The Microbiome in Cancer Immunotherapy

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Immunobiology Overview

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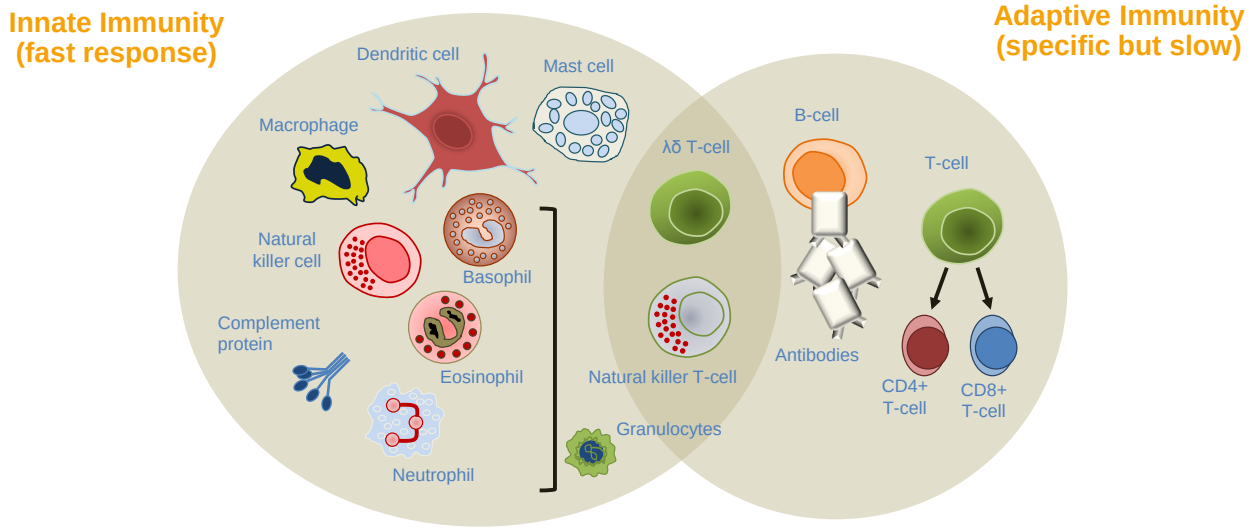
Common Types of Immunotherapy

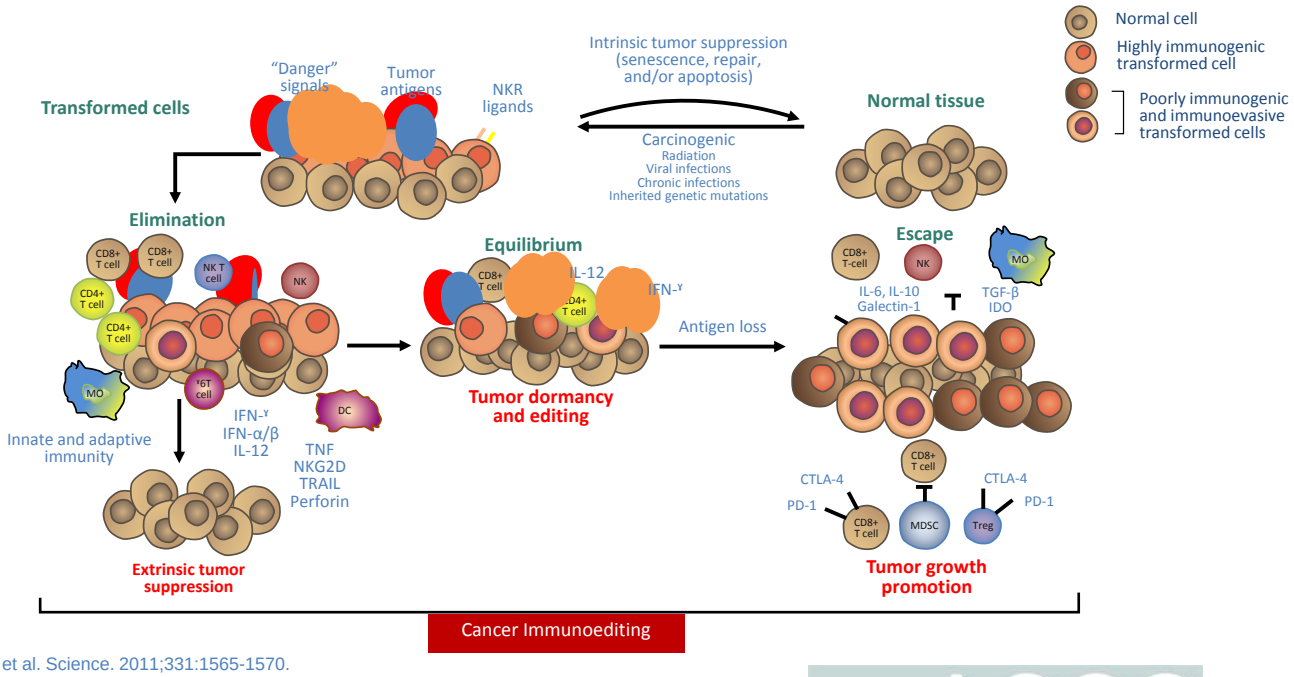
- Vaccines
  - Peptide/Protein/Tumor cell lysates
  - Viral
  - Dendritic Cell
  - Oncolytics
- Small molecule agonists and inhibitors
  - IDO
  - TGF-beta
- Cytokines
  - IL-2
- Immune checkpoint blockade
  - CTLA-4
  - PD-1, PD-L1
- Cellular therapy
  - CARs, TCRs

Immune System Function and Immune Response



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

Basic Concepts in Tumor Immunology: Immunoediting



Schreiber RD, et al. Science. 2011;331:1565-1570.

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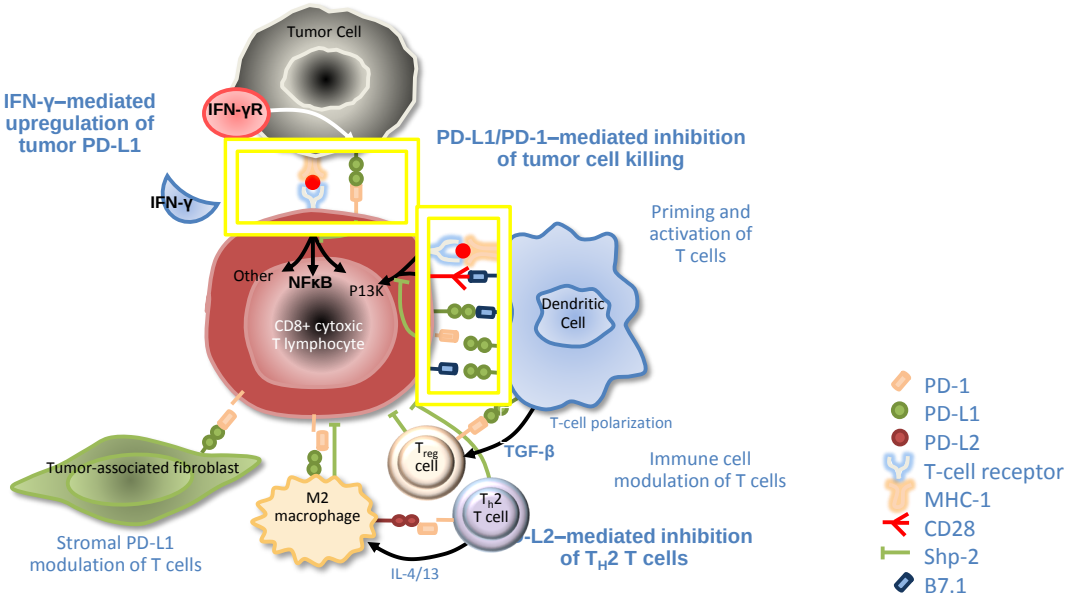
Immunologic Synapses Within Tumor Microenvironment



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

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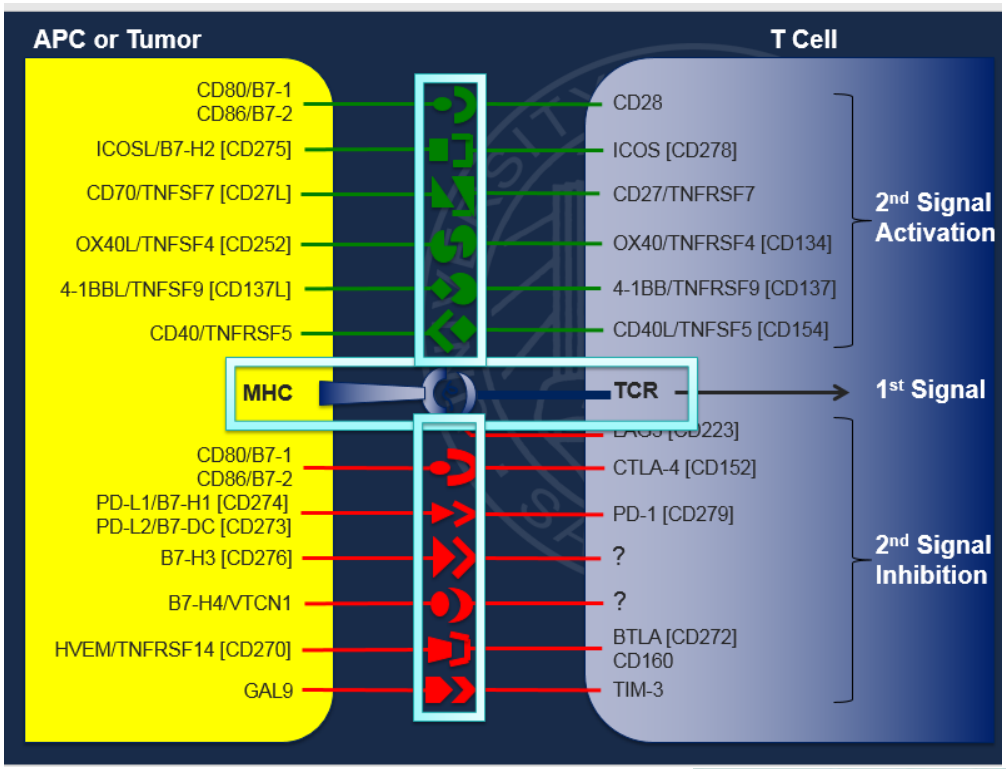

Clinical Biomarkers

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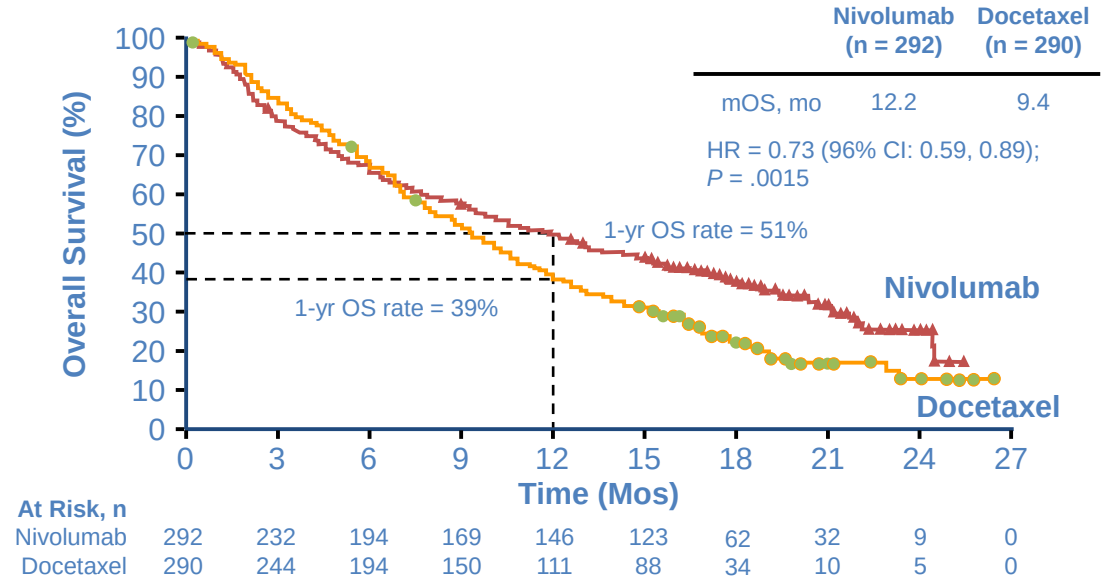
CheckMate 057: OS in NSCLC-nonsquamous



Paz-Ares L, et al. ASCO 2015. Abstract LBA109

PD-L1 IHC

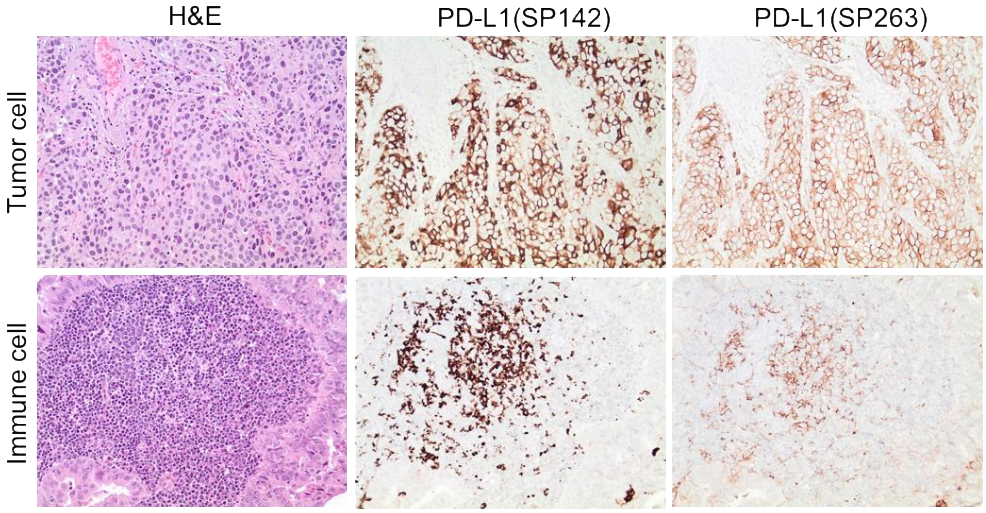
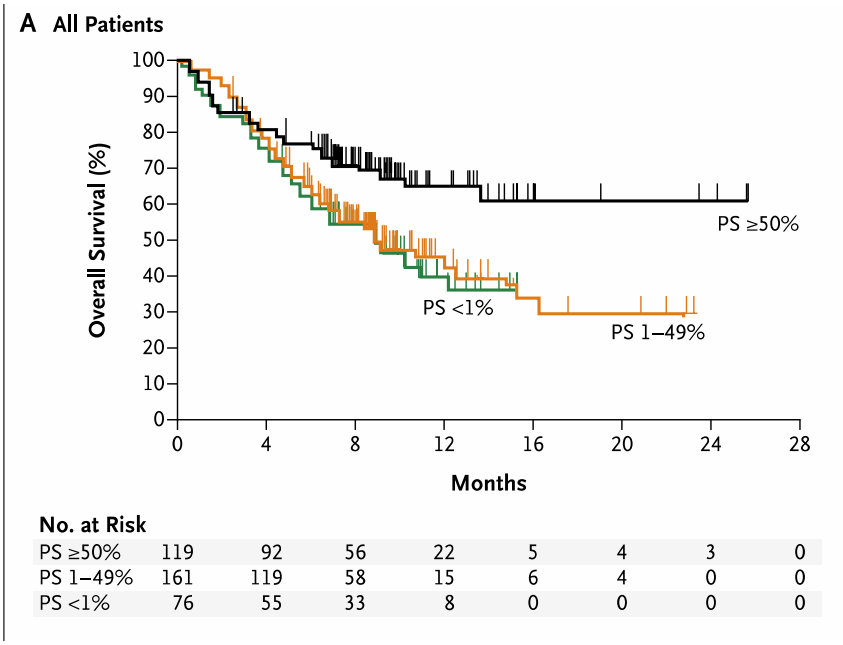


Figure 1: Staining with PD-L1 monoclonal antibodies in tumor and immune cells. Histology of urothelial carcinoma (upper panels) and metastatic lung adenocarcinoma (lower panels). Tissues were stained with hematoxylin-eosin and PD-L1 monoclonal antibodies (SP142 and SP263, respectively).

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

Biomarker Enrichment - OS in NSCLC with Pembrolizumab

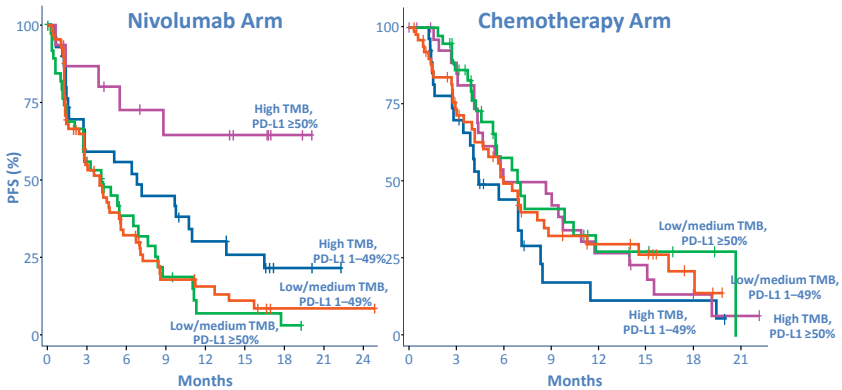


No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

- PD-L1 expression on tumor membrane
- 50% cutoff point

Garon et al. NEJM 2015

PFS by TMB Subgroup & PD-L1 Expression
CheckMate-026 TMB Analysis: Nivolumab in First-line NSCLC



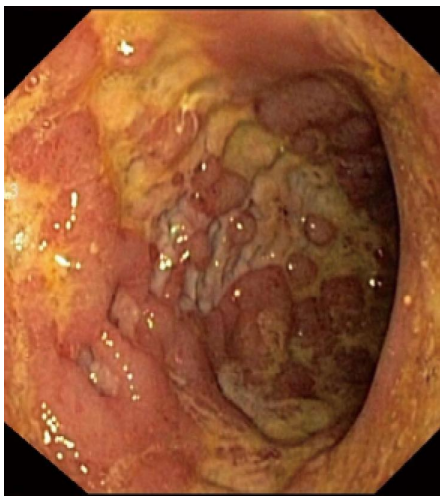
No. at Risk																
High TMB, PD-L1 ≥50%	16	13	10	8	8	6	2	0	0	32	24	13	12	7	5	2	1
High TMB, PD-L1 1–49%	31	17	16	13	8	6	2	1	0	28	18	9	3	2	2	2	0
Low/medium TMB, PD-L1 ≥50%	41	21	12	6	2	2	1	0	0	41	30	14	10	5	4	2	0
Low/medium TMB, PD-L1 1–49%	70	33	18	9	7	5	1	1	1	53	35	23	13	10	8	3	0

Peters S, et al. *AACR*. 2017. Abstract CT082.

The Intersection of the Gut and the Immune System

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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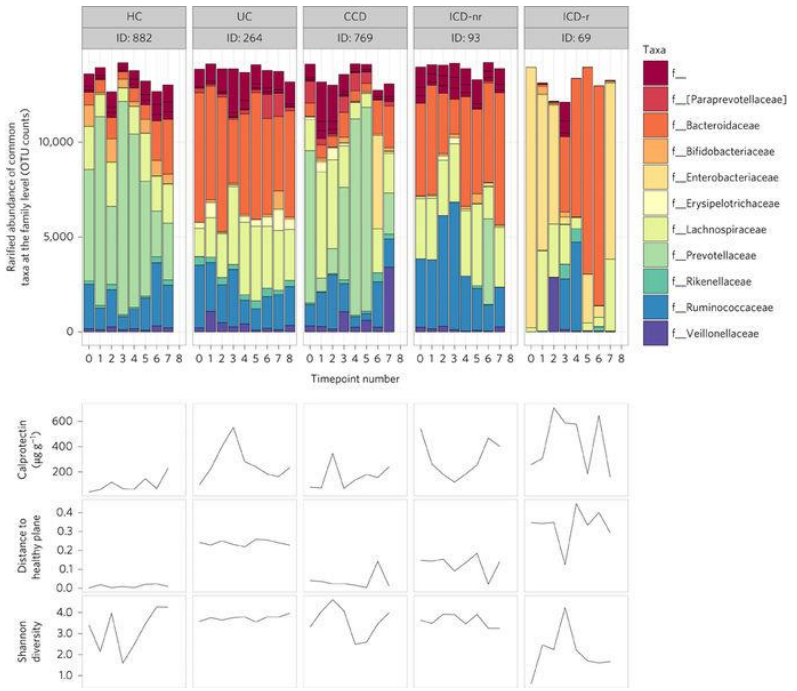
Microbiota in Inflammatory Bowel Disease

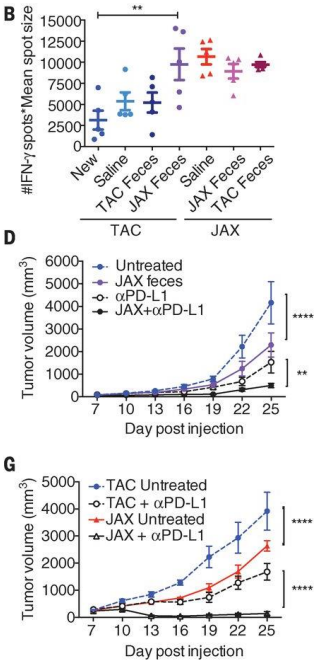


Major differences in microbiome profile between HC (healthy control) and:

- 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

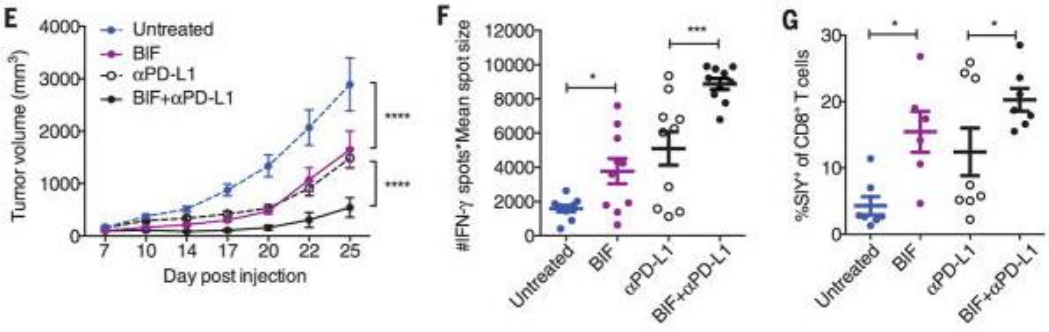
Microbiome Modulates Response to Immunotherapy



- 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).

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

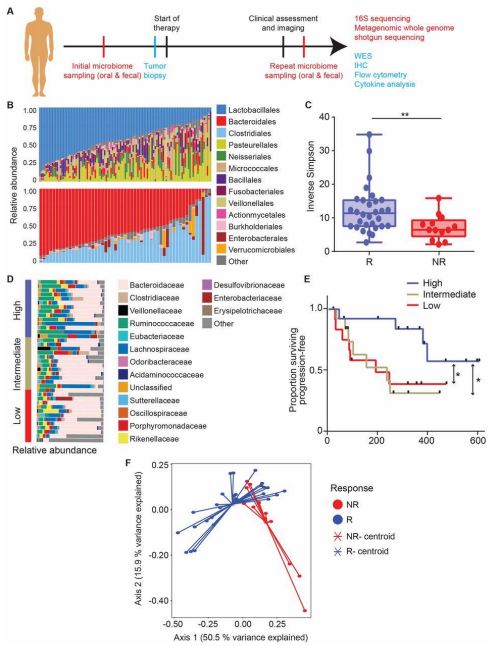
Which bacterial species?



- 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

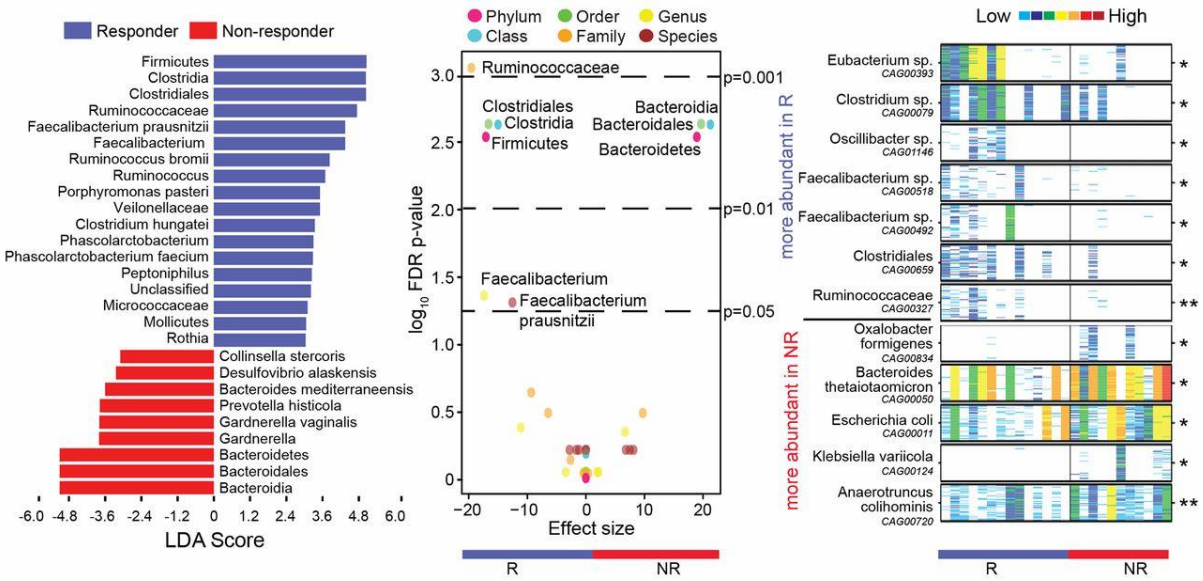
Sivan et al. Science 2015;350:1084-1089

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



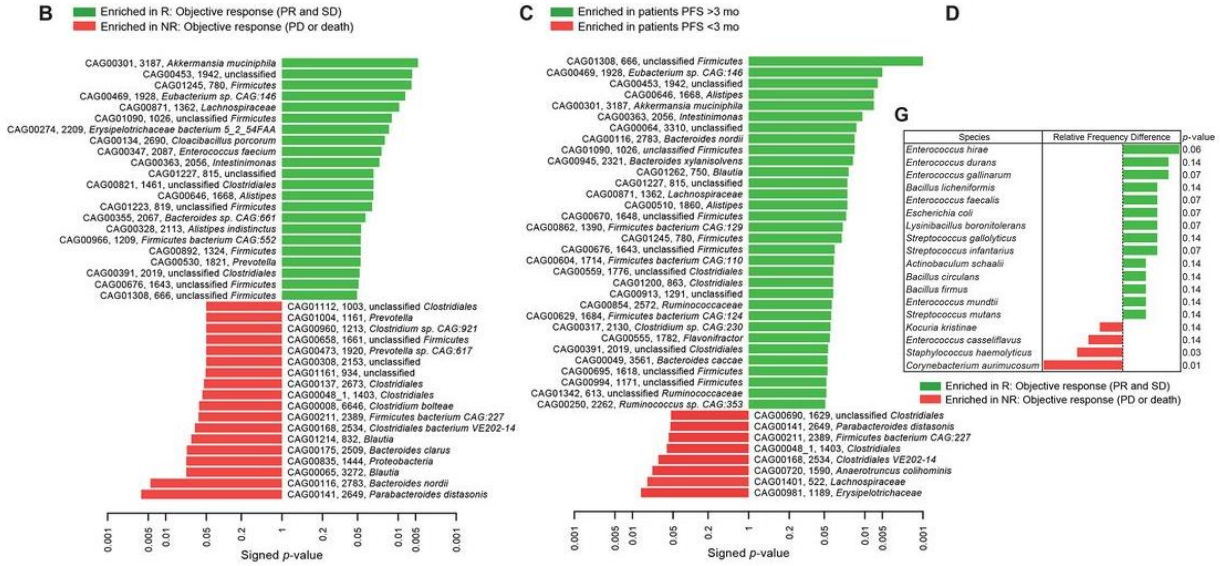
V. Gopalakrishnan et al. Science 2017;science.aan4236

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



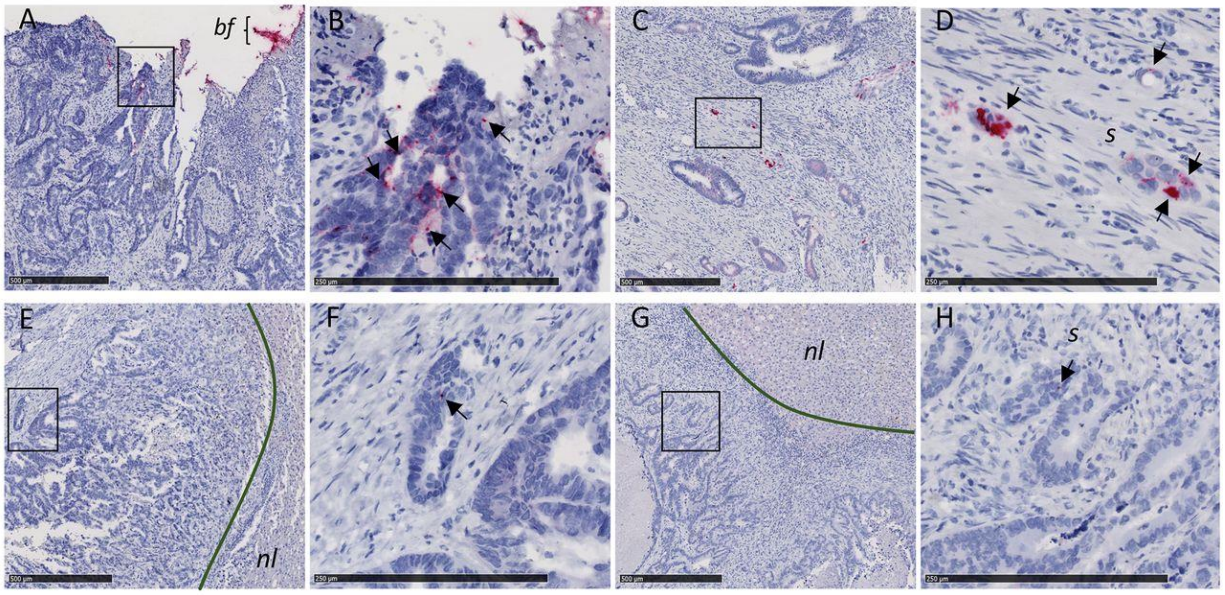
V. Gopalakrishnan et al. Science 2017;science.aan4236

Gut bacteria influence response to anti-PD-1



Bertrand Routy et al. Science 2017;science.aan3706

Fusobacterium nucleatum RNA present in colon primary tumors and metastasis



Susan Bullman et al. Science 2017;science.aal5240

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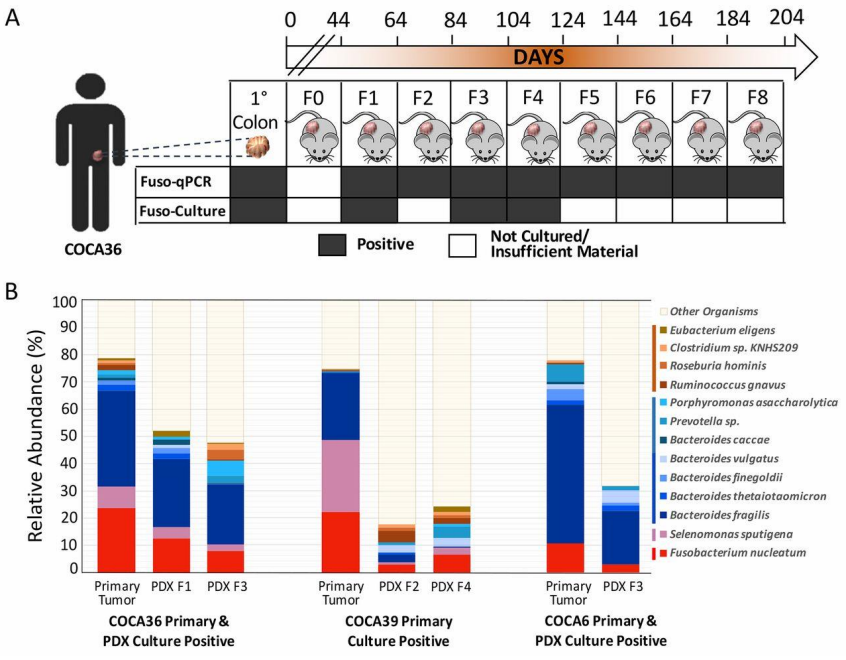
Fusobacterium persist in patient-derived xenografts



Susan Bullman et al. Science 2017;science.aal5240

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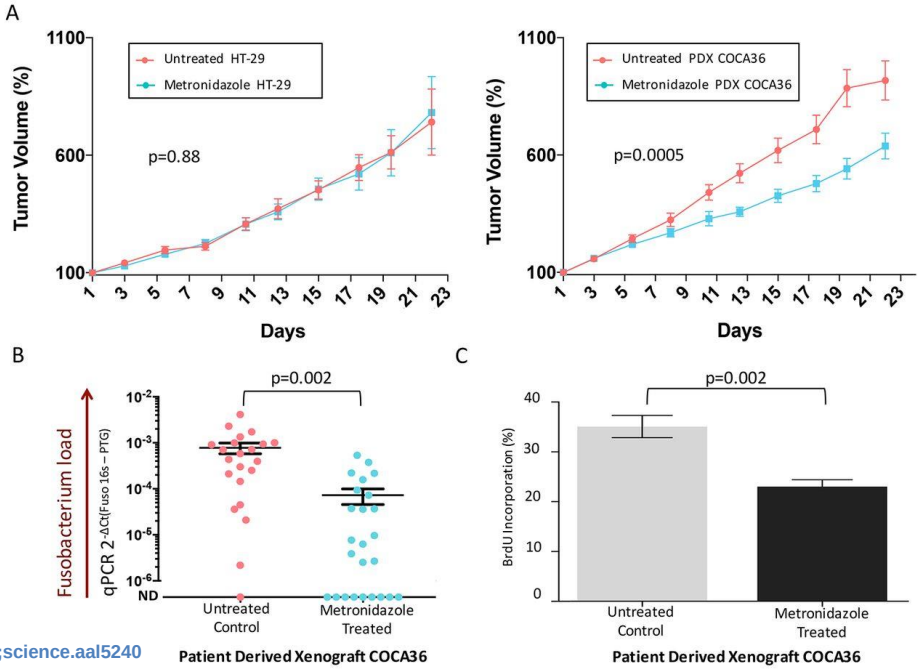
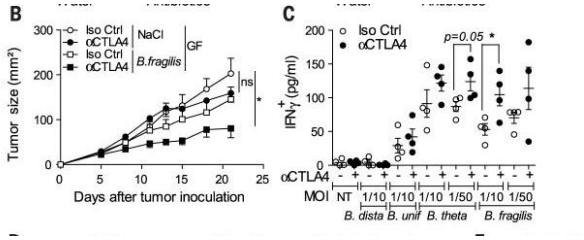
Treatment of Fusobacterium colonized PDX with metronidazole reduces tumor growth in mice

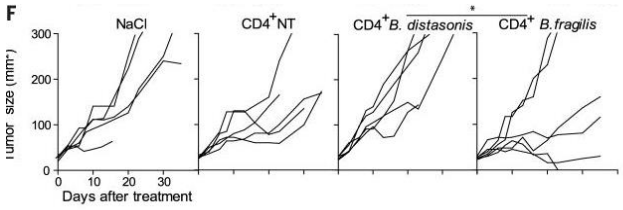


Susan Bullman et al. Science 2017;science.aal5240

What about other immune checkpoints? Anti-CTLA-4



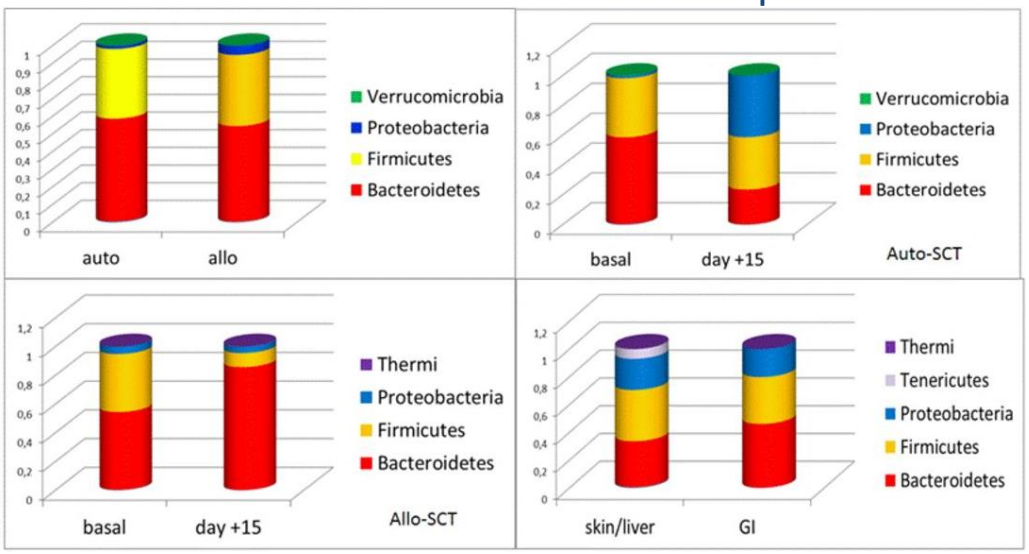
In mice, anti-CTLA-4 seems to work best with Bacteroides fragilis.



T cell (CD4) responses to B. fragilis specifically were associated with reductions in tumor size.

Vétizou et al. Science 2015;350:1079-1084

What about bone marrow transplant?



- After auto-SCT there was an increase of Proteobacteria and a reduction of Bacteroidetes
- After allo-SCT there was an increase of Bacteriodetes and a reduction of Firmicutes
- Patients who developed graft versus host disease (GvHD) harbored more Firmicutes and Proteobacteria and less Bacteroidetes

Chiusolo et al. Blood 2015;126:1953

Potential Mechanisms

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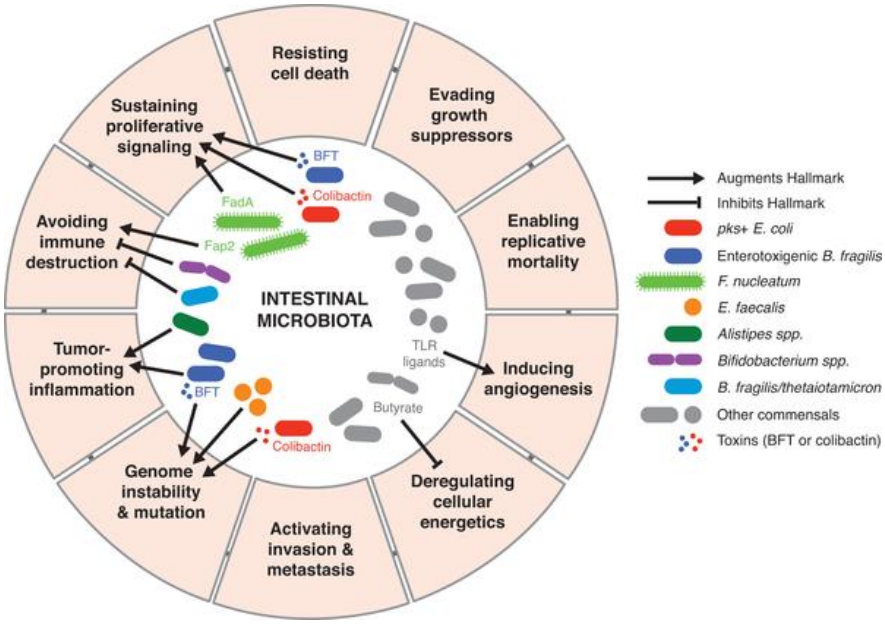
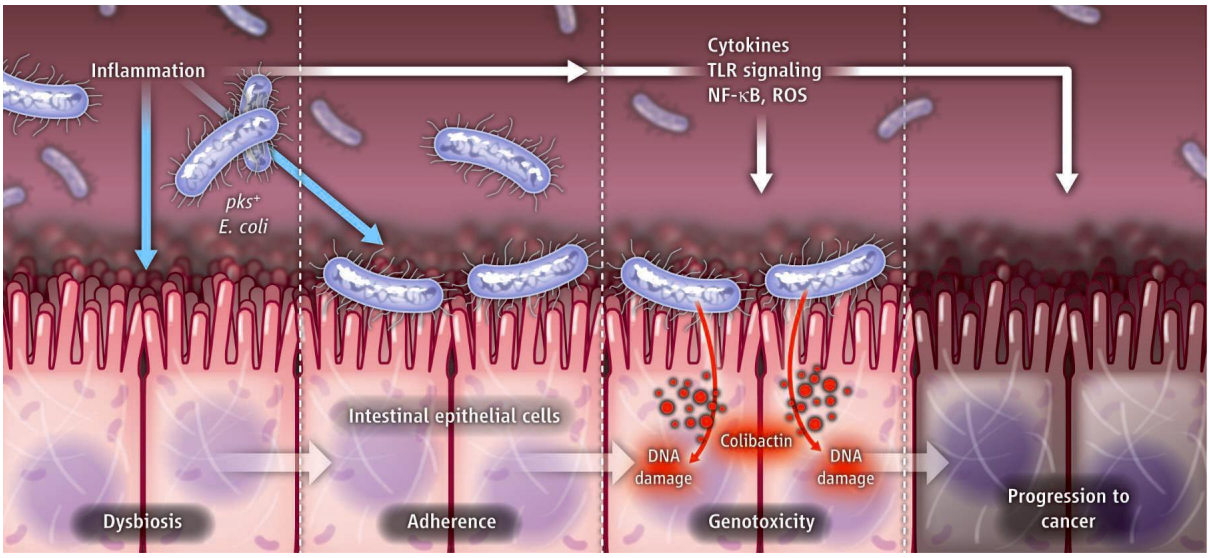
How Different Bacterial–induced Mechanisms can Lead to Cancer



Fulbright LE, Ellermann M, Arthur JC (2017) The microbiome and the hallmarks of cancer. PLOS Pathogens 13(9): e1006480. https://doi.org/10.1371/journal.ppat.1006480
http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006480

Bacteria can stimulate inflammation, and vice versa



Schwabe Science 2012

Specific bacterial mechanisms of oncogenesis

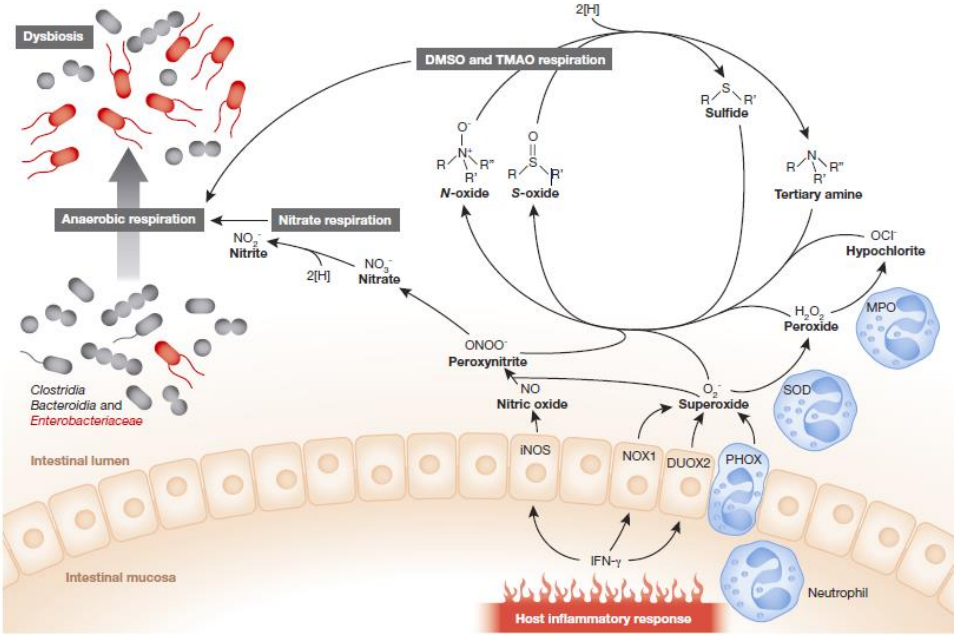
Intestinal bacteria	Bacterial mechanism	Hallmark affected	Mouse models	References
enterotoxigenic *Bacteroides fragilis* (ETBF)	*B. fragilis* toxin (BFT)	sustaining proliferative signaling	WT mice	[3]
		genome instability and mutations	$Apc^{Min/+}$	[21]
	unknown mechanism	tumor-promoting inflammation	$Apc^{Min/+}$	[10]
Fusobacterium nucleatum	FadA adhesin	sustaining proliferative signaling	xenograft model	[4]
	Fap2 adhesin	avoiding immune destruction	$Apc^{Min/+}$	[14] [13]
pks+ Escherichia coli	colibactin	genome instability and mutations	in vitro cellular assays	[19]
			AOM/$Il10^{-/-}$	[20]
		sustaining proliferative signaling	AOM/DSS xenograft model	[5]
Enterococcus faecalis	unknown mechanism	genome instability and mutations	allograft model	[22]
Alistipes spp.	unknown mechanism	tumor-promoting inflammation	$Il10^{-/-}$ $Lcn2^{-/-}$	[12]
Bifidobacterium spp.	unknown mechanism	inhibits avoiding immune destruction	subcutaneous B16.SIY melanoma	[15]
Bacteroides thetaiotamicron and *B. fragilis*	unknown mechanism	inhibits avoiding immune destruction	MCA205 sarcoma, Ret melanoma, and MC38 CRC xenograft	[16]

Abbreviations: AOM, azoxymethane; Apc, adenomatosis polyposis coli; CRC, colorectal cancer; DSS, dextran sodium sulfate; *Il10*, interleukin 10; *Lcn2*, lipocalin2; Min, multiple intestinal neoplasia

https://doi.org/10.1371/journal.ppat.1006480.t001

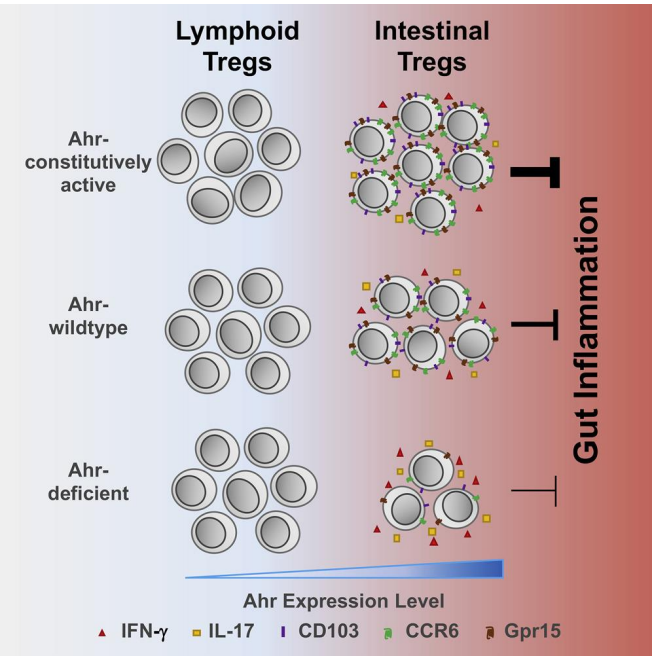
Fulbright LE, Ellermann M, Arthur JC (2017) The microbiome and the hallmarks of cancer. PLOS Pathogens 13(9): e1006480. https://doi.org/10.1371/journal.ppat.1006480
http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006480

Microbiome and Metabolome are Connected



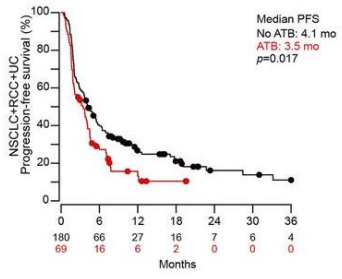
Sebastian E. Winter, Christopher A. Lopez & Andreas J. Bäumler, EMBO reports VOL 14, p. 319-327 (2013)

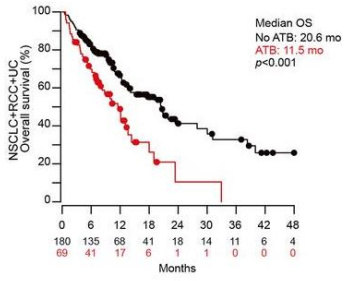
Metabolic receptors (aryl hydrocarbon) promote Tregs

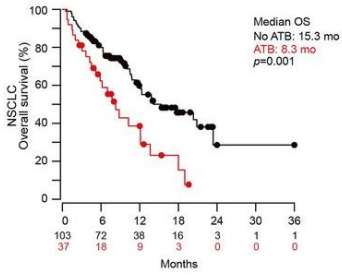


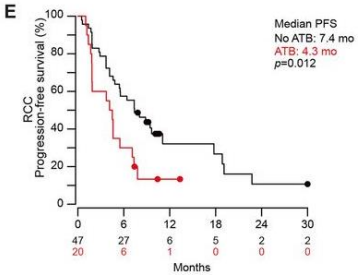
Ye et al. Cell Reports 2017 21, 2277-2290DOI: (10.1016/j.celrep.2017.10.114)

Antibiotics compromise the efficacy of PD-1 blockade in cancer patients?





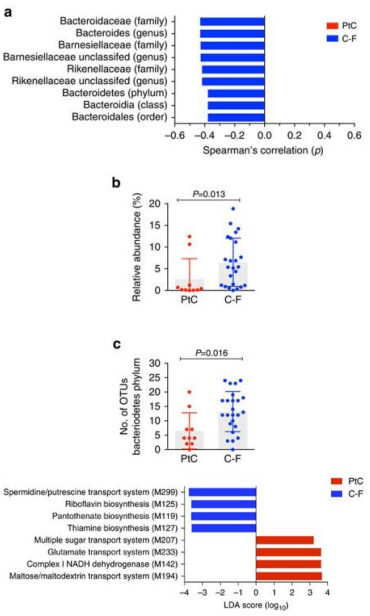




- Antibiotic effect or patient population effect?
- Judicious use of antibiotics is important regardless

Bertrand Routy et al. Science 2017;science.aan3706

Microbiome protection from immune-related colitis



- Patients with melanoma receiving ipilimumab had less immune-related colitis if they had higher bacteroides spp
- Increase in Thiamine and Riboflavin protective from colitis
  - Levels decreased in Crohn's

Dubin et al. Nat Comm 2017

Translational Research Directions

- Stool microbiota are important in oncogenesis
  - Whether direct modulation of bacteria (probiotics/antibiotics) OR
  - Understanding and modifying their downstream immune effects is more important is unknown
- At a population level, most patients with these microbiota signatures do not develop cancer
  - Understanding host factors key
- Bacteria modify tumor-promoting inflammation, and the tumor microenvironment modifies bacteria
  - What is the inciting event?
  - What is the most important to modify?
- Many bacterial species in these studies are on both responder and nonresponder lists – need larger, prospectively defined datasets
  - Increased clarity with shotgun sequencing in prospective cohorts

Clinical Questions

- Should we be giving probiotics to cancer patients receiving immunotherapy?
  - Not yet
    - Bifidobacterium?
    - Non-toxic bacteroides?
- Should we be giving antibiotics to cancer patients receiving immunotherapy?
  - Judiciously
    - For antibiotics resistance and for microbiome interaction with immunotherapy
- Can microbiome influence cancer development
  - Personalized probiotics as prevention
  - May be a key public health intervention going forward

Questions?

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