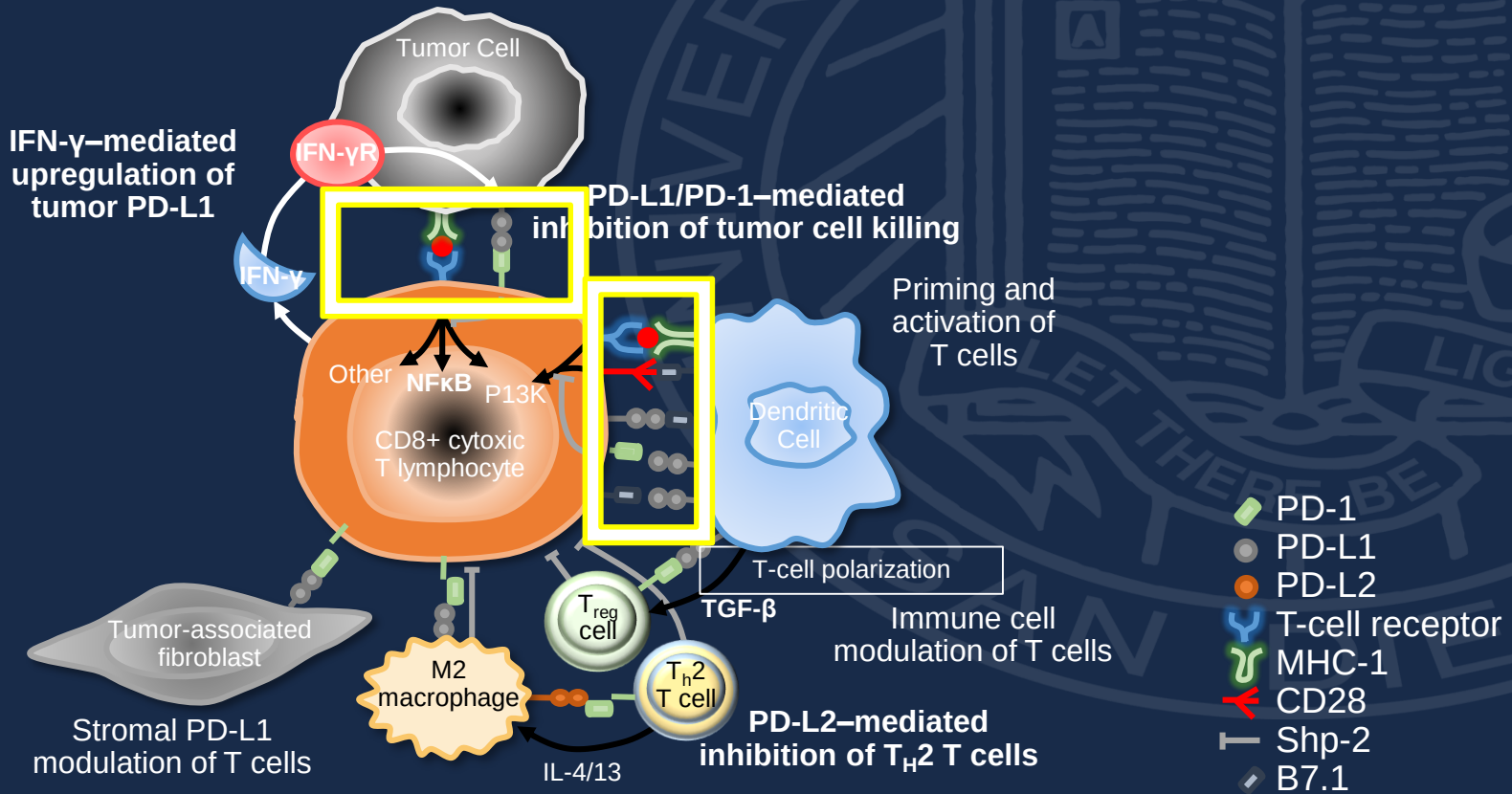
Immunologic Synapses Within Tumor Microenvironment



Sznol M, et al. Clin Cancer Res. 2013;19:1021-1034.

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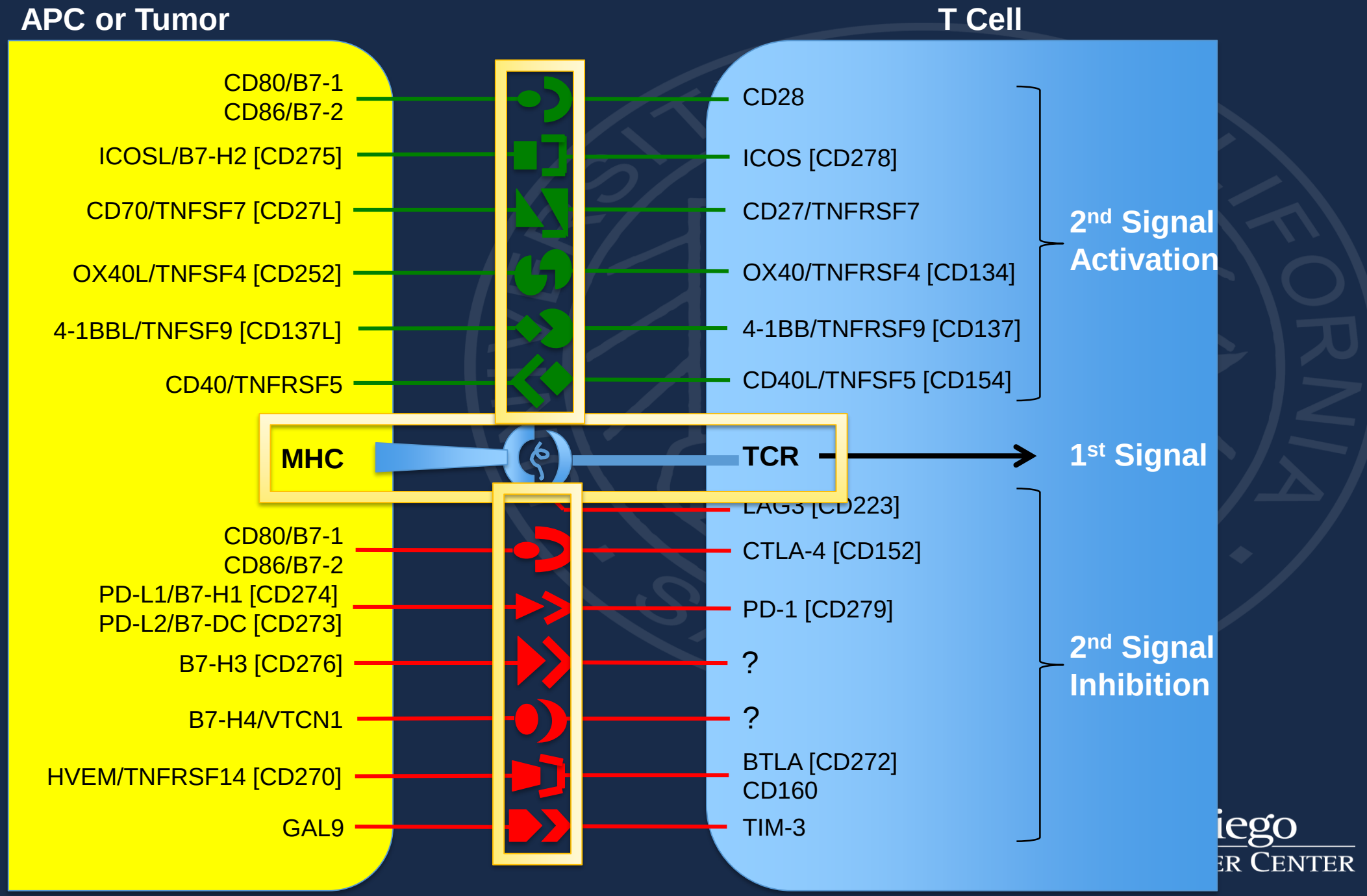
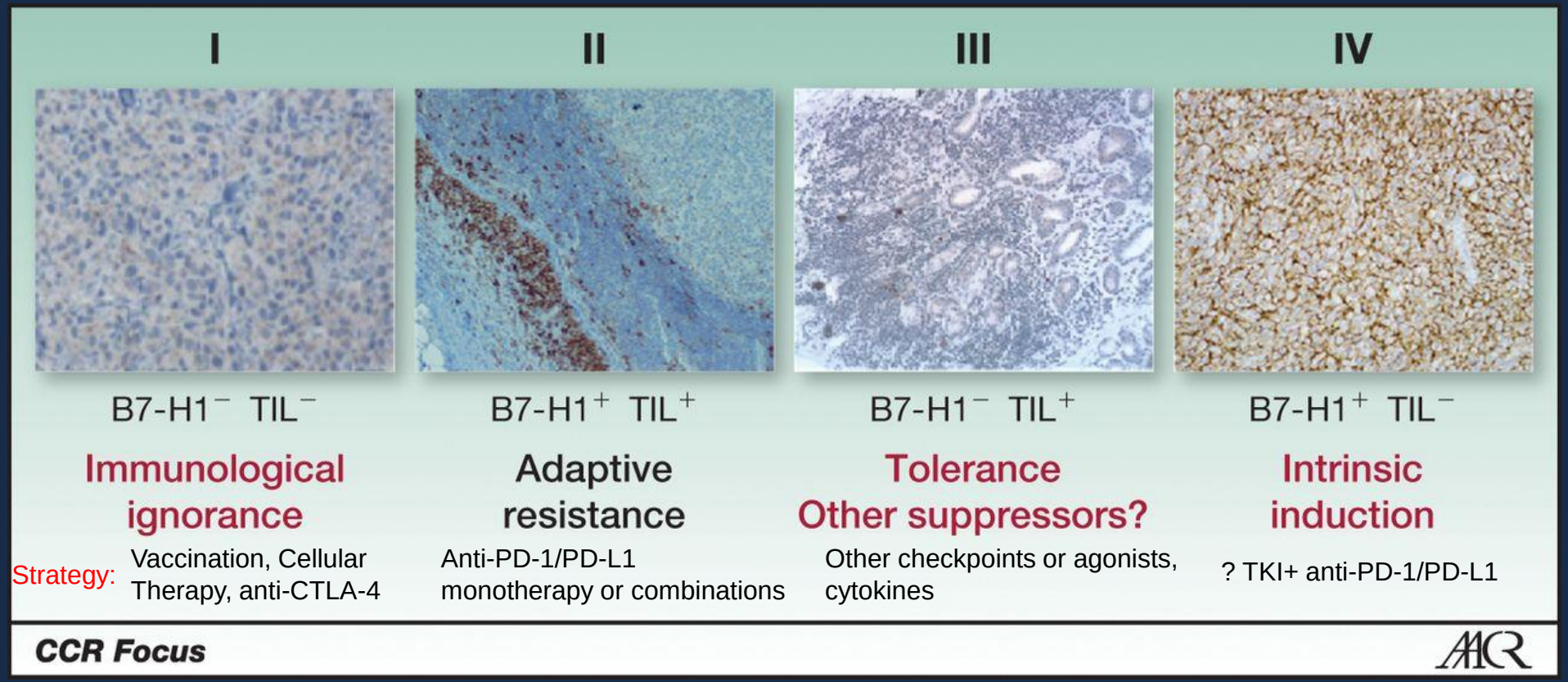

APC or Tumor
T Cell
CD80/B7-1
CD86/B7-2
ICOSL/B7-H2 [CD275]
CD70/TNFSF7 [CD27L]
OX40L/TNFSF4 [CD252]
4-1BBL/TNFSF9 [CD137L]
CD40/TNFRSF5
CD28
ICOS [CD278]
CD27/TNFRSF7
OX40/TNFRSF4 [CD134]
4-1BB/TNFRSF9 [CD137]
CD40L/TNFSF5 [CD154]
2nd Signal Activation
MHC
TCR
1st Signal
LAG3 [CD223]
CD80/B7-1
CD86/B7-2
CTLA-4 [CD152]
PD-L1/B7-H1 [CD274]
PD-L2/B7-DC [CD273]
PD-1 [CD279]
B7-H3 [CD276]
?
B7-H4/VTCN1
?
HVEM/TNFRSF14 [CD270]
BTLA [CD272]
CD160
GAL9
TIM-3
2nd Signal Inhibition

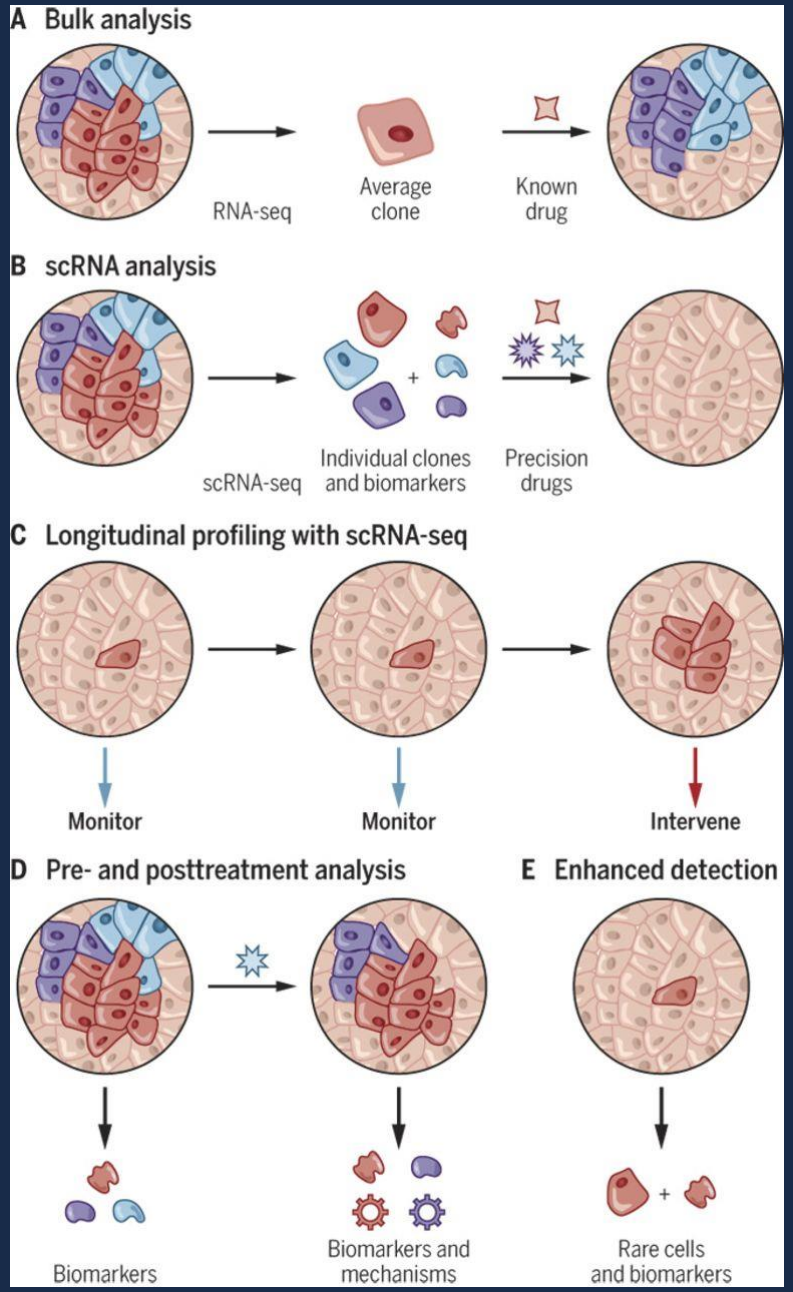
PD-L1 (B7-H1) expression and T cell infiltrate: primary resistance



Mario Sznol, and Lieping Chen Clin Cancer Res 2013;19:1021-1034

Clinical Cancer Research
AACR American Association for Cancer Research

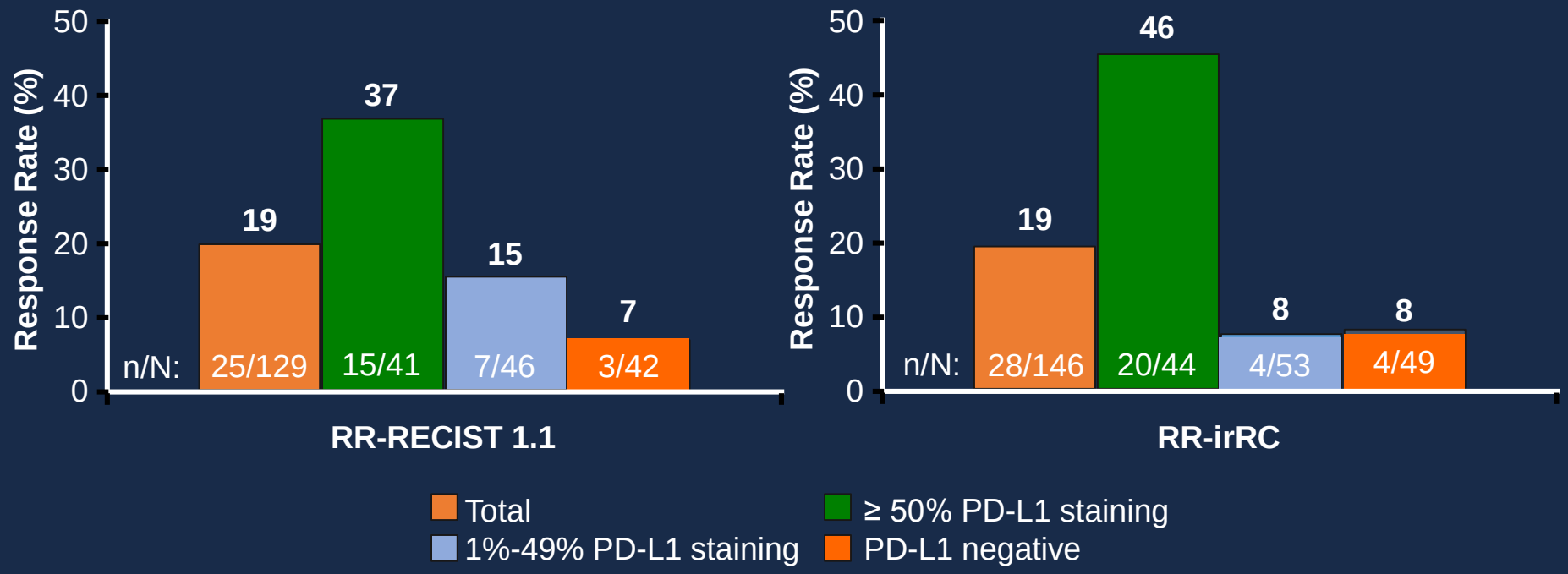
scRNA-seq in cancer: Losing the Forest for the Trees?



Alex K. Shalek and Mikael Benson Sci Transl Med 2017;9:eaan4730

Immunotherapy Biomarkers

PD-L1 IHC in Clinic: Pembrolizumab response rate by PD-L1 IHC in NSCLC



Gandhi L, et al. AACR 2014. Abstract CT105.

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Response Rate by PD-L1 IHC Expression

Therapy	Histology	PD-L1 IHC strata	ORR
Nivolumab (anti-PD-1, BMS)	Melanoma	+ -	44% 17%
	NSCLC	+ -	67% 8%
	Multiple (melanoma, RCC, NSCLC, CRC, mCRPC)	+ -	36% 0%
Pembrolizumab (anti-PD-1, Merck)	Melanoma	+ -	51% 6%
	NSCLC	+ -	67% 0%
MPDL3280A (anti-PD-L1, Roche)	Multiple (melanoma, RCC, NSCLC, CRC, gastric)	+ -	39% 13%
	NSCLC	+ -	100% 15%
	Bladder	+ -	52% 11%

Patel, Kurzrock Mol Canc Ther 2015

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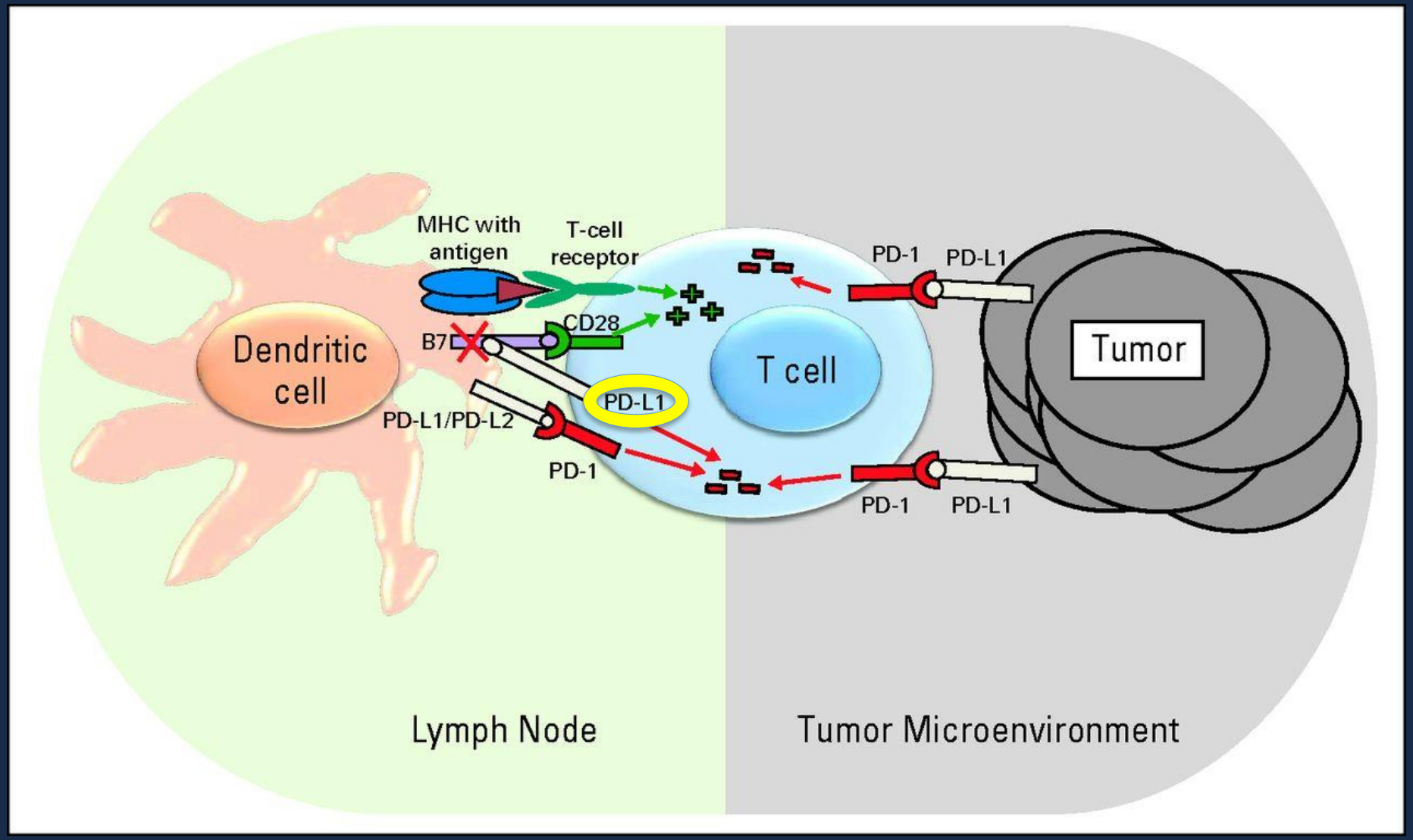
PD-L1 Expression– on Tumor and on Immune Cells



Michael A. Postow et al. JCO doi:10.1200/JCO.2014.59.4358 JOURNAL OF CLINICAL ONCOLOGY ASCO

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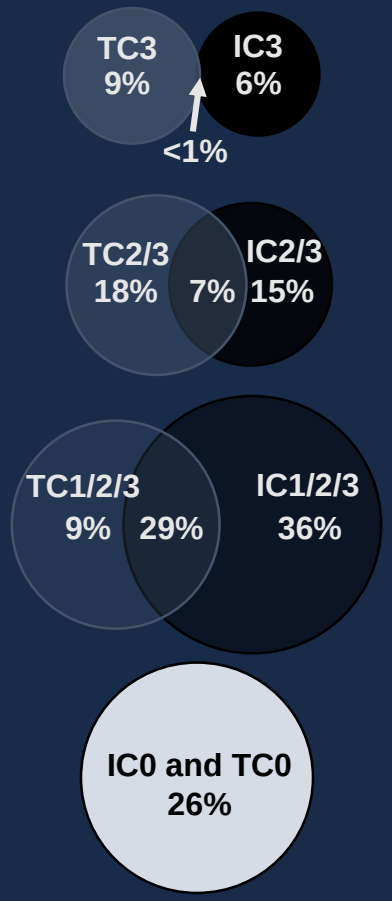
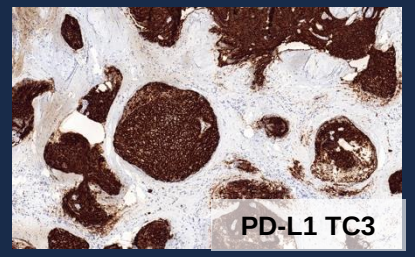
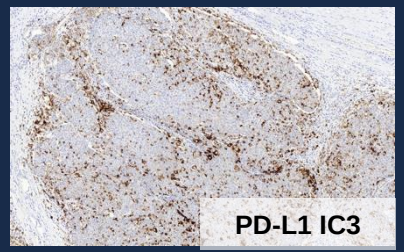
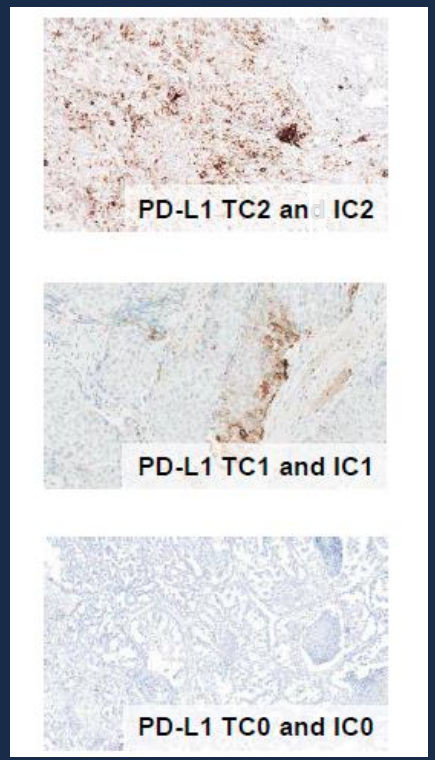
SP142 PD-L1 positive subsets in NSCLC









- In addition to subsets of tumors with PD-L1 expression on both TC and host-derived IC, NSCLC is further characterized by tumors that express PD-L1 exclusively on IC or TC
- TC3 and IC3 represent distinct populations with <1% overlap in NSCLC

IC=immune cells; TC=tumor cells

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Schmid P, et al. Poster. ESMO. 2015 (abstr P269).

M2.AZ.Lung.Clinical.121

*Roche **Sponsored** Study

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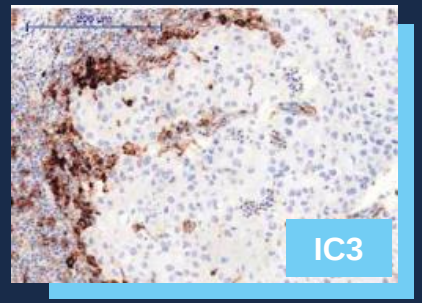
Summary of Characteristics for TC3 and IC3 NSCLC Tumors

Sclerotic
Desmoplastic
Associated with EMT
Regulated by methylation
Intrinsic PD-L1 regulation

PD-L1 TC3 tumors exhibit a desmoplastic and sclerotic TME with low intra-epithelial and stromal IC

PD-L1 TC3 vs IC3 NSCLC tumors have distinct tumor TME



PD-L1 IC3 tumors represent immune-rich/CD8 high tumors

Adaptive PD-L1 regulation
Intra-epithelial/stromal IC
Presence of T_{eff} cells
CD8 IHC

- Despite the differences in TME, both TC and IC predict for clinical benefit to atezolizumab

IC=immune cells; TC=tumor cells; TME=tumor microenvironment

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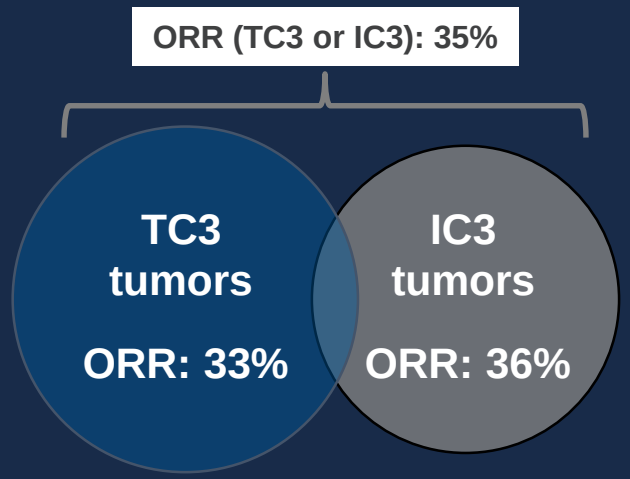
Either Patients With TC3 or IC3 Tumors Showed Enriched Response to Atezolizumab



*Roche **Sponsored** Study

PD-L1 Status	ORR (RECIST v1.1) Pooled Analysis From Phase I and II NSCLC Atezolizumab Trials[a]	
	n	% (95% CI)
TC3 (TC high)	45	33 (20-49)
IC3 (IC high)	42	36 (22-52)
TC3 or IC3	81	35 (24-56)
TC0 and IC0	69	9 (3-18)

[a]Data from pooled ORR analysis in second line+ NSCLC PCD4989g (data cutoff, Dec 2, 2014), FIR (cohort 2; data cutoff Jan 7, 2015) and POPLAR (data cutoff, Jan 30, 2015) trials

IC=immune cells; RECIST=Response Evaluation Criteria in Solid Tumors; TC=tumor cells

Schmid P, et al. Poster. ESMO. 2015 (abstr P269).

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Comparison of SP263 and SP142 at UCSD

	PD-L1 (SP142)		
PD-L1 (SP263)	Positive	Negative	Total
Positive	7% (6)	(7%) 6	12
Negative	15% (13)	71% (62)	75
Total	22% (19)	78% (68)	87

Positive for Tumor or Immune Cell
SP142: TC2-TC3, IC2-IC3 scoring
SP263: 25% tumor or immune cell staining

- SP142 stained more tumors positive than SP263 in serial sections
- Why is this different than Blueprint?
  - Different tumor types (not just lung)
  - Different scoring for positivity (TC/IC2 vs TC/IC1)
  - And differential immune staining

Nakasaki, Jacobs, Fadare, Patel, Hansel (pending)

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Comparison of SP263 and SP142 at UCSD

	Total			
	N = 87 (%)	TC positive	IC positive	TC-IC dual positive
PD-L1 (SP142)				
Negative	68 (78.1)	-	-	-
Positive	19 (21.8)	10 (11.5)	11 (12.6)	2 (2.3)
PD-L1 (SP263)				
Negative	75 (86.2)	-	-	-
Positive	12 (13.8)	12 (13.8)	0 (0)	0 (0)

- SP263 appears to stain tumor cell PD-L1 better
- SP142 appears to stain immune cell PD-L1 better
- Another reason testing for both on serial sections may be superior strategy

Nakasaki, Jacobs, Fadare, Patel, Hansel (pending)

Under the Scope

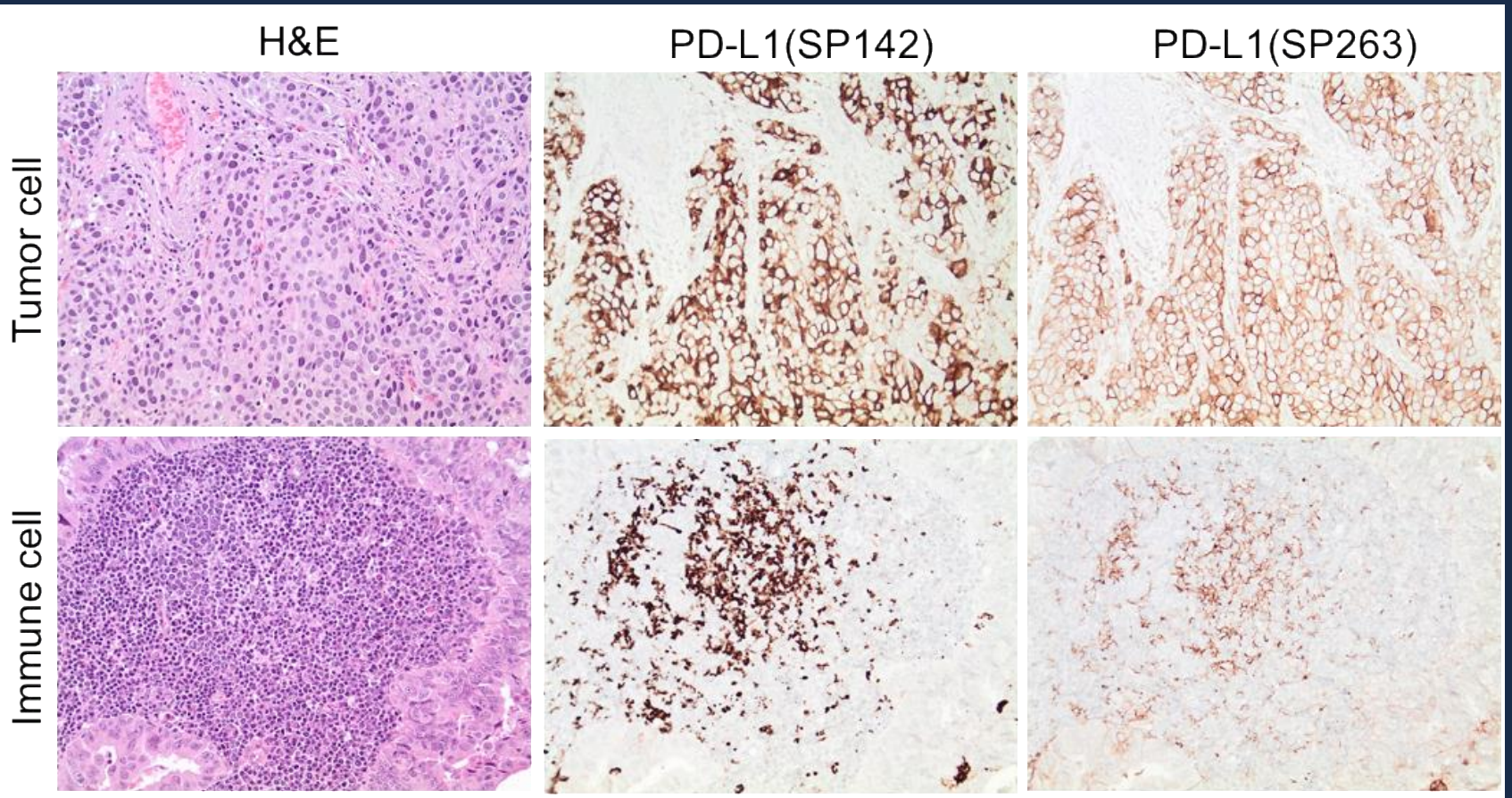

Figure 1: Staining with PD-L1 monoclonal antibodies in tumor and immune cells. Histology of urothelial carcinoma (upper panels) and metastatic lung adenocarcinoma (lower panels). Tissues were stained with hematoxylin-eosin and PD-L1 monoclonal antibodies (SP142 and SP263, respectively).

Nakasaki, Jacobs, Fadare, Patel, Hansel (pending)

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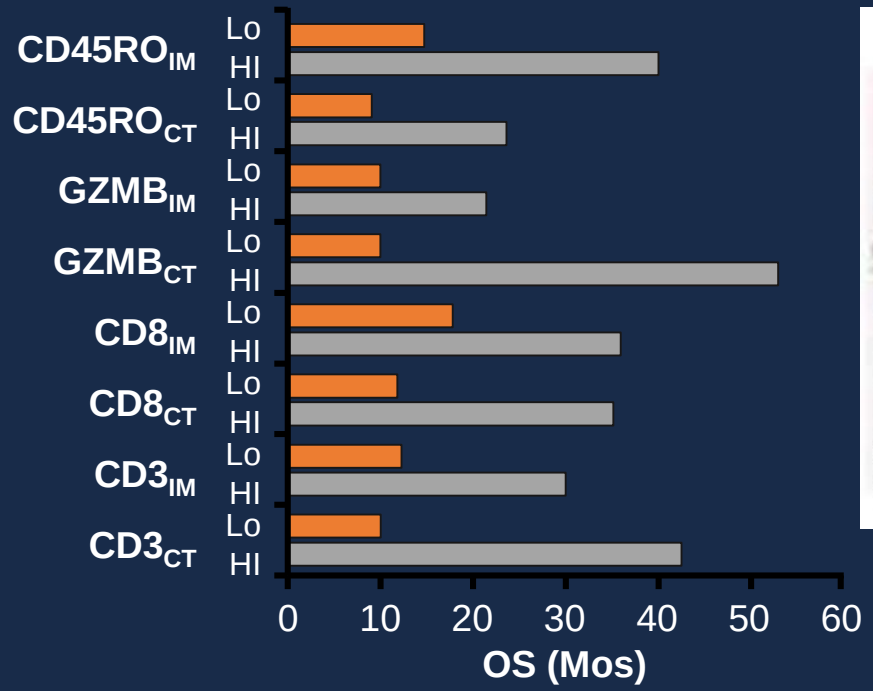
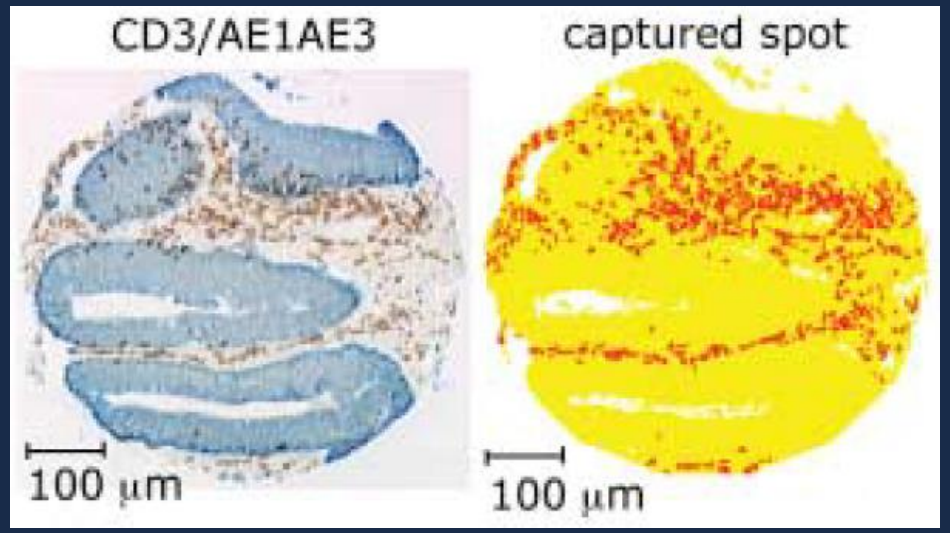
ImmunoScore in colorectal cancer





- Has prognostic value on par with classical TNM staging

Galon J, et al. Science. 2006;313:1960-1964.

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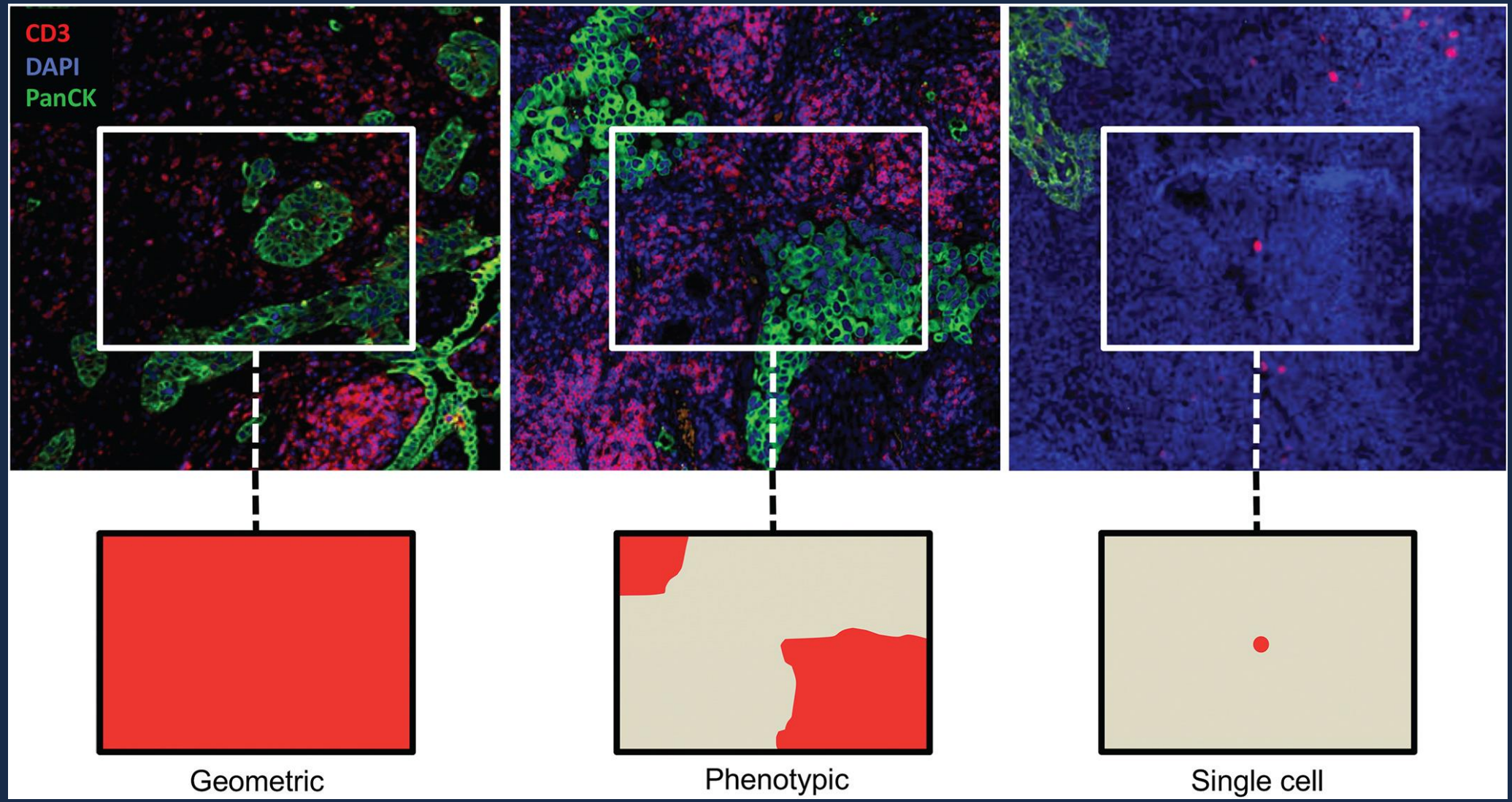
Selection of Region of Interest Within Tumor Microenvironment



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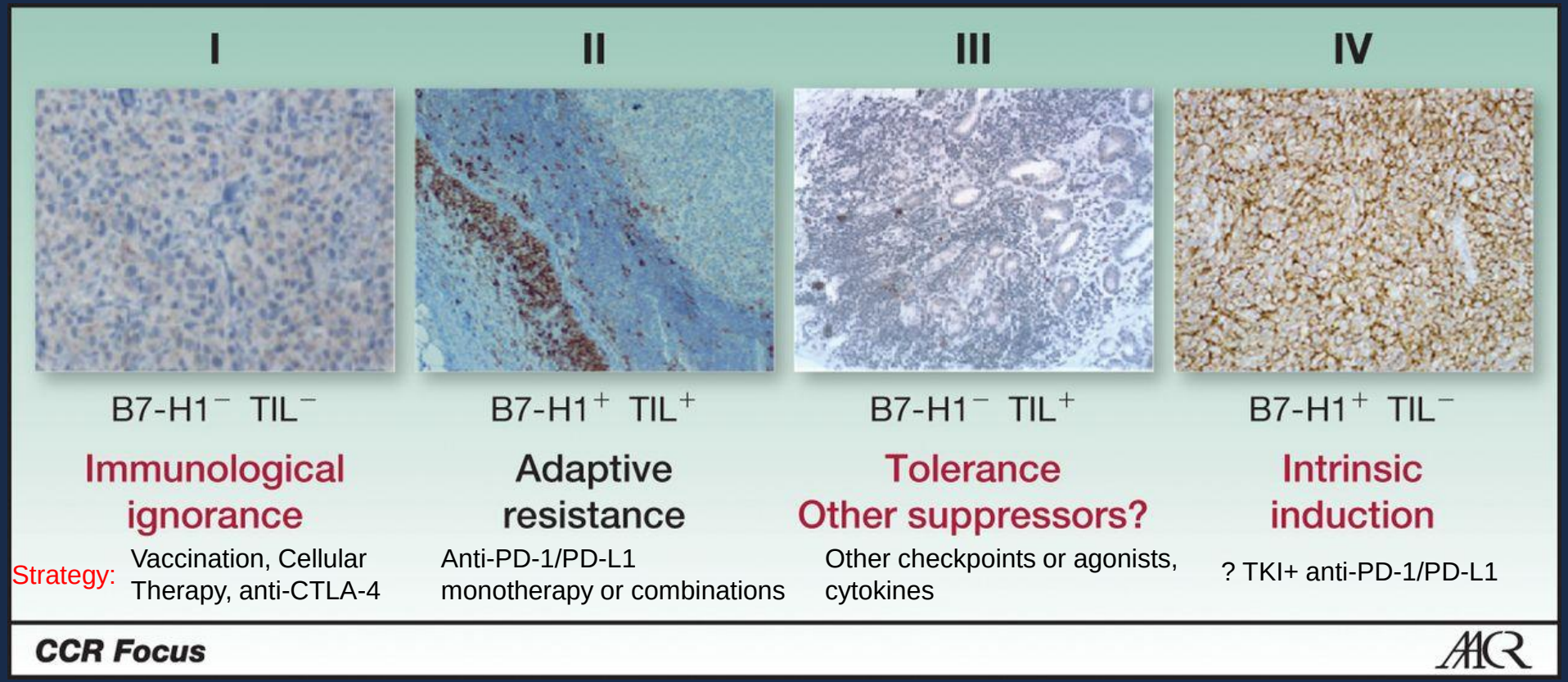
The Journal of Pathology, Volume: 247, Issue: 5, Pages: 650-661, First published: 20 December 2018, DOI: (10.1002/path.5223)

PD-L1 (B7-H1) expression and T cell infiltrate: primary resistance



Mario Sznol, and Lieping Chen Clin Cancer Res 2013;19:1021-1034

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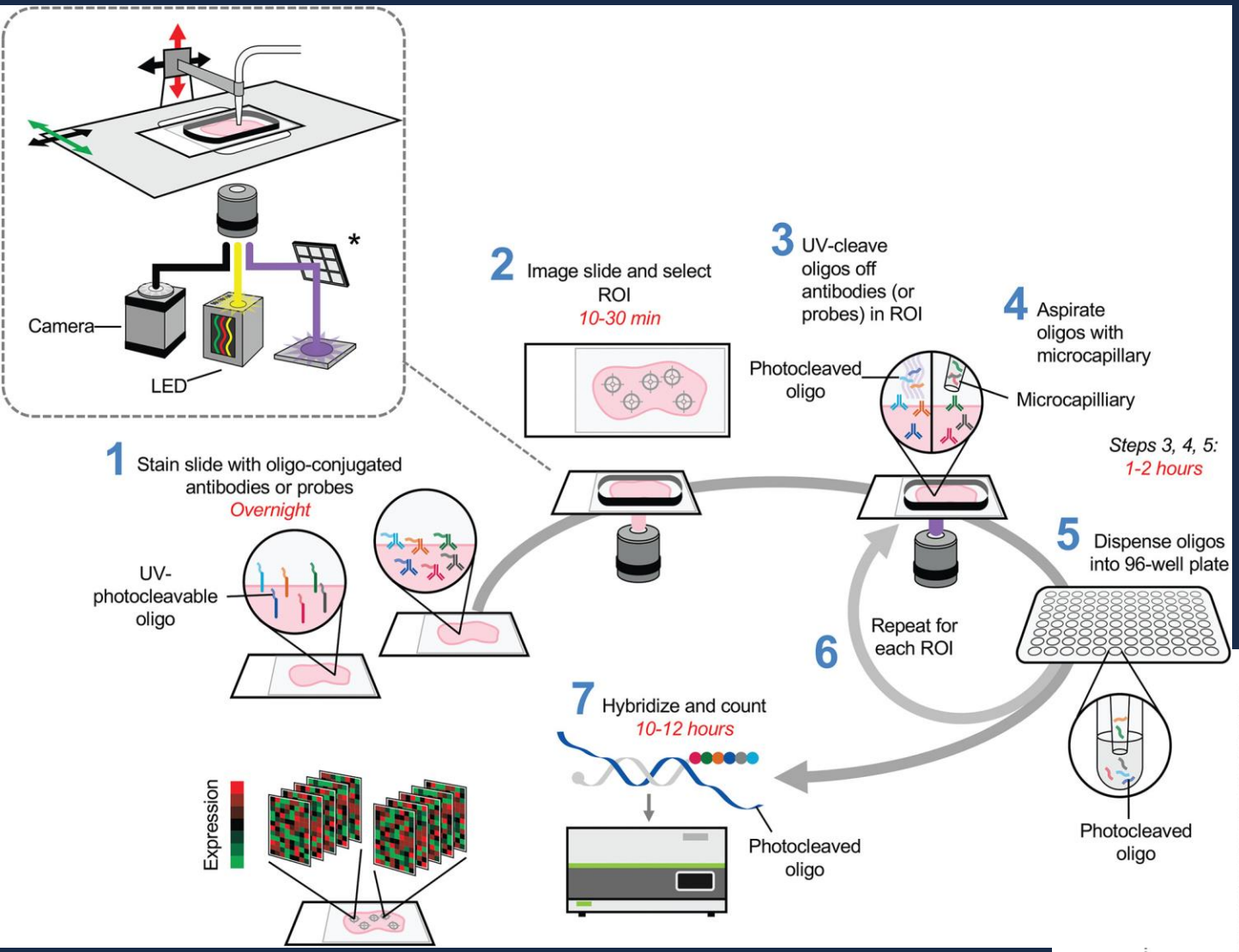
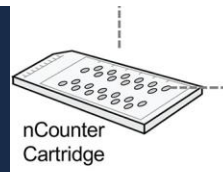
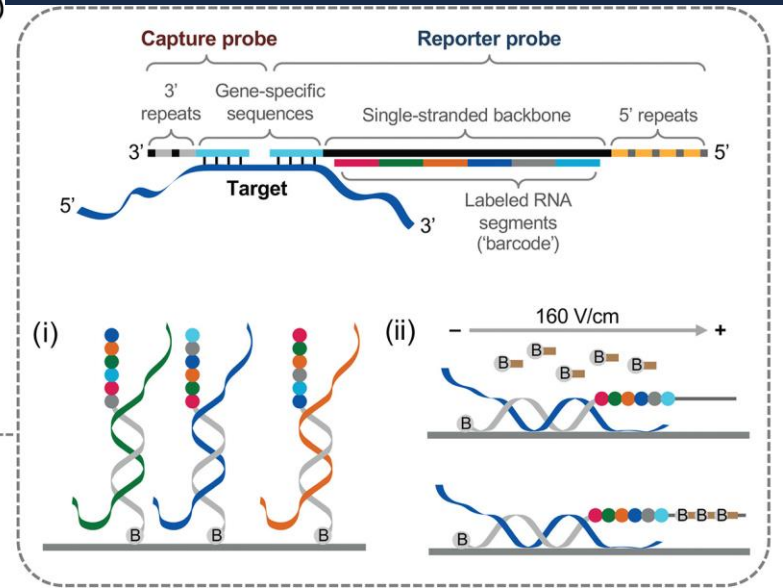
Workflow for Spatial Interrogation (nanoSting GeoMX/DSP)







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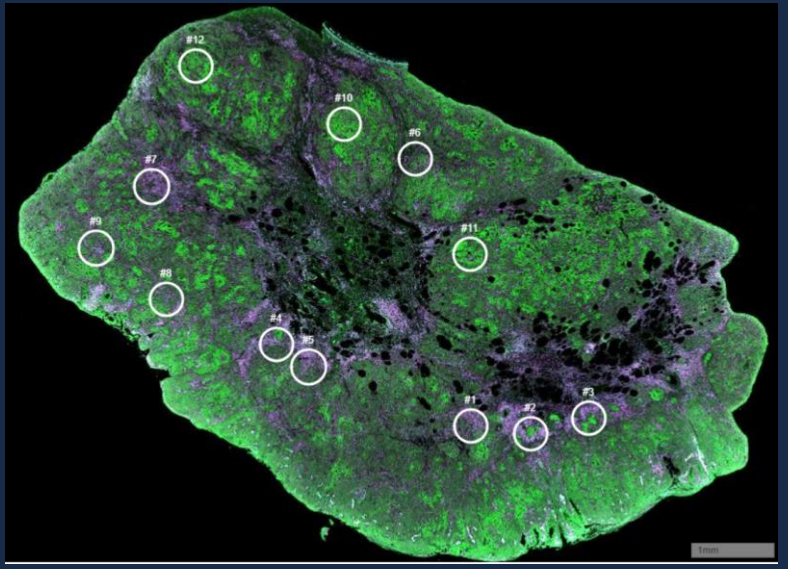
#3		7500

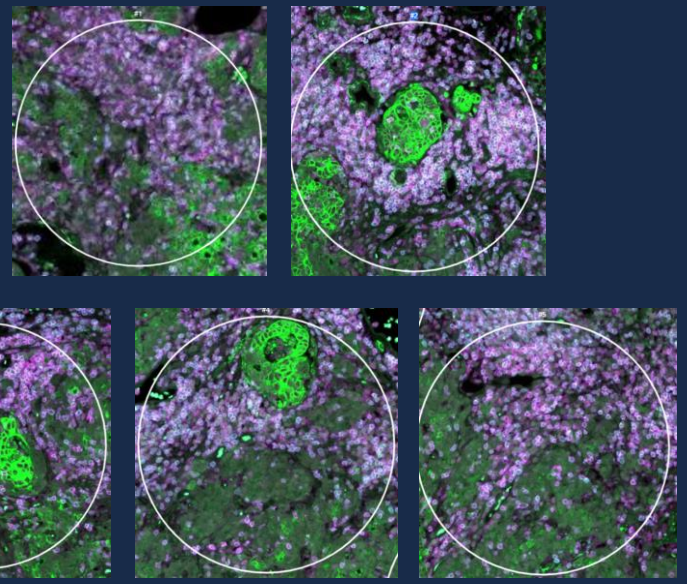
The Journal of Pathology, Volume: 247, Issue: 5, Pages: 650-661, First publish



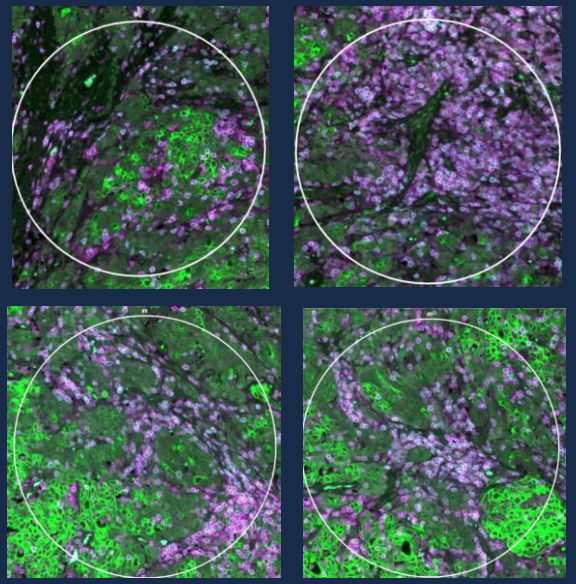
Assessment of Immune Stroma in MSI-H vs MSS Colon Cancer: Effect of Spatial Context

CD45-enriched hotspots

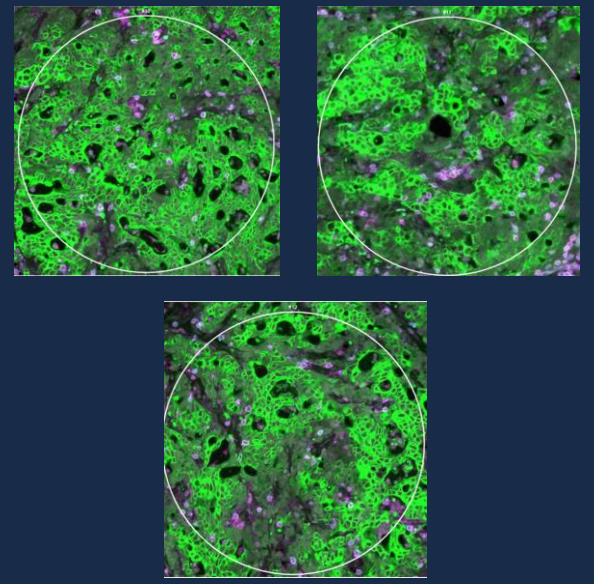
Invasive Margin (IM)



Tumor Center (CT)



Cytokeratin-enriched (Tumor)



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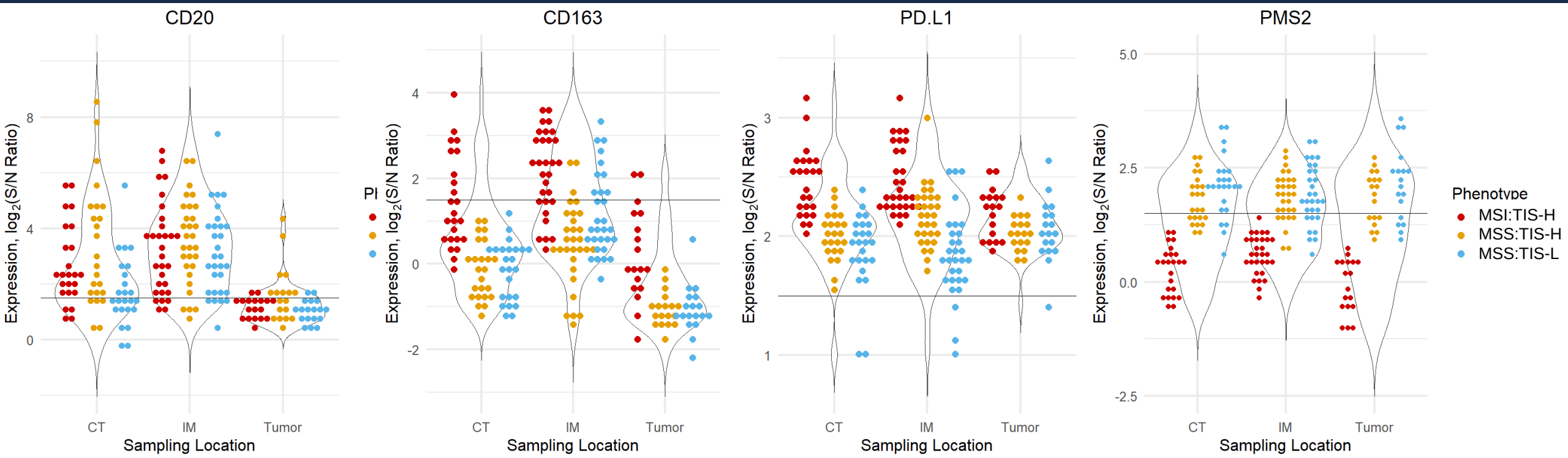
Church. SITC 2018

Differences in B cell and macrophage populations by sampling location



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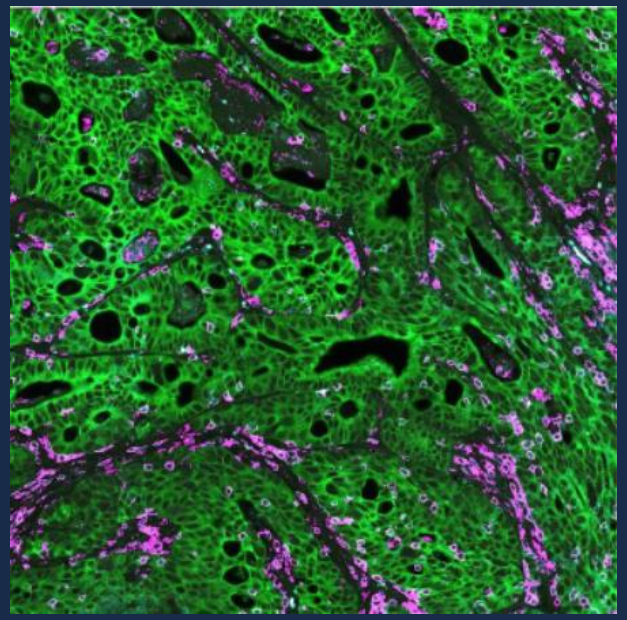
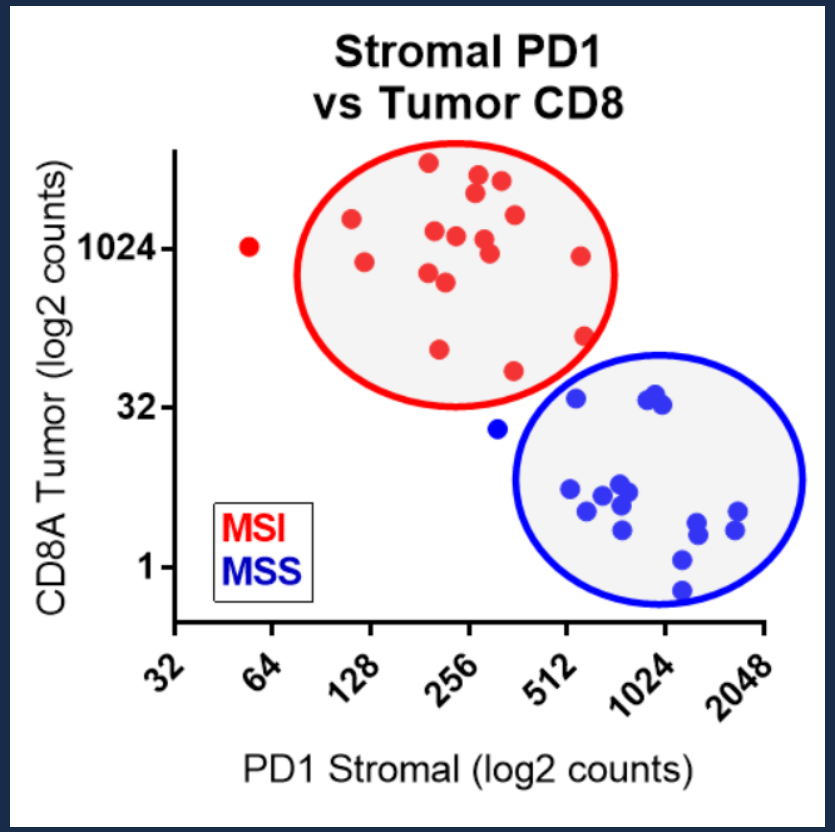
Segmentation Profiling of Colon Cancer



Stromal

Tumor



MSS mCRC has stromal PD-1, MSI-H mCRC has high tumoral CD8

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Church. SITC 2018

The Intersection of the Gut and the Immune System

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Immune Checkpoint Inhibitor Colitis

- Ipilimumab-induced ileocolitis with deep ulcerations in the colon

Slangen RM, et al. World J Gastrointest Pharmacol Ther. 2013;4:80-82.

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Microbiota in Inflammatory Bowel Disease

Major differences in microbiome profile between HC (healthy control) and:

- Ulcerative colitis (UC)
- Collagenous colitis (CC)
- Colonic Crohn's Dz (CCD)
- Ileal Crohn's Dz-not resected (ICD-nr)
- Ileal Crohn's Dz-resected (ICD-r)

Halfvarson, Knight, Jansson. Nat Micro 2017

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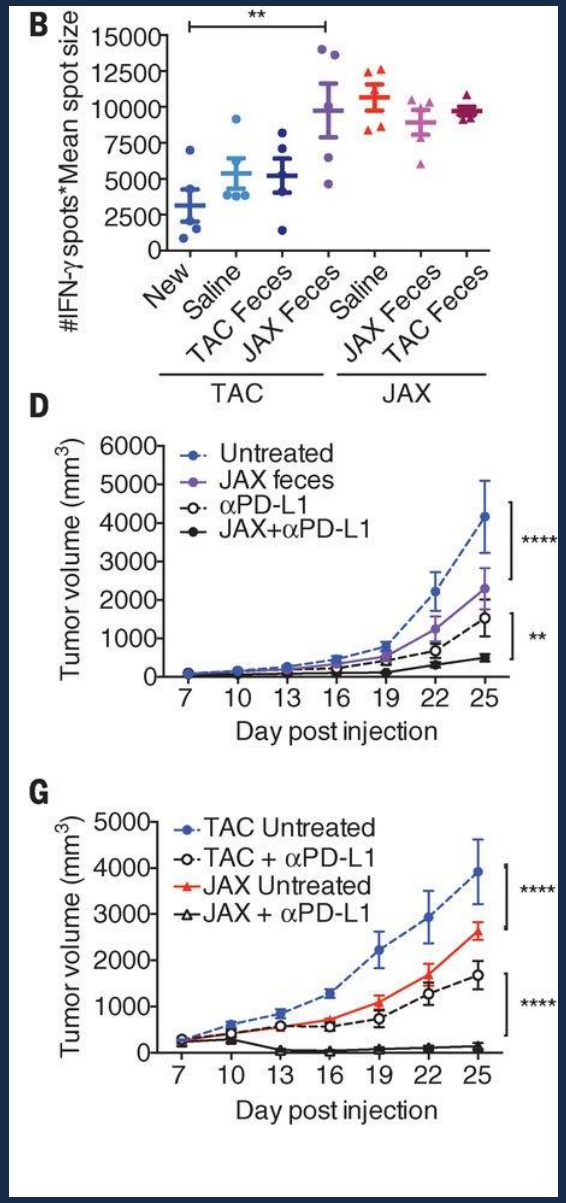
Microbiome Modulates Response to Immunotherapy



- Where a mouse was ordered seemed to determine response to anti-PD-L1 (JAX vs TAC)
- This difference was driven by gut microbiota
- The commensal microbial composition can influence spontaneous antitumor immunity, as well as a response to immunotherapy with αPD-L1 mAb.
  - Combination treatment with both JAX fecal transfer and αPD-L1 mAb improved tumor control (Fig. D)
  - αPD-L1 alone was significantly more efficacious in JAX mice compared with TAC mice (Fig. G).

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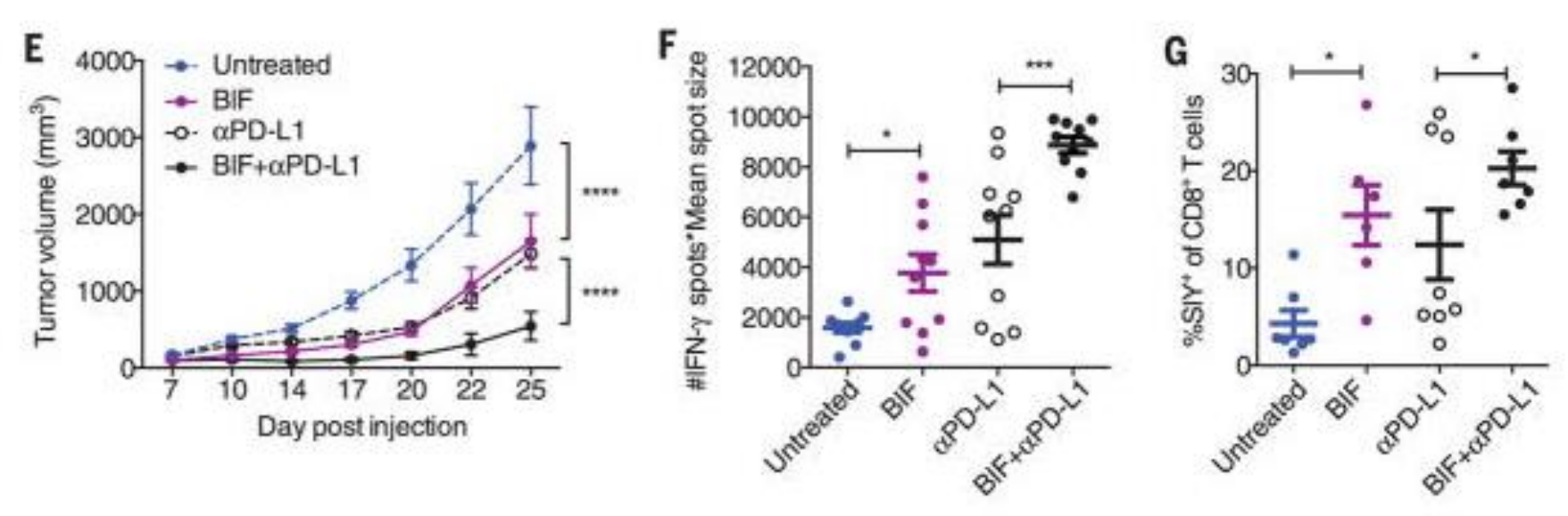
Sivan et al. Science 2015;350:1084-1089

Which bacterial species?



- Bifidobacterium (BIF) seemed to be the sensitizing bacterial strain
- Transfer of BIF into deficient mice led to improved anti-tumor responses with anti-PD-L1

Sivan et al. Science 2015;350:1084-1089

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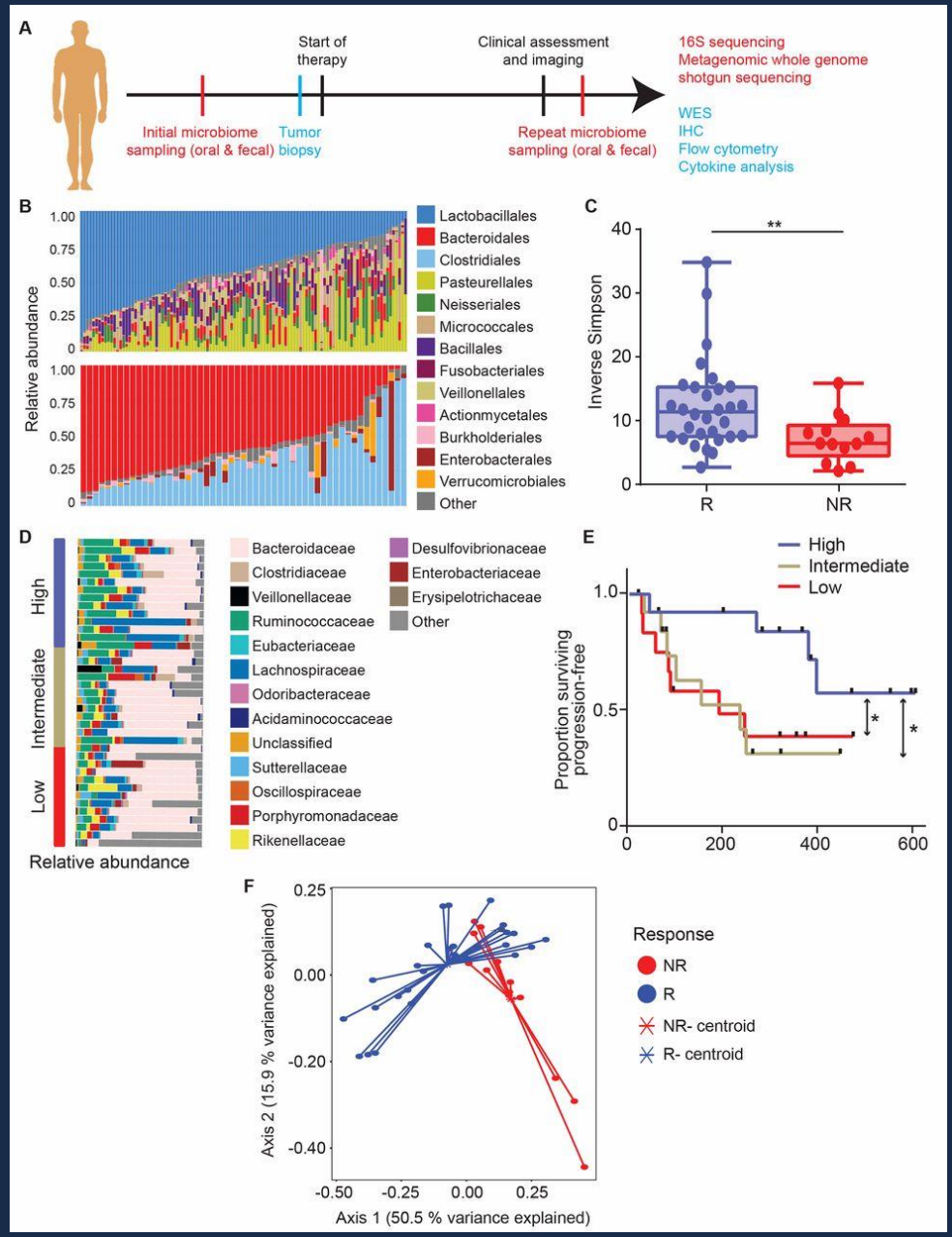
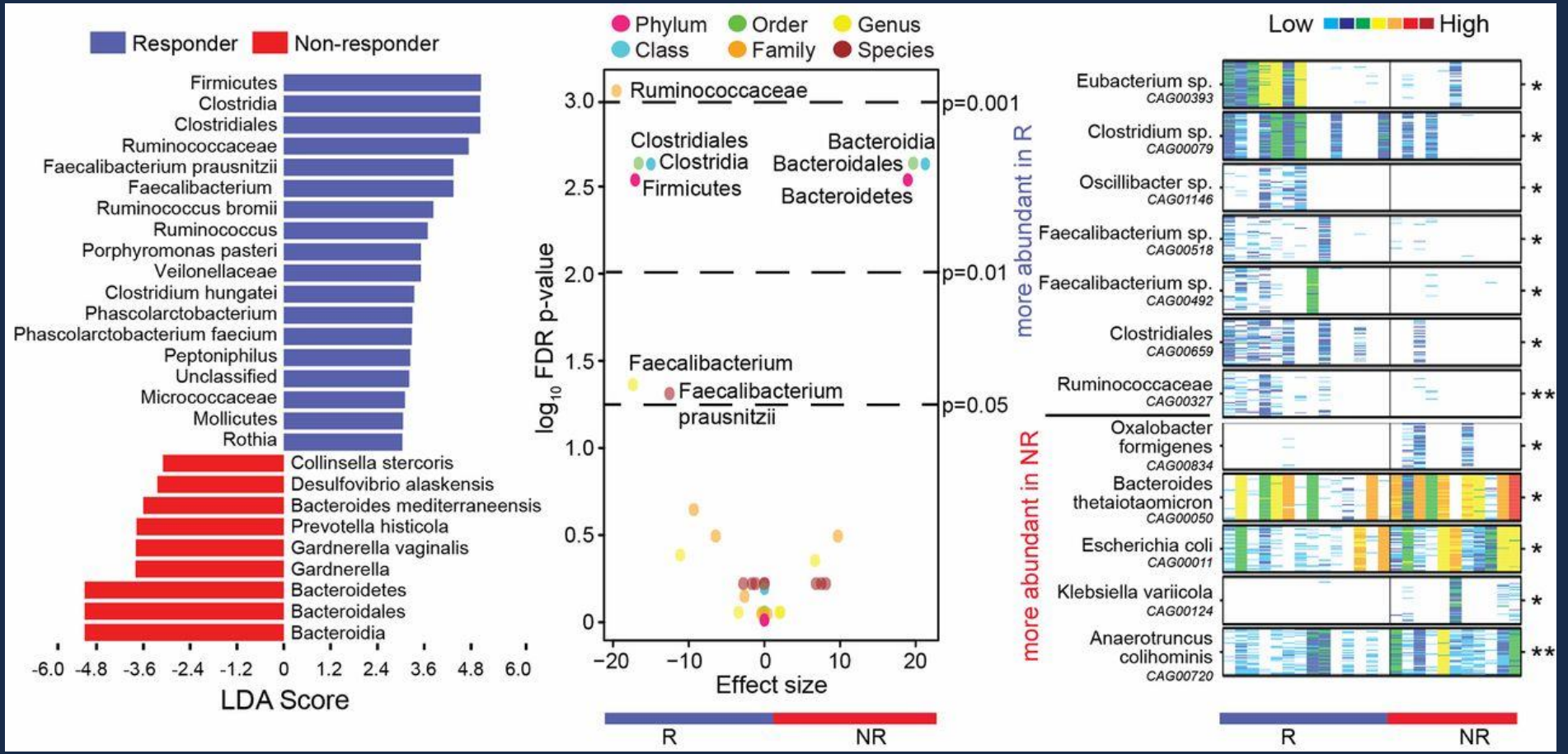
Melanoma patients with more gut microbiome diversity response better to anti-PD-1



V. Gopalakrishnan et al. Science 2017;science.aan4236

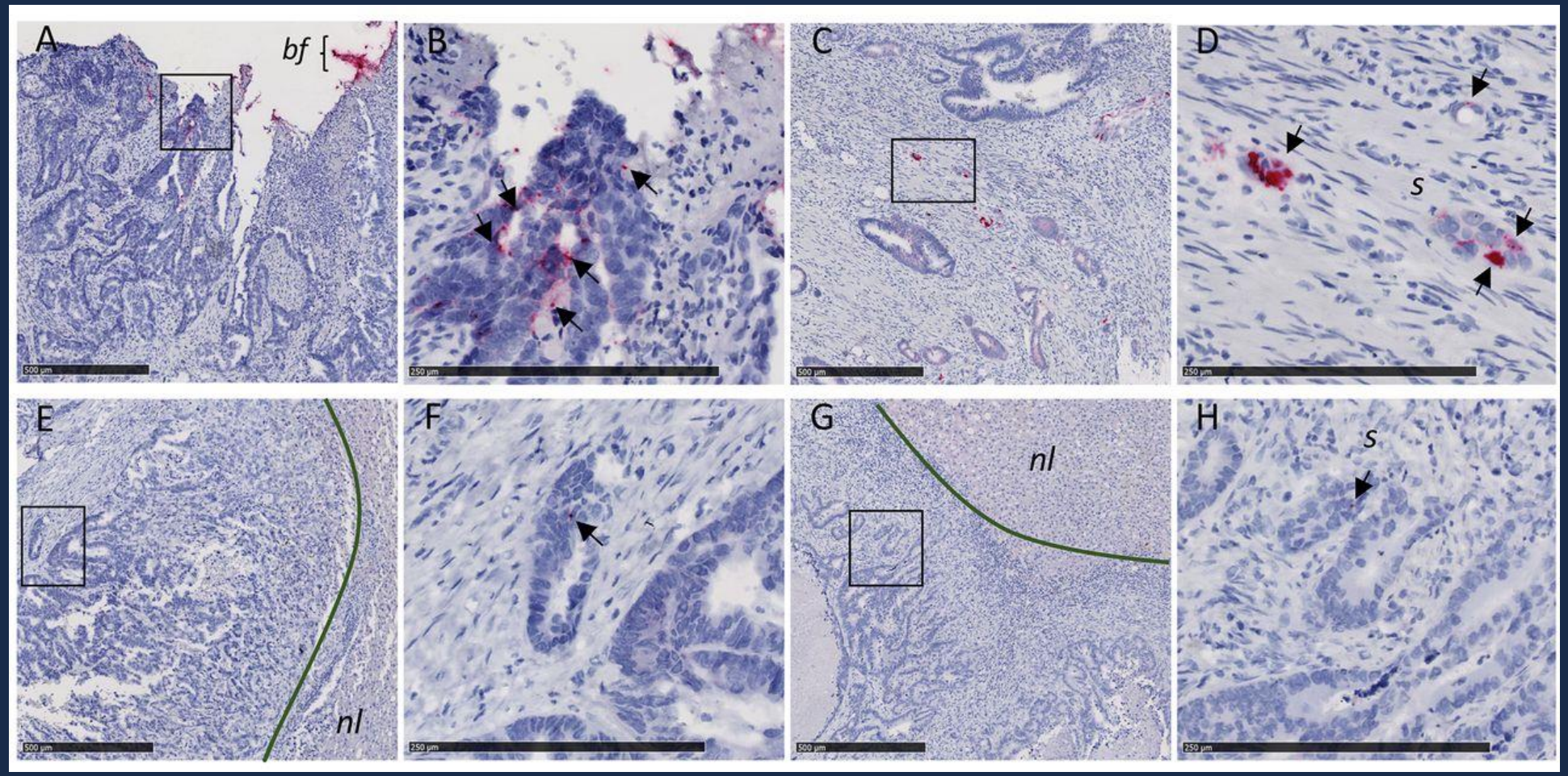
Published by AAAS

Different Bacteria Portend Response or Resistance to Anti-PD-1 in Melanoma



V. Gopalakrishnan et al. Science 2017;science.aan4236

Fusobacterium nucleatum RNA present in colon primary tumors and metastasis



Susan Bullman et al. Science 2017;science.aal5240

Summary

- Cancer immunotherapy has revolutionized cancer treatment, with melanoma as the forerunner but now a multitude of tumor types
- PD-L1 is an imperfect biomarker in the clinic, and newer biomarkers such as TMB have not informed clinic practice
  - PD-L1 negative melanoma patients respond to anti-PD-1
- Spatial context of immune infiltrate can provide unique information about relevant immunosuppressive pathways at key tumor-immune synapses
- The microbiome can influence response to immunotherapy
  - Metabolomics may be central to this effect
  - Intratumoral microbiome and fungome may affect oncogenesis

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Questions?

Sandip Pravin Patel, MD

Email: patel@ucsd.edu

Twitter: @PatelOncology

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