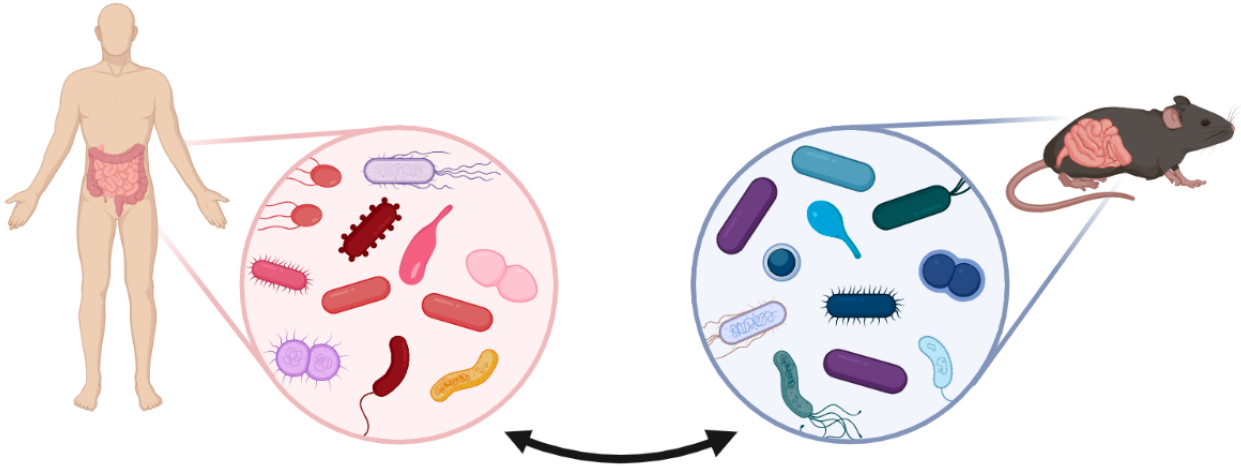
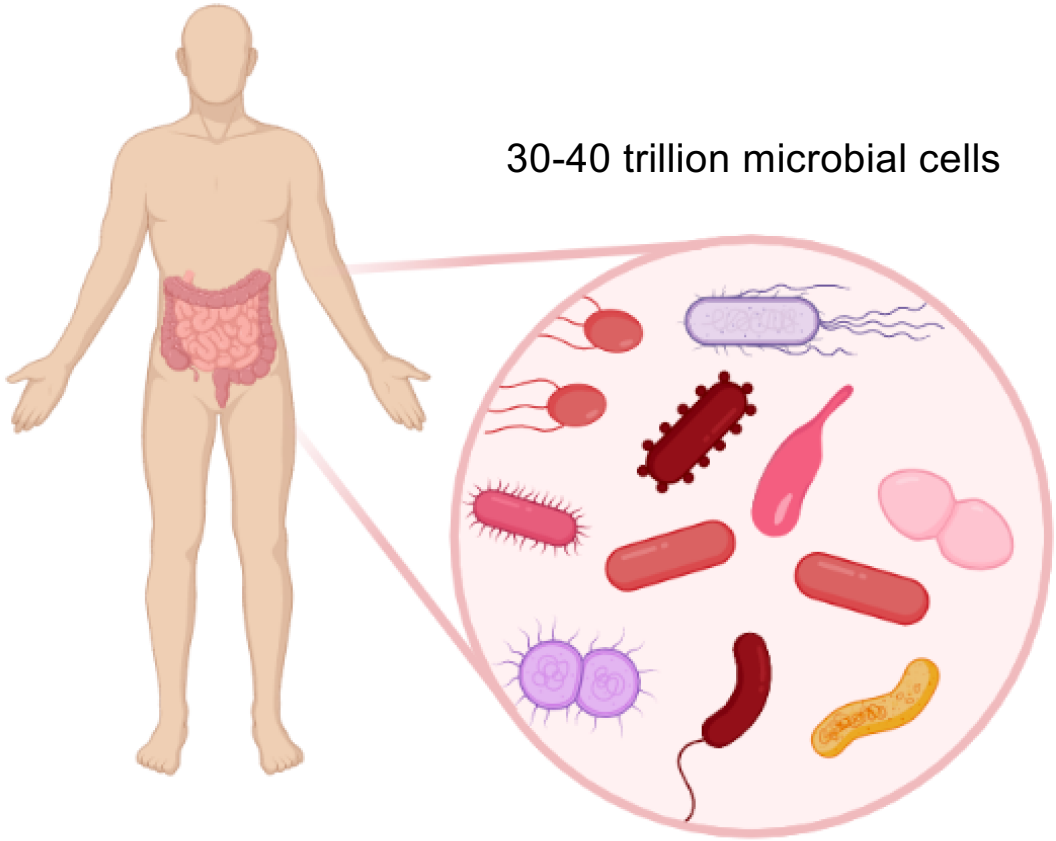
Intestinal microbiota in immune responses and pathogen resistance



Virginia Pedicord, Ph.D.
vap33@cam.ac.uk

UNIVERSITY OF CAMBRIDGE

The microbiota is a highly dynamic organ



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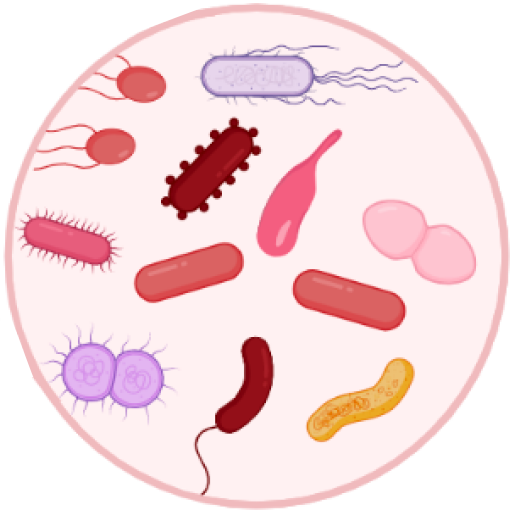
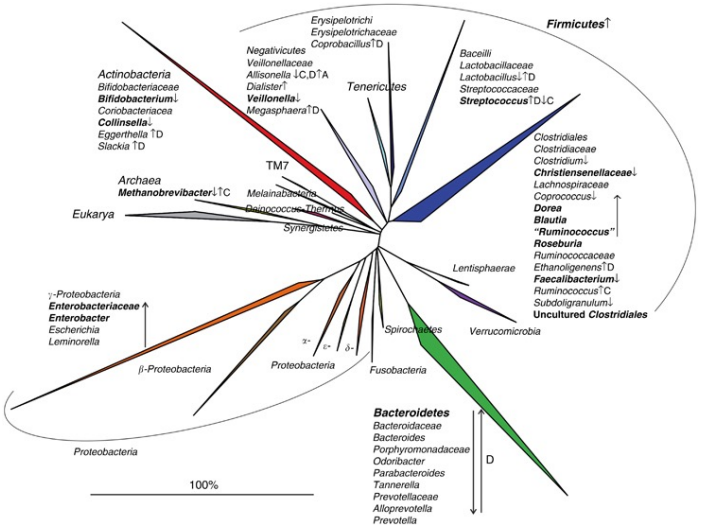
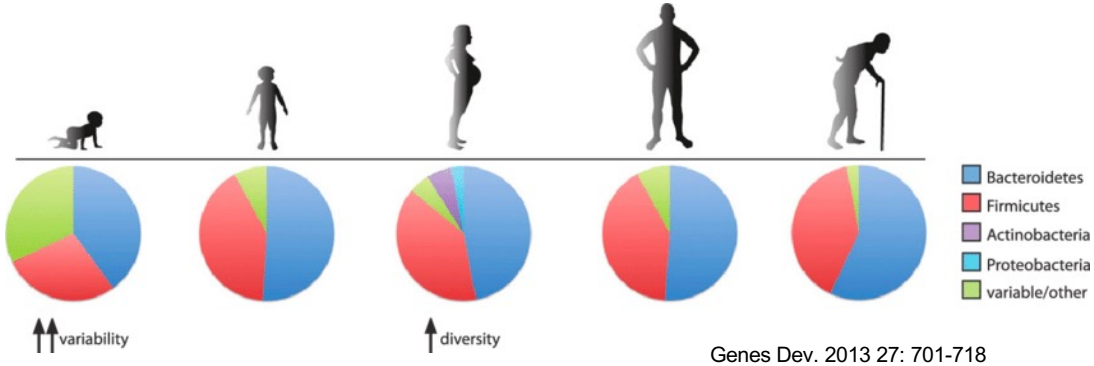


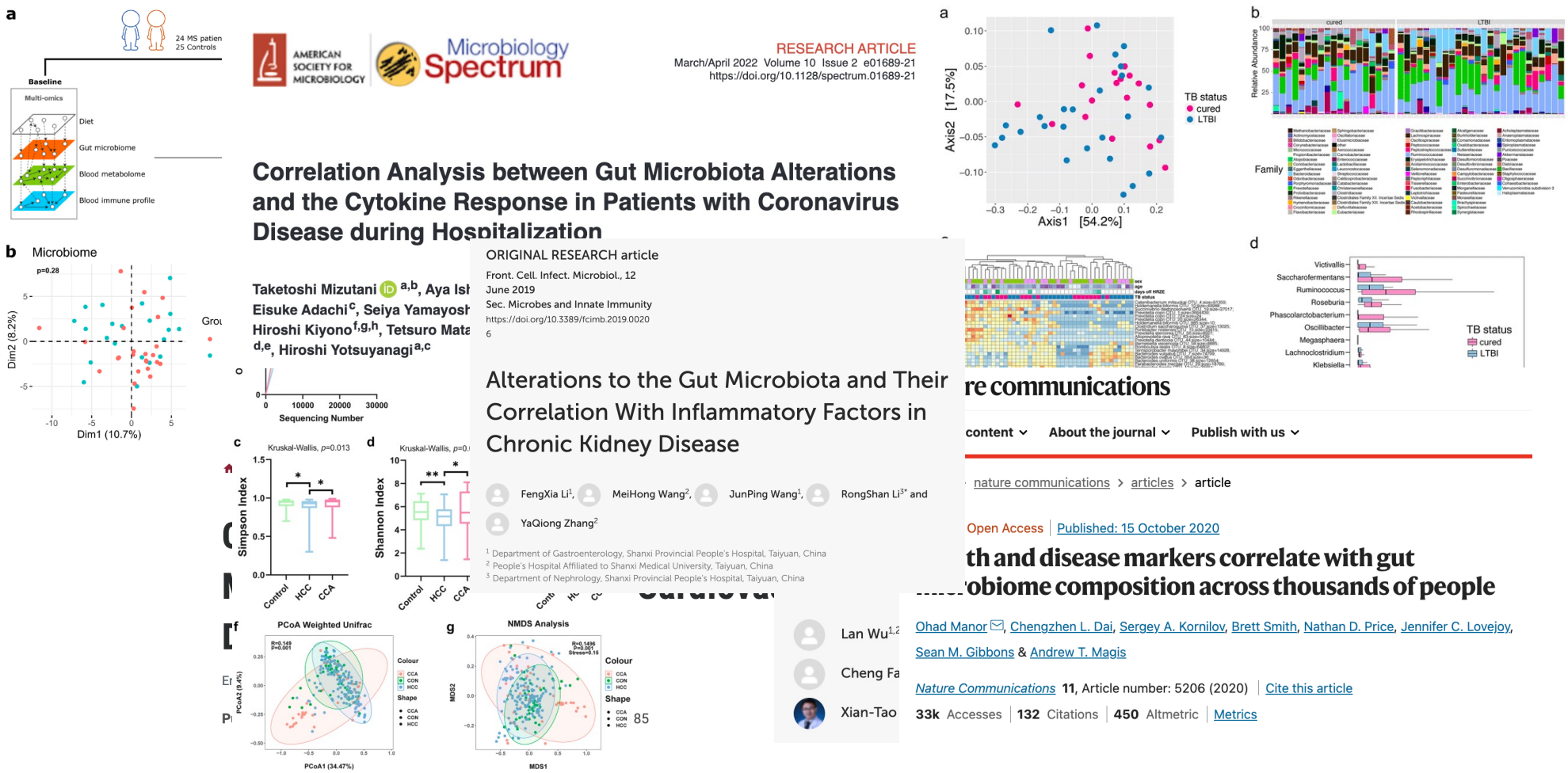


The American Journal of Gastroenterology Volume 110 | February 2015

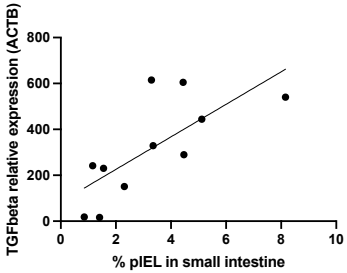


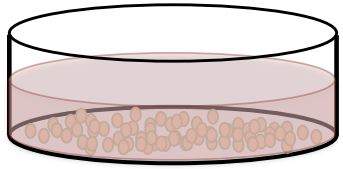
Genes Dev. 2013 27: 701-718

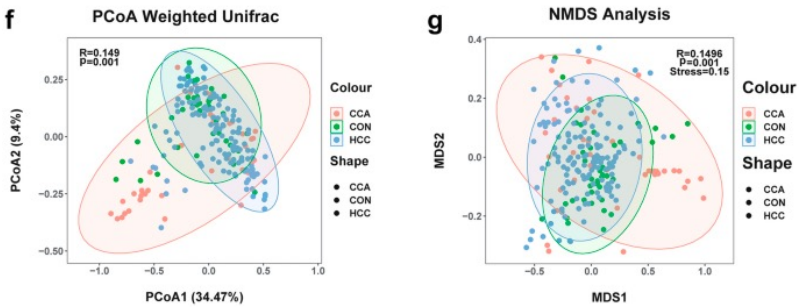
Numerous members of the microbiota have been correlated with health and disease



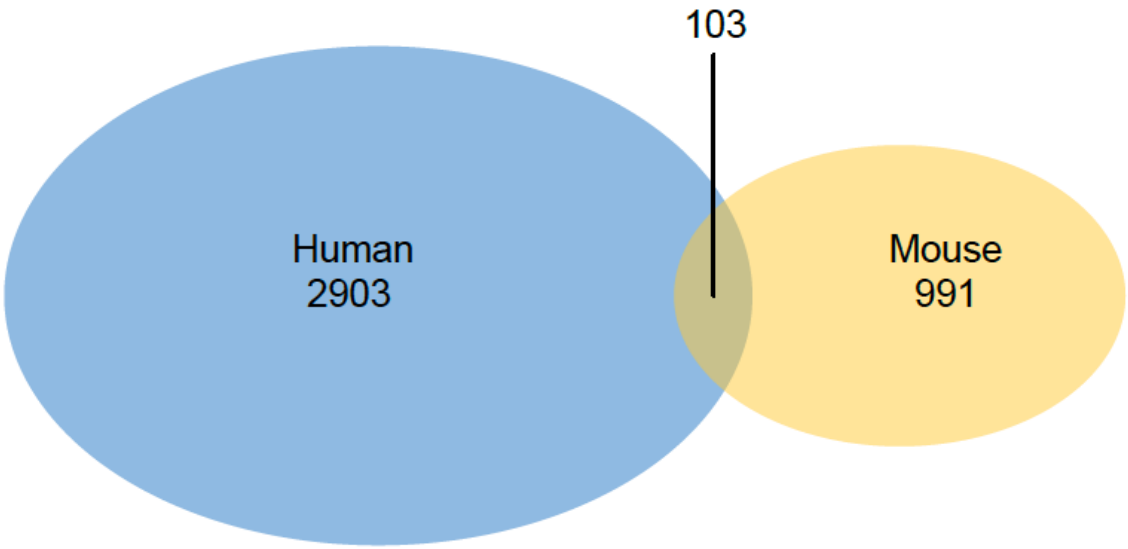
How do we go from correlation to mechanism?





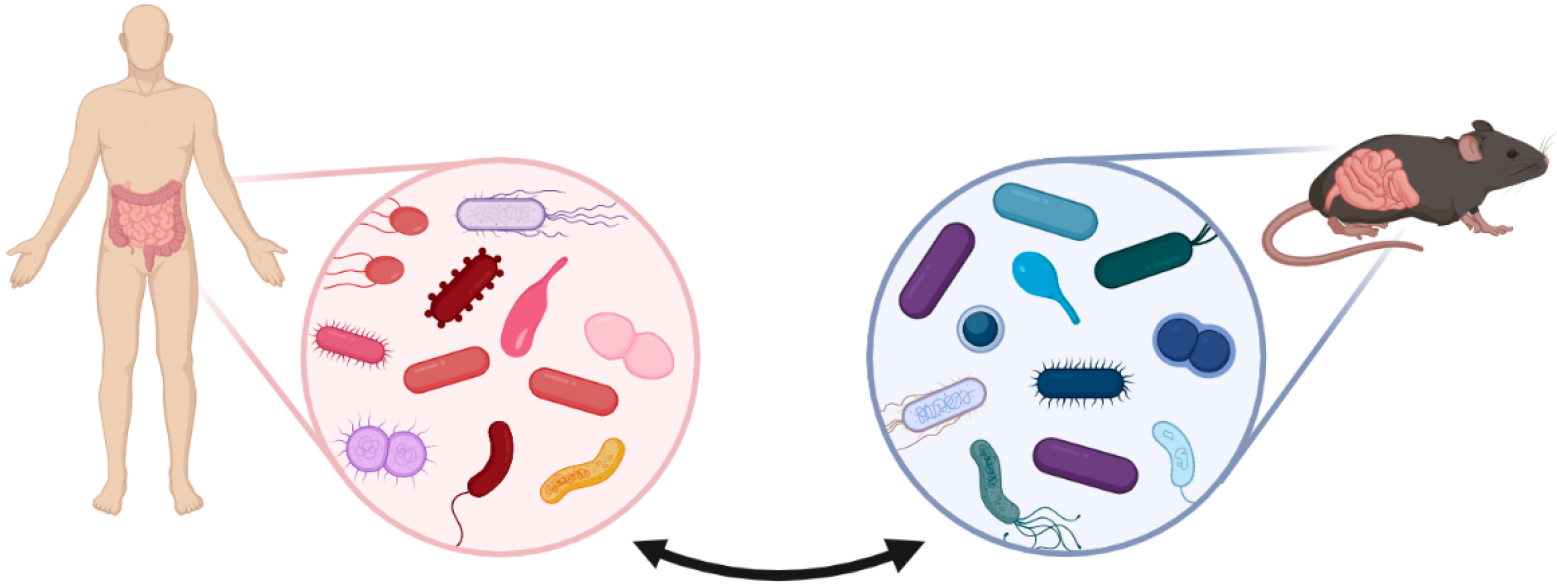


The human and mouse microbiotas are taxonomically distinct (<3% overlap)

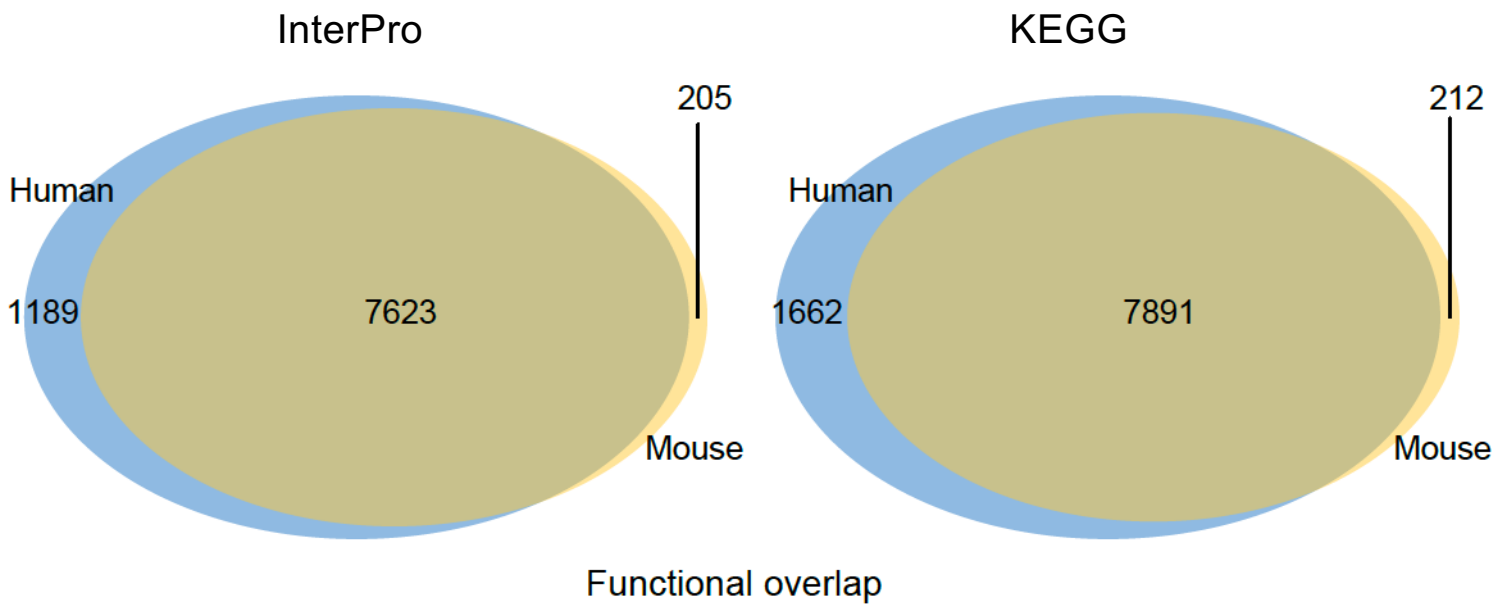


Taxonomic overlap

So how can we translate findings between patients and mice (and other model organisms)?



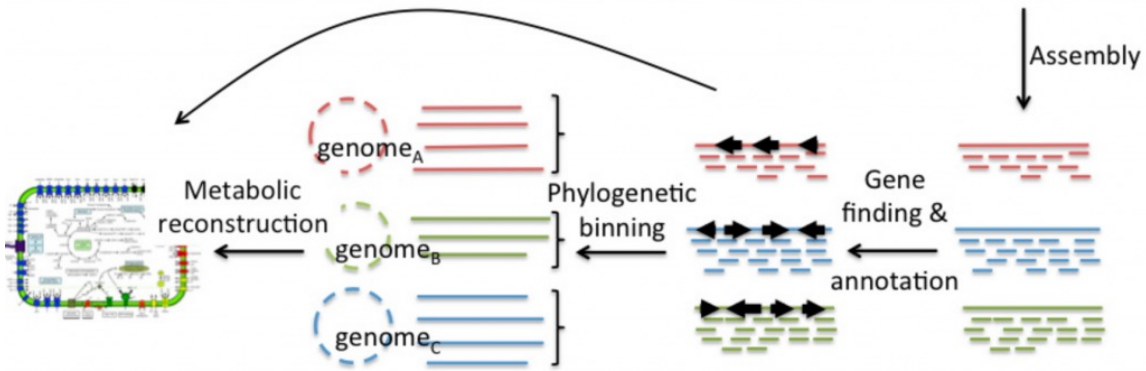
The human and mouse microbiotas share many of the same functions



→ Find functionally equivalent species and genes between the human and mouse microbiotas

Functional metagenomics reveals the skills and tools encoded by an individual's gut microbiome

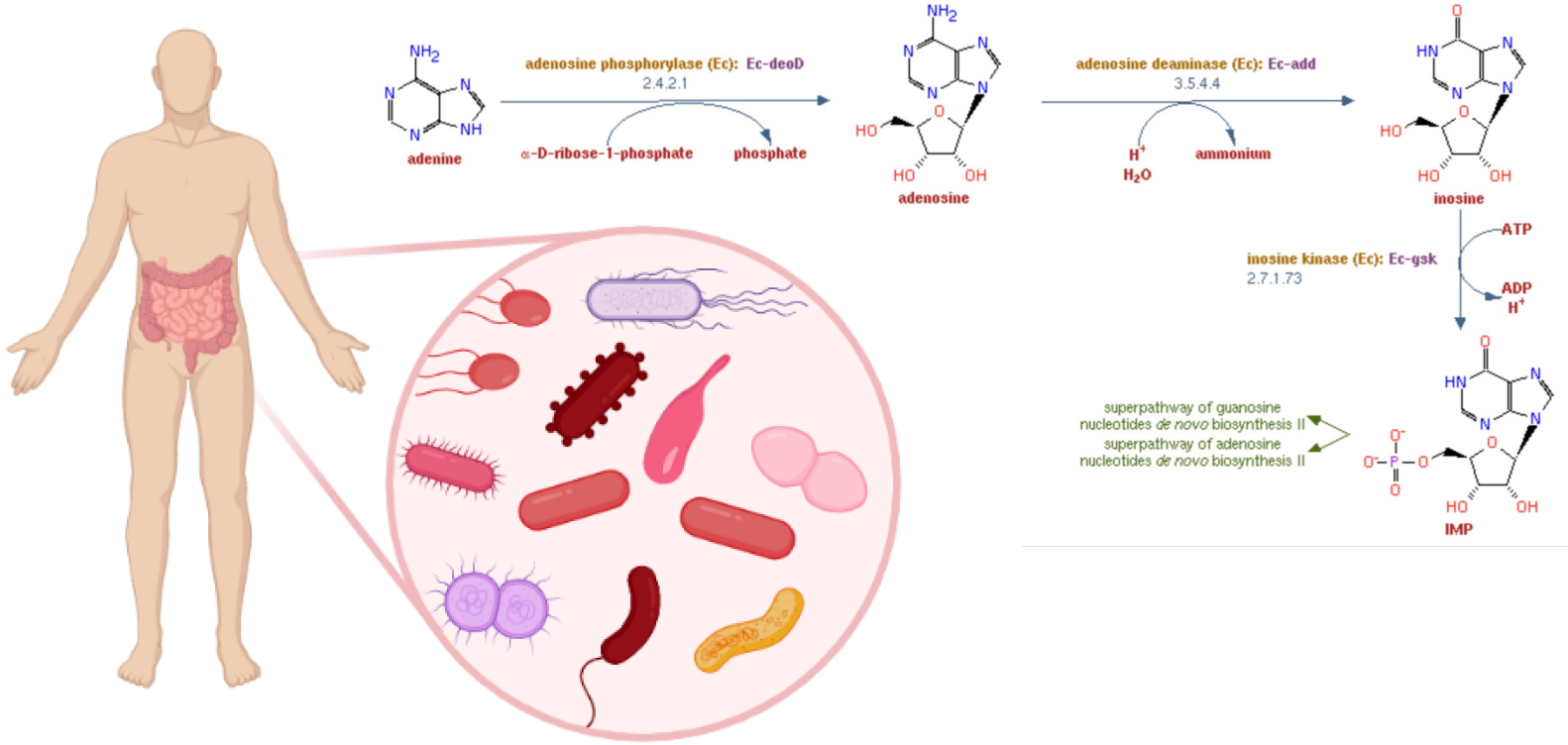
- Contig assembly
- Metagenome-assembled genomes (MAGs)



- Pangenomes
- Computational tools

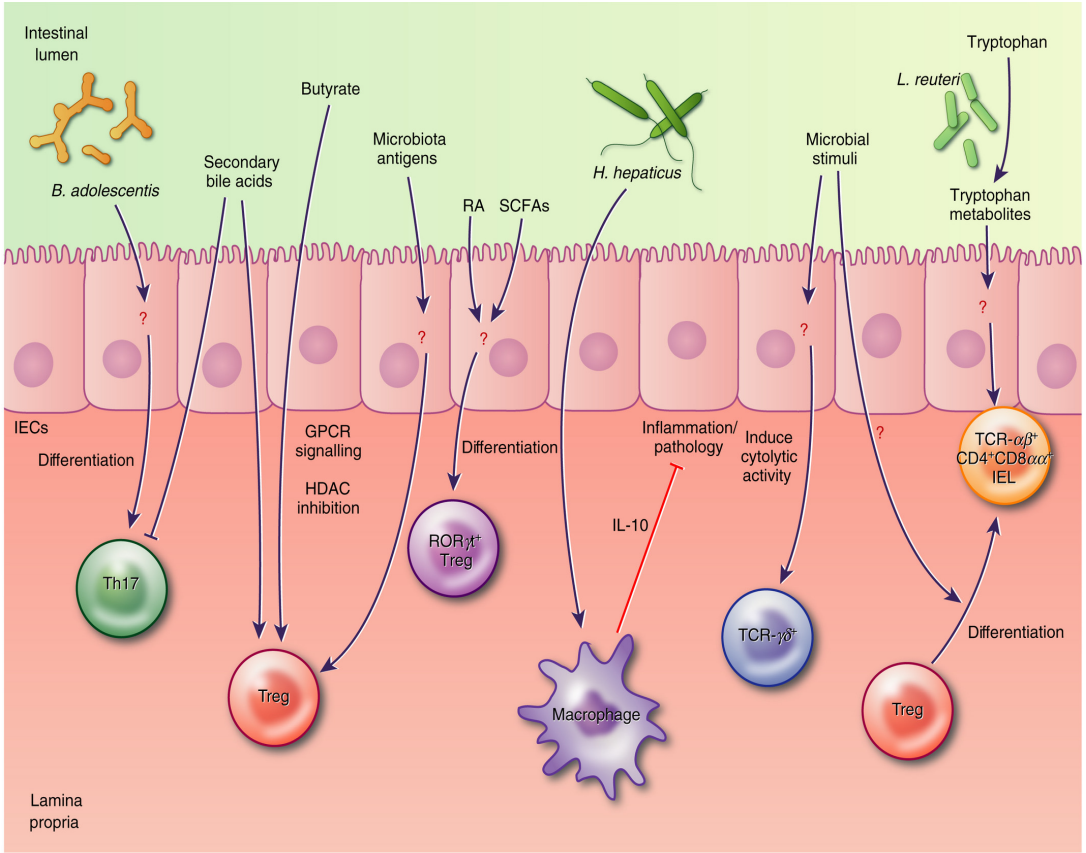
  → ORF/gene-level functional annotation

Functional metagenomics gives us access to the metabolic activity and outputs of the gut microbiome



How can we apply this to understanding effects on host immunity and disease?

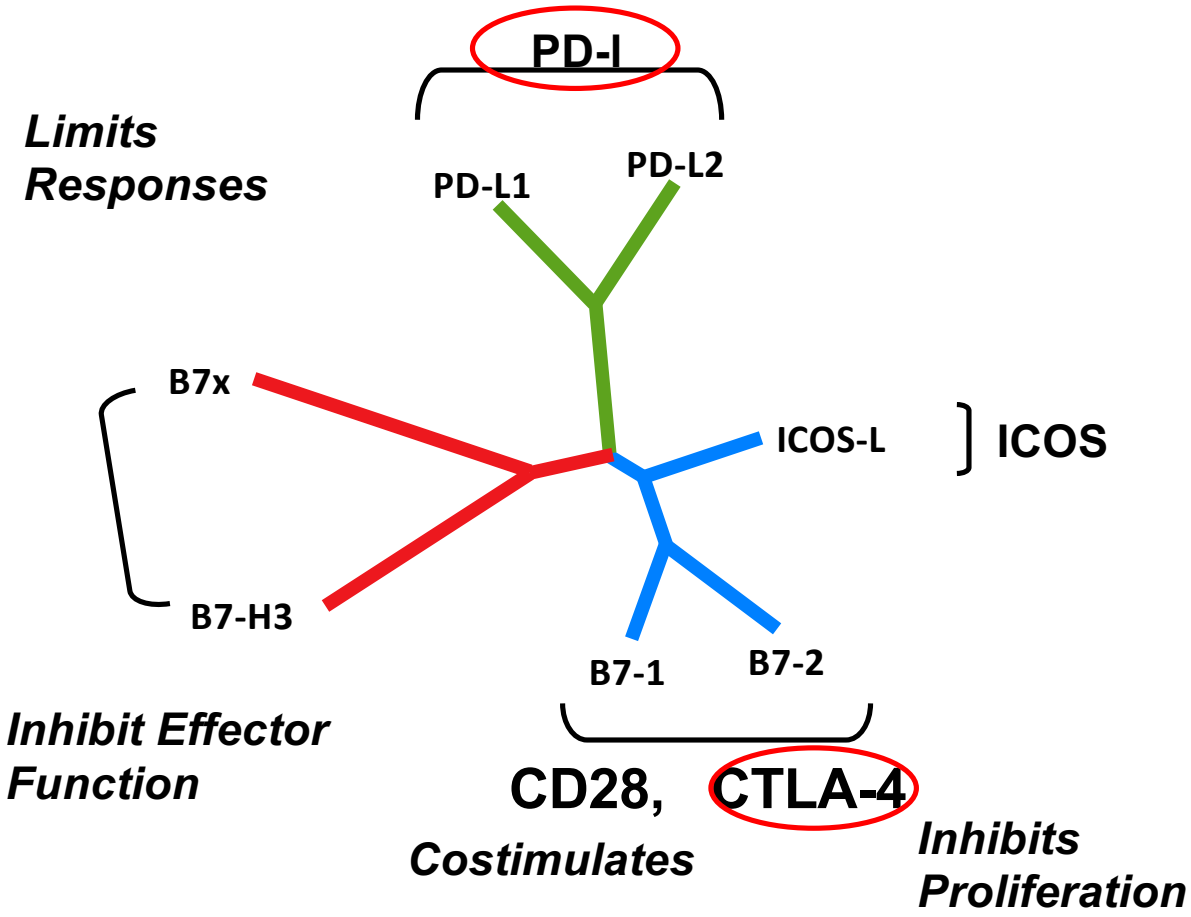
Common microbial metabolites and cell wall components modulate immune cell function

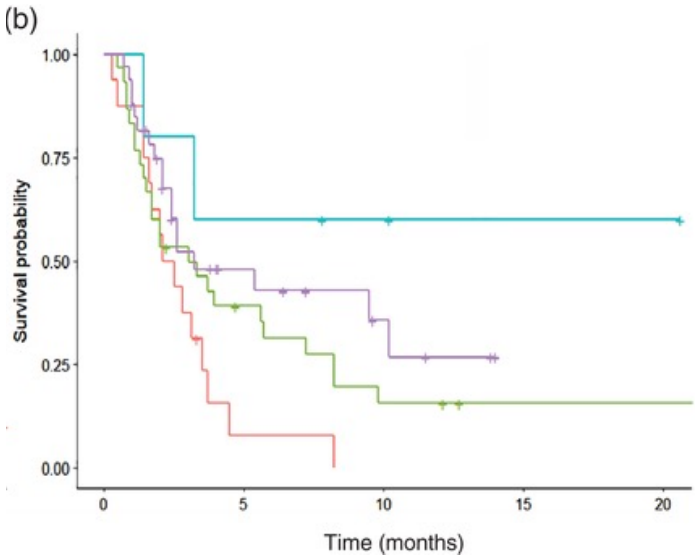


Immunology, Volume: 158, Issue: 4, Pages: 267-280.

Role of the microbiome in cancer immunotherapy efficacy

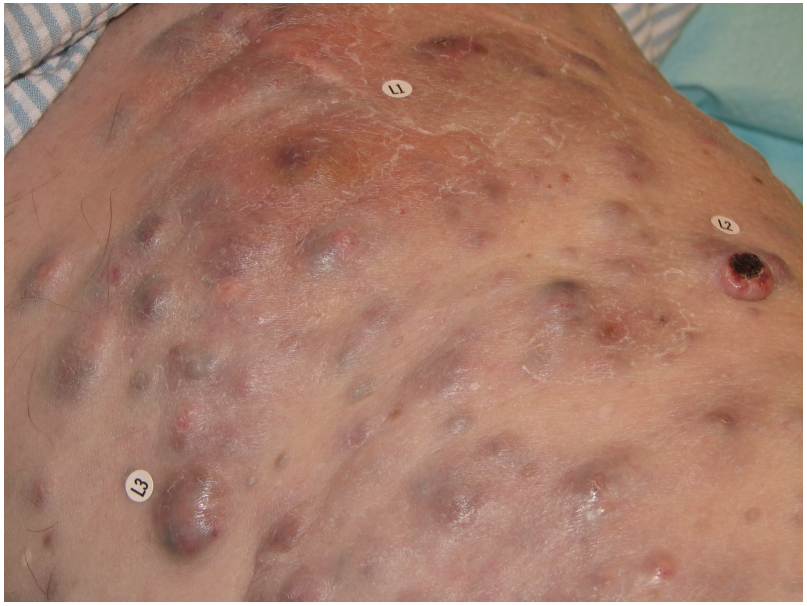
Immune Checkpoint Inhibitors (ICIs) unleash immune responses to cancer

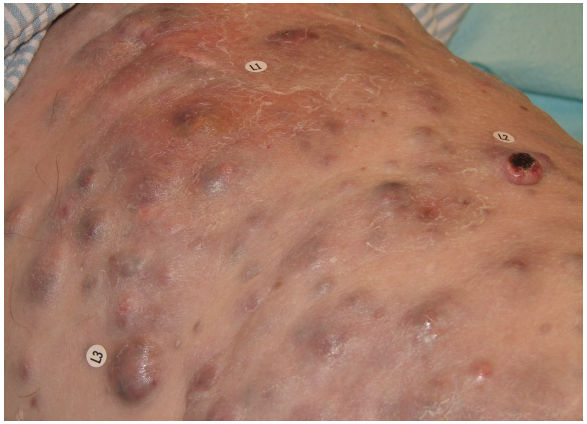




Kuo, et al. (2019). Thoracic Cancer. 10. 10.1111/1759-7714.13057.

Baseline 28/11/06





Wolchok (MSKCC)

9/1/07 12/2/07

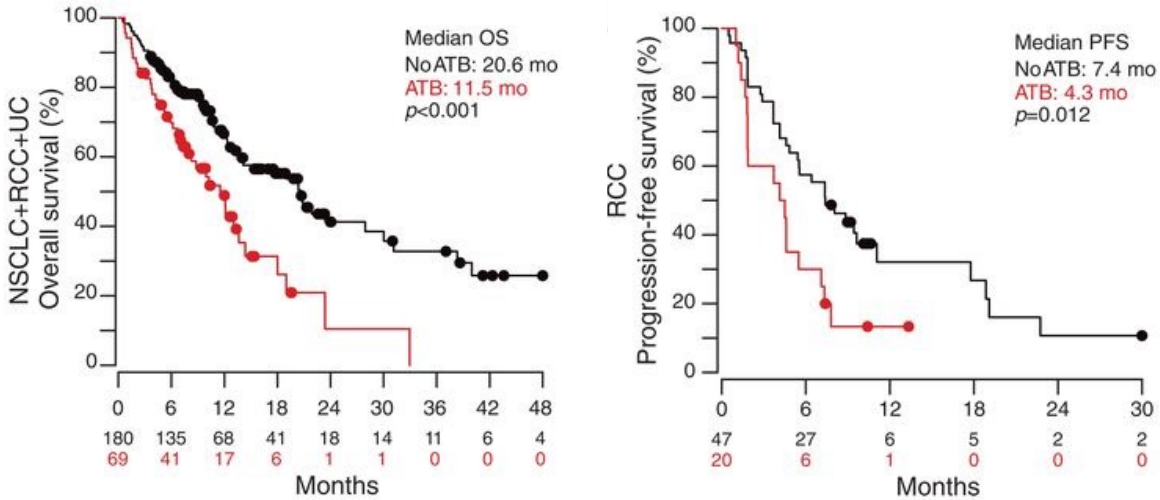
6 Weeks 10 Weeks

Wolchok (MSKCC)

The gut microbiome plays a crucial role in immunotherapy efficacy

CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors



Routy et al., Science 2018

Gut microbiota composition has been associated with patient responses to cancer immunotherapy

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Cross-cohort gut microbiome … immune checkpoint inhibitor … melanoma

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Article | Published: 03 February 2022

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Nature Medicine **28**, 315–324 (2022) | Cite this article

9307 Accesses | **23** Citations | **132** Altmetric | Metrics

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associated with malignant di…

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Mykhaylo Usyk, Abhishek Pandey, Richard B. Haye… Weber & Jiyoung Ahn

Genome Medicine **13**, Article number: 160 (2021)

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[a]Research Center of Translational Medicine, Shanghai Children's Hospital, Shanghai Institute of Immunology, State Key Laboratory of Oncogenes and Related Genes, Shanghai Jiao Tong University School of Medicine, Shanghai 200240, China; [b]Shanghai Institute of Immunology, Translational Medicine Center, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200240, China; [c]HHMI, Stanford University School of Medicine, Stanford, CA 94305; [d]Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA 94305; [e]Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, CA 94305; [f]Department of Bioengineering and ChEM-H, Stanford University and Chan Zuckerberg Biohub, Stanford, CA 94305; and [g]Department of Pathology, Stanford University School of Medicine, Stanford, CA 94305

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Gut microbiota composition has been associated with patient responses to cancer immunotherapy

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Article | Published: 28 February 2022

Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1

John A. McCulloch, Diwakar Davar, Richard R. Rodrigues, Jonathan H. Badger, Jennifer R. Fang, Alicia M. Cole, Ascharya K. Balaji, Marie Vetizou, Stephanie M. Prescott, Miriam R. Fernandes, Raquel G. F. Costa, Wuxing Yuan, Rosalba Salcedo, Erol Bahadiroglu, Soumen Roy, Richelle N. DeBlasio, Robert M. Morrison, Joe-Marc Chauvin, Quanquan Ding, Bochra Zidi, Ava Lowin, Saranya Chakka, Wentao Gao, Ornella Pagliano, ... Amiran K. Dzutsev + Show authors

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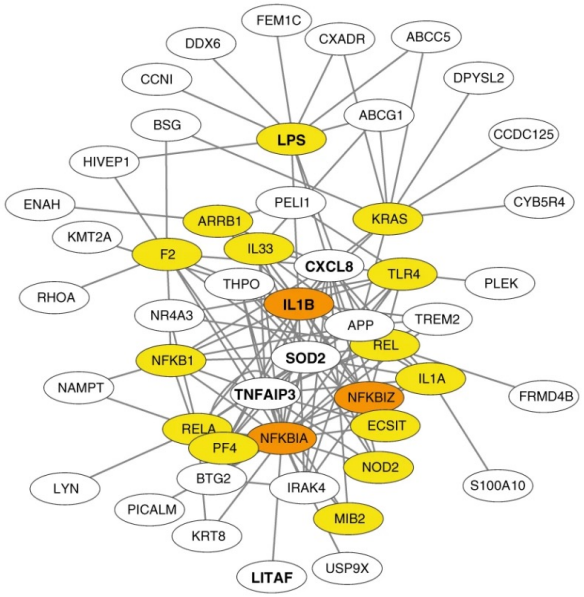
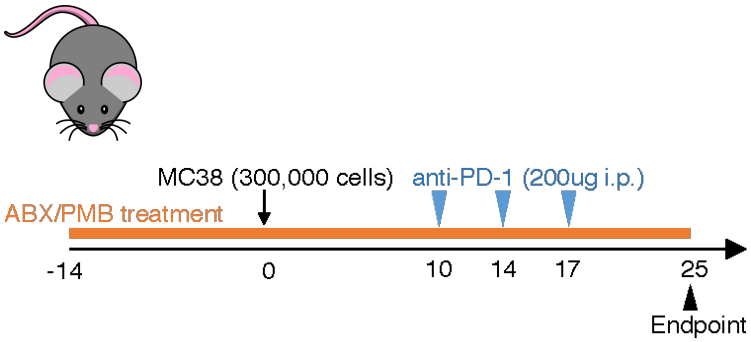


"Collectively, our findings hint that an unfavorable gut microbiome enriched in Gram-negative bacteria may promote an LPS-dominated inflammatory signature in the gut, resulting in systemic inflammation manifested by elevated NLR and poor response to anti-PD-1."

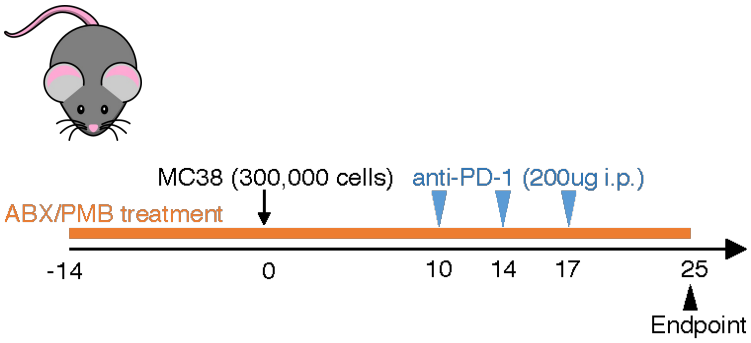
Will blocking LPS and depleting Gram-negative gut bacteria improve immunotherapy efficacy?

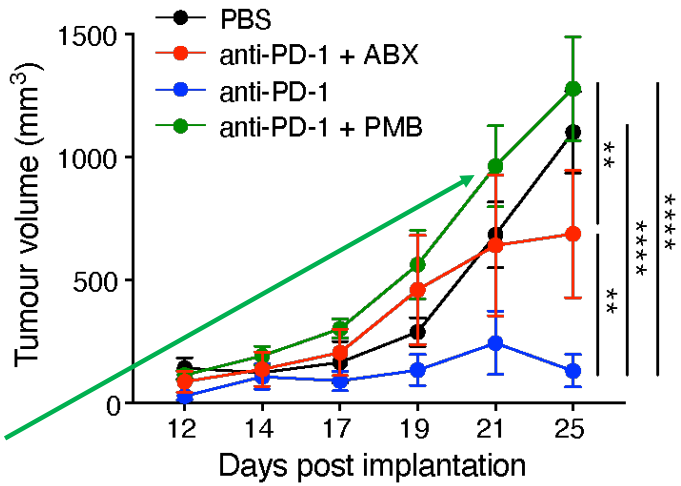


Polymyxin B (PMB) blocks LPS and kills many Gram-negative bacteria

Paula Kuo
Roychoudhuri Lab

Will blocking LPS and depleting Gram-negative gut bacteria improve immunotherapy efficacy?





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Will blocking LPS and depleting Gram-negative gut bacteria improve immunotherapy efficacy?

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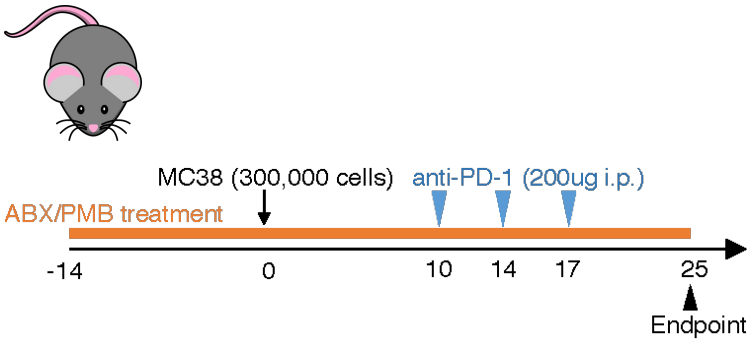
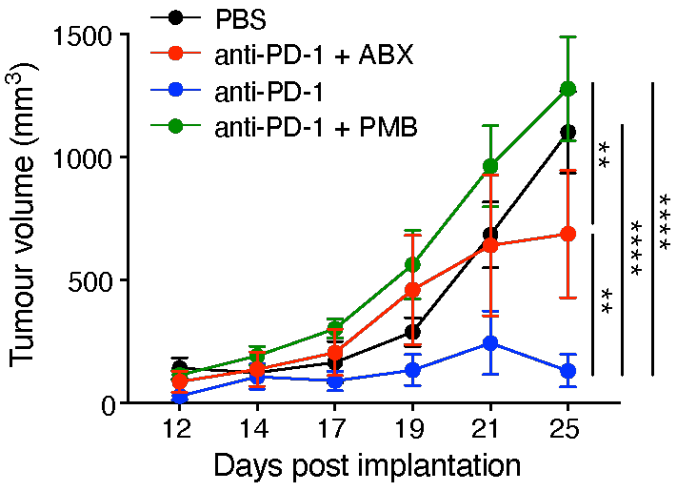
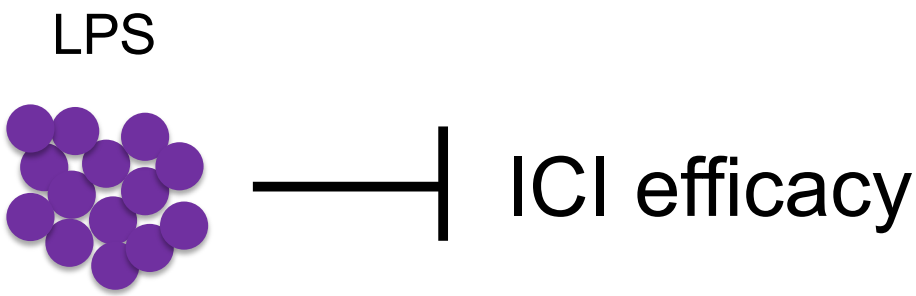




Blocking LPS and Gram-negative bacteria <u>abolishes</u> anti-PD-1 responses

Paula Kuo
Roychoudhuri Lab

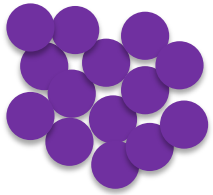
So if Gram-negative bacteria and LPS are bad for immunotherapy efficacy…

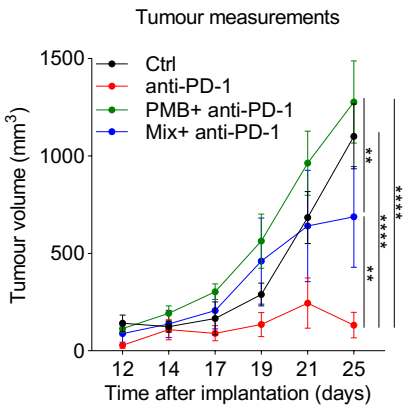


Why doesn't PMB improve anti-PD-1 responses instead of abolishing them?

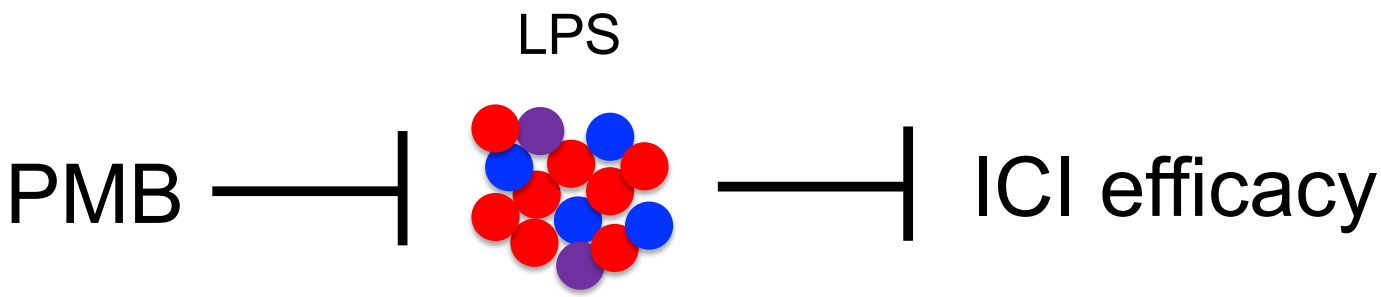
LPS

???

PMB ⊣  ⊣ ICI efficacy

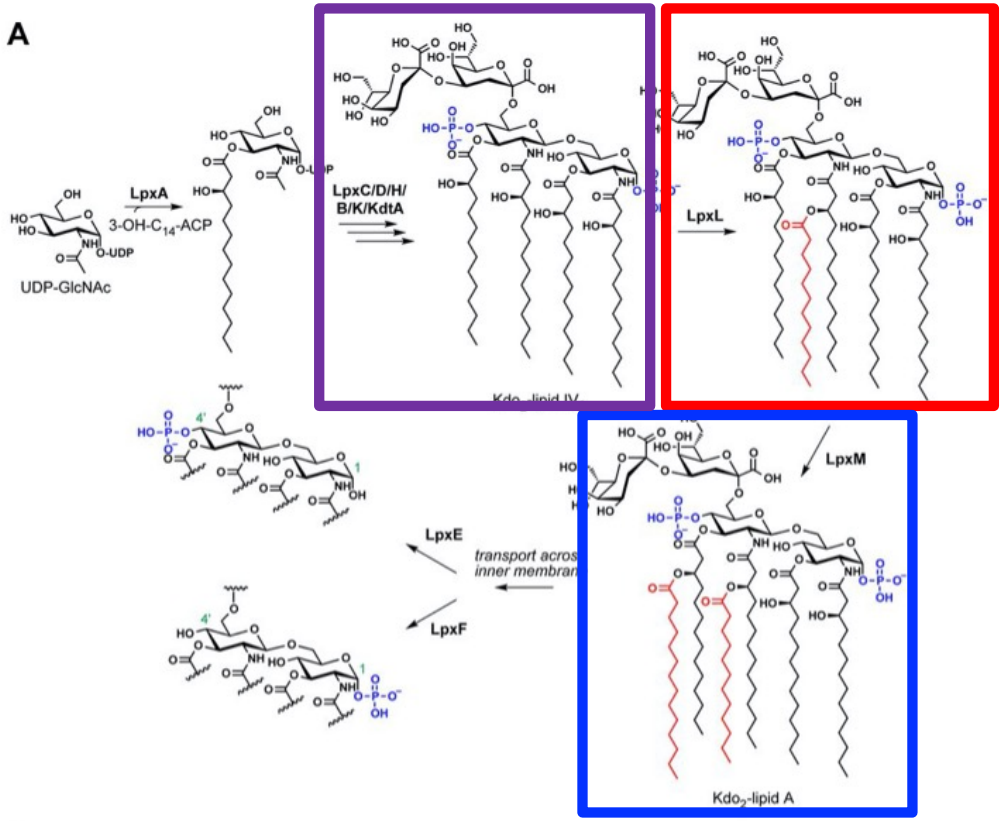


Not all LPS are the same!



Ben Beresford-Jones

The number of LPS lipid A acyl chains affects immune stimulation



tetra-acylated = weak TLR4 agonism

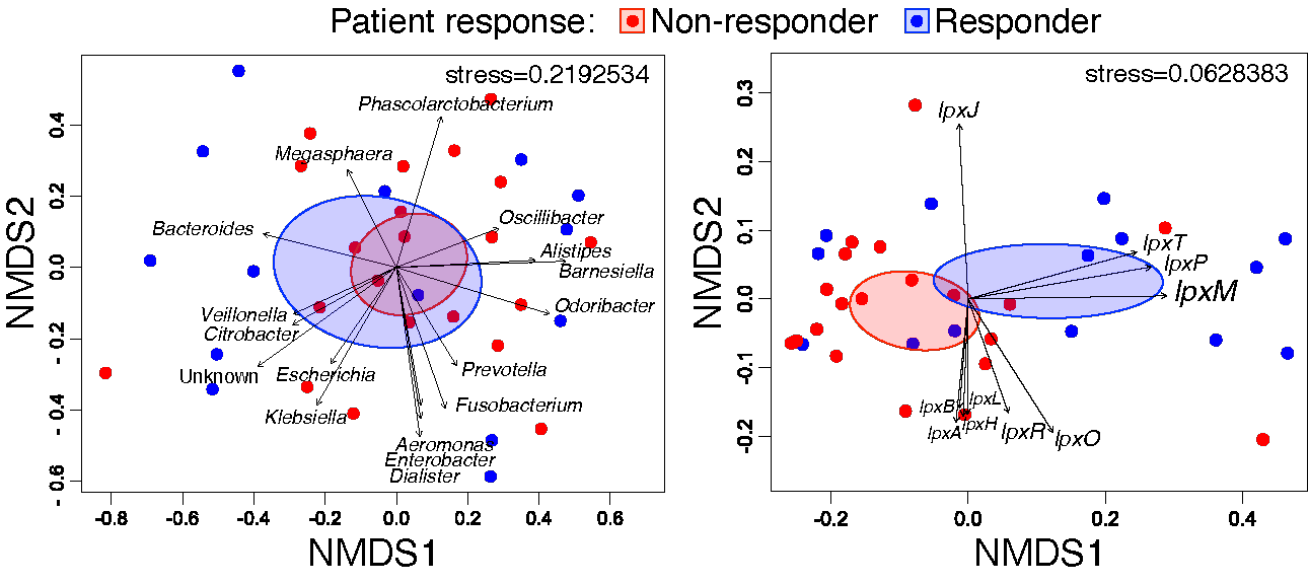
penta-acylated = weak TLR4 agonism

hexa-acylated = strong TLR4 agonism

Ben Beresford-Jones

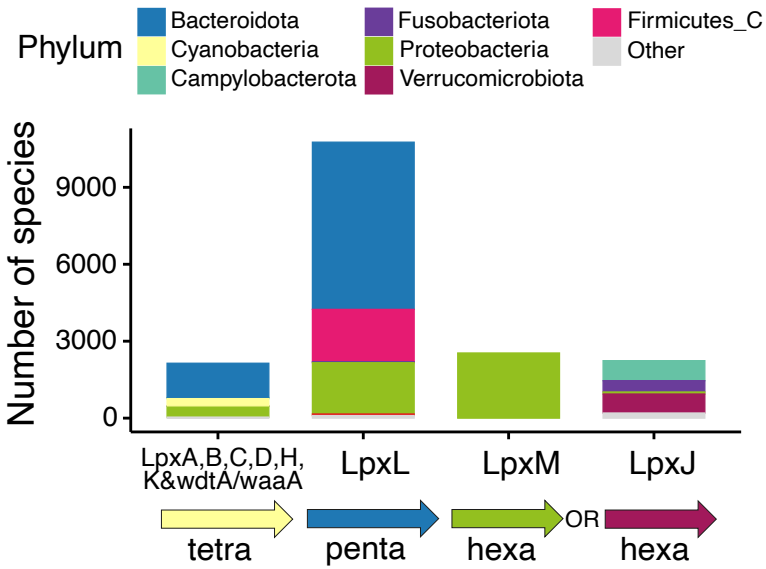
https://doi.org/10.1128/mBio.02289-17

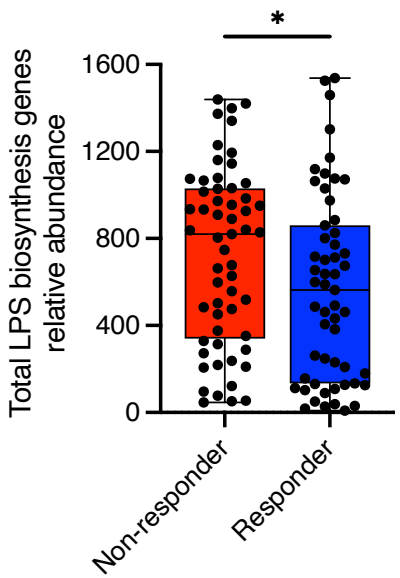
Clustering by function rather than taxonomy segregates immunotherapy responders



Puspendu Sardar

Gram-negative bacteria and total LPS correlate with <u>non-response</u> to anti-PD-1 in melanoma patients



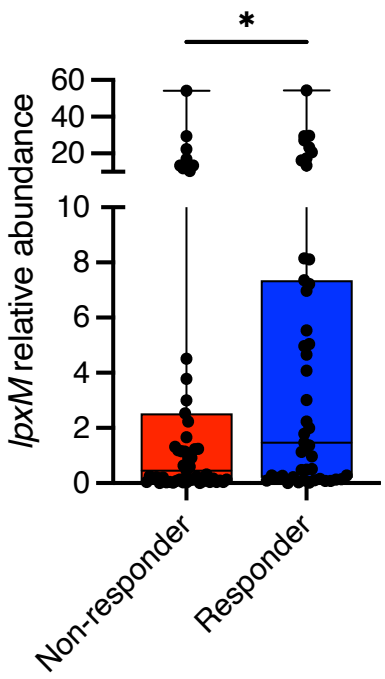


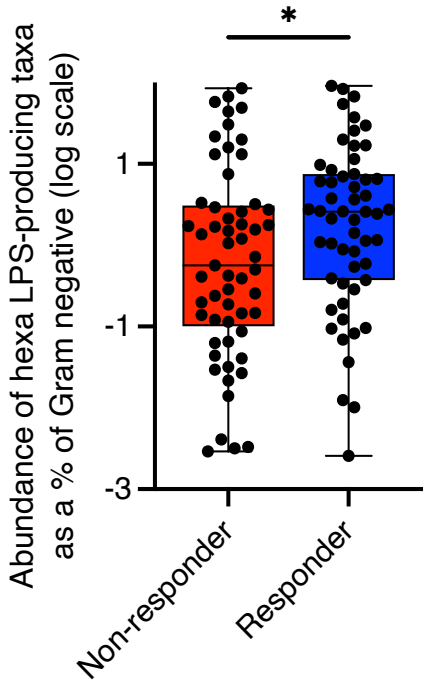
Puspendu Sardar

Ben Beresford-Jones

fecal metagenomes
112 melanoma patients treated with anti-PD-1
7 clinical studies from 4 different countries

Hexa LPS-producers are higher in melanoma patients that respond to anti-PD-1



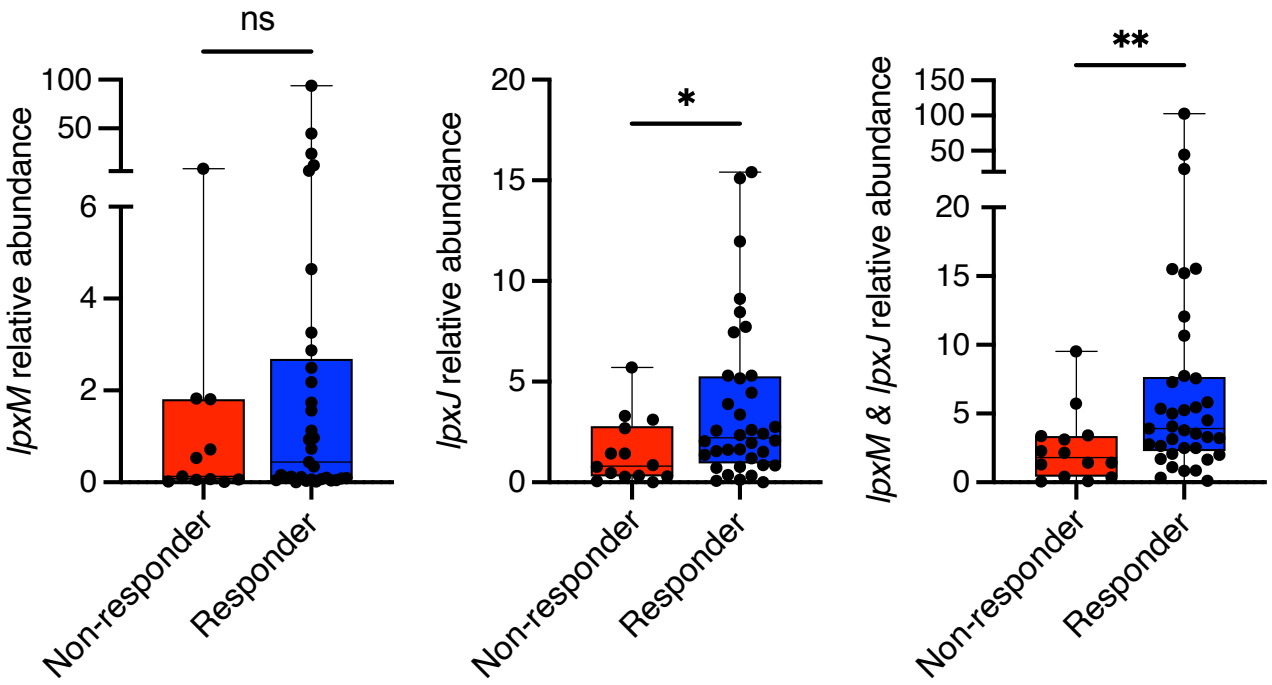


fecal metagenomes
112 melanoma patients treated with anti-PD-1
7 clinical studies from 4 different countries

Puspendu Sardar

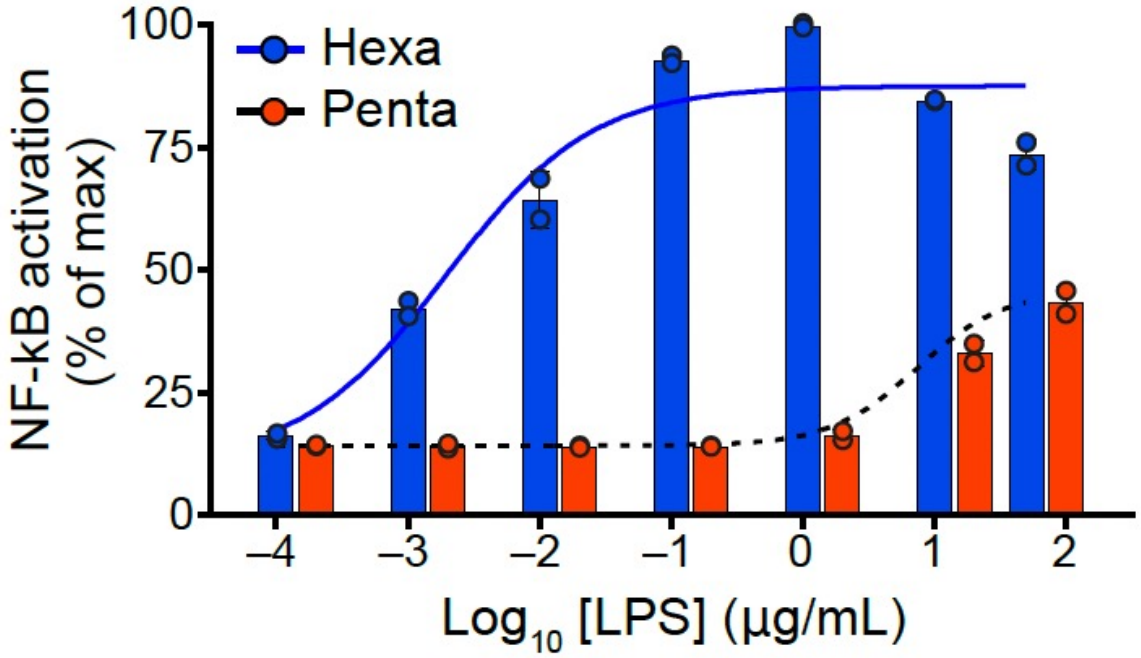
Ben Beresford-Jones

Hexa-acylation signature is also associated with RCC responders



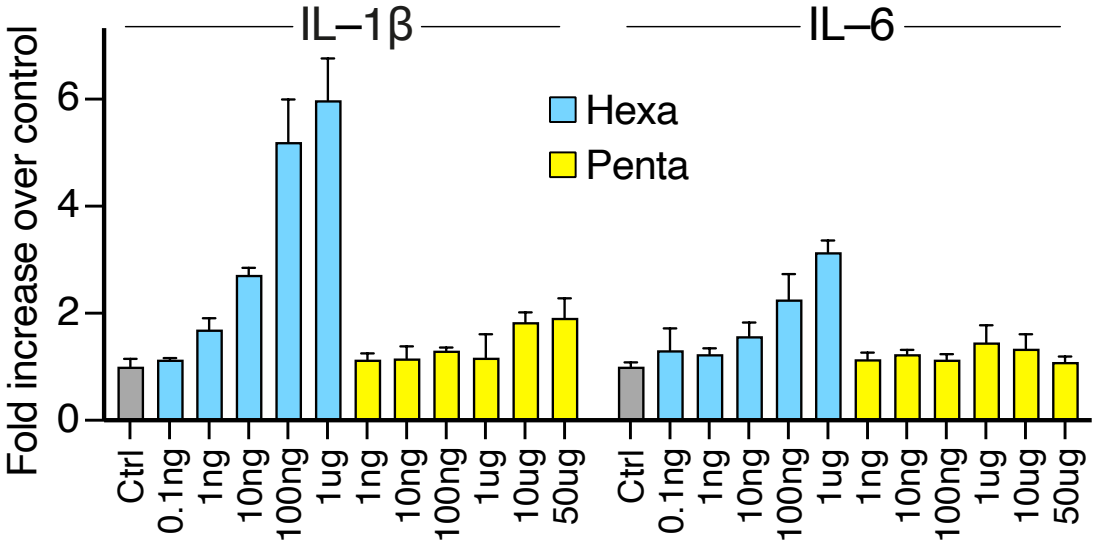
fecal metagenomes
50 RCC patients treated with anti-PD-1
single study

Hexa LPS potently induces immune activation



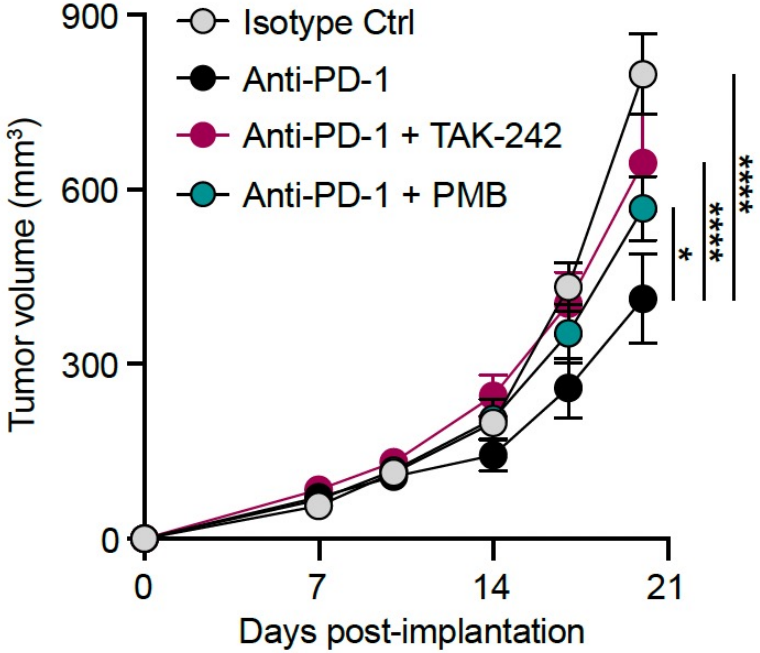
Satoshi Suyama

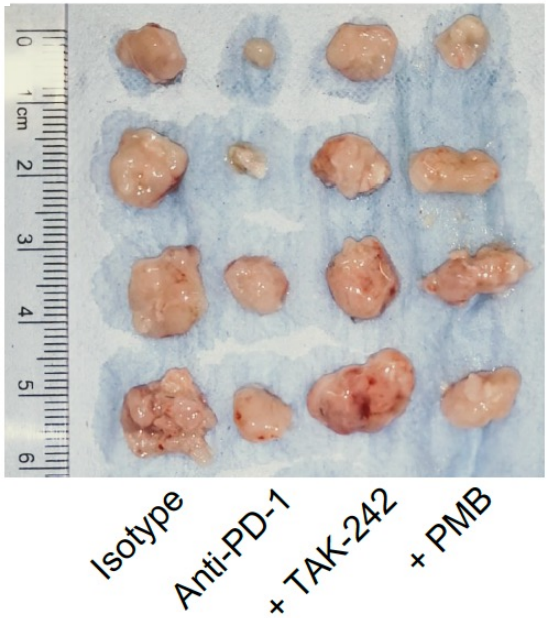
Hexa LPS potently induces cytokine secretion

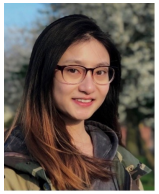


Satoshi Suyama

Depletion of hexa-producing bacteria and blockade of TLR4 abrogate anti-PD-1 efficacy

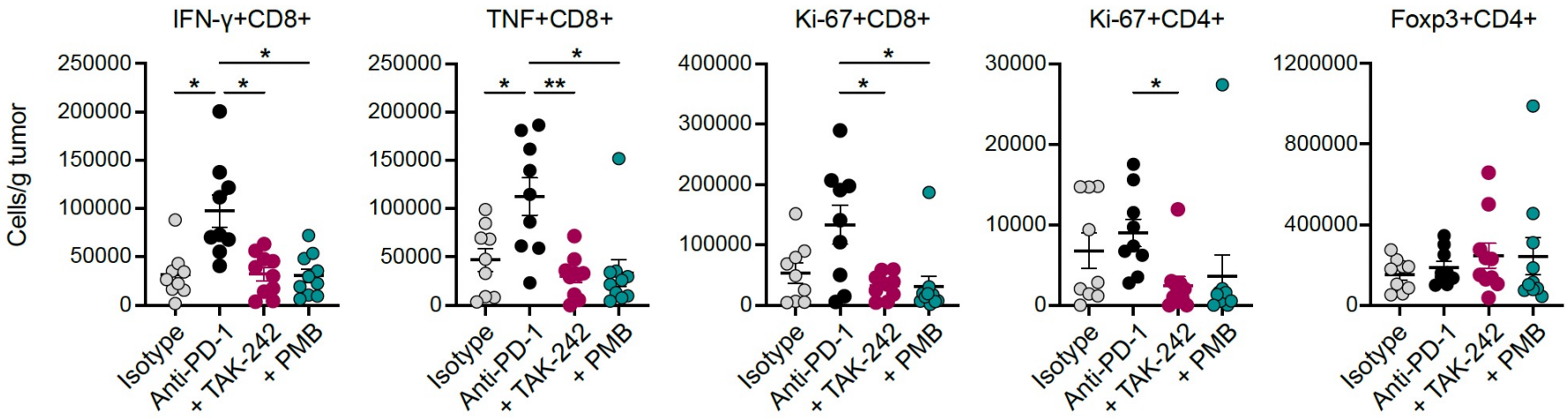


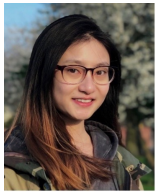




Wangmingyu Xia

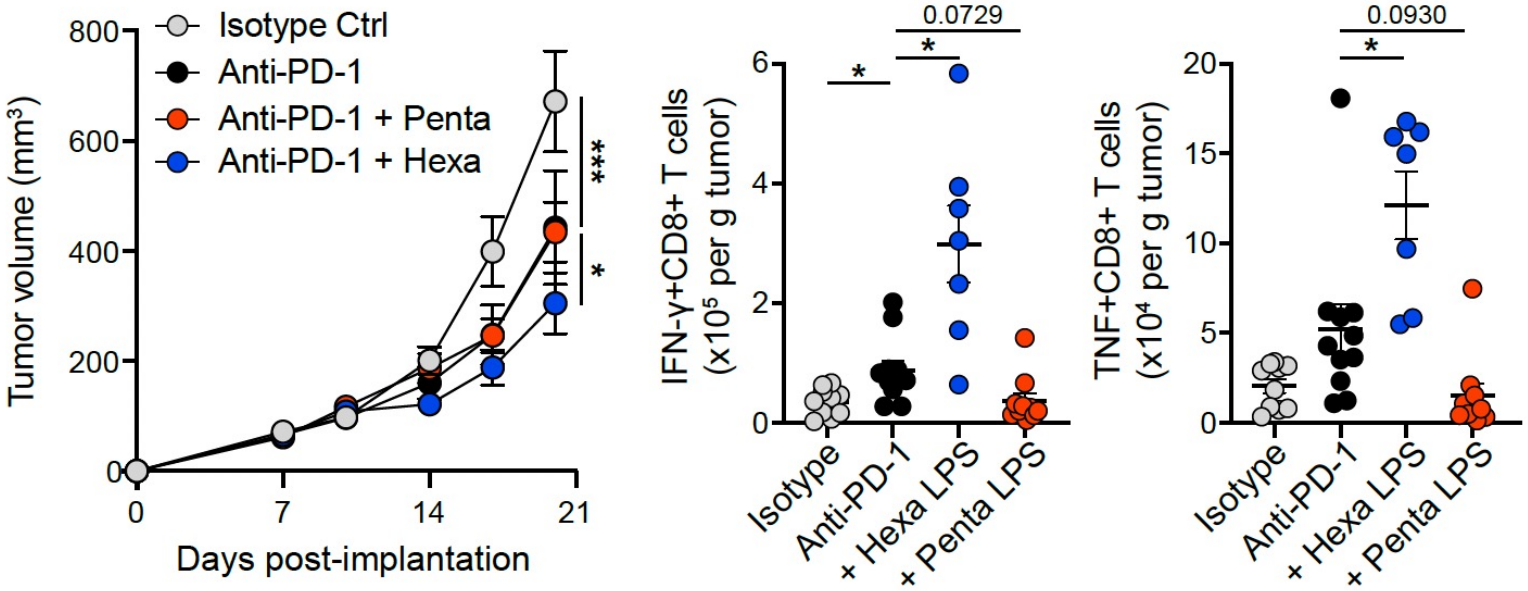
Depletion of hexa-producing bacteria and blockade of TLR4 abrogate anti-PD-1 efficacy

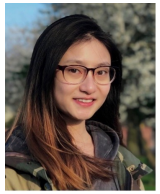




Wangmingyu Xia

Oral supplementation with hexa LPS increases anti-tumour immunity and anti-PD-1 efficacy

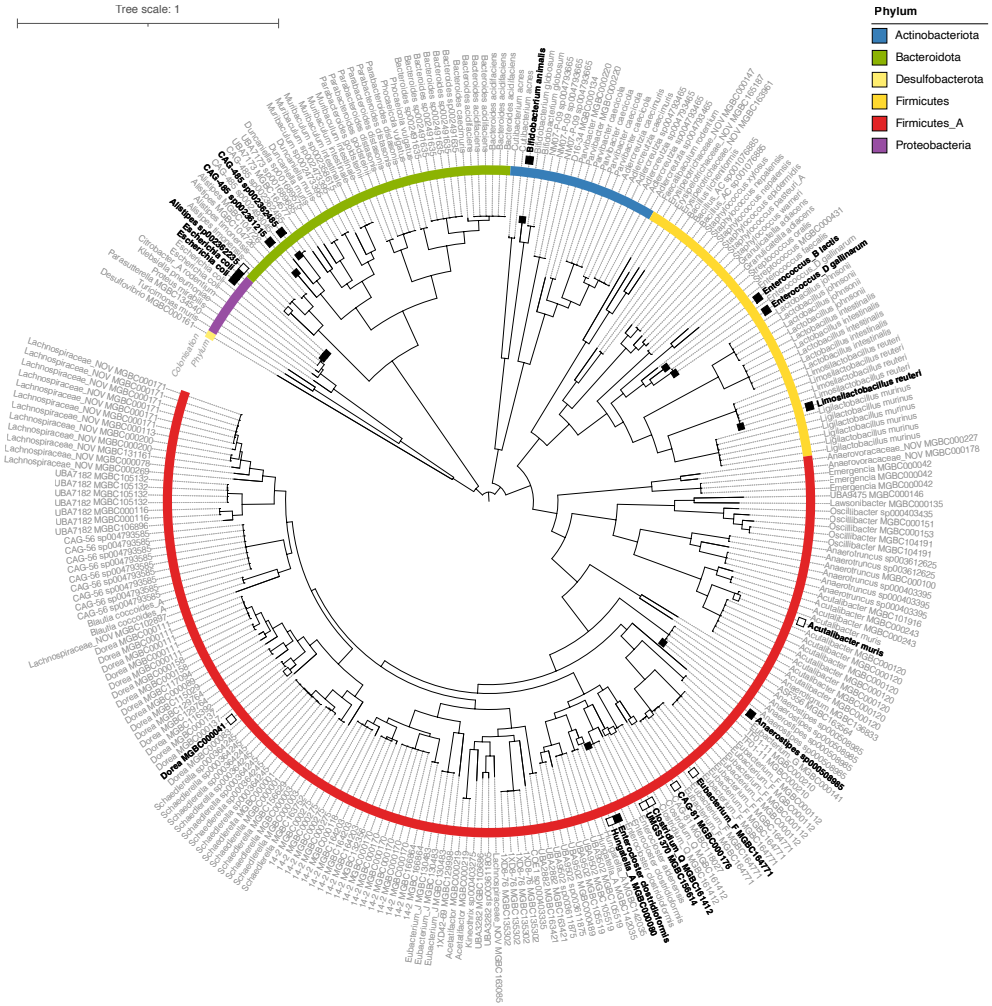




Wangmingyu Xia

Role of the microbiome in protection against enteric infection

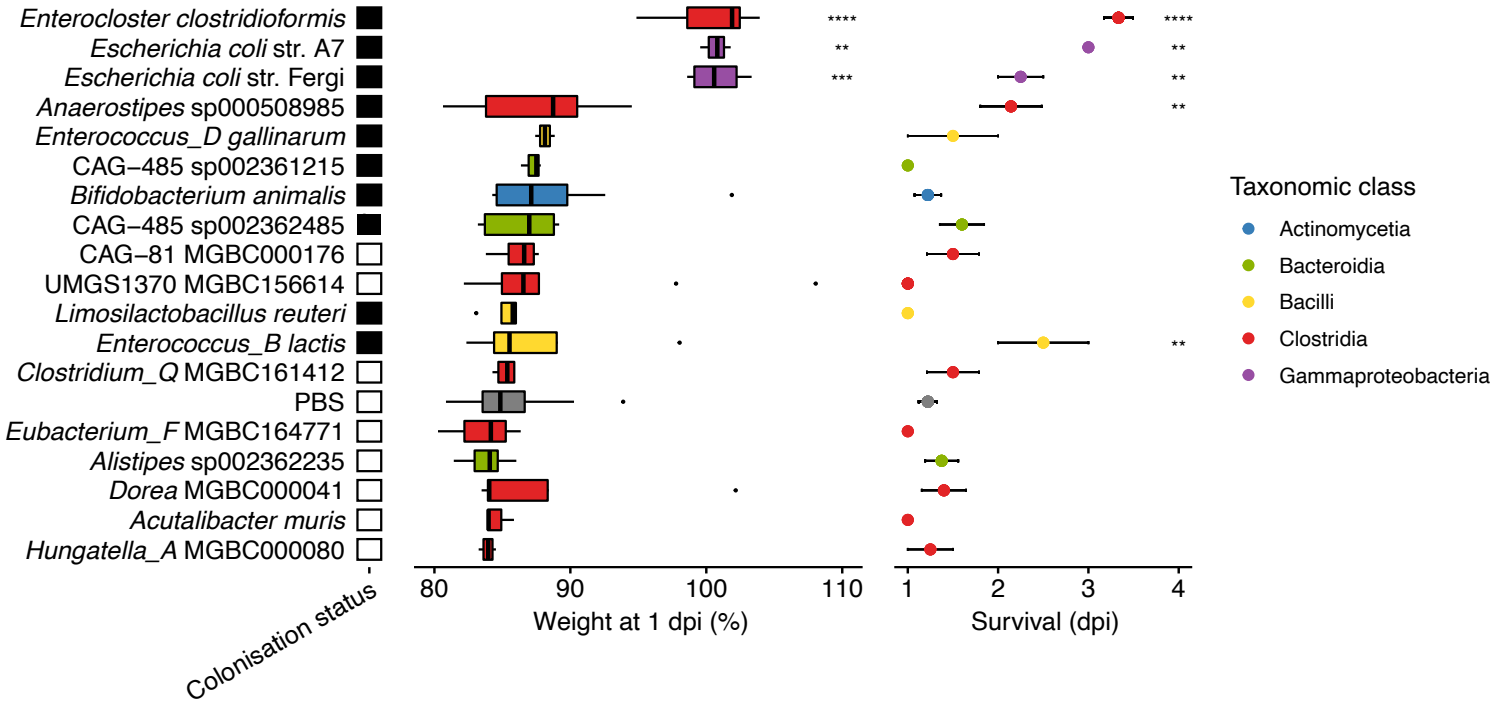
Screening for protective commensals against *S.* Typhimurium



18 commensal species screened, representing five phyla

Ben Beresford-Jones

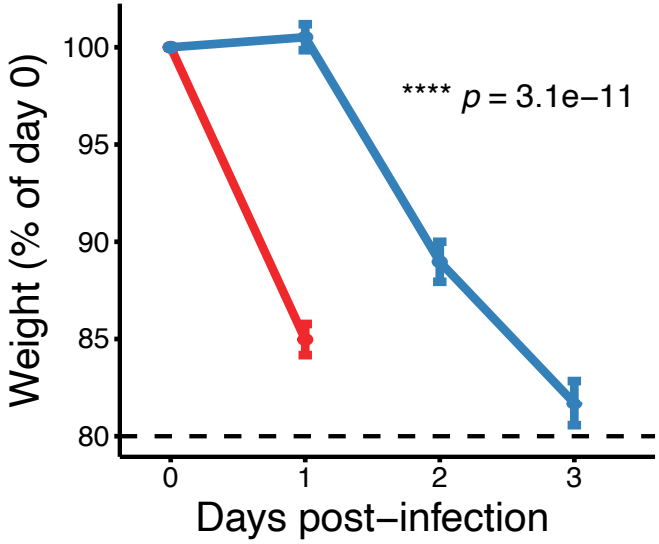
Monocolonisation with specific commensals induces resistance to *Salmonella* Typhimurium

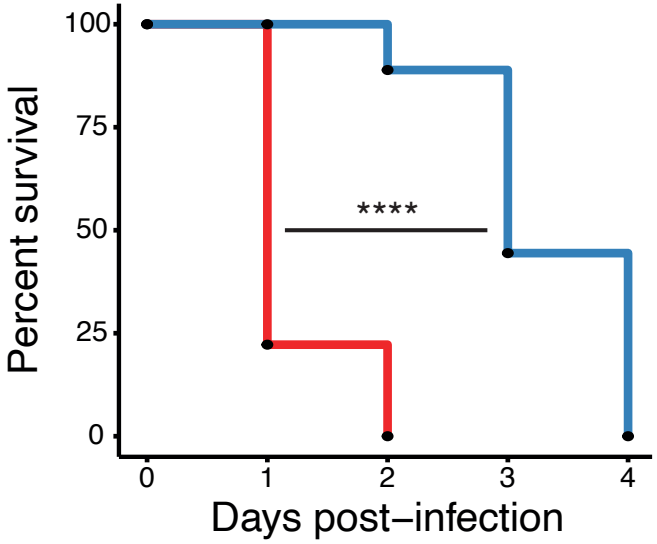


- GF mice monocolonised for 2 weeks prior to infection with a low dose (10^2 CFU/mouse) of *Salmonella* Typhimurium (*S.*Tm)

Ben Beresford-Jones

Enterocloster clostridioformis prolongs germ-free mouse survival following *S.* Typhimurium infection

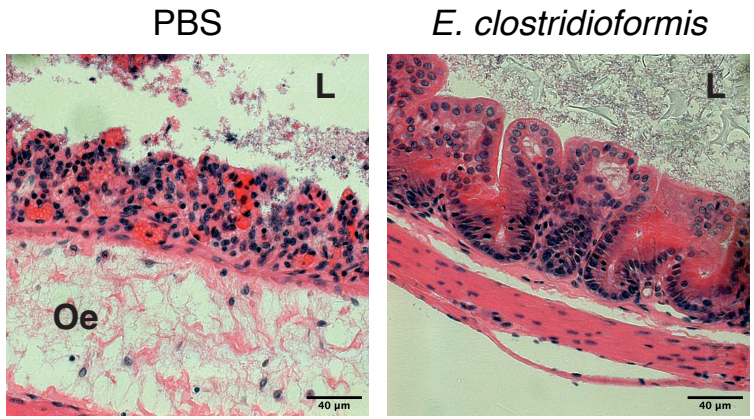


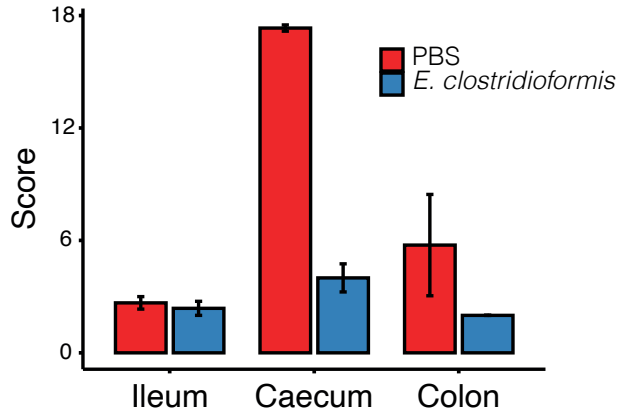


PBS
E. clostridioformis

Ben Beresford-Jones

Enterocloster clostridioformis leads to decreased epithelium pathology after *S.* Typhimurium infection

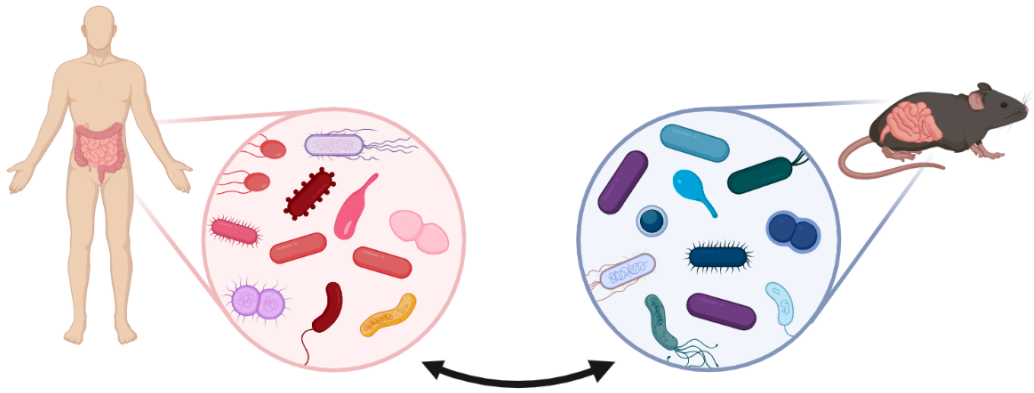




Ben Beresford-Jones

Summary:

- Human → Mouse: A patient microbiome signature of response to immunotherapy identifies a gut microbial metabolite that enhances anti-PD-1 efficacy.
- Mouse → Human: A gut microbial metabolite orchestrates epithelial cell-mediated differentiation of anti-inflammatory intestinal T cells.
- An applied a screen of mouse commensal bacteria identified a novel host-commensal interaction that mediates protection against *S.* Typhimurium pathogenesis *in vivo*.
- Examining microbiota function facilitates translation between mouse and human studies to reveal the mechanisms of microbiota modulation of host immunity.



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