The New Role of the Microbiome in Lung Cancer Immunotherapy

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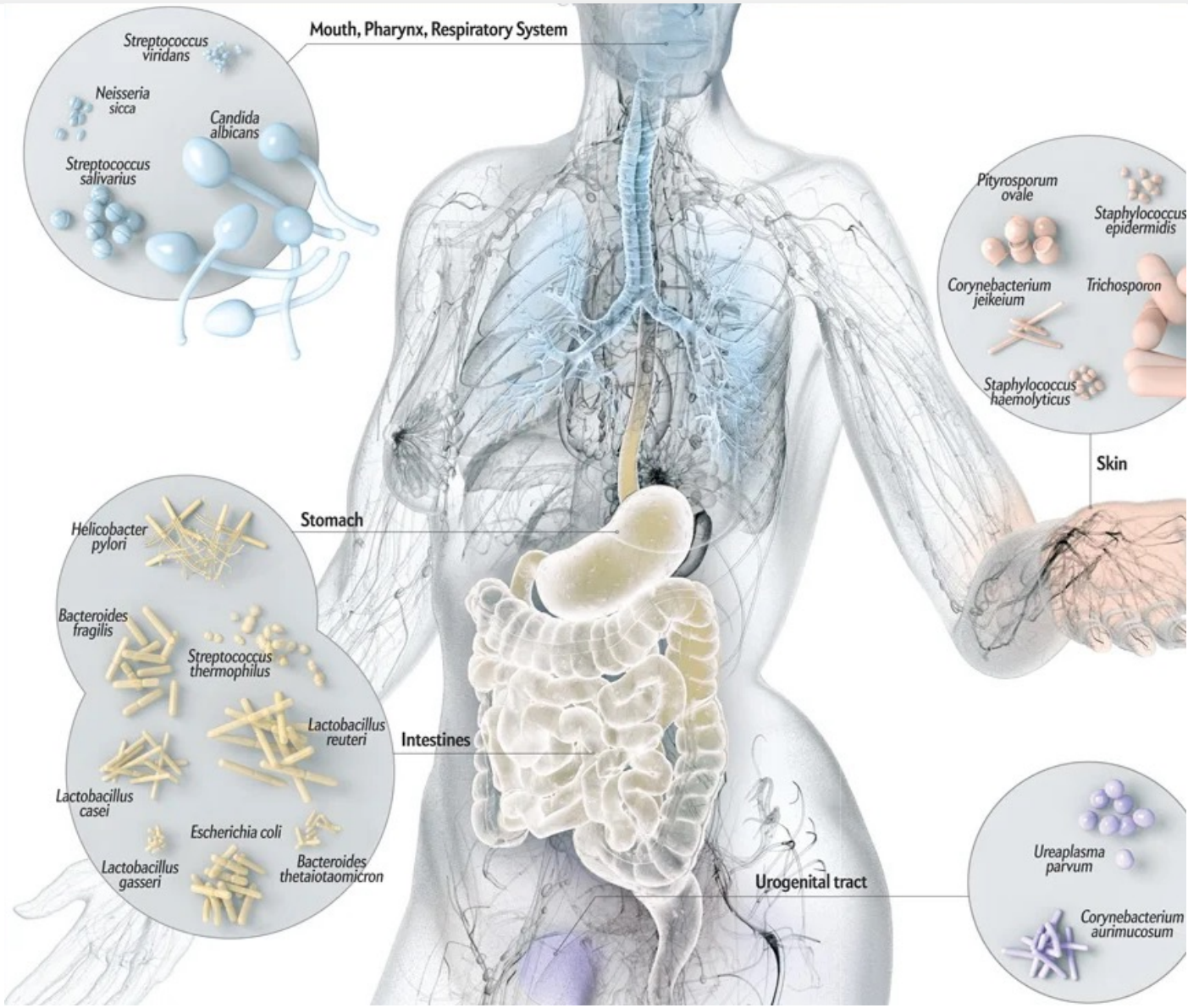
With thanks to Dan Spakowicz in our group who does this work!

The Microbiome

- On you and in you are as many microbe cells as human (~10 trillion of each)
  - 100X more microbe genes
- Associated with health and disease
- Interacts with the immune system
- Can be changed



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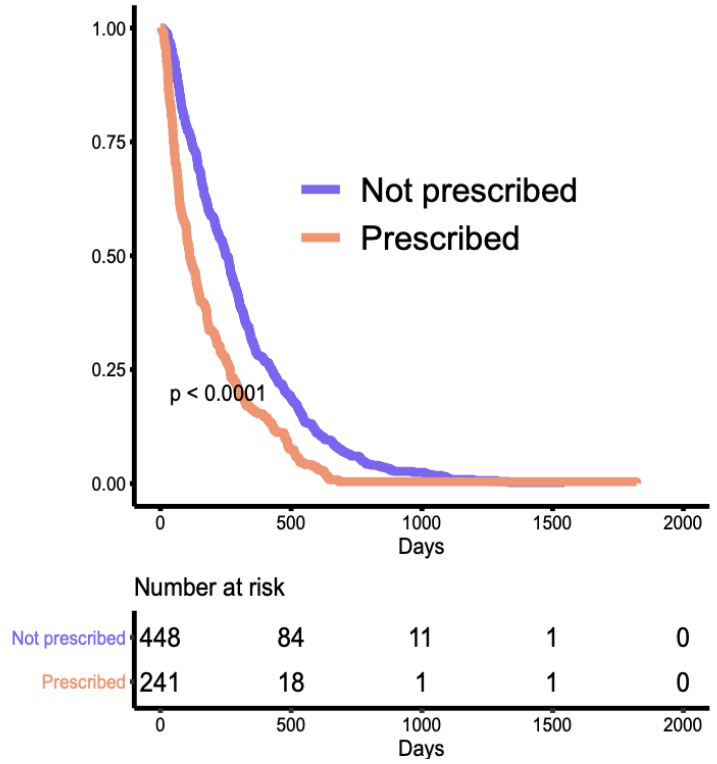
Shorter overall survival in patients who received antibiotics at the time of immunotherapy start

Table 1. Cohort characteristics

Overall n	689
BMI (mean (sd))	27.76 (6.62)
Age (mean (sd))	62.27 (13.21)
Sex = Male (%)	402 (58.3)
ECOG (%)	
····0	185 (31.0)
····1	272 (45.6)
····2	113 (19.0)
···>2	26 (4.4)
CCI = 0-1 (%)	458 (66.7)
Cancer (%)	
··Bladder Cancer	32 (4.9)
··Head and Neck Carcinoma	42 (6.5)
··Melanoma	184 (28.4)
··Non-Small Cell Lung Cancer	152 (23.5)
··Renal Cell Carcinoma	65 (10.0)
··Sarcoma	21 (3.2)
··Other	152 (23.5)
Staging (%)	
····1	1 (0.2)
····2	4 (0.7)
····3	44 (7.2)
····4	547 (90.0)
····Unknown	12 (2.0)

Effect of ABx within 28 days of start of IO



Spakowicz and Hoyd *et al.* BMC Cancer (2020)

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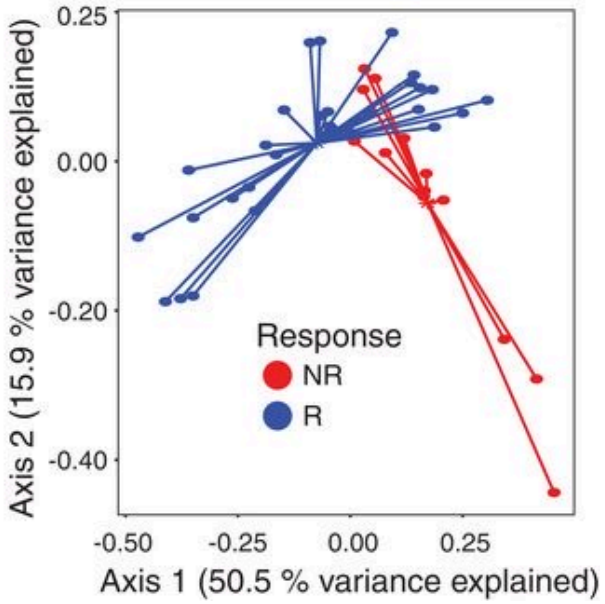
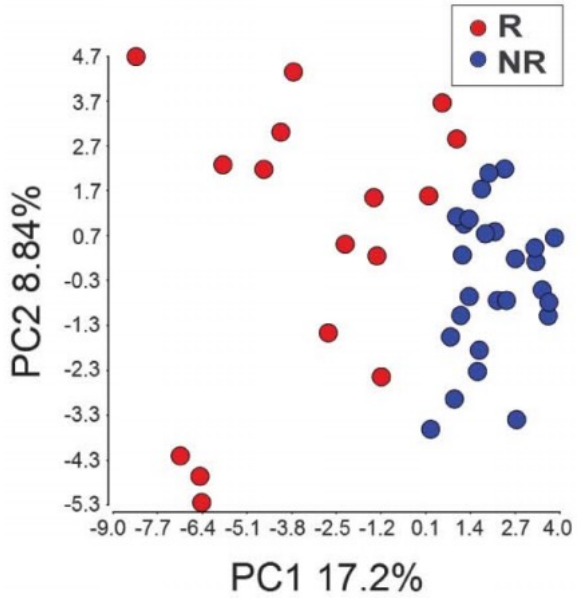
Microbiome as a Biomarker

- Response to immune checkpoint inhibitors predictable from pre-treatment stool



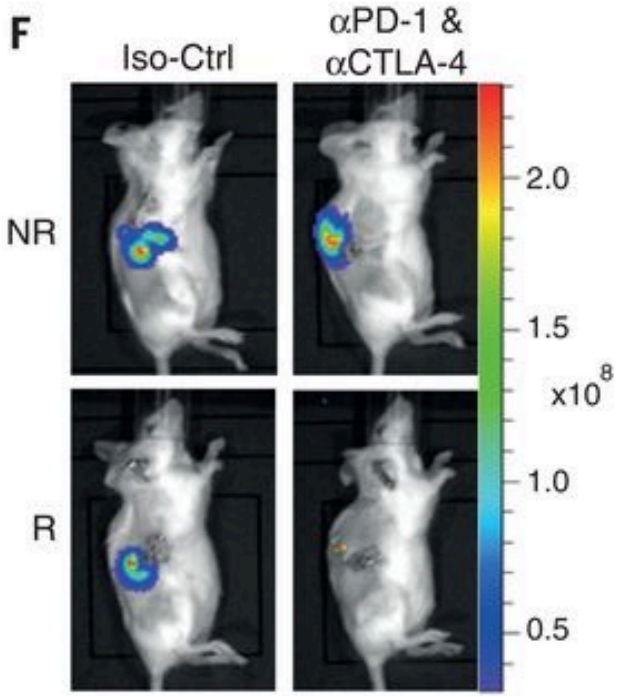
Gopalakrishnan et al Science 2018



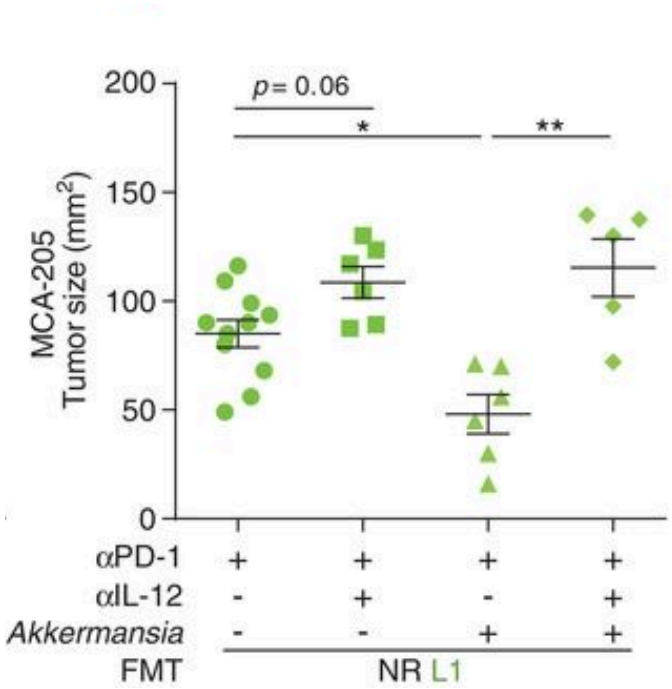
Matson et al Science 2018

Akkermansia modifies IO response

Response to immune checkpoint inhibitors is transferred to mice via patients' pre-treatment stool



A. muciniphila alters response to immune checkpoint inhibitors in an IL-12 dependent manner



Routy *et al. Science* (2018)

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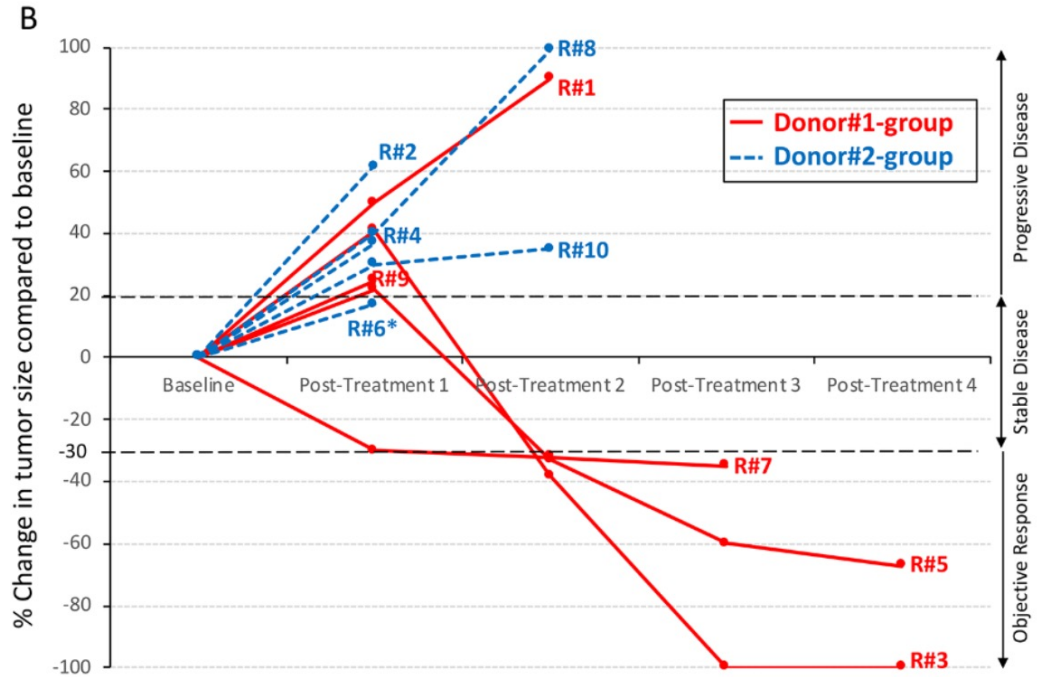
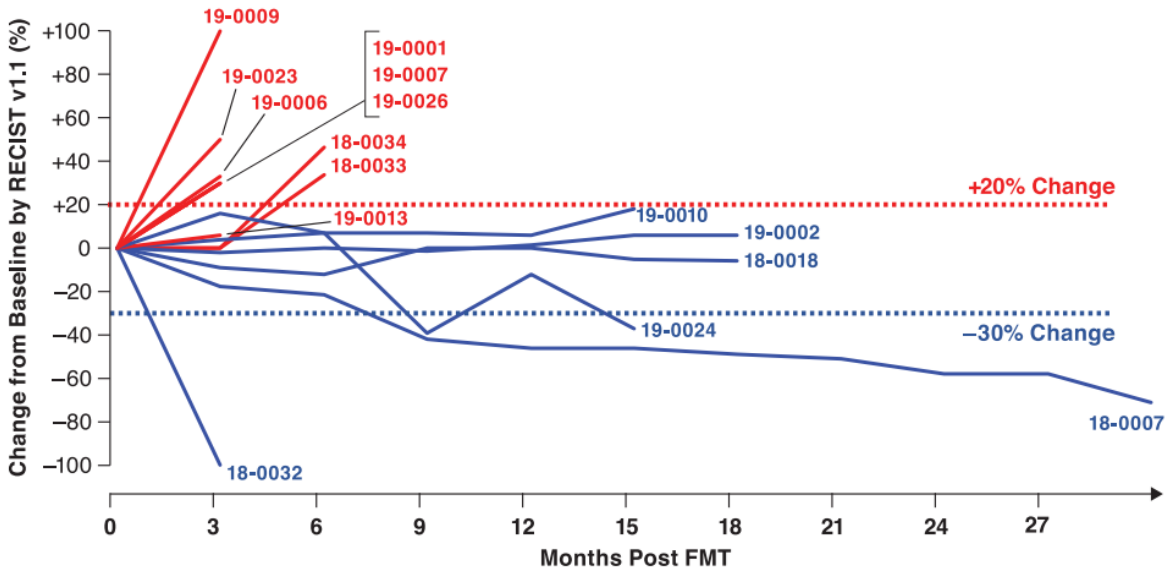
Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients

Treated with ICI -> Progression -> FMT -> Treated with ICI



[Baruch et al (’20) Science]



[Davar et al (’21) Science]

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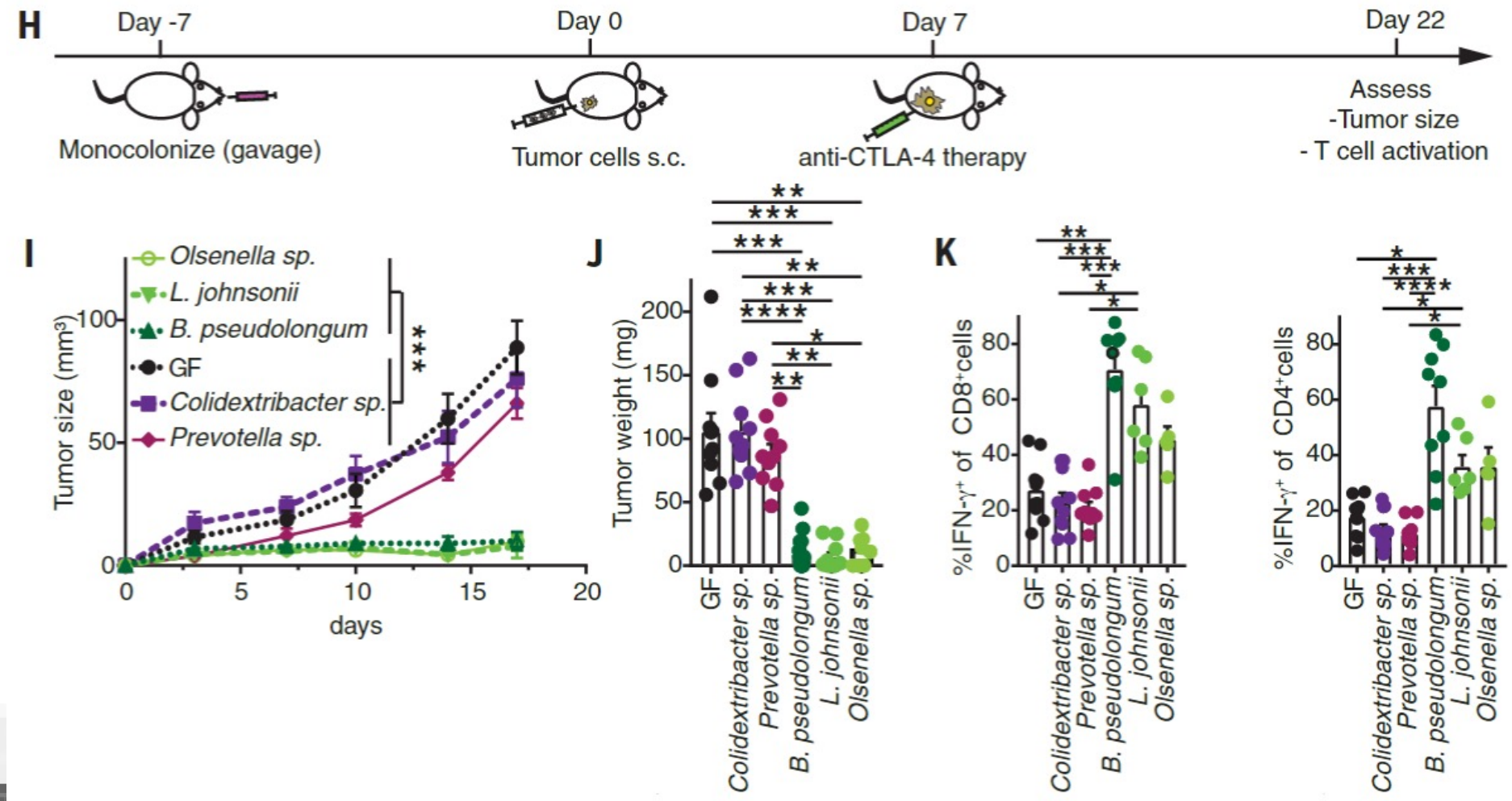
Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy

Mager et al, Science, 2020



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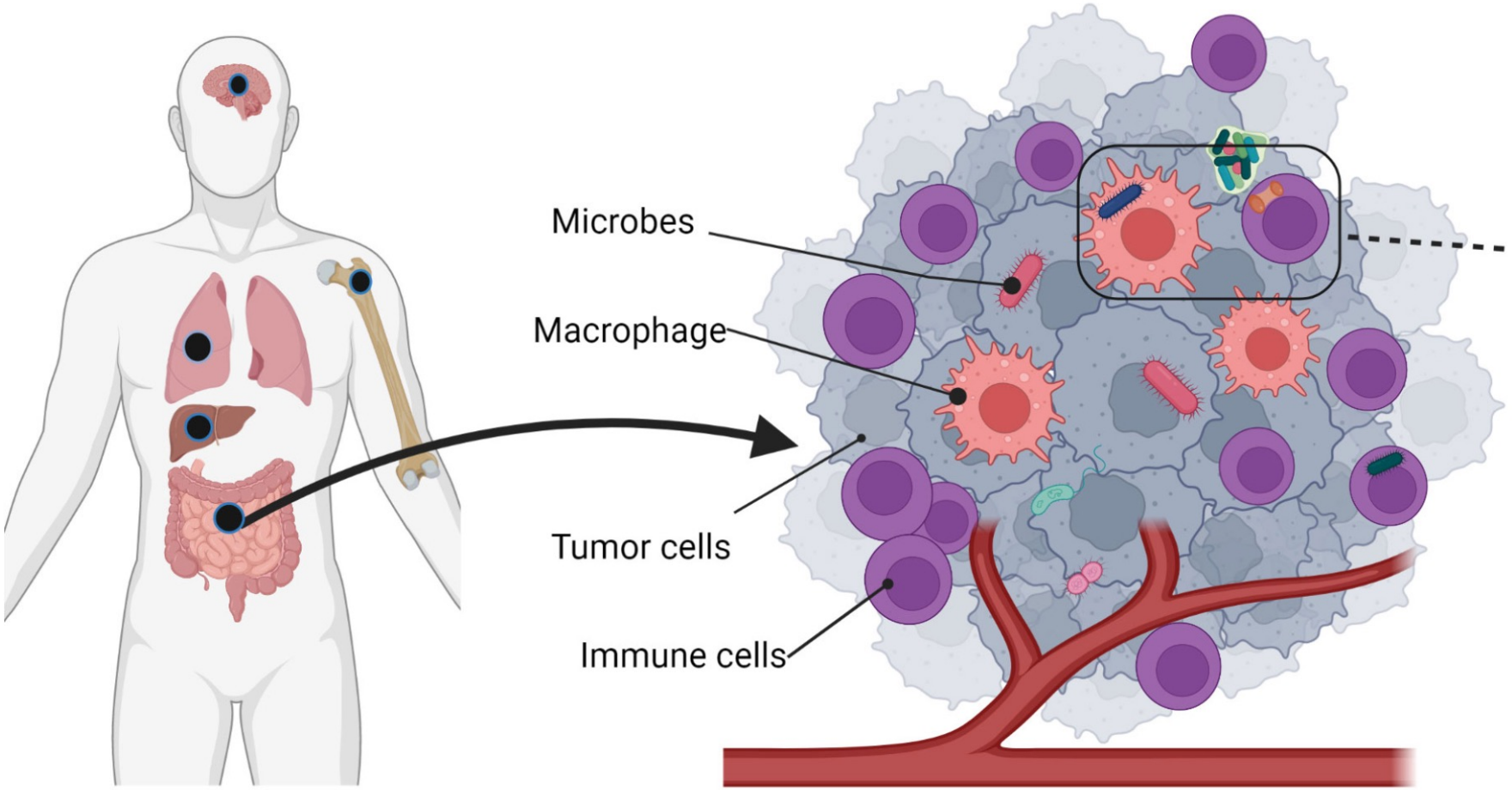
The tumor microbiome

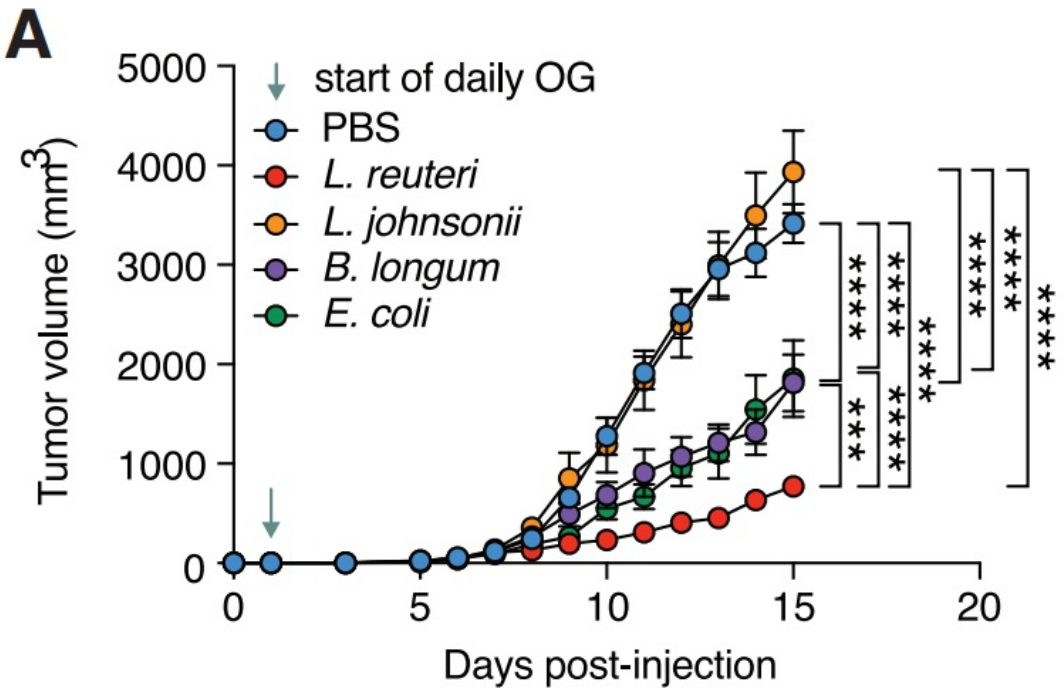


Cross-talk between tumors, microbes, and immune cells

Zhou et al *Frontiers Onc* (2022)

Dietary tryptophan metabolite released by intratumoral Lactobacillus reuteri facilitates immune checkpoint inhibitor treatment

- Some immune-modulating effects may derive from the tumor microbiome
  - Bender et al Cell 2023



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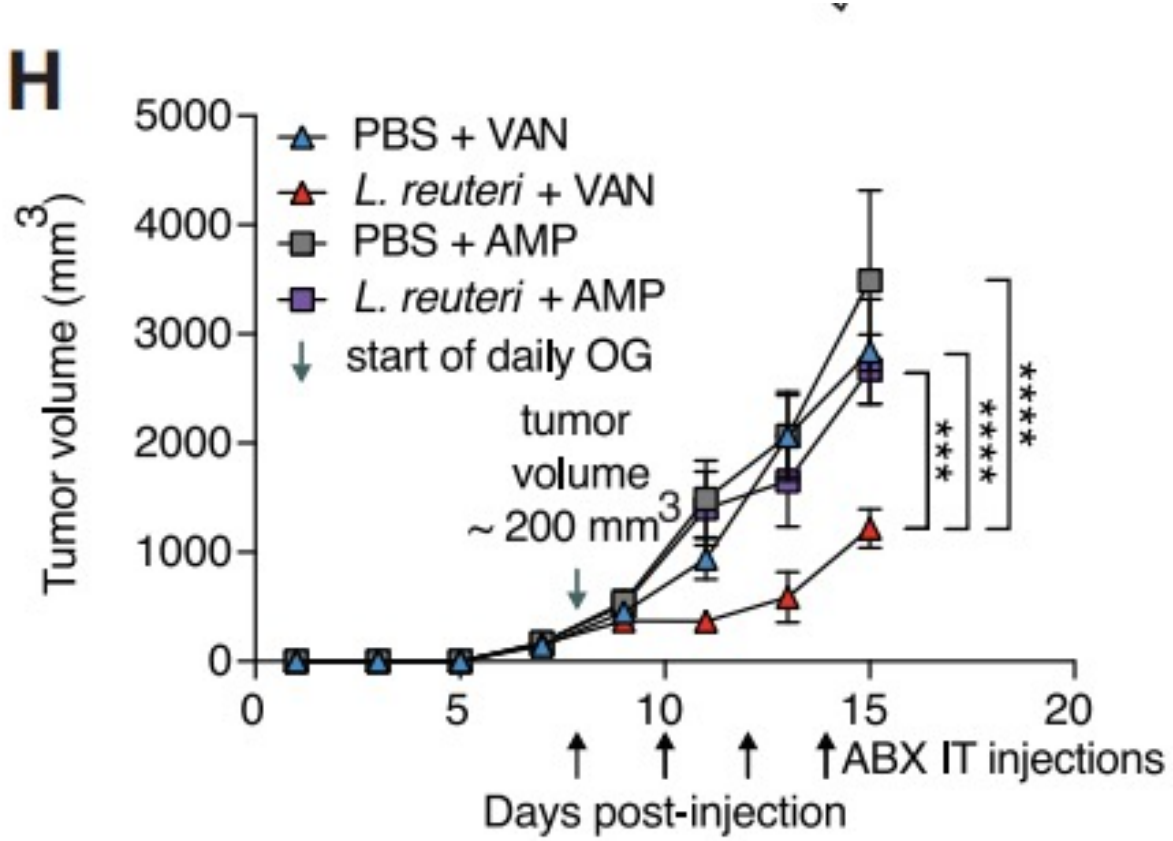
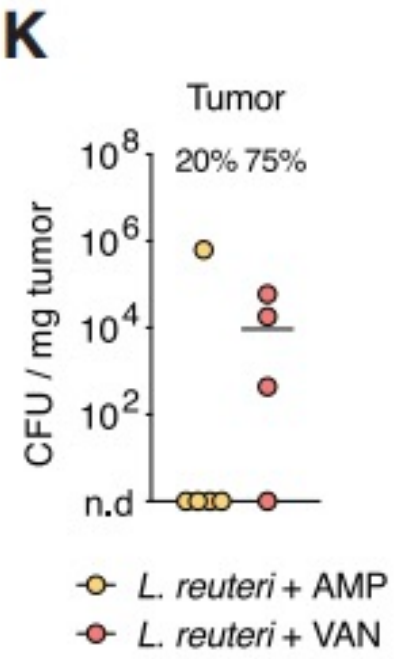
Depleting Lr in the tumor, but not the gut, affects tumor volume





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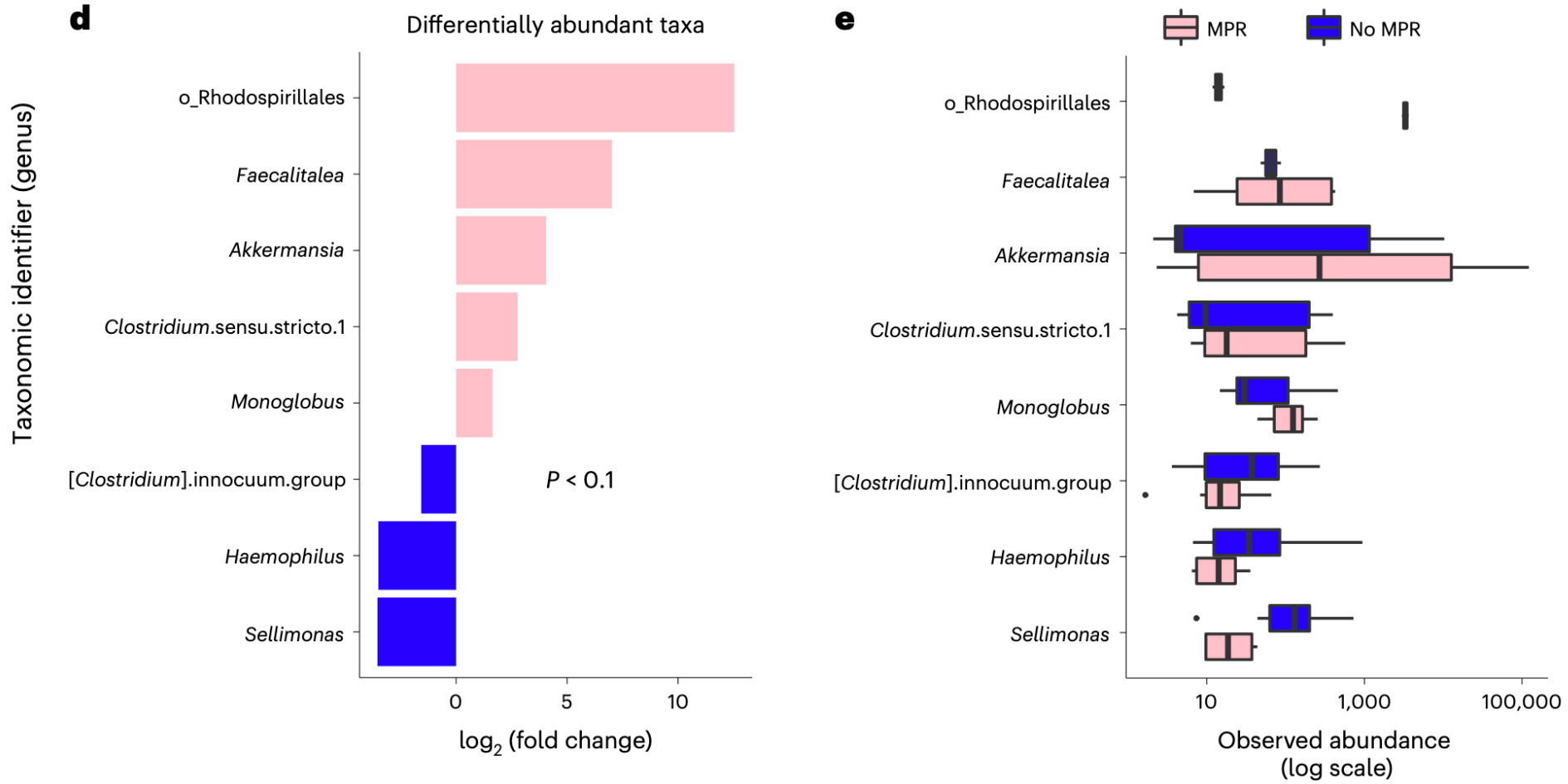
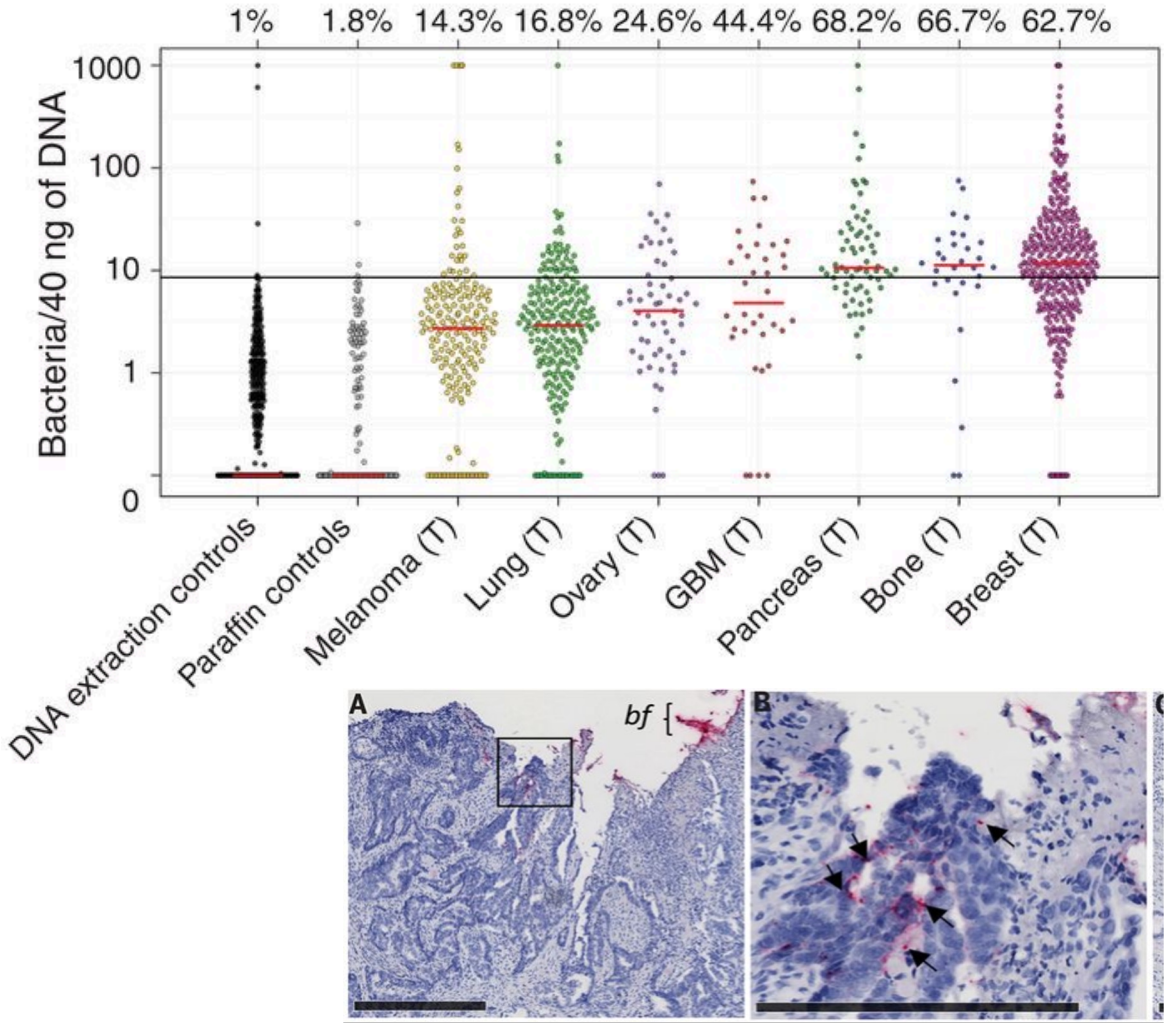
Fecal microbiome and pathR in NEOSTAR



Cascone et al, NM 2023

Intra-tumor microbes affect cancer

- *Fusobacterium nucleaum* found in tumors, liver metastases & persist in pdx models CRC (Bullman et al Science 2017)
- *Gammaproteobacteria* degrade gemcitabine (Geller et al Science 2018)
- *Malassezia* drives PDA tumor growth (Aykut et al Nature 2019)



Nejman et al *Science* (2020)

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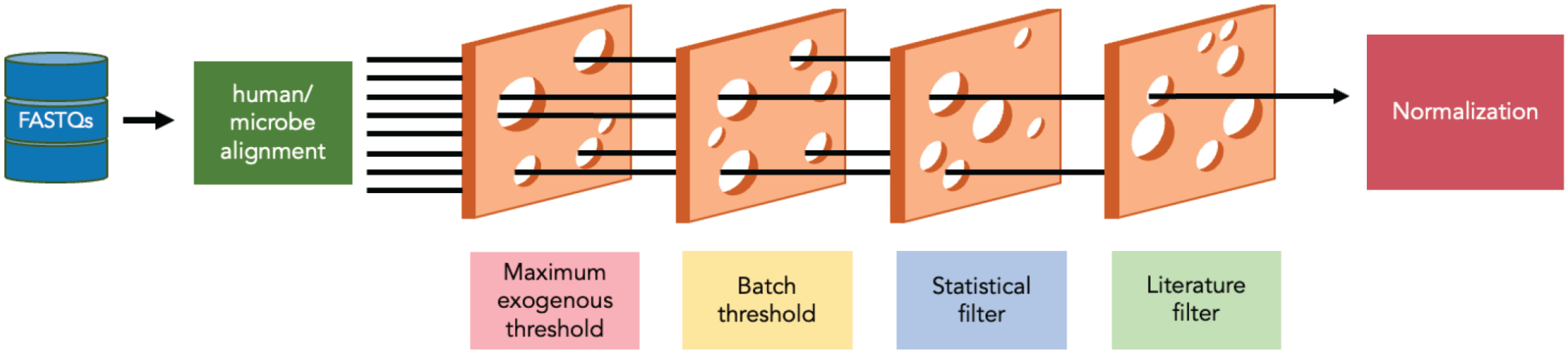
Exploring the microbiome in tumor RNAseq data



- {exotic} (exogenous sequences in tumors and immune cells) Hoyd *et al. CRC* (2023)
- A high false positive rate requires stringent, conservative filters
- Sparse, heterogeneous microbe abundances require many samples to observe a signal
- Validation is critical

Next Step: Apply to larger dataset

- Oncology Research Information Exchange Network (ORIEN) inter-member project
  - ORIEN = 19 cancer centers that share a protocol for the collection, processing, and sharing of biospecimens and clinical data
    - Tumor goes to Aster Insights for sequencing
    - Researchers have access to RNAseq & WES through HBOC
    - Large clinical dataset, harmonized across institutions
- Goals:
  - Test a hypothesis about the determinants of the tumor microbiome
    - *Hypothesis: microbes' presence in tumors is a function of the **(1) tumor microenvironment** and **(2) immune system activity** more so than the tumor primary site/histology*
  - Provide a resource to the community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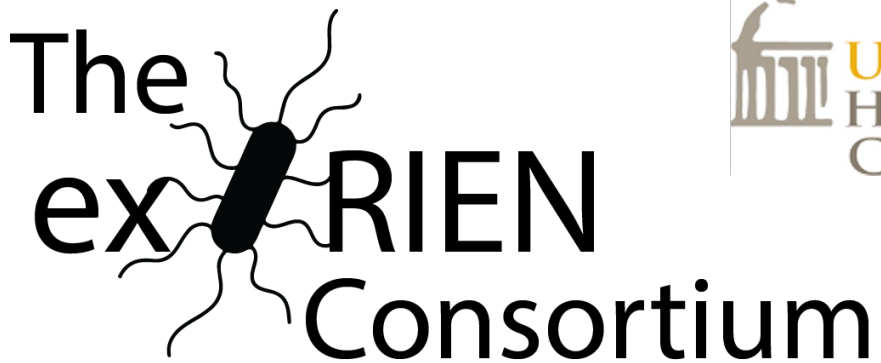
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ORIEN

Processed ORIEN and TCGA datatsets

ORIEN

N = 2892

Cancer (Primary Location)	
COAD	500 (17.3)
Cecum	38 (7.6)
Colon	428 (85.6)
Rectum	34 (6.8)
LUAD	261 (9.0)
Lung	260 (99.6)
Other	1 (0.38)
LUSC	127 (4.4)
Lung	126 (99.2)
Other	1 (0.79)
PAAD	156 (5.4)
Pancreas	156 (100)
READ	95 (3.3)
Rectum	95 (100)
SARC	691 (23.9)
Abdomen	17 (2.46)
Bone	45 (6.51)
Colon	4 (0.58)
Intestine	25 (3.62)
Lung	7 (1.01)
Pancreas	2 (0.29)
Rectum	2 (0.29)
Retroperitoneum	95 (13.7)
Skin	2 (0.29)
Soft Tissue	316 (45.7)
Stomach	56 (8.10)
Uterus	28 (4.05)
Other	92 (13.3)
SCLC	26 (0.9)
Lung	25 (96.2)
Other	1 (3.84)

Cancer (Primary Location) cont.	
SKCM	138 (4.8)
Rectum	1 (0.72)
Skin	121 (87.7)
Soft Tissue	1 (0.72)
Other	15 (10.9)
THCA	539 (18.6)
Thyroid	539 (100)
Other CR	39 (1.3)
Cecum	8 (20.5)
Colon	27 (69.2)
Rectum	4 (10.3)
Other Lung	104 (3.6)
Lung	103 (99.0)
Other	1 (0.96)
Other Pancreatic	216 (7.5)
Pancreas	216 (100)

Sex (%)	
Male	1418 (49.0)
Female	1474 (51.0)

Age (%)	
10-19	15 (0.5)
20-29	120 (4.1)
30-39	207 (7.2)
40-49	397 (13.7)
50-59	691 (23.9)
60-69	794 (27.5)
70-79	530 (18.3)
80-89	128 (4.4)
90+	10 (0.3)

TCGA

N = 2720

Cancer (Primary Location)	
COAD	478 (17.6)
Cecum	87 (18.2)
Colon	382 (79.9)
Rectum	7 (1.5)
Other	2 (0.4)
LUAD	533 (19.6)
Lung	531 (99.6)
Other	2 (0.4)
LUSC	502 (18.5)
Lung	495 (98.6)
Other	7 (1.4)
PAAD	177 (6.5)
Pancreas	177 (100)
READ	166 (6.1)
Colon	6 (3.6)
Rectum	156 (94.0)
Other	2 (1.2)

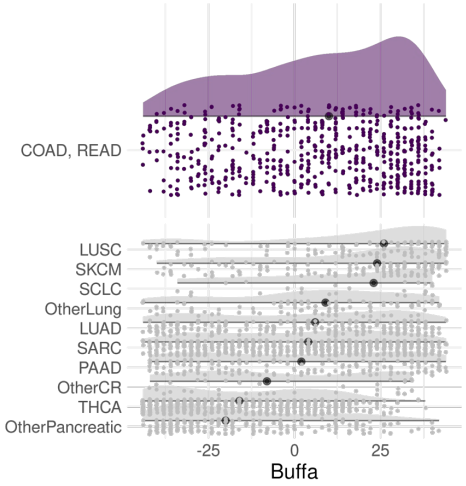
Sex (%)	
Male	1371 (50.5)
Female	1349 (49.5)

Cancer (Primary Location) cont.	
SARC	259 (9.5)
Bone	2 (0.8)
Colon	1 (0.4)
Retroperitoneum	98 (37.8)
Soft Tissue	117 (45.2)
Stomach	2 (0.8)
Uterus	29 (11.2)
Other	10 (3.9)
SKCM	
Skin	103 (100)
THCA	502 (18.5)
Thyroid	502 (100)

Age (%)	
10-19	12 (0.4)
20-29	62 (2.3)
30-39	157 (5.9)
40-49	262 (9.8)
50-59	510 (19.1)
60-69	762 (28.5
70-79	695 (26.0)
80-89	210 (7.9)

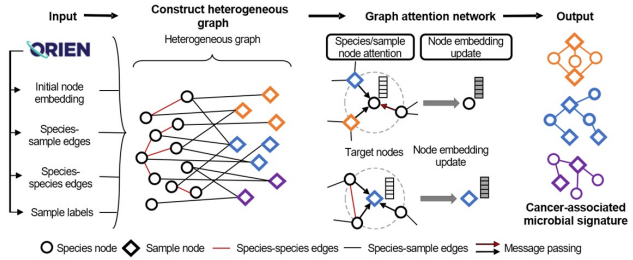
Nic Denko (OSU)

- Hypoxia and response to radiation in rectal cancer



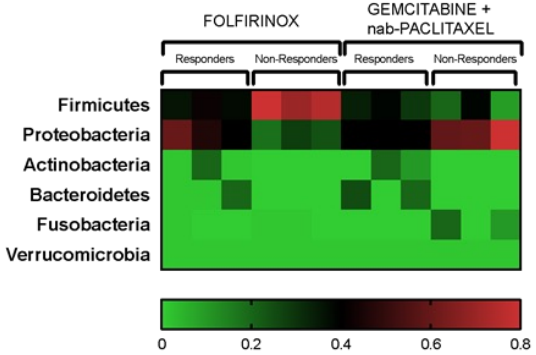
Qin Ma (OSU)

- pyMEGA: a deep learning package for identifying cancer-associated tissue-resident microbes



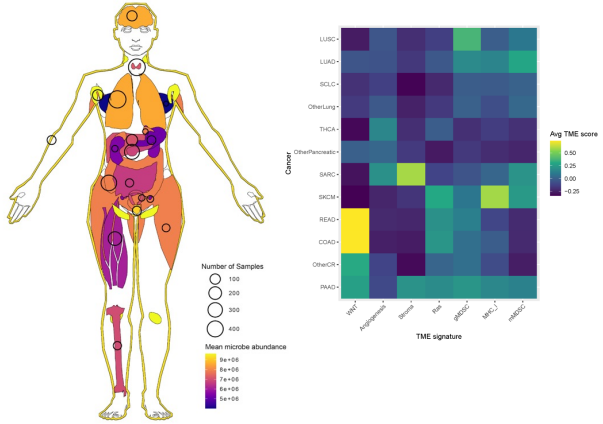
Carlos Chan (Ulowa)

- Chemotherapy outcomes in pancreatic cancer

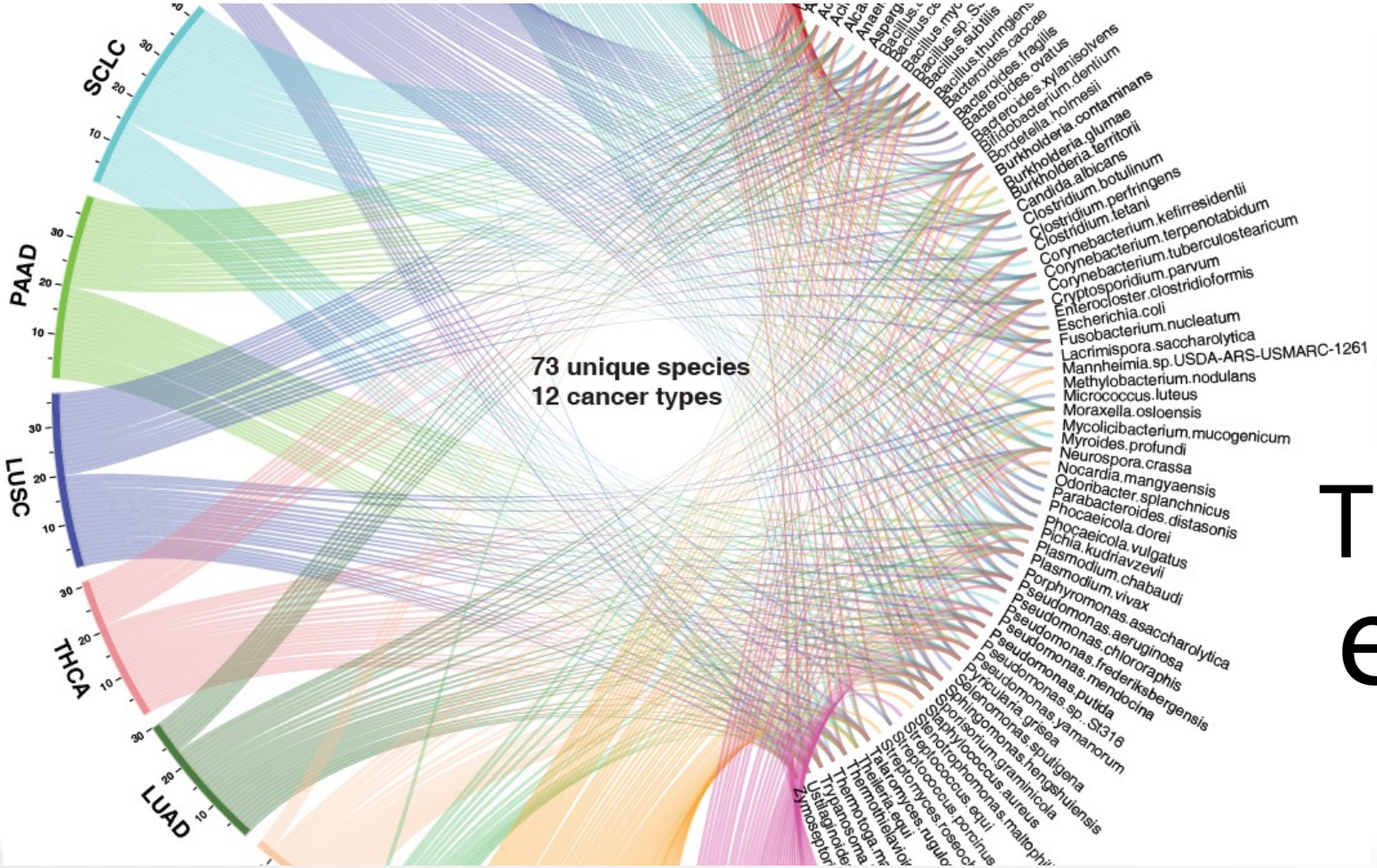


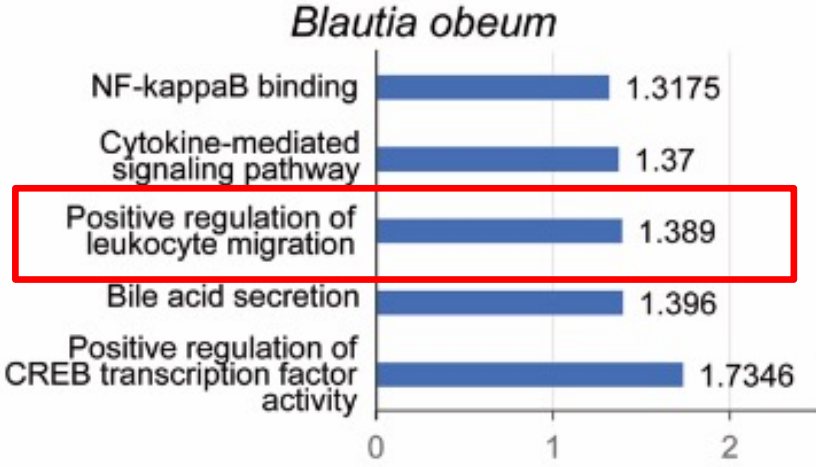
Dan Spakowicz (OSU)

- Association with features of the tumor microenvironment



Deep learning models predict strong interactions with host expression





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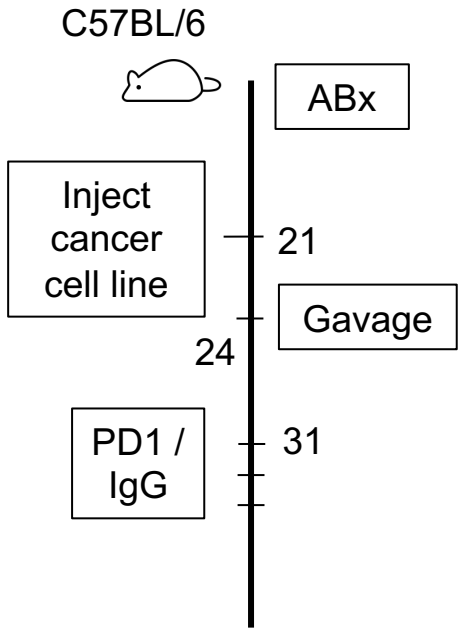
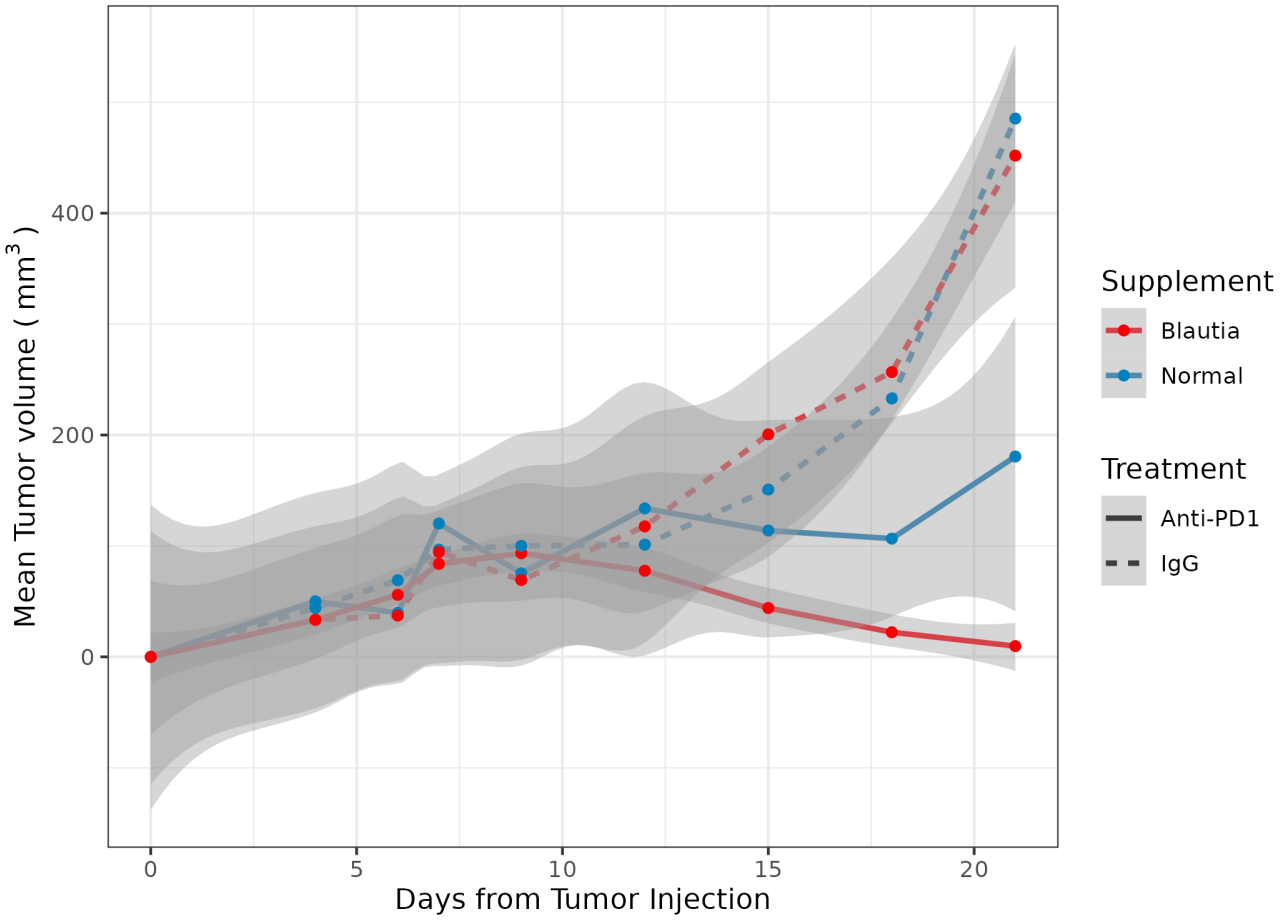
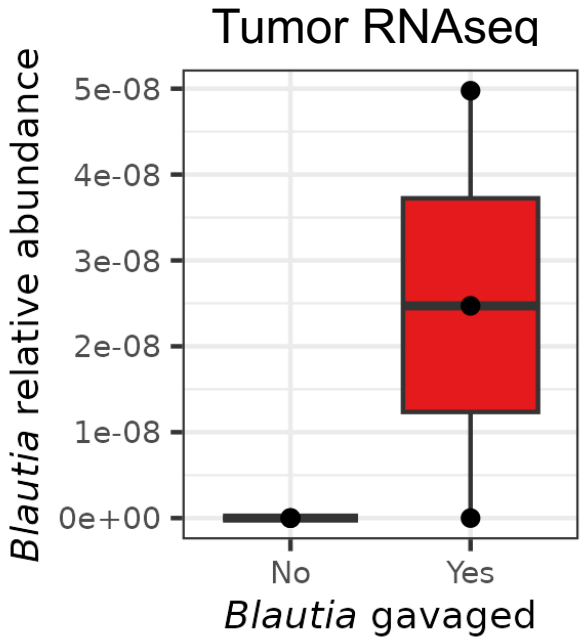
Blautia supplementation increases lymphocyte migration into tumors: immunotherapy response assay







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Starting December 5: Microbiome RIG

- New structure for microbiome research within ORIEN
- Rolling projects/submissions
- Monthly meetings
- Larger dataset (~20k)
- All tumor types
- Uses exotic 2.0

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ORIEN MICROBIOME RESEARCH INTEREST GROUP CHARTER

BACKGROUND

Aligning with the ORIEN Mission of accelerating cancer discovery and delivering hope through collaborative learning and partnerships, the purpose of a Research Interest Group (RIG) is to encourage research opportunities between ORIEN member institutions/faculty as well as with industry partners. RIGs also provide a forum for experts to exchange ideas, identify areas for collaboration, and provide input on ORIEN research initiatives. RIGs will also serve in advisory roles to Aster Insights in developing industry-sponsored research collaborations, including but not limited to disease/tissue-specific data and scientific matters related to the ORIEN TCC and Avatar Programs.

MISSION STATEMENTS

The Microbiome Research Interest Group will be established with the following goals:

- To bring together ORIEN clinicians and scientists who are dedicated to advancing the understanding of microbes' role in cancer
- To foster collaborations that seek to use the microbiome to address challenges and unmet needs in cancer research by leveraging ORIEN data, resources, and expertise
- To provide a resource to the community by developing and maintaining high-quality processes for the identification and quantification of non-human sequences in the ORIEN data corpus

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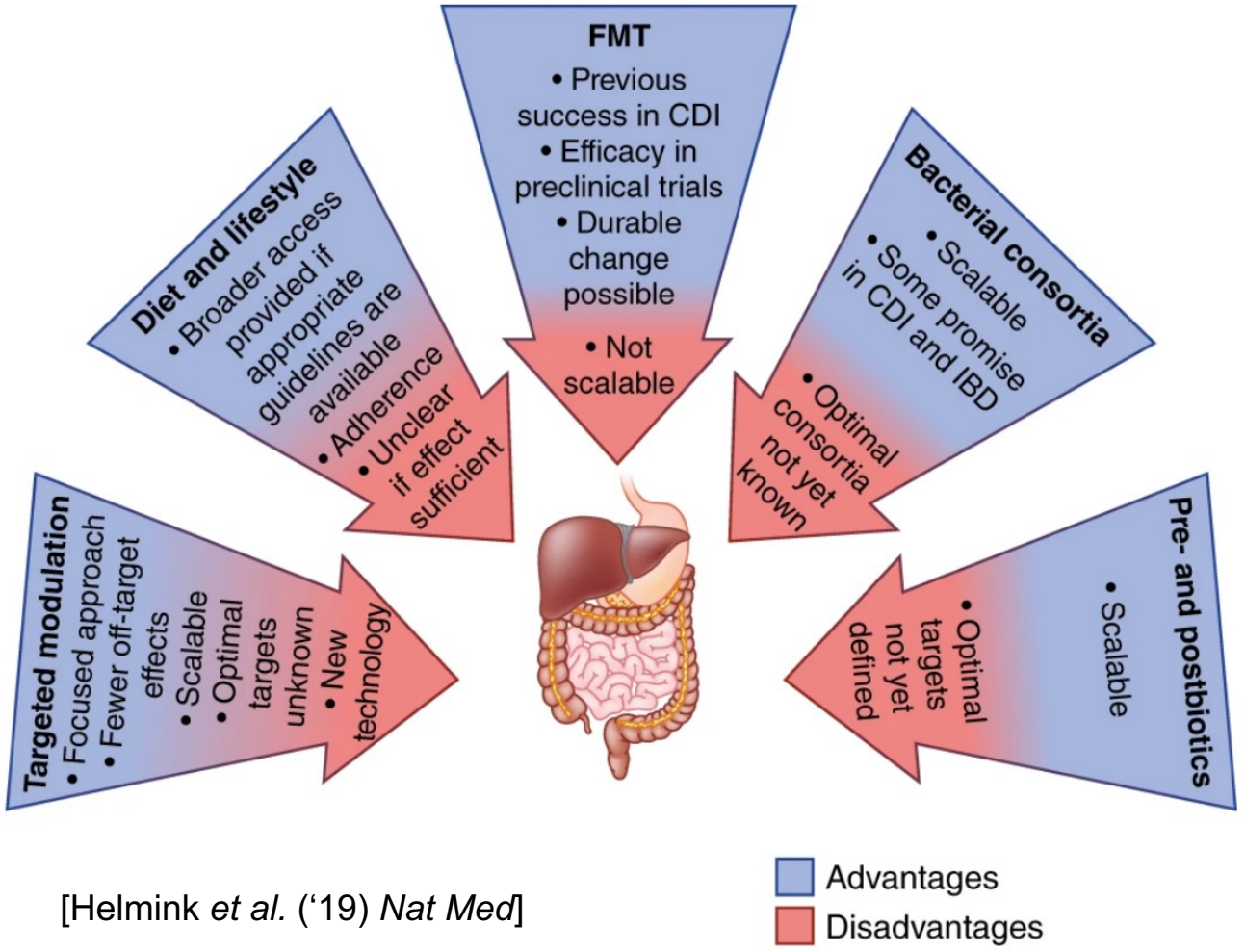
Microbiome may predict outcomes and microbiome modulation may improve cancer immunotherapy outcomes



[Helmink *et al.* (‘19) *Nat Med*]

- Additional benefits of diet and lifestyle-based modification
  - Likely to be a part of any microbiome modification strategy (*e.g.*, maintenance of probiotics)
  - Treatment durability, prevention
  - Patient-controlled

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