Microbiota e tumori: stato dell’arte e prospettive

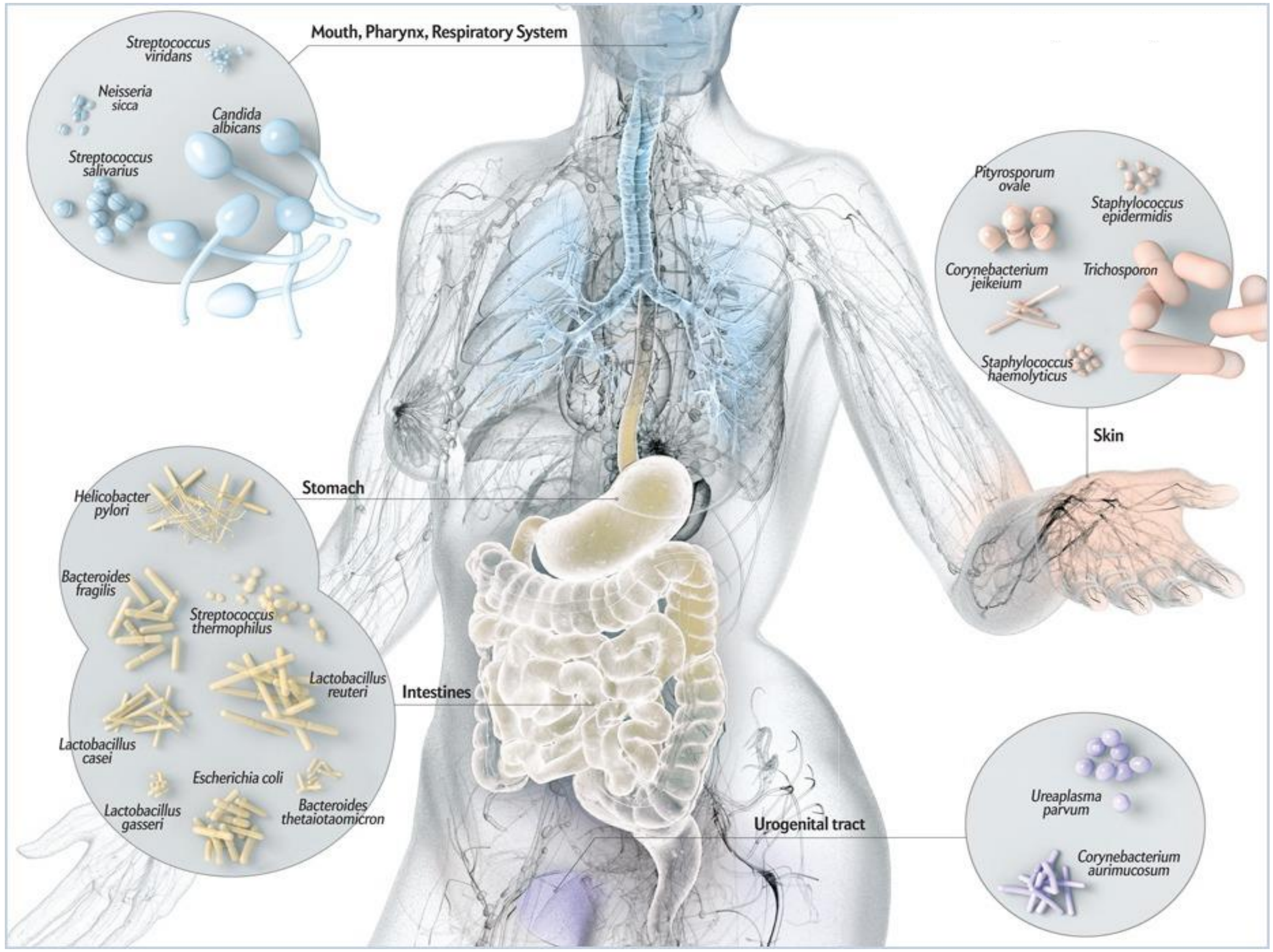
Prof.ssa Federica Facciotti

Dipartimento di Biotecnologie e Bioscienze
Università degli Studi di Milano-Bicocca

E-mail: federica.facciotti@unimib.it

The gut is the major site of contact in the body for foreign antigens

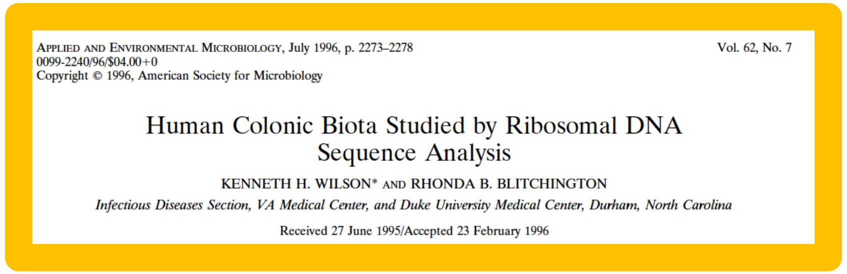
”the entire microbial community living in symbiosis with our body„



10 times more microbial cells than mammalian cells

100 times more genes

Resident microbiota consisting of 1010 – 1012 organisms per gram of luminal content.



Applied and Environmental Microbiology, July 1996, p. 2273–2278 Vol. 62, No. 7
0099-2240/96/$04.00+0
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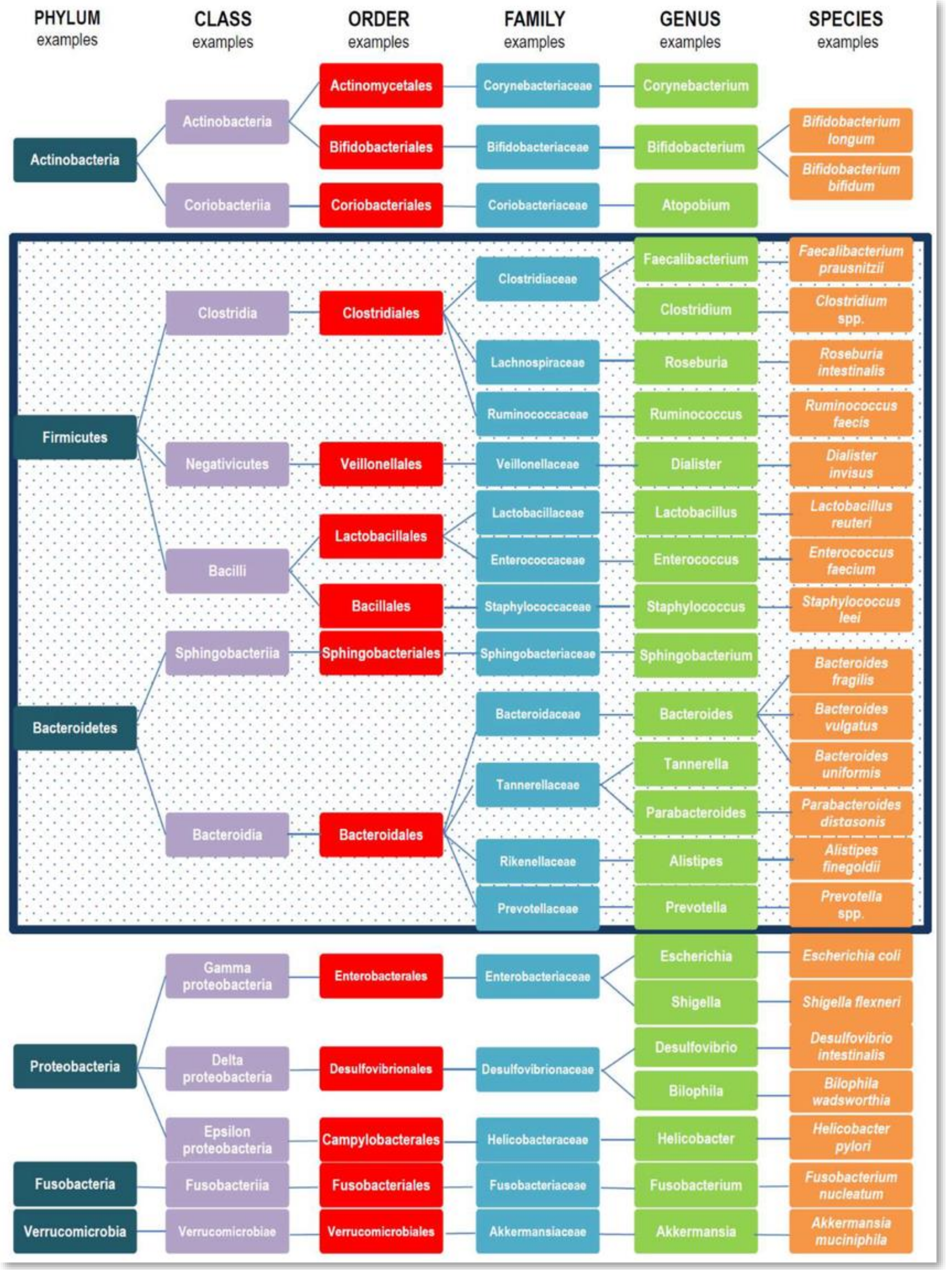
Human Colonic Biota Studied by Ribosomal DNA Sequence Analysis

KENNETH H. WILSON* and RHONDA B. BLITCHINGTON

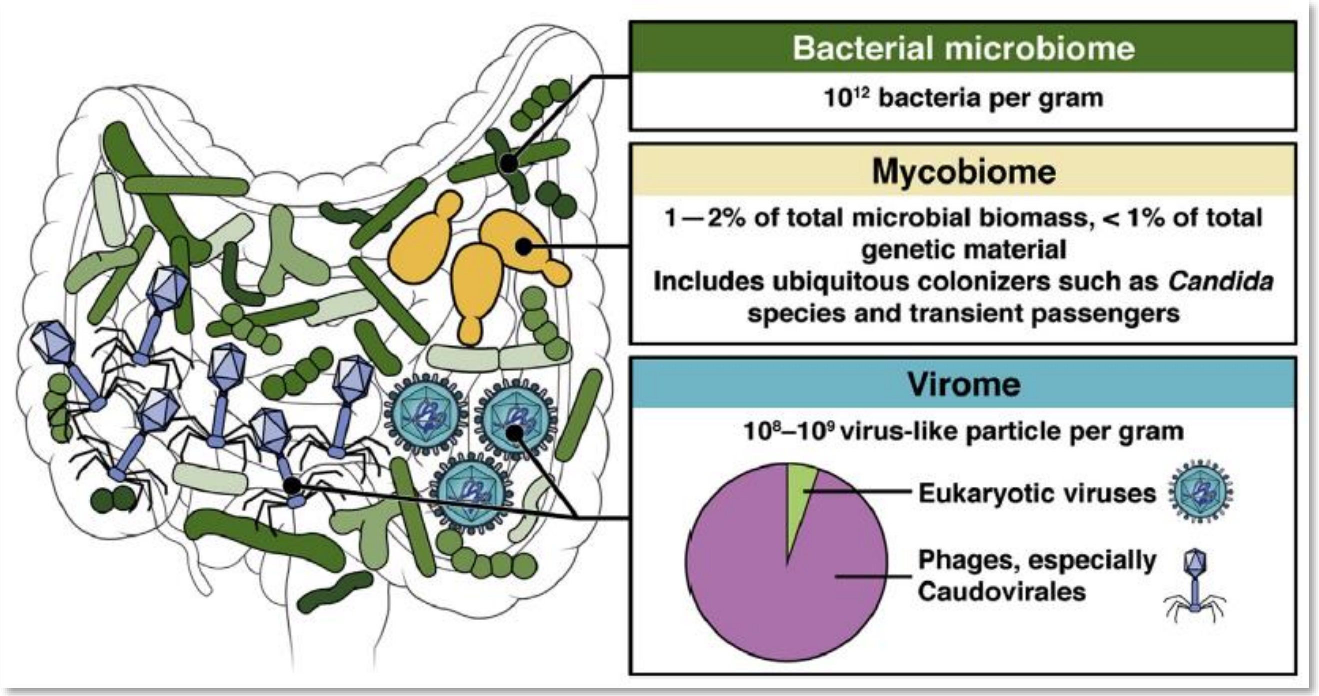
Infectious Diseases Section, VA Medical Center, and Duke University Medical Center, Durham, North Carolina

Received 27 June 1995/Accepted 23 February 1996

The microbiome as a superorganism



PHYLUM examples	CLASS examples	ORDER examples	FAMILY examples	GENUS examples	SPECIES examples
Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	Corynebacterium	
		Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium	*Bifidobacterium longum*
					Bifidobacterium bifidum
	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	Atopobium	
Firmicutes	Clostridia	Clostridiales	Clostridiaceae	Faecalibacterium	*Faecalibacterium prausnitzii*
				Clostridium	*Clostridium spp.*
			Lachnospiraceae	Roseburia	*Roseburia intestinalis*
			Ruminococcaceae	Ruminococcus	*Ruminococcus faecis*
	Negativicutes	Veillonellales	Veillonellaceae	Dialister	*Dialister invisus*
	Bacilli	Lactobacillales	Lactobacillaceae	Lactobacillus	*Lactobacillus reuteri*
			Enterococcaceae	Enterococcus	*Enterococcus faecium*
		Bacillales	Staphylococcaceae	Staphylococcus	*Staphylococcus leei*
Bacteroidetes	Sphingobacteriia	Sphingobacteriales	Sphingobacteriaceae	Sphingobacterium	
	Bacteroidia	Bacteroidales	Bacteroidaceae	Bacteroides	*Bacteroides fragilis*
					Bacteroides vulgatus
					Bacteroides uniformis
			Tannerellaceae	Tannerella	
				Parabacteroides	*Parabacteroides distasonis*
			Rikenellaceae	Alistipes	*Alistipes finegoldii*
			Prevotellaceae	Prevotella	*Prevotella spp.*
Proteobacteria	Gamma proteobacteria	Enterobacterales	Enterobacteriaceae	Escherichia	*Escherichia coli*
				Shigella	*Shigella flexneri*
	Delta proteobacteria	Desulfovibrionales	Desulfovibrionaceae	Desulfovibrio	*Desulfovibrio intestinalis*
				Bilophila	*Bilophila wadsworthia*
	Epsilon proteobacteria	Campylobacterales	Helicobacteraceae	Helicobacter	*Helicobacter pylori*
Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	Fusobacterium	*Fusobacterium nucleatum*
Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiales	Akkermansiaceae	Akkermansia	*Akkermansia muciniphila*



Bacterial microbiome

10^{12} bacteria per gram

Mycobiome

1—2% of total microbial biomass, < 1% of total genetic material

Includes ubiquitous colonizers such as *Candida* species and transient passengers

Virome

10^8–10^9 virus-like particle per gram

Iliev DI, et al. Gastroenterology 2021;160:1050–1066

Factors influencing the composition and function of the microbiota

Geographic origin

lifestyle

diet

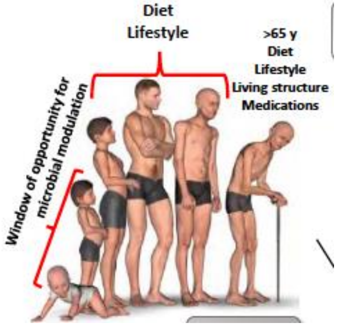
hygien

antibiotics

genetics

Mode of delivery

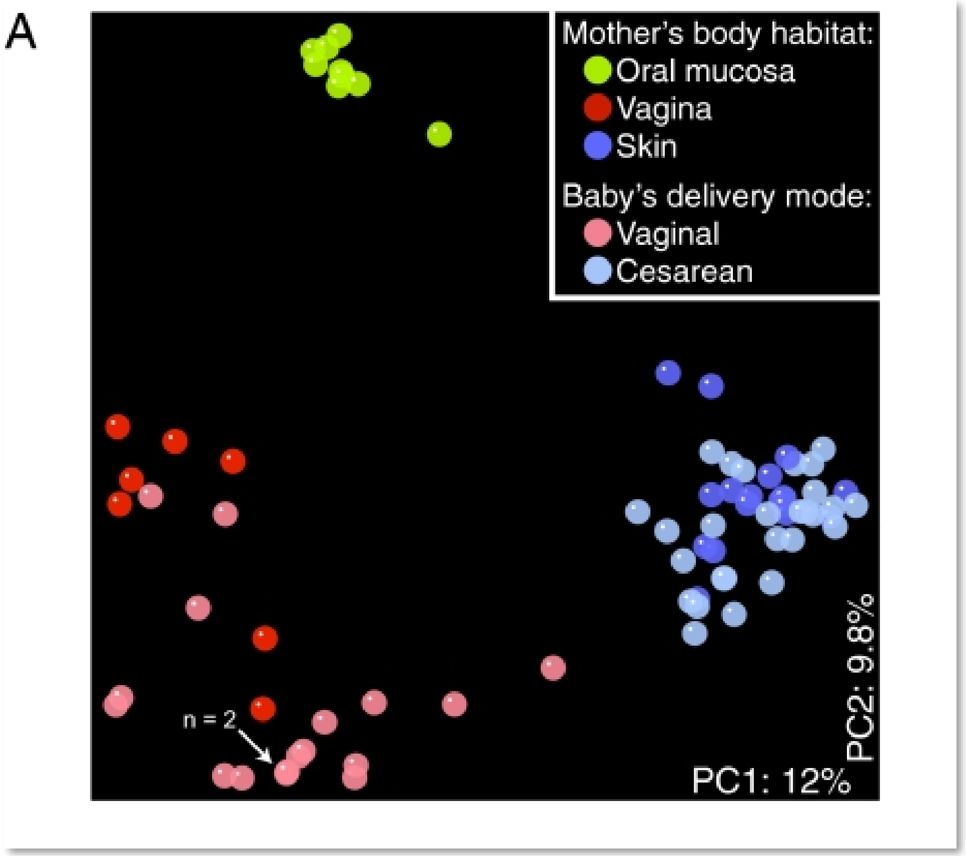
age



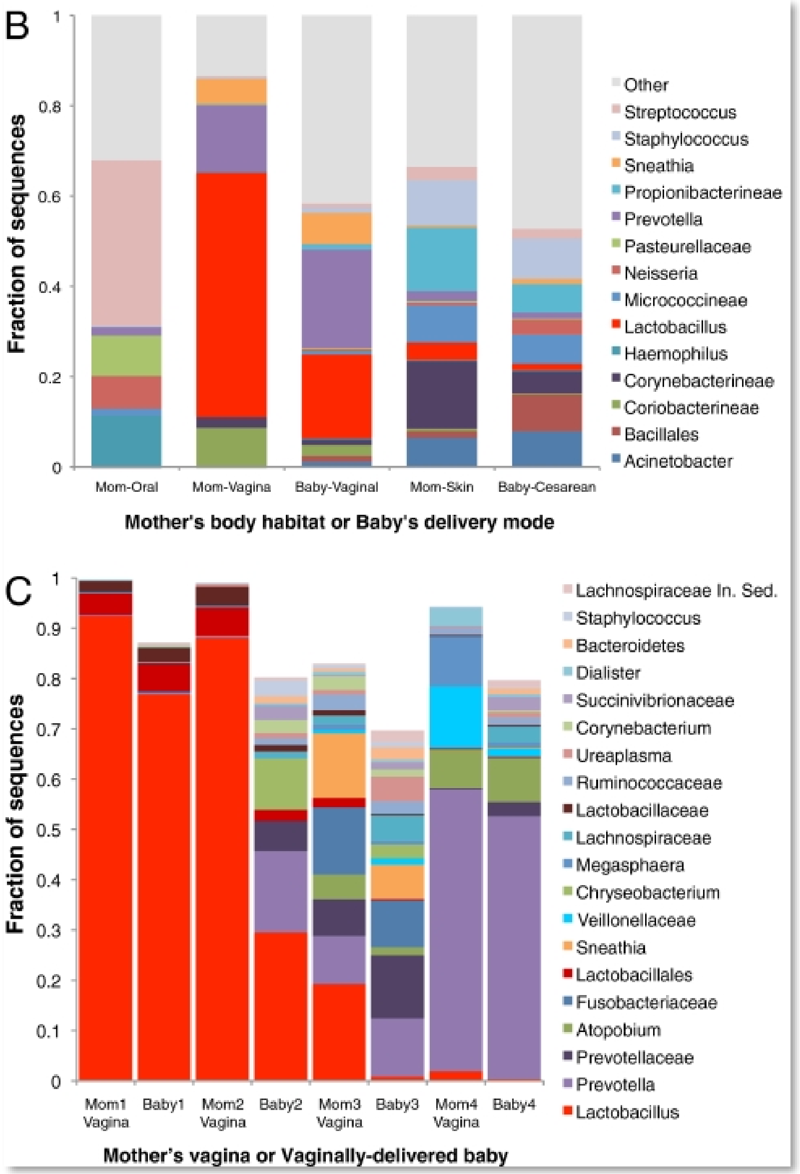
normobiosis

dysbiosis

Microbiota is acquired at birth and during lactation

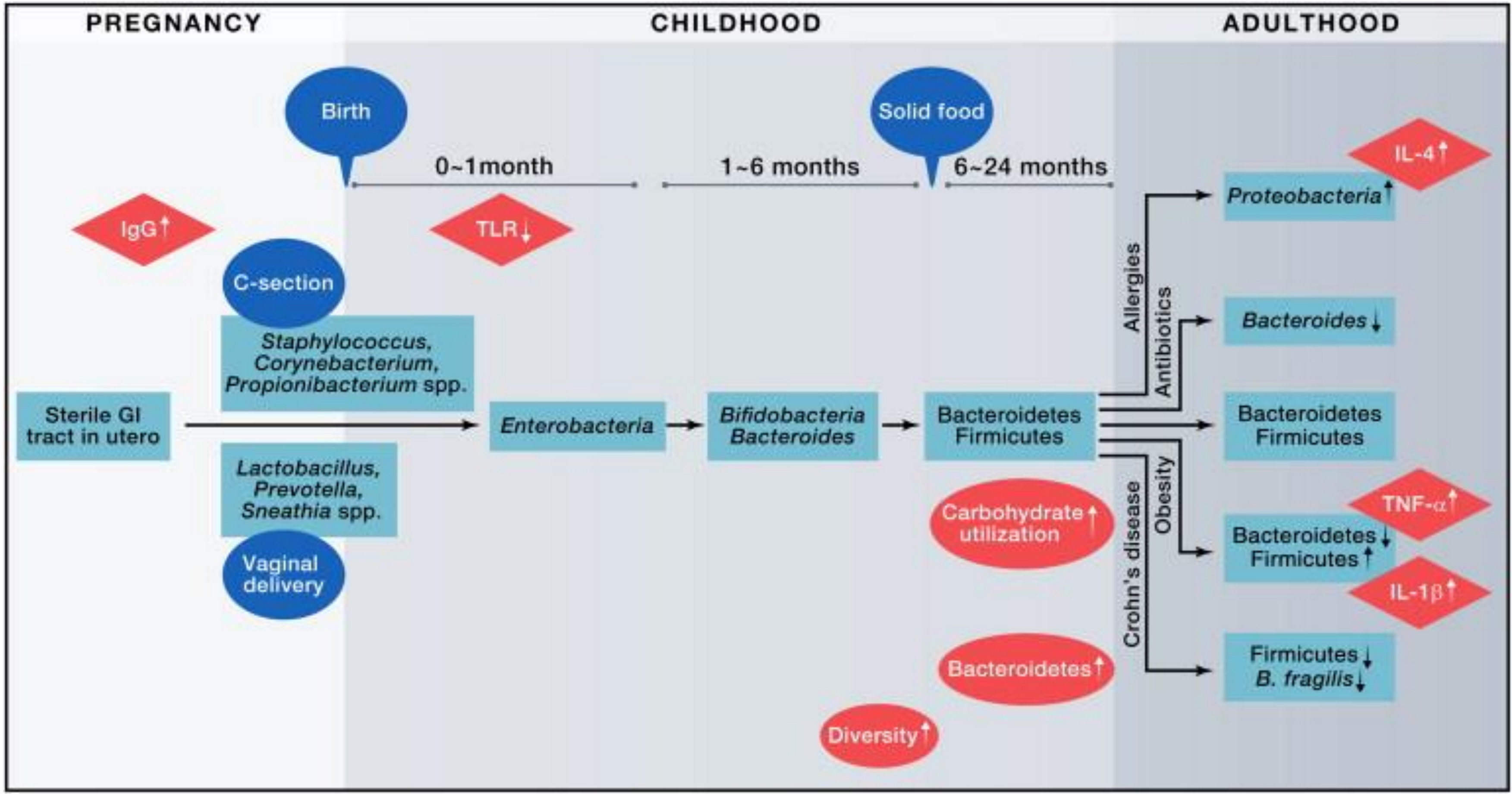


C-section: typical skin taxa, including Staphylococcus spp
Vaginally delivered: Lactobacillus, Prevotella, Atopobium, or Sneathia spp.



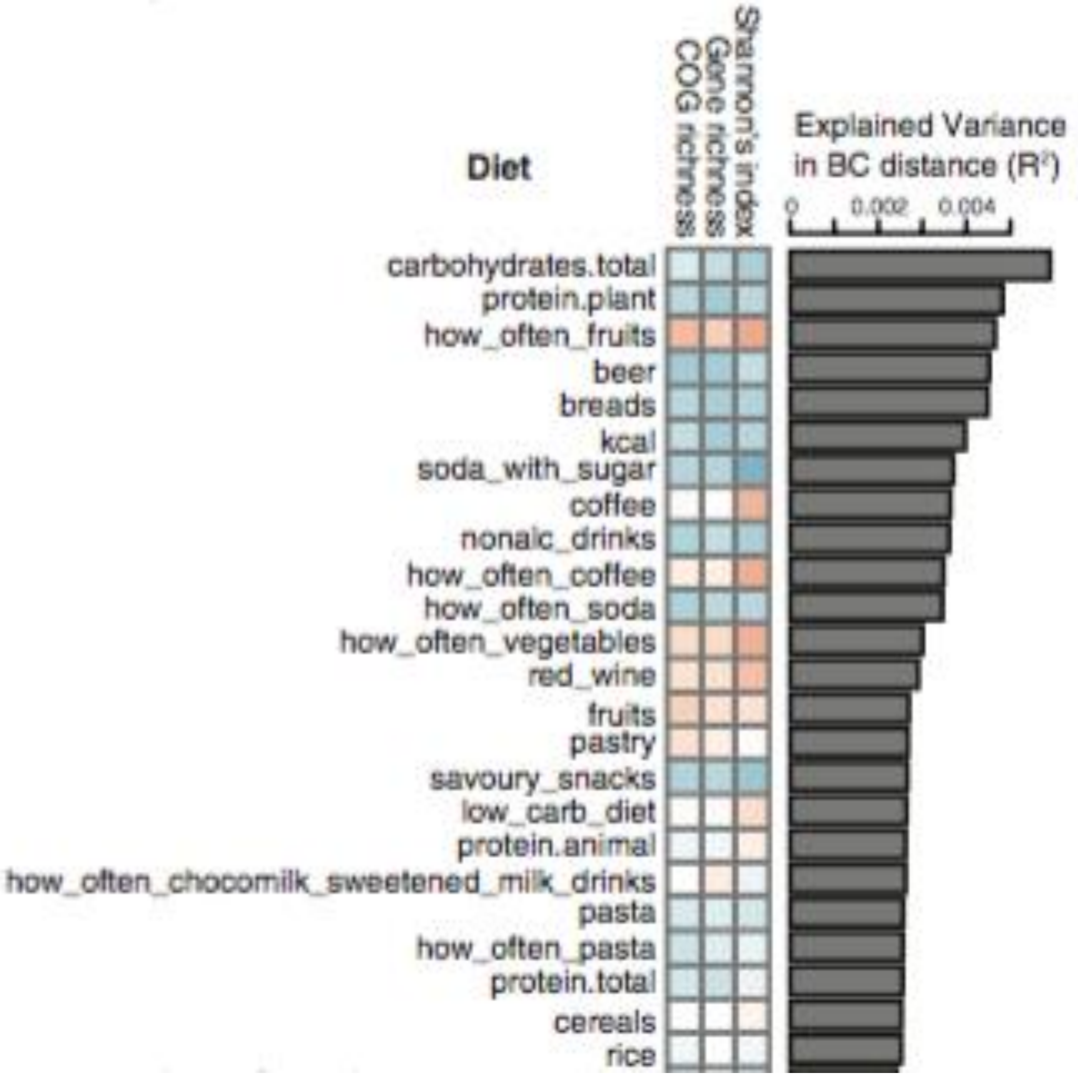
Dominguez-bello Proc Natl Acad Sci U S A. 2010 June 29; 107(26): 11971–11975

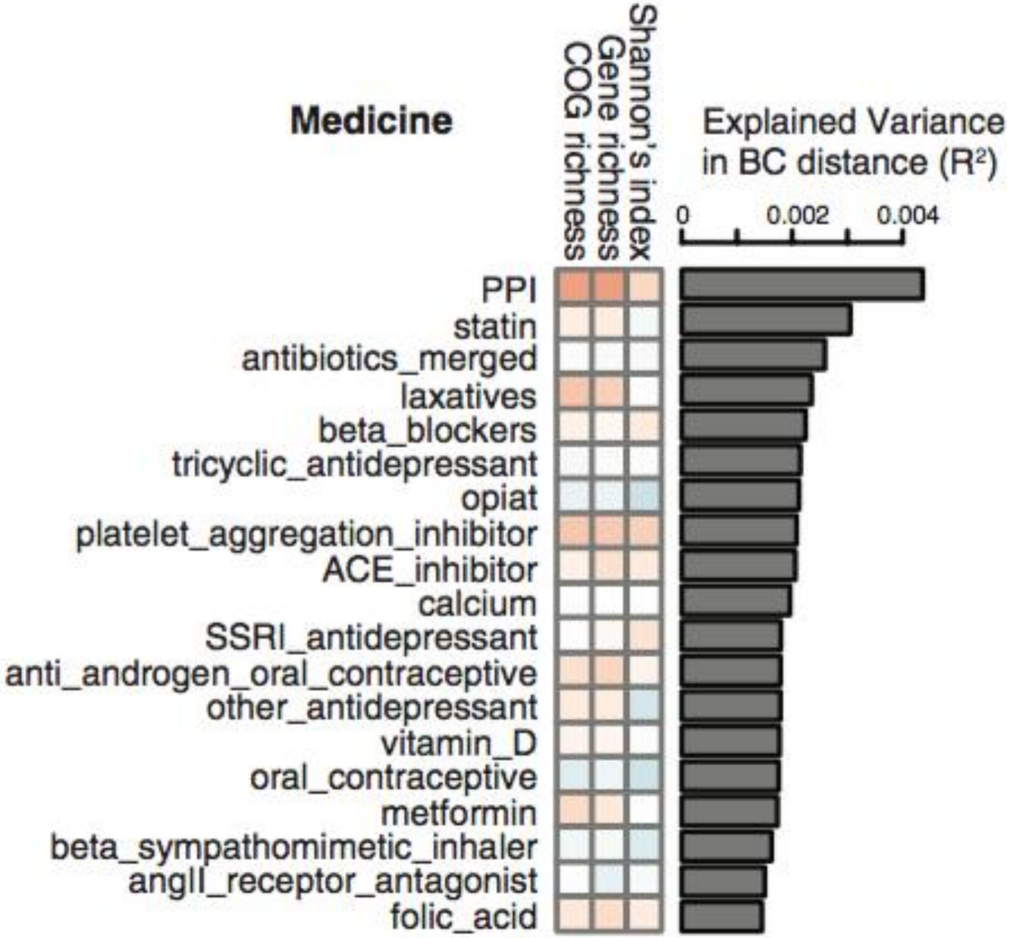
Establishment of the microbiota



Clemente et al. Cell 148, (2012), Pages 1258–1270

Diet and drugs can affect the microbiota



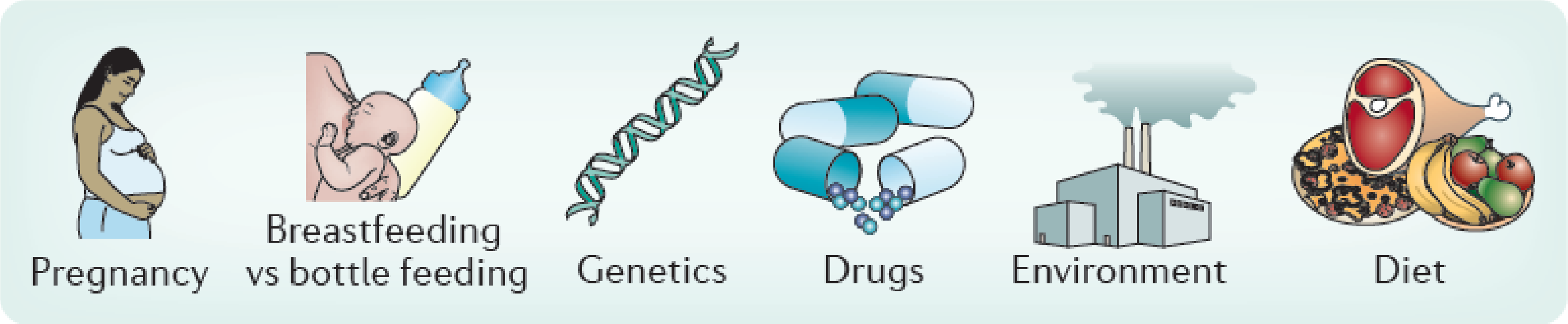


Zhernakova et al. Science 2016

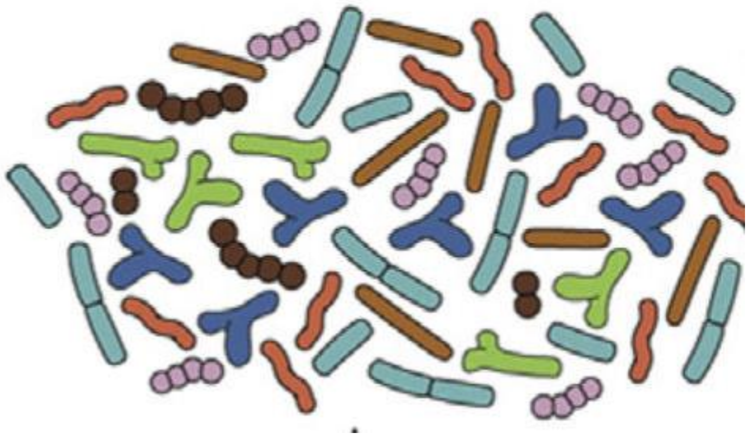
Functions of the intestinal microbiome

- Food breakdown
- Vitamin metabolism
- Brain development
- Immune system maturation
- Defense against pathogens

From EUBIOSIS to DYSBIOSIS

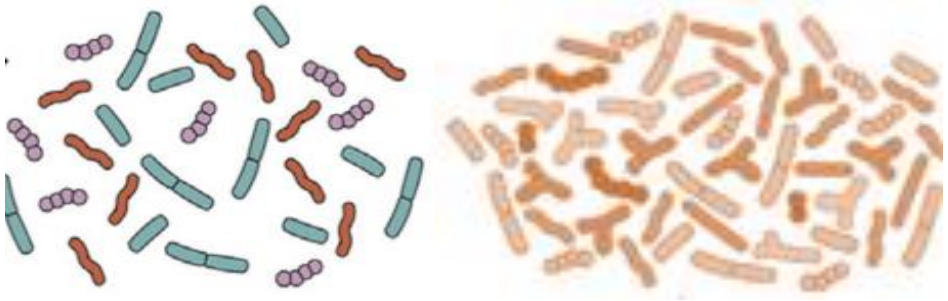


Healthy microbiota



Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

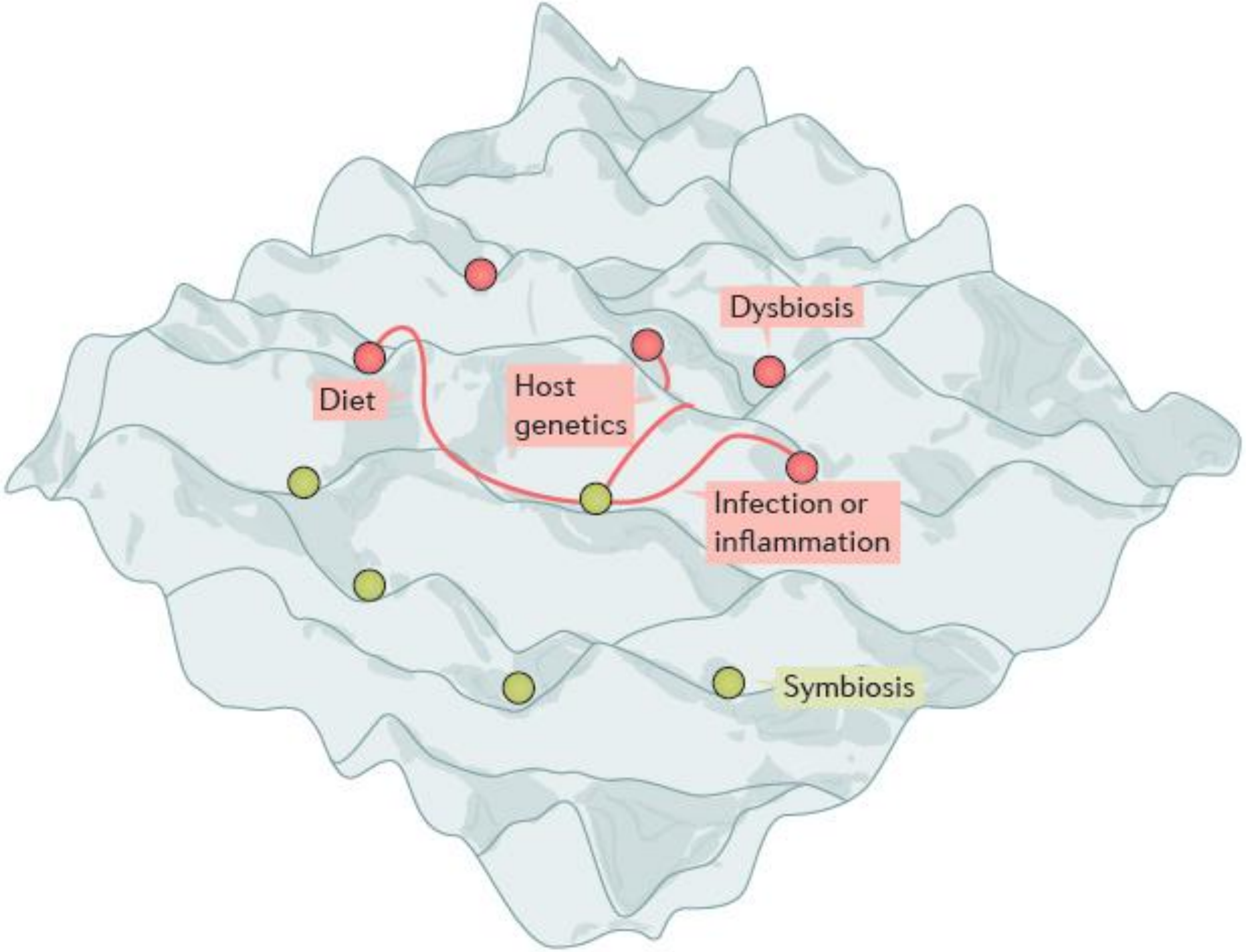
Dysbiosis
(Loss of eubiosis)



Quantity

Quality

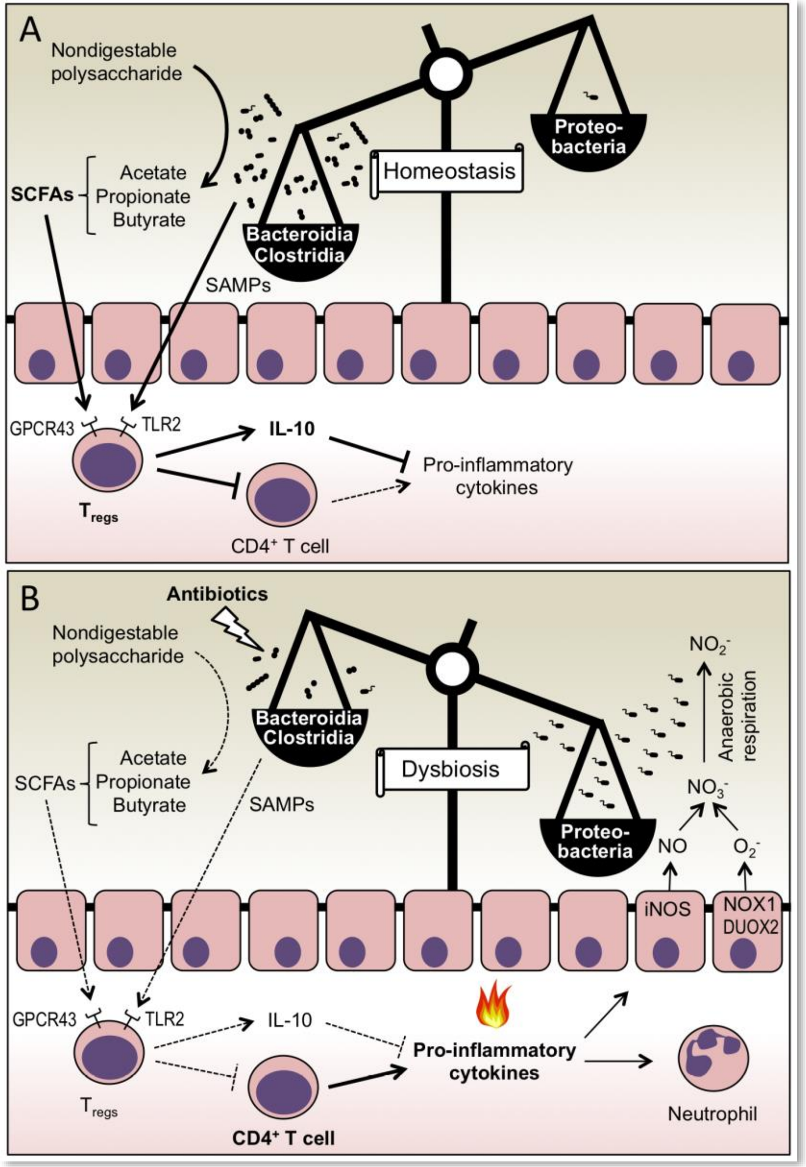
struttura del microbiota è dinamica



Resilience of the gut microbiota = the capacity to return to the original state upon perturbation. “Pathologic” dysbiosis occurs when a set of environmental and host-related factors exceed the resistance and resilience of the microbiota

Is the microbiome relevant for human health (and for clinicians)?

Colonization Resistance: Battle of the Bugs or (failed) interaction with the Host?



Acute dysbiosis : described with the "Anna Karenina principle"

"All healthy microbiomes are alike but dysbiotic communities are all dysbiotic in their own ways" (Zaneveld et al 2017).

Examples of Diseases in which the Microbiota has been involved:

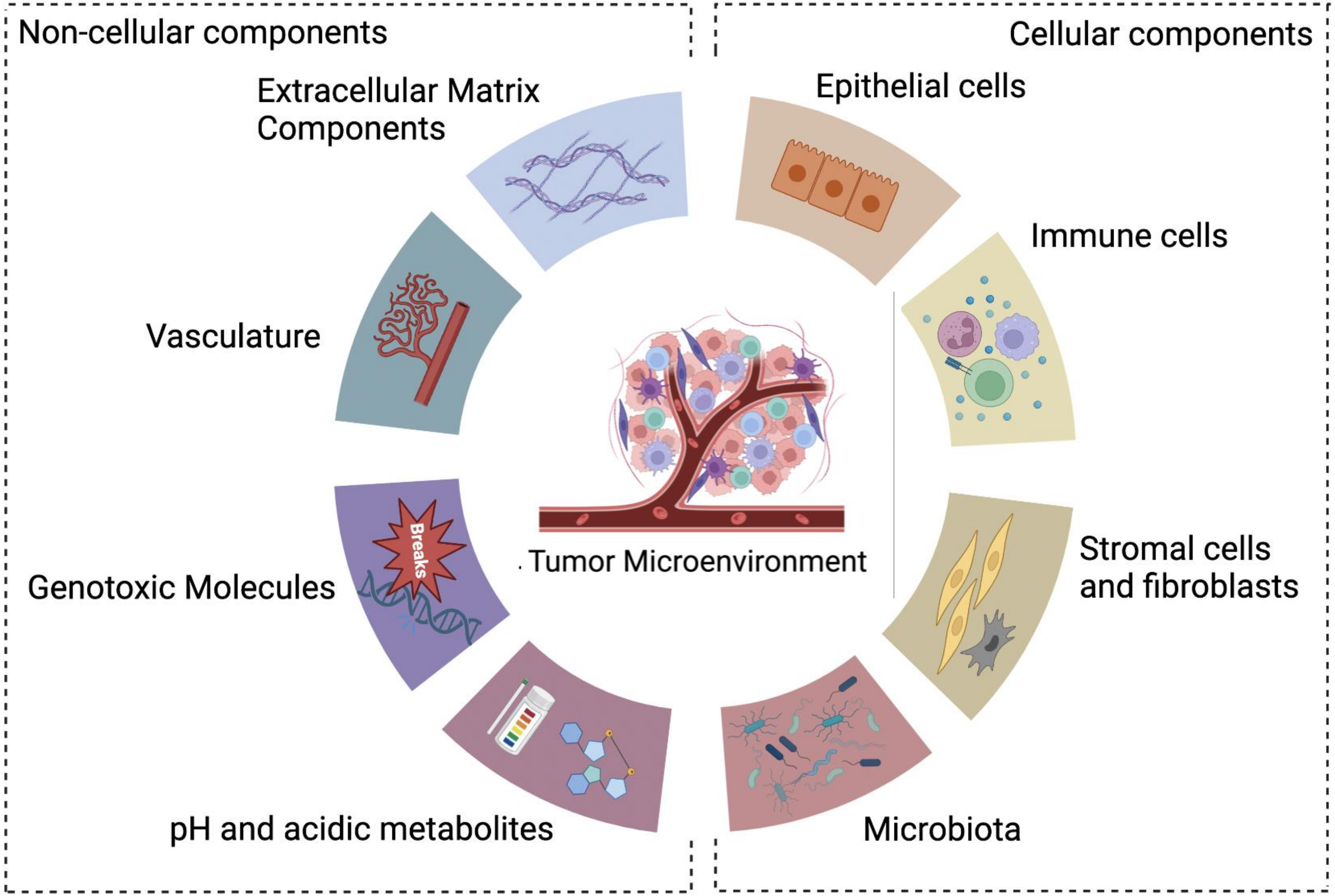
- Parkinson's Disease
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Inflammatory Bowel Diseases
- Liver Diseases
- GVHD and Hematologic Malignancies
- Colo-Rectal Cancer
- Many Others (MDR, Metabolic Diseases, etc.).....

Alanna M. Spees AM, et al. PLoS Pathog. 2013;9(11):e1003730

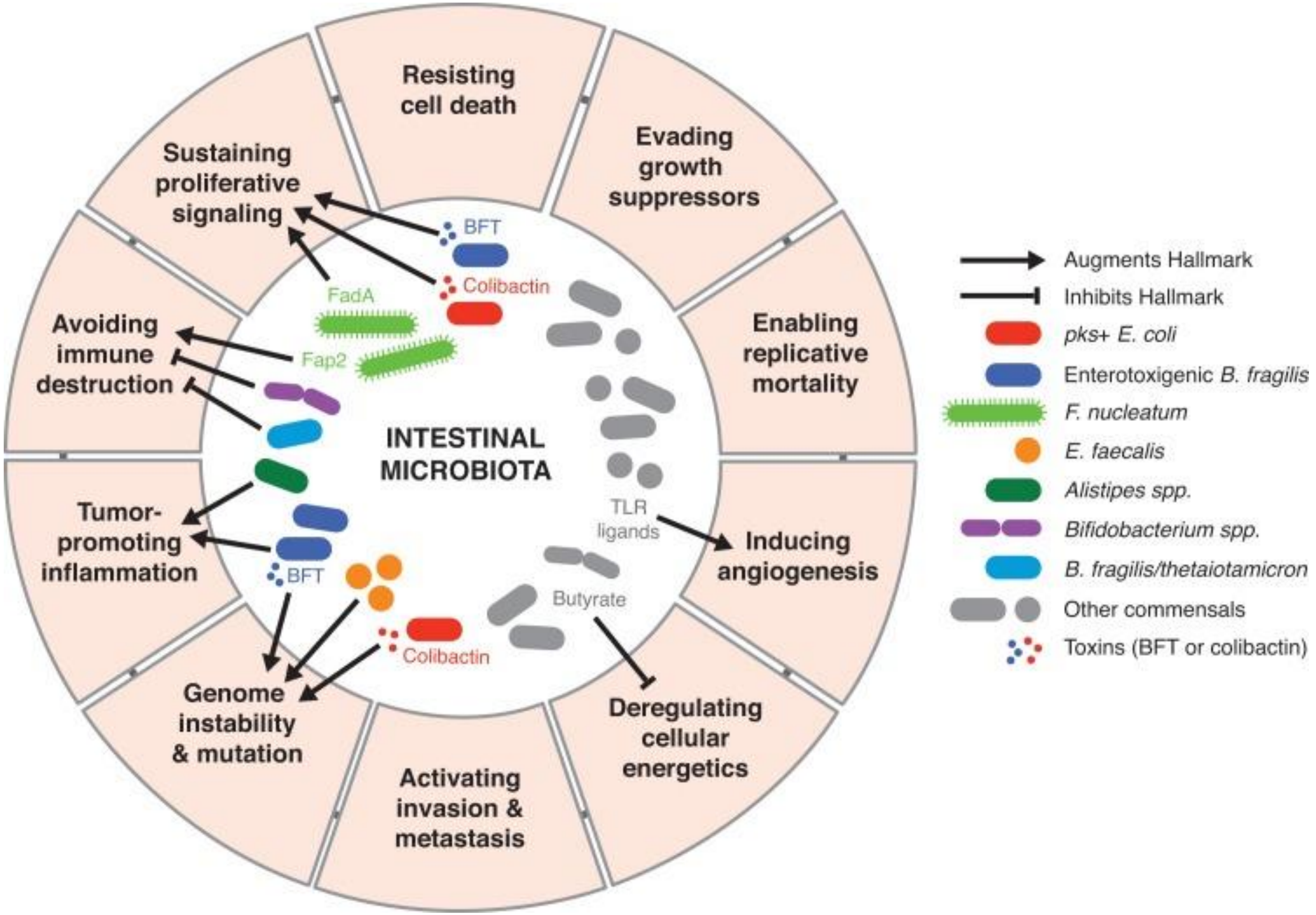
How can we use the info?

- Risk prediction
- Stratification for best treatment
- theraphy

L'ambiente tumorale: microbiota e sistema immunitario partecipano attivamente



Gut microbiota influences carcinogenesis

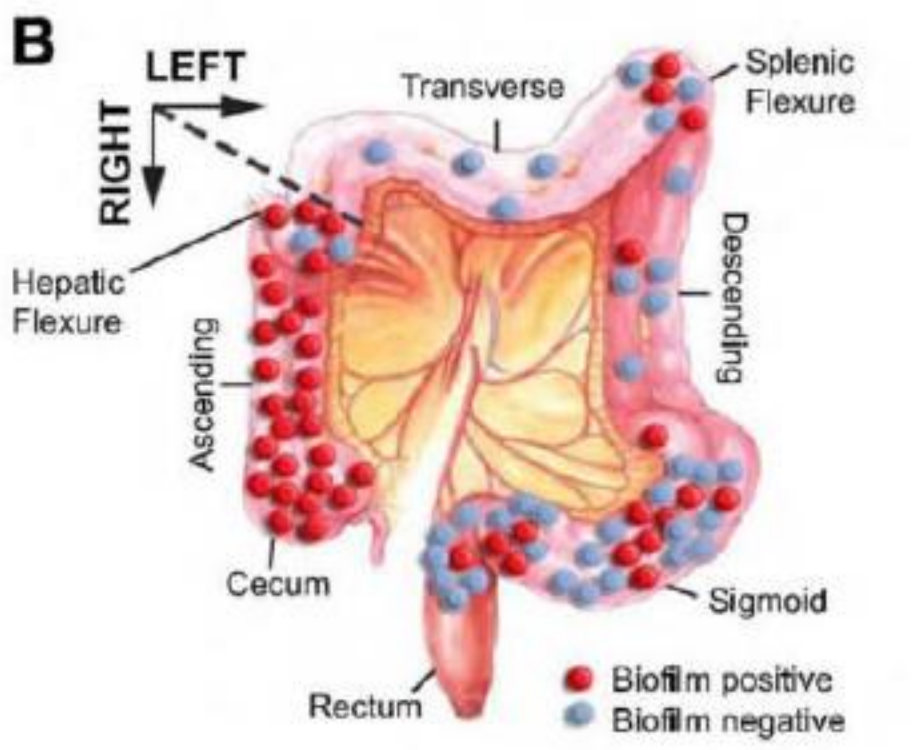


Fulbright *et al* 2017 PLoS Pathog

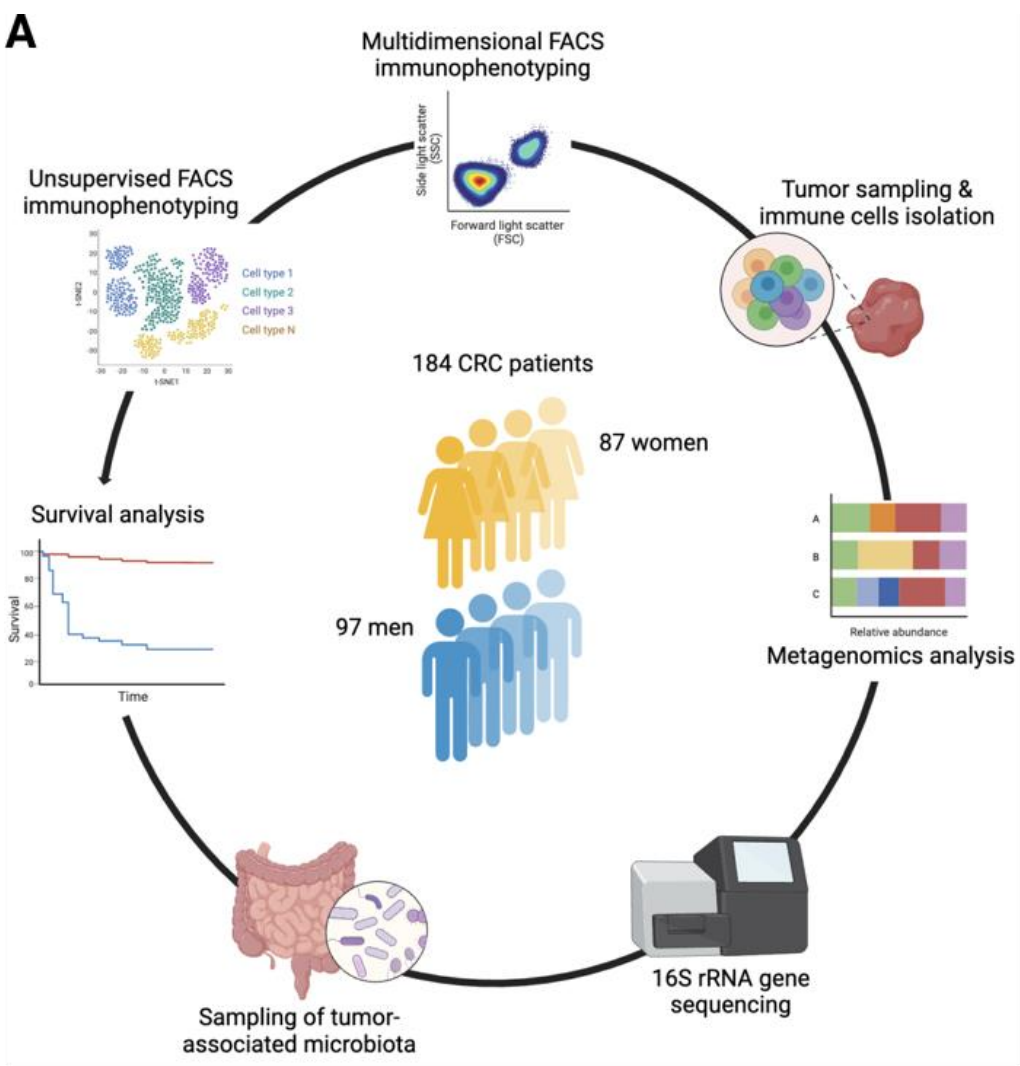
F. nucleatum

- Higher abundance in CRC patients
- Intratumoral/tumoral localization
- **Biofilm production**

- MoA: FadA activates pathway E-cadherin-B catenin
- pro-tumorigenic environment
- Inhibits IS by Fap2-TIGIT
- Upreglates miRNA21 (>> cancer cells proliferation)

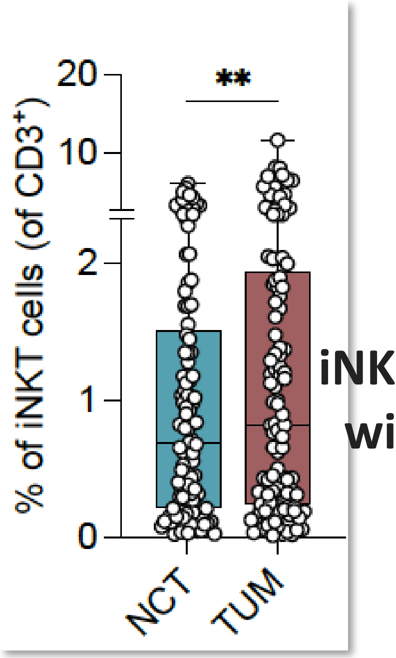


How TME-microbiome-T cells interact in CRC patients and its functional outcome



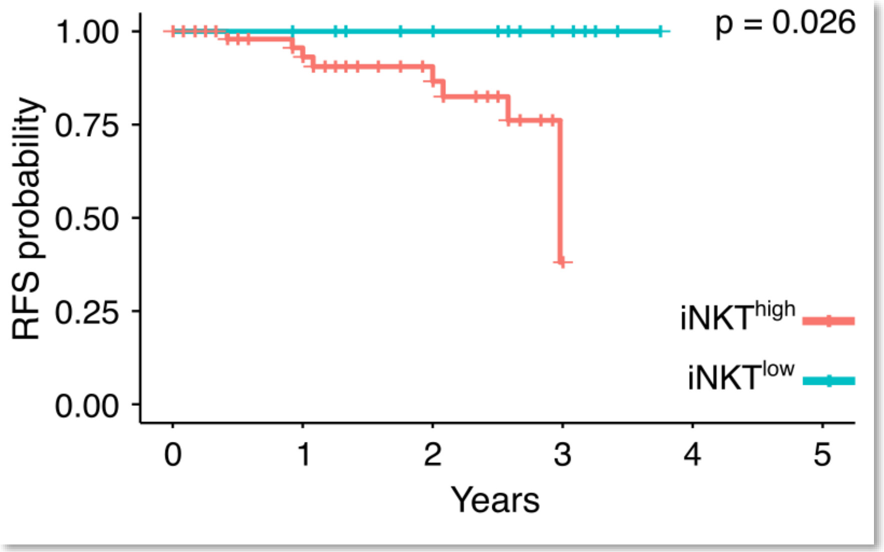
1. Sustain a suppressive microenvironment
2. Inhibit killing capabilities
3. Regional compartimentalization

CRC lesions are infiltrated by iNKT cells

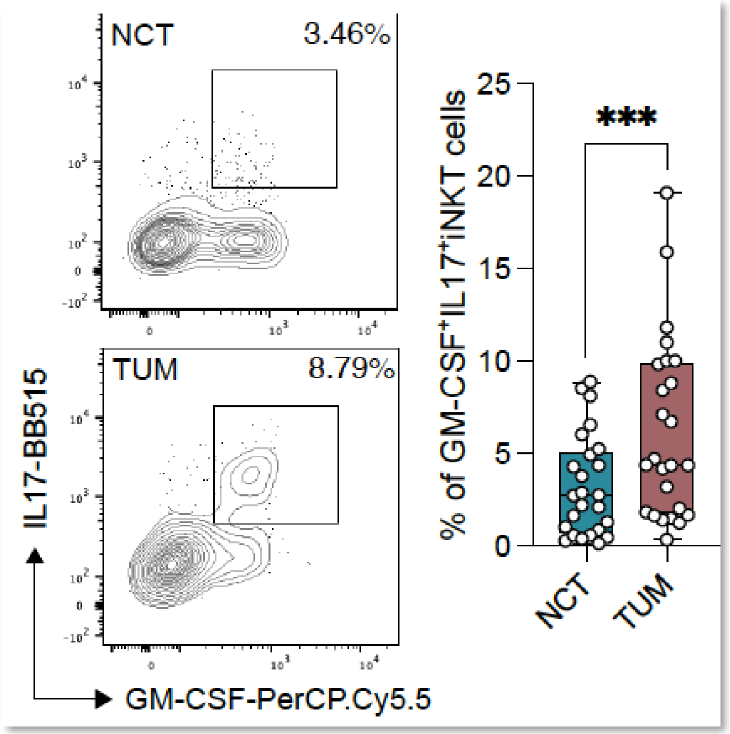


BUT

iNKT cell infiltration correlates with poor patient outcomes



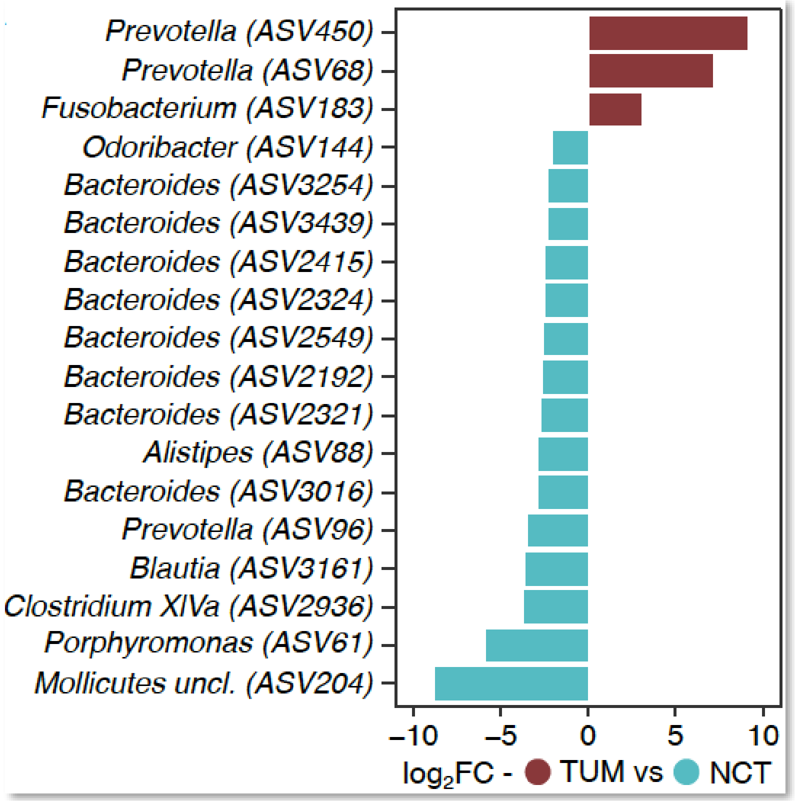
Intratumor iNKT cell show a GMCSF+IL17+ phenotype

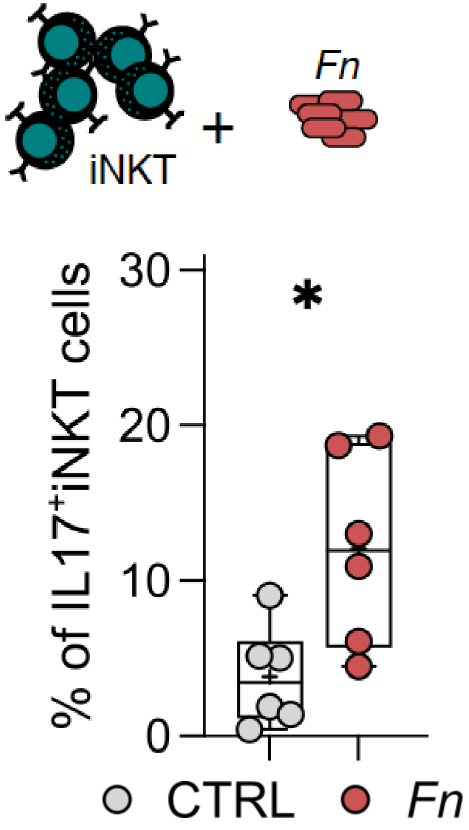


Lattanzi*, Strati*, 2023; Mucosal Immun

F. nucleatum induces iNKT17 cells

Microbiome profiling highlights the presence of IT Prevotella and F.nucleatum

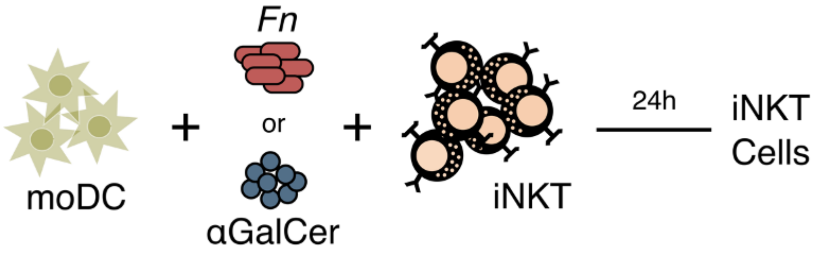




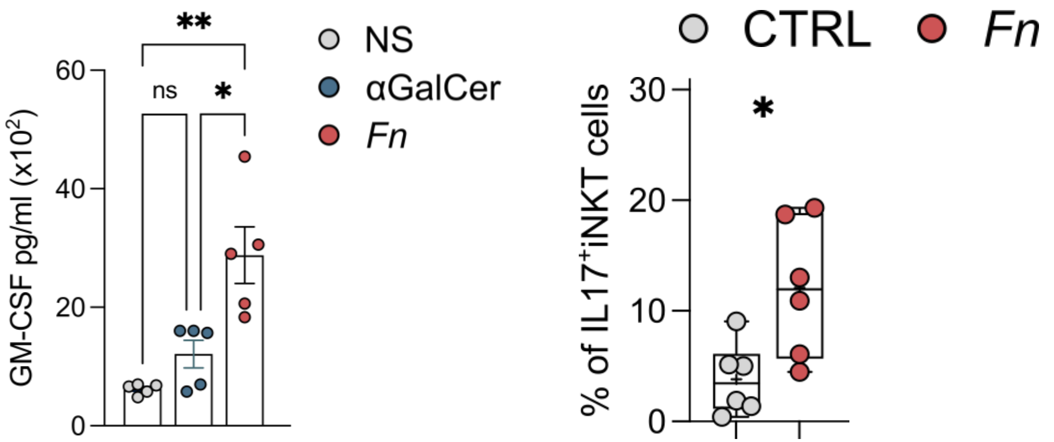
F.nucleatum induces IL17 secretion by iNKT cells

Lattanzi*, Strati*, 2023; Mucosal Immun

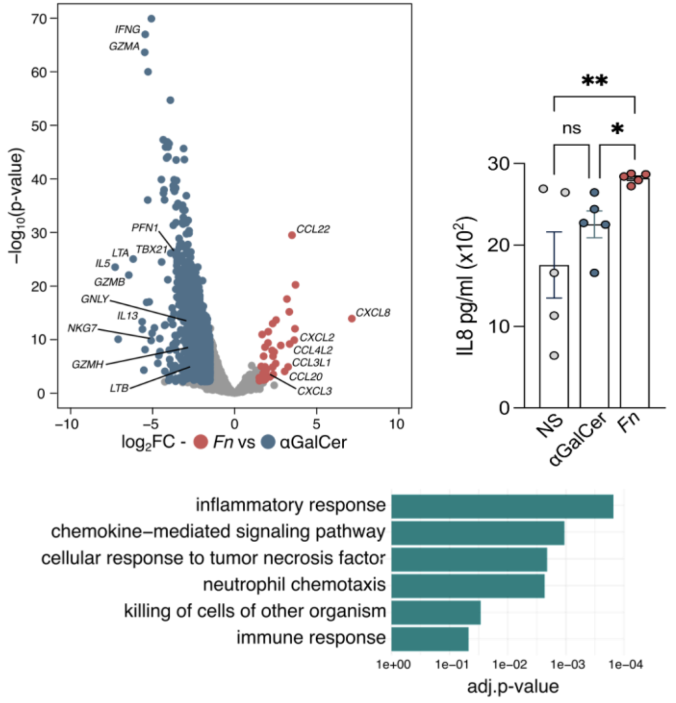
Functional consequences of Fn-iNKT interaction



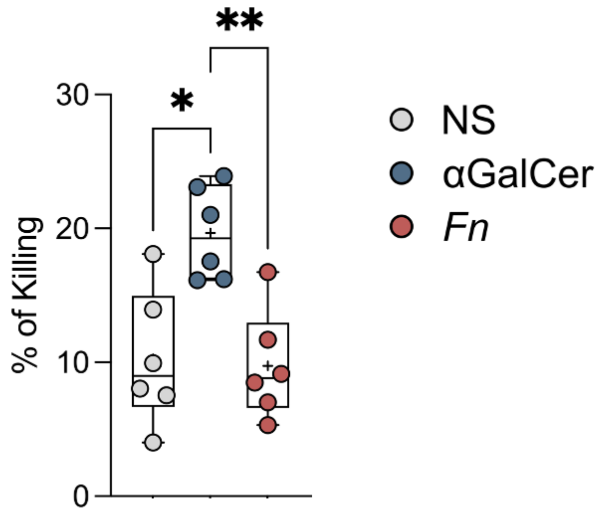
Induces GMCSF and IL17 production



Promotes iNKT-mediated neutrophils recruitment

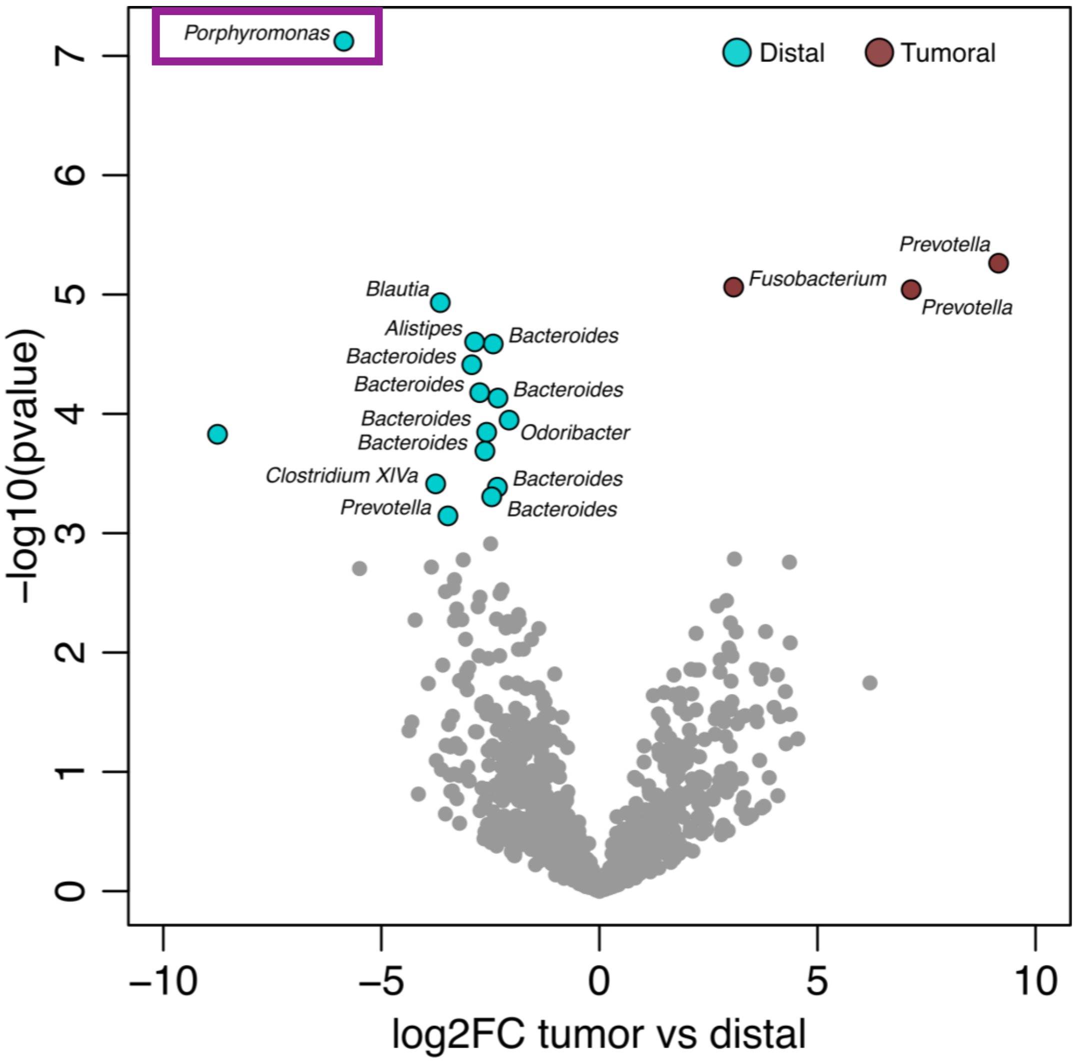


Inhibits killing capability



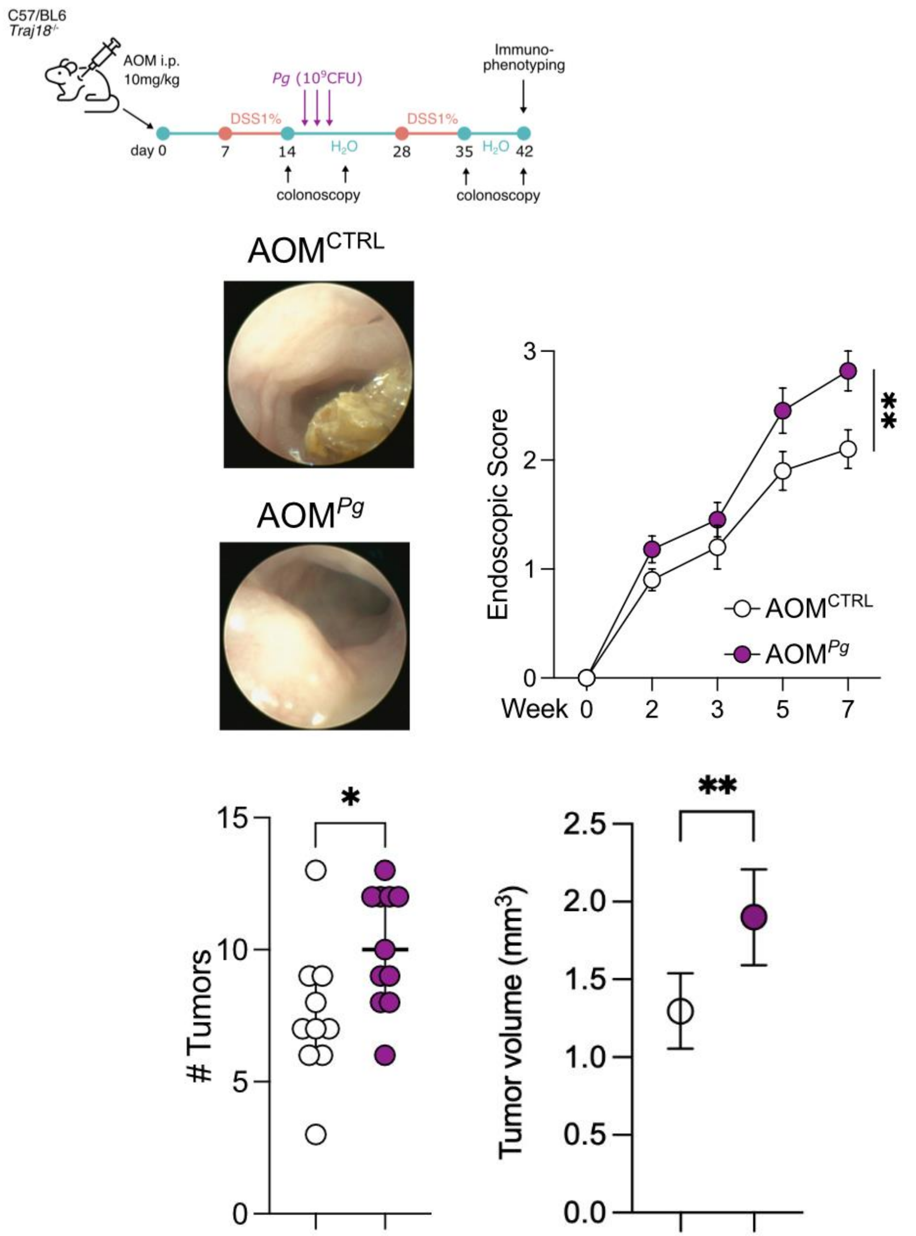
Lattanzi, Strati Mucosal Immunology 2023

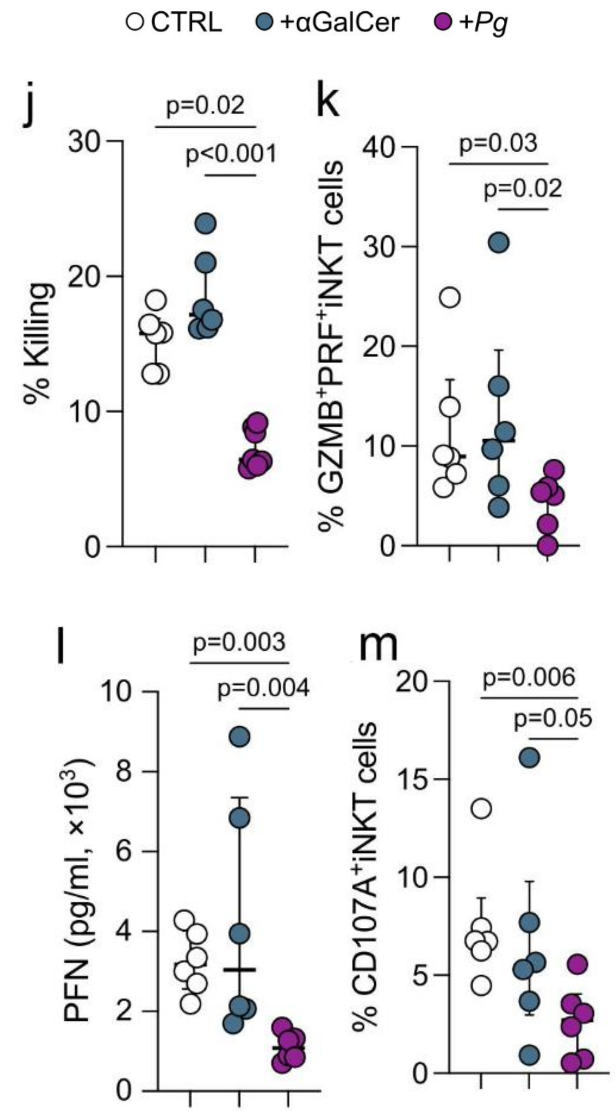
Distal tissues are enriched in Porphyromonas Gingivalis



Diaz- Basabe et al., 2024 Gut

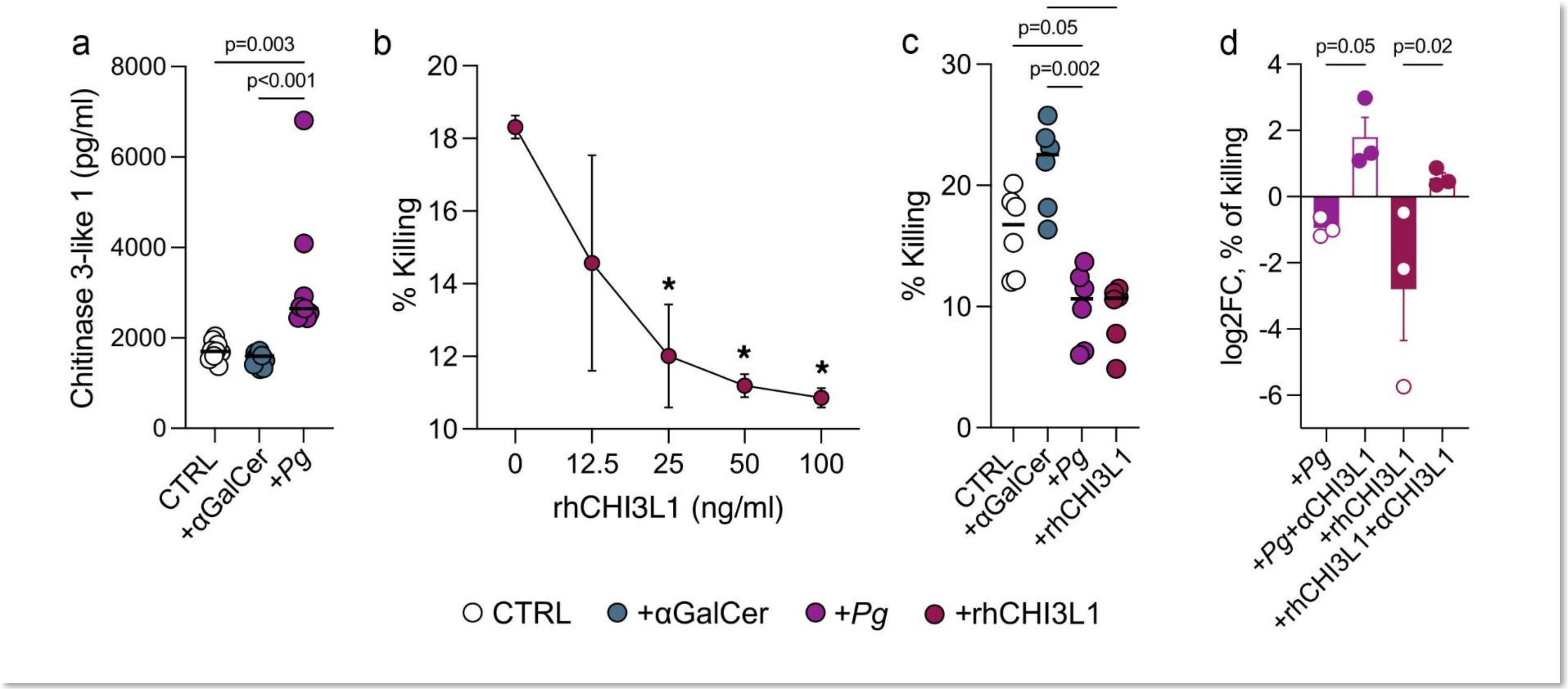
P. gingivalis impairs iNKT cell cytotoxicity



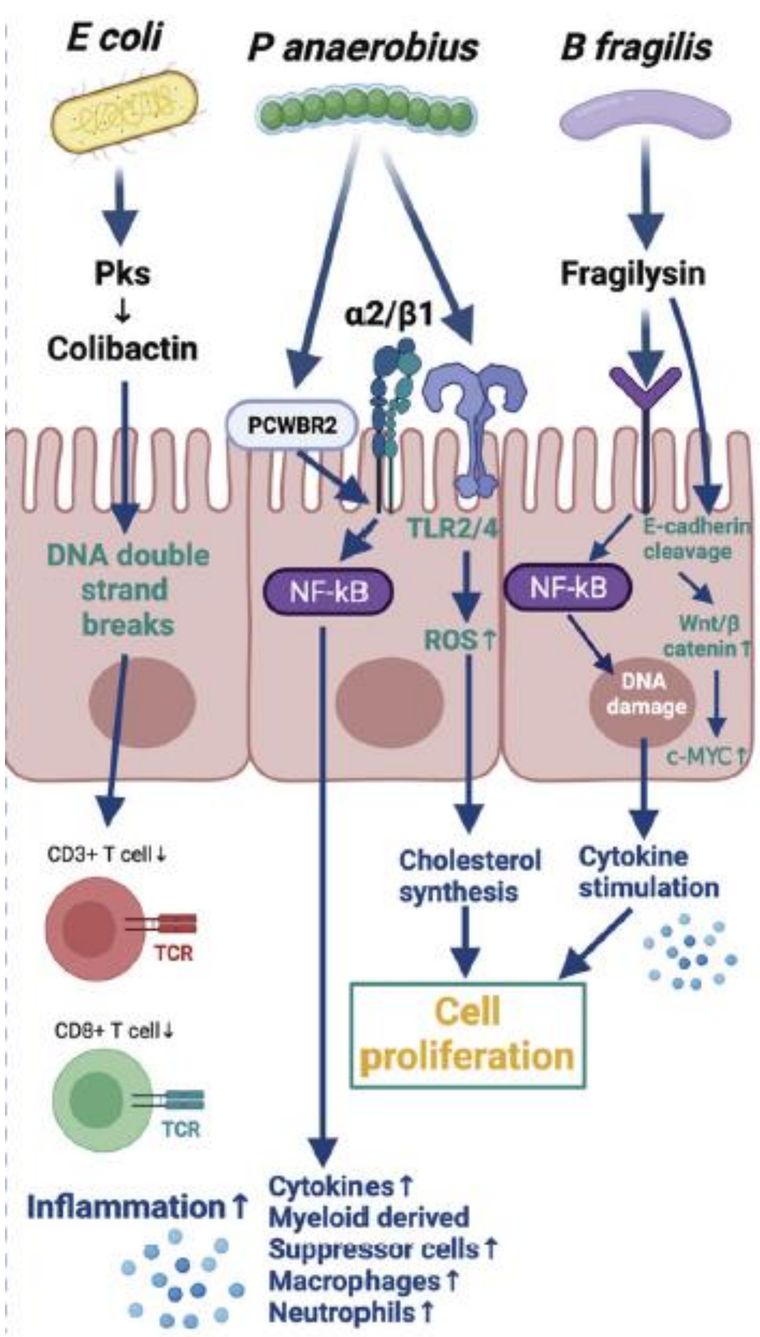


Diaz-Basabe et al., 2024 Gut

P. gingivalis exerts its effect on iNKT cells through CHI3L1



Diaz-Basabe et al., 2024 Gut

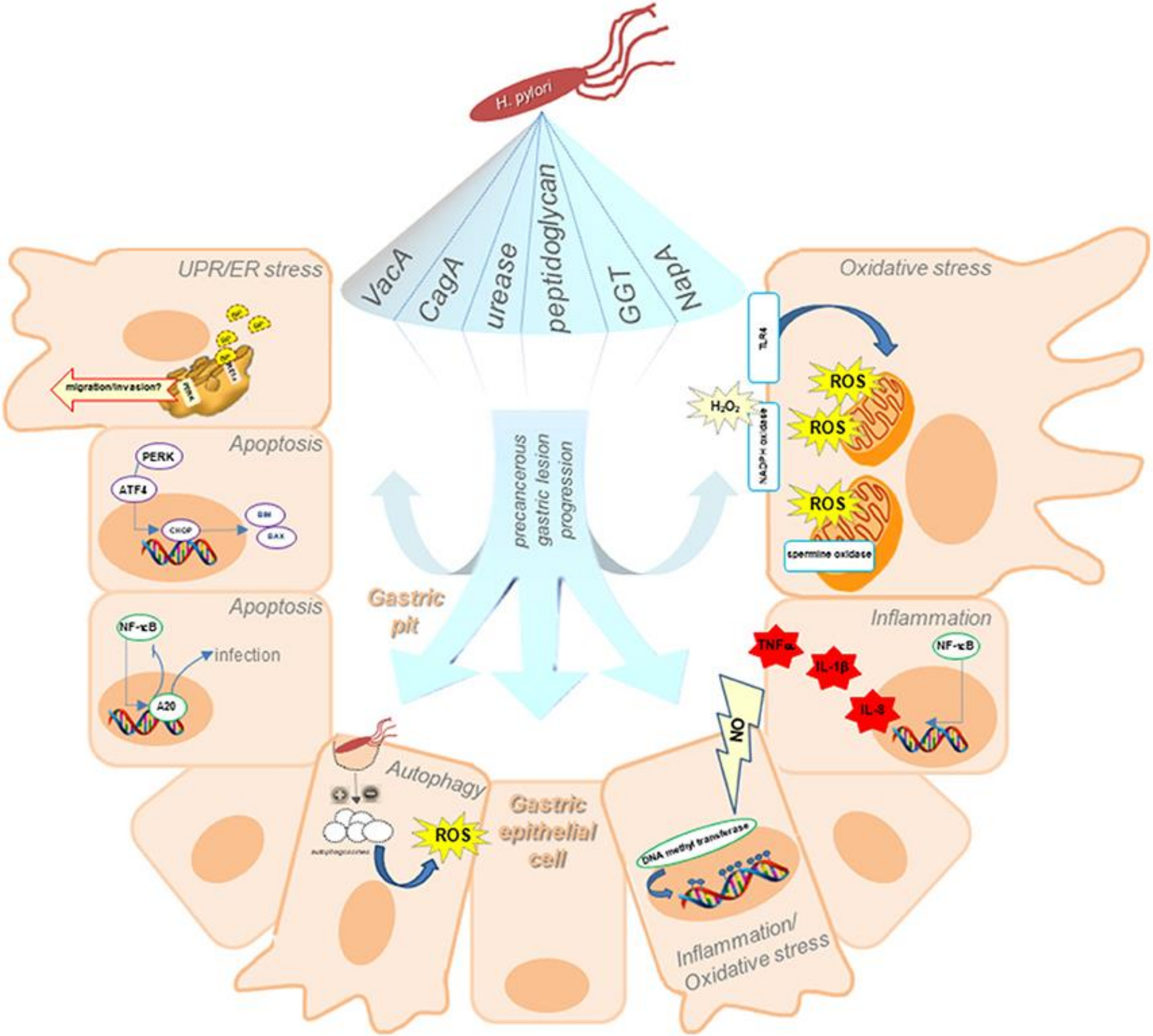


E coli , B fragilis, P anaerobius

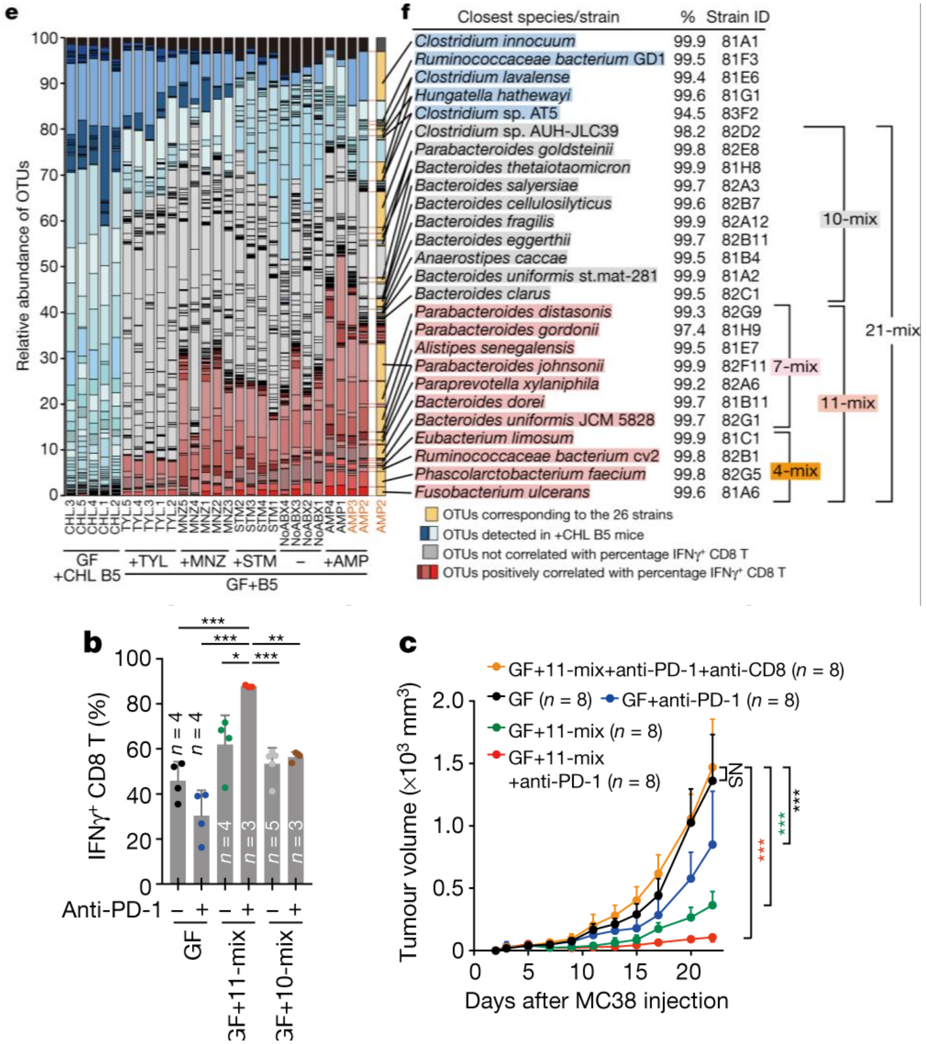
- Produce TOXINS
- Activate pathways of DNA damage, pro-inflammatory responses and TLRs interaction
- pathways NFK-B/Wnt/Bcatenin
- >>>cell proliferation

- **E. coli** > pks (DNA double strands breaks)
- **B.fragilis** > fragilysin > wnt patwhay
- **P. anaerobius** > a2b1 > proliferative pathway

H. pylori

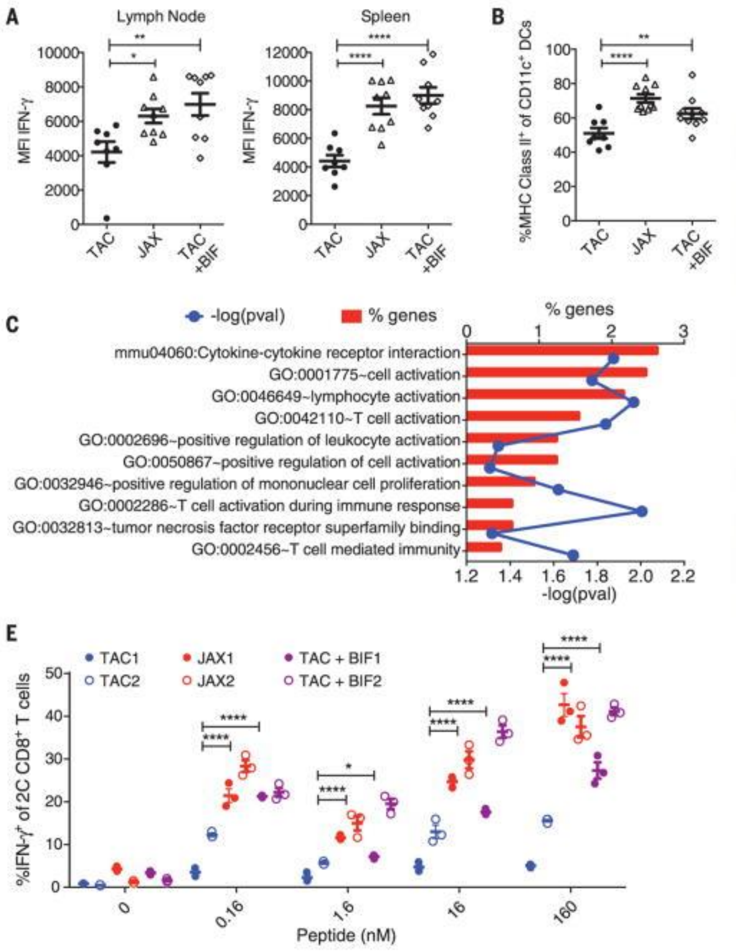

H. pylori
VacA
CagA
urease
peptidoglycan
GGT
NapA
precancerous gastric lesion progression
Gastric pit
UPR/ER stress
migration/invasion?
PERK
Apoptosis
PERK
ATF4
CHOP
BIM
BAX
Apoptosis
NF-κB
infection
A20
Autophagy
autophagosomes
ROS
Gastric epithelial cell
Oxidative stress
TLR4
H_2O_2
NADPH oxidase
ROS
ROS
ROS
spermine oxidase
Inflammation
TNFα
IL-1β
IL-8
NF-κB
NO
DNA methyl transferase
Inflammation/ Oxidative stress

Positive outcomes

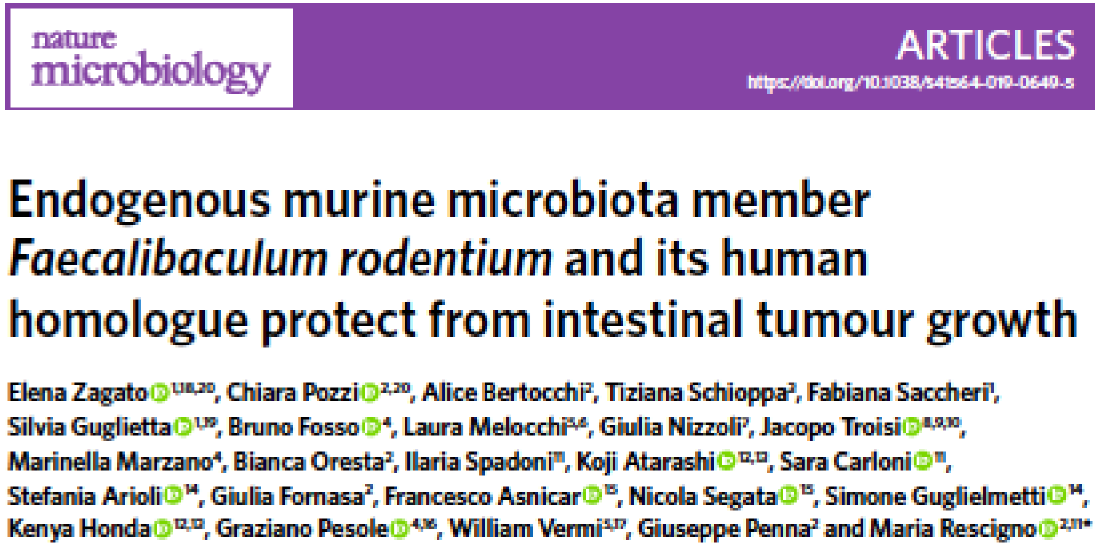


Closest species/strain	%	Strain ID
Clostridium innocuum	99.9	81A1
Ruminococcaceae bacterium GD1	99.5	81F3
Clostridium lavalense	99.4	81E6
Hungatella hathewayi	99.6	81G1
Clostridium sp. AT5	94.5	83F2
Clostridium sp. AUH-JLC39	98.2	82D2
Parabacteroides goldsteinii	99.8	82E8
Bacteroides thetaiotaomicron	99.9	81H8
Bacteroides salyersiae	99.7	82A3
Bacteroides cellulosilyticus	99.6	82B7
Bacteroides fragilis	99.9	82A12
Bacteroides eggerthii	99.7	82B11
Anaerostipes caccae	99.5	81B4
Bacteroides uniformis st.mat-281	99.9	81A2
Bacteroides clarus	99.5	82C1
Parabacteroides distasonis	99.3	82G9
Parabacteroides gordonii	97.4	81H9
Alistipes senegalensis	99.5	81E7
Parabacteroides johnsonii	99.9	82F11
Paraprevotella xylaniphila	99.2	82A6
Bacteroides dorei	99.7	81B11
Bacteroides uniformis JCM 5828	99.7	82G1
Eubacterium limosum	99.9	81C1
Ruminococcaceae bacterium cv2	99.8	82B1
Phascolarctobacterium faecium	99.8	82G5
Fusobacterium ulcerans	99.6	81A6

- 🟨 OTUs corresponding to the 26 strains
- ▨ OTUs detected in +CHL B5 mice
- ▨ OTUs not correlated with percentage IFNγ+ CD8 T
- 🟥 OTUs positively correlated with percentage IFNγ+ CD8 T



Tanoue T, Morita S, Plichta DR, et al. A defined commensal Consortium elicits CD8 T cells and anti-cancer immunity. Nature 2019;565:600–5.
Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD- L1 efficacy. Science 2015;350:1084–9.



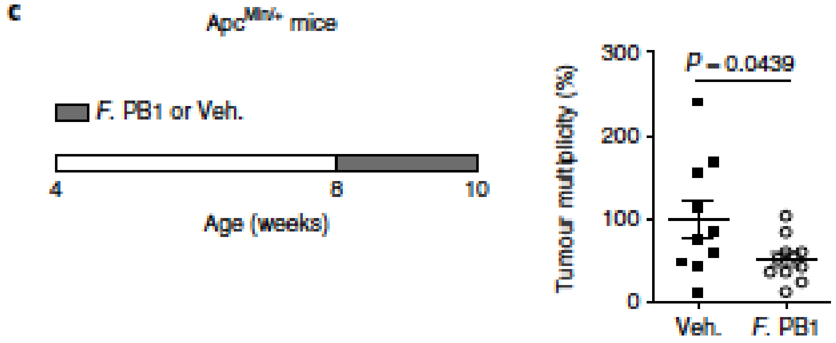
nature microbiology

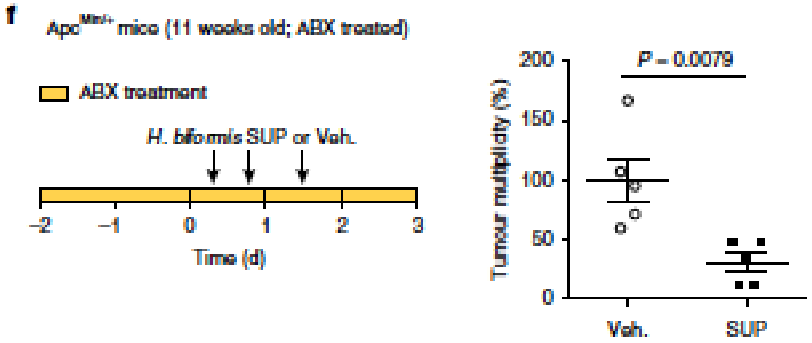
ARTICLES

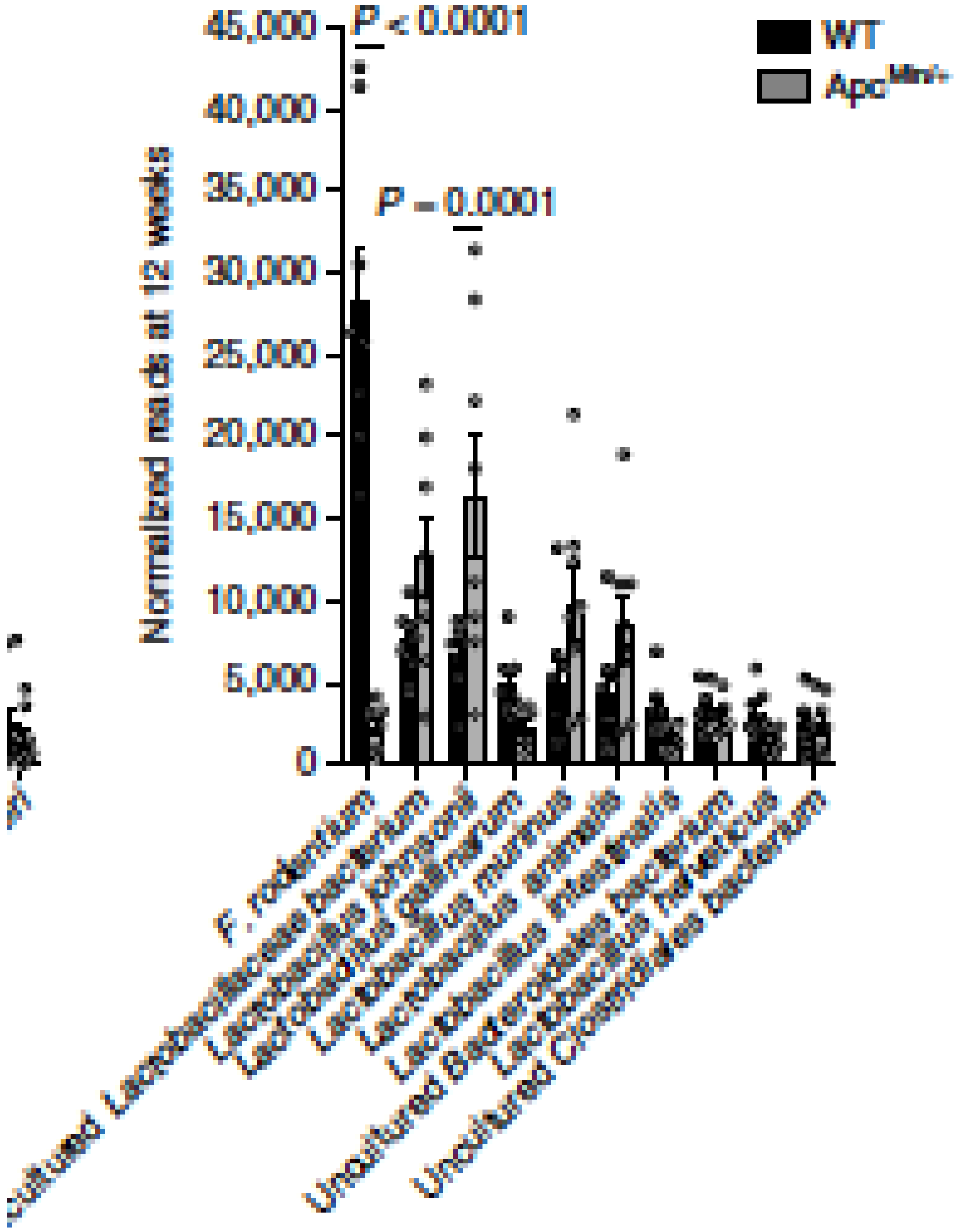
https://doi.org/10.1038/s41564-019-0649-5

Endogenous murine microbiota member *Faecalibaculum rodentium* and its human homologue protect from intestinal tumour growth

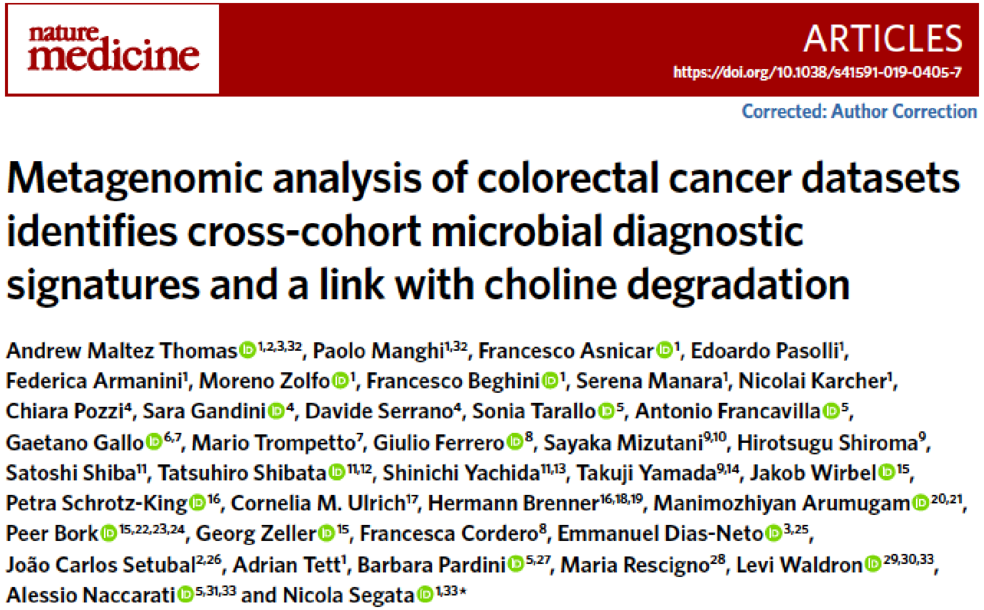
Elena Zagato[1,18,20], **Chiara Pozzi**[2,20], **Alice Bertocchi**[2], **Tiziana Schioppa**[2], **Fabiana Saccheri**[1], **Silvia Guglietta**[1,19], **Bruno Fosso**[4], **Laura Melocchi**[5,6], **Giulia Nizzoli**[7], **Jacopo Troisi**[8,9,10], **Marinella Marzano**[4], **Bianca Oresta**[2], **Ilaria Spadoni**[11], **Koji Atarashi**[12,13], **Sara Carloni**[11], **Stefania Arioli**[14], **Giulia Fornasa**[2], **Francesco Asnicar**[15], **Nicola Segata**[15], **Simone Guglielmetti**[14], **Kenya Honda**[12,13], **Graziano Pesole**[4,16], **William Vermi**[5,17], **Giuseppe Penna**[2] and **Maria Rescigno**[2,11*]







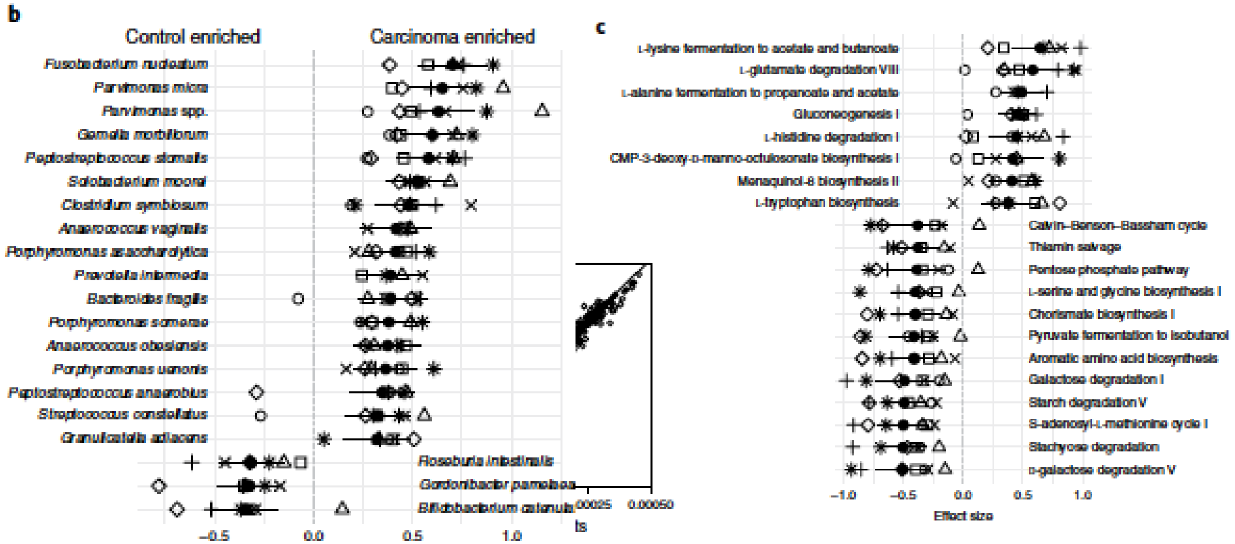
Microbiome Signatures

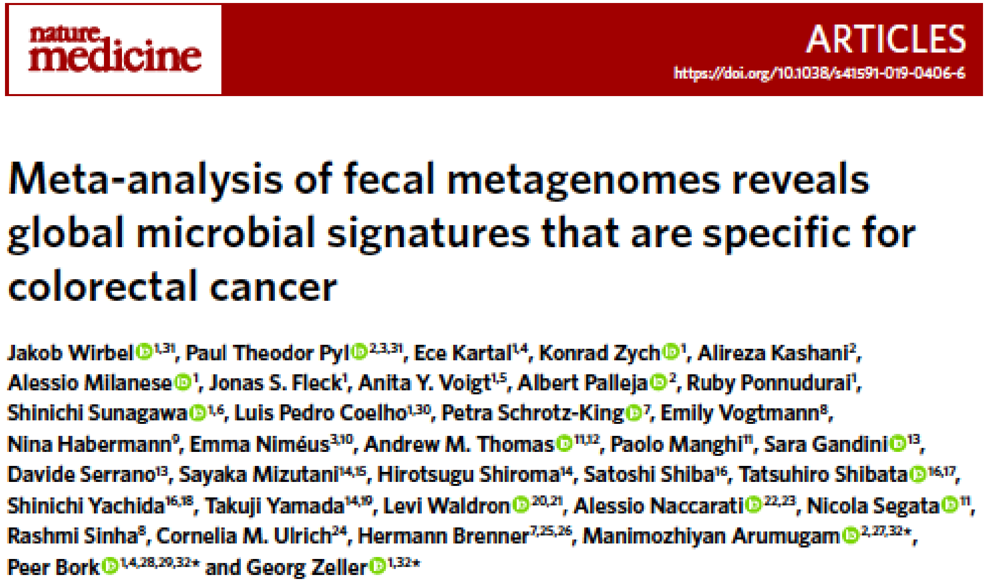

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-019-0405-7
Corrected: Author Correction

Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation

Andrew Maltez Thomas[1,2,3,32], Paolo Manghi[1,32], Francesco Asnicar[1], Edoardo Pasolli[1], Federica Armanini[1], Moreno Zolfo[1], Francesco Beghini[1], Serena Manara[1], Nicolai Karcher[1], Chiara Pozzi[4], Sara Gandini[4], Davide Serrano[4], Sonia Tarallo[5], Antonio Francavilla[5], Gaetano Gallo[6,7], Mario Trompetto[7], Giulio Ferrero[8], Sayaka Mizutani[9,10], Hirotsugu Shiroma[9], Satoshi Shiba[11], Tatsuhiro Shibata[11,12], Shinichi Yachida[11,13], Takuji Yamada[9,14], Jakob Wirbel[15], Petra Schrotz-King[16], Cornelia M. Ulrich[17], Hermann Brenner[16,18,19], Manimozhiyan Arumugam[20,21], Peer Bork[15,22,23,24], Georg Zeller[15], Francesca Cordero[8], Emmanuel Dias-Neto[3,25], João Carlos Setubal[2,26], Adrian Tett[1], Barbara Pardini[5,27], Maria Rescigno[28], Levi Waldron[29,30,33], Alessio Naccarati[5,31,33] and Nicola Segata[1,33]*

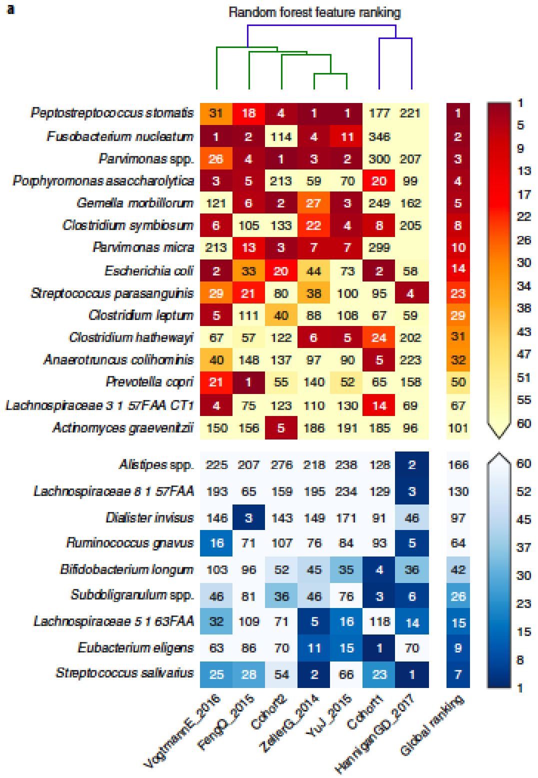
764 CRC



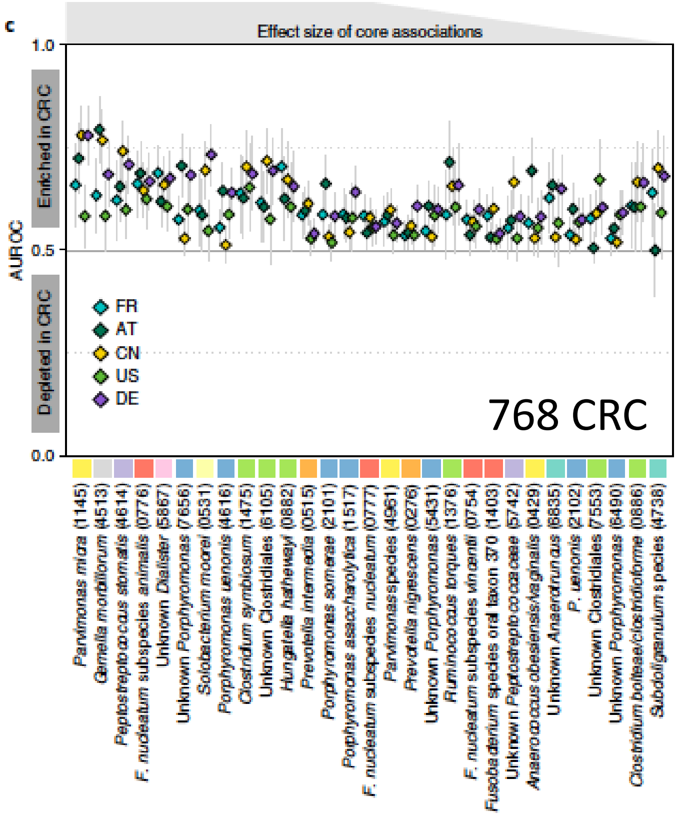

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-019-0406-6

Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer

Jakob Wirbel[1,31], Paul Theodor Pyl[2,3,31], Ece Kartal[1,4], Konrad Zych[1], Alireza Kashani[2], Alessio Milanese[1], Jonas S. Fleck[1], Anita Y. Voigt[1,5], Albert Palleja[2], Ruby Ponnudurai[1], Shinichi Sunagawa[1,6], Luis Pedro Coelho[1,30], Petra Schrotz-King[7], Emily Vogtmann[8], Nina Habermann[9], Emma Niméus[3,10], Andrew M. Thomas[11,12], Paolo Manghi[11], Sara Gandini[13], Davide Serrano[13], Sayaka Mizutani[14,15], Hirotsugu Shiroma[14], Satoshi Shiba[16], Tatsuhiro Shibata[16,17], Shinichi Yachida[16,18], Takuji Yamada[14,19], Levi Waldron[20,21], Alessio Naccarati[22,23], Nicola Segata[11], Rashmi Sinha[8], Cornelia M. Ulrich[24], Hermann Brenner[7,25,26], Manimozhiyan Arumugam[2,27,32]*, Peer Bork[1,4,28,29,32]* and Georg Zeller[1,32]*



	VogtmannE_2016	FengQ_2015	Cohort2	ZellerG_2014	YuJ_2015	Cohort1	HanniganGD_2017	Global ranking
Peptostreptococcus stomatis	31	18	4	1	1	177	221	1
Fusobacterium nucleatum	1	2	114	4	11	346		2
Parvimonas spp.	26	4	1	3	2	300	207	3
Porphyromonas asaccharolytica	3	5	213	59	70	20	99	4
Gemella morbillorum	121	6	2	27	3	249	162	5
Clostridium symbiosum	6	105	133	22	4	8	205	8
Parvimonas micra	213	13	3	7	7	299		10
Escherichia coli	2	33	20	44	73	2	58	14
Streptococcus parasanguinis	29	21	80	38	100	95	4	23
Clostridium leptum	5	111	40	88	108	67	59	29
Clostridium hathewayi	67	57	122	6	5	24	202	31
Anaerotruncus colihominis	40	148	137	97	90	5	223	32
Prevotella copri	21	1	55	140	52	65	158	50
Lachnospiraceae 3 1 57FAA CT1	4	75	123	110	130	14	69	67
Actinomyces graevenitzii	150	156	5	186	191	185	96	101
Alistipes spp.	225	207	276	218	238	128	2	166
Lachnospiraceae 8 1 57FAA	193	65	159	195	234	129	3	130
Dialister invisus	146	3	143	149	171	91	46	97
Ruminococcus gnavus	16	71	107	76	84	93	5	64
Bifidobacterium longum	103	96	52	45	35	4	36	42
Subdoligranulum spp.	46	81	36	46	76	3	6	26
Lachnospiraceae 5 1 63FAA	32	109	71	5	16	118	14	15
Eubacterium eligens	63	86	70	11	15	1	70	9
Streptococcus salivarius	25	28	54	2	66	23	1	7



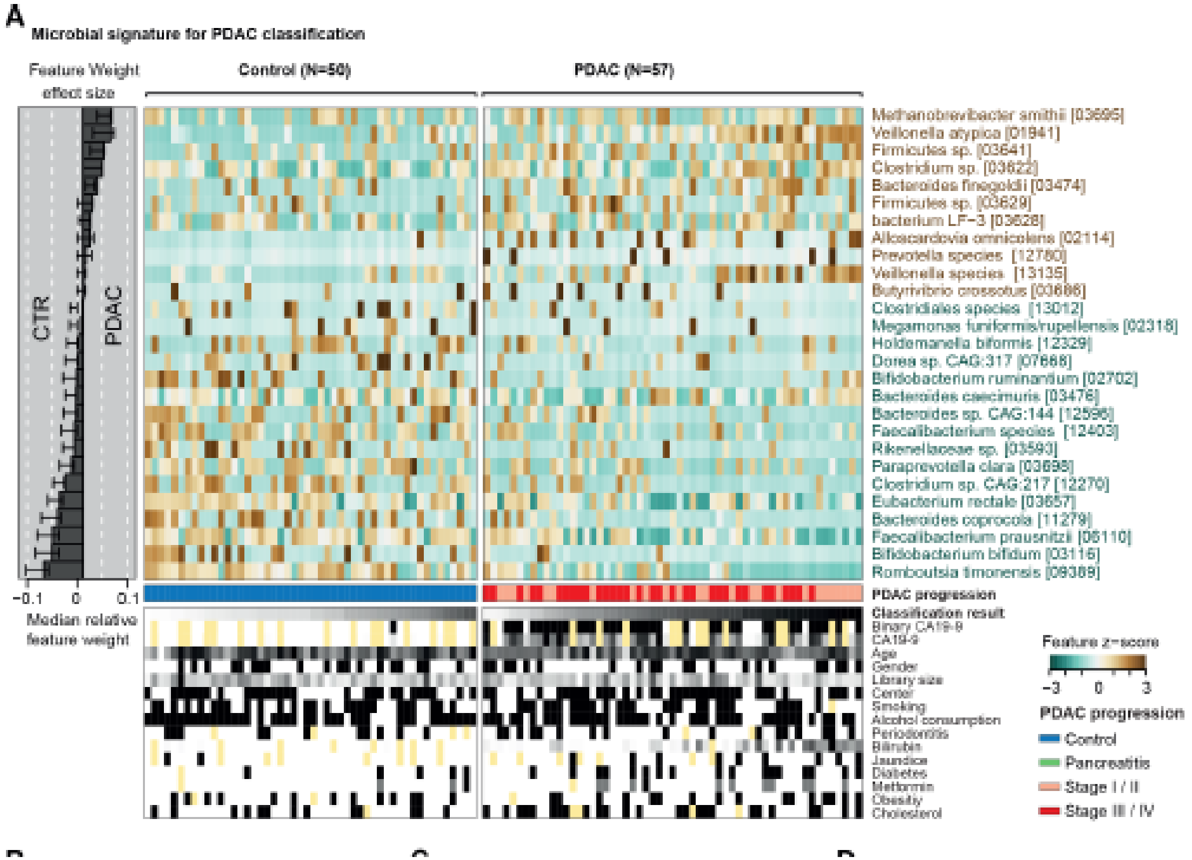
768 CRC

A faecal microbiota signature with high specificity for pancreatic cancer

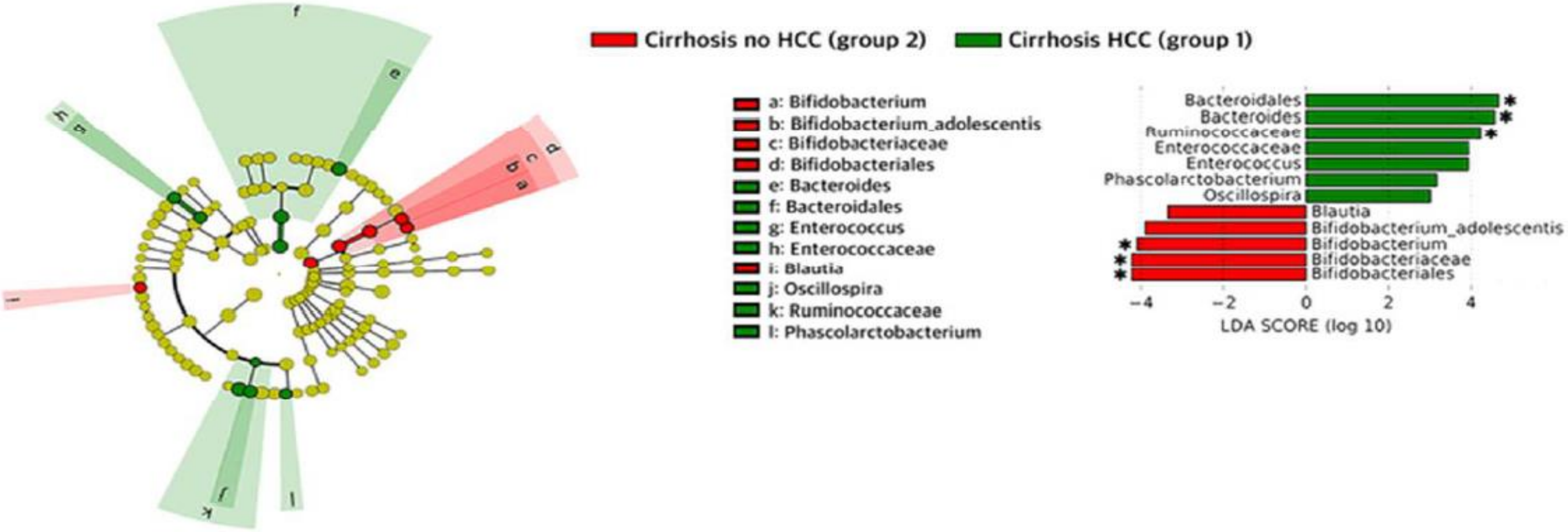
Ece Kartal ,[1,2] Thomas S B Schmidt ,[1] Esther Molina-Montes ,[3,4] Sandra Rodríguez-Perales ,[4,5] Jakob Wirbel ,[1,2] Oleksandr M Maistrenko ,[1] Wasiu A Akanni ,[1] Bilal Alashkar Alhamwe ,[6] Renato J Alves ,[1] Alfredo Carrato ,[4,7,8] Hans-Peter Erasmus,[9] Lidia Estudillo ,[3,4] Fabian Finkelmeier,[9,10] Anthony Fullam ,[1] Anna M Glazek,[1] Paulina Gómez-Rubio,[3,4] Rajna Hercog,[11] Ferris Jung ,[11] Stefanie Kandels ,[1] Stephan Kersting ,[12,13] Melanie Langheinrich ,[13] Mirari Márquez,[3,4] Xavier Molero,[14,15,16] Askarbek Orakov ,[1] Thea Van Rossum ,[1] Raul Torres-Ruiz ,[4,5] Anja Telzerow ,[11] Konrad Zych ,[1] MAGIC Study investigators, PanGenEU Study investigators, Vladimir Benes ,[11] Georg Zeller ,[1] Jonel Trebicka ,[9,17] Francisco X Real ,[4,18,19] Nuria Malats ,[3,4] Peer Bork [1,20,21,22]

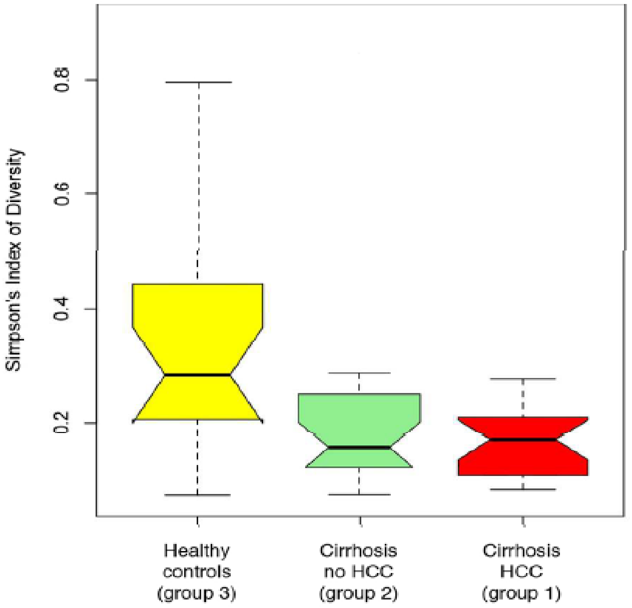
What are the new findings?

- Stool microbiota-based classifiers are described that predict PDAC with high accuracy and specificity, independent of disease stage, with potential as agents for non-invasive diagnostics.
- A faecal metagenomic classifier identified PDAC with an accuracy of 0.84 area under the receiver operating characteristic curve (AUROC) in a Spanish cohort, based on 27 species. The accuracy improved to up to 0.94 AUROC when combined with the less specific carbohydrate antigen (CA) 19–9 serum marker.
- The classifier was validated in an independent German PDAC cohort (0.83 AUROC), and PDAC disease specificity was confirmed against 25 publicly available metagenomic study populations with various health conditions (n=5792).
- The presence of marker taxa enriched in faecal samples (*Veillonella*, *Streptococcus*, *Akkermansia*) and also taxa with differential abundance in healthy and tumour pancreatic tissues (*Bacteroides*, *Lactobacillus*, *Bifidobacterium*) was validated by fluorescence *in situ* hybridisation.



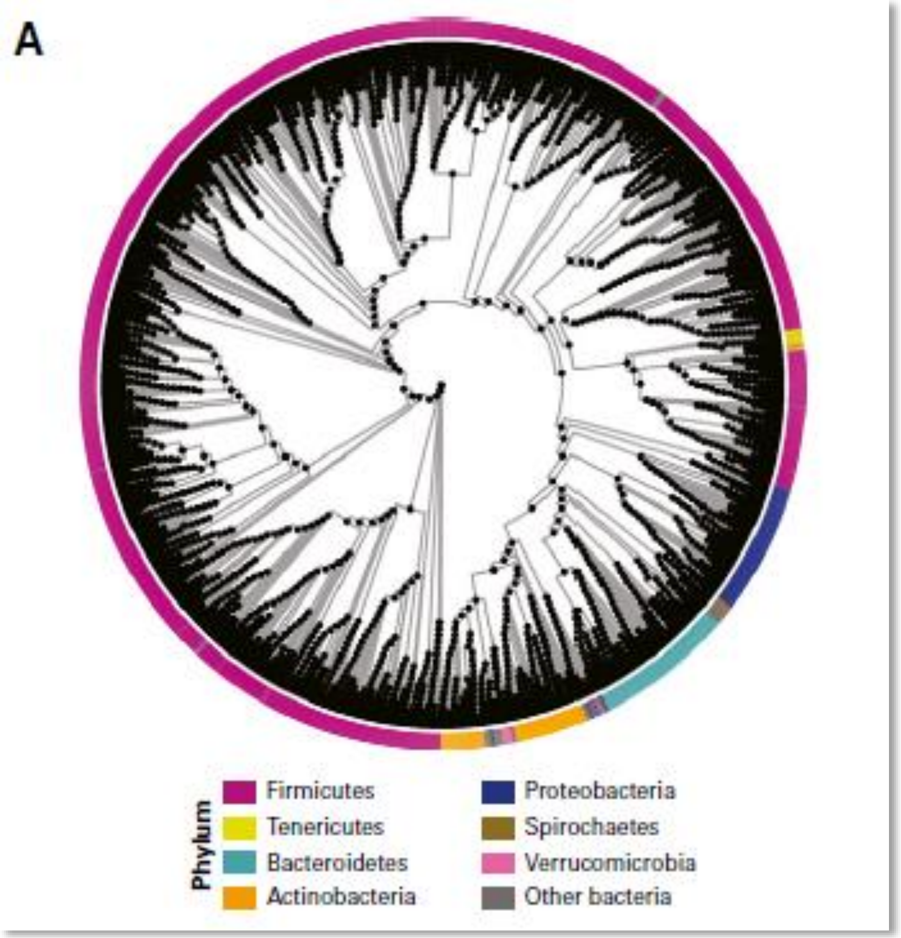
Gut microbiome can predict disease progression
From liver cirrhosis to HCC

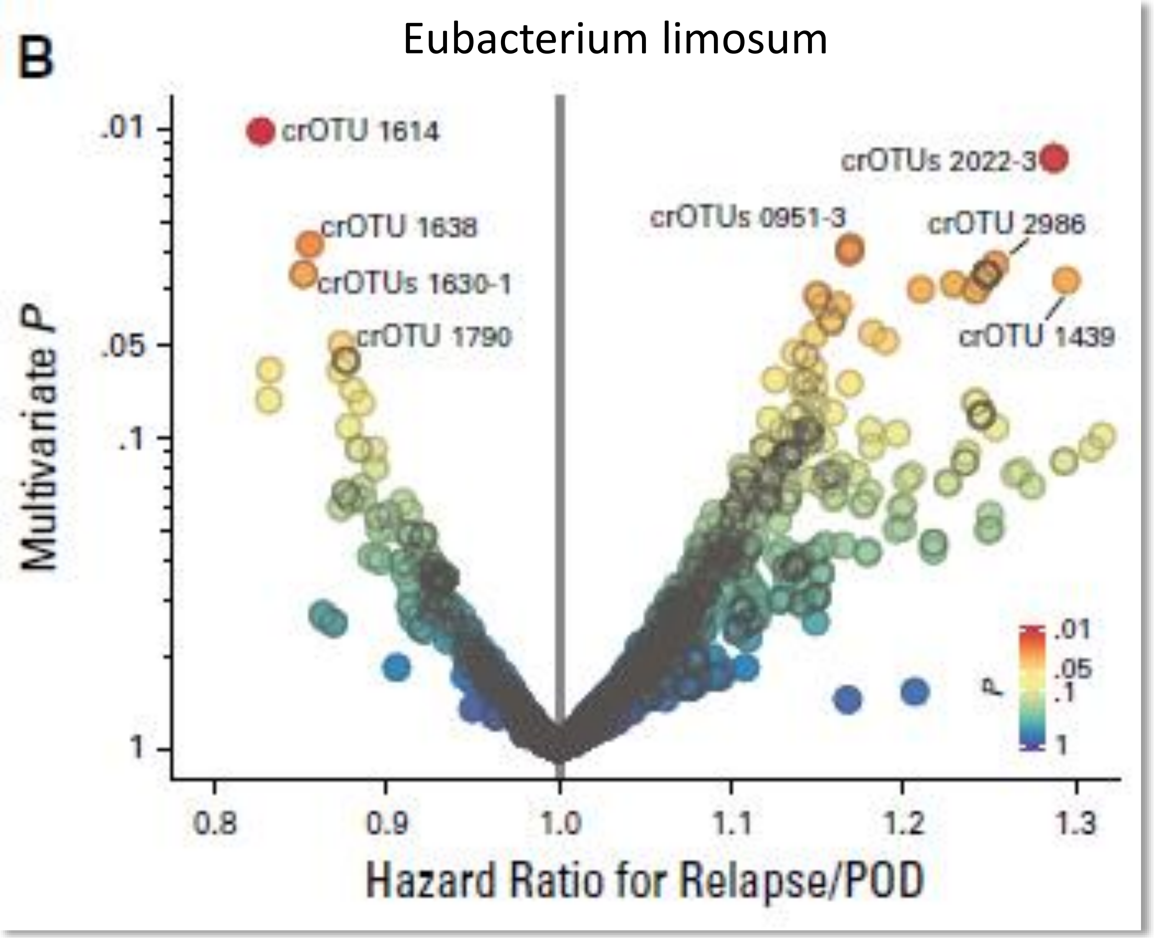




Ponziani, Hepatology 2018

Intestinal Microbiota and Relapse After Hematopoietic-Cell Transplantation

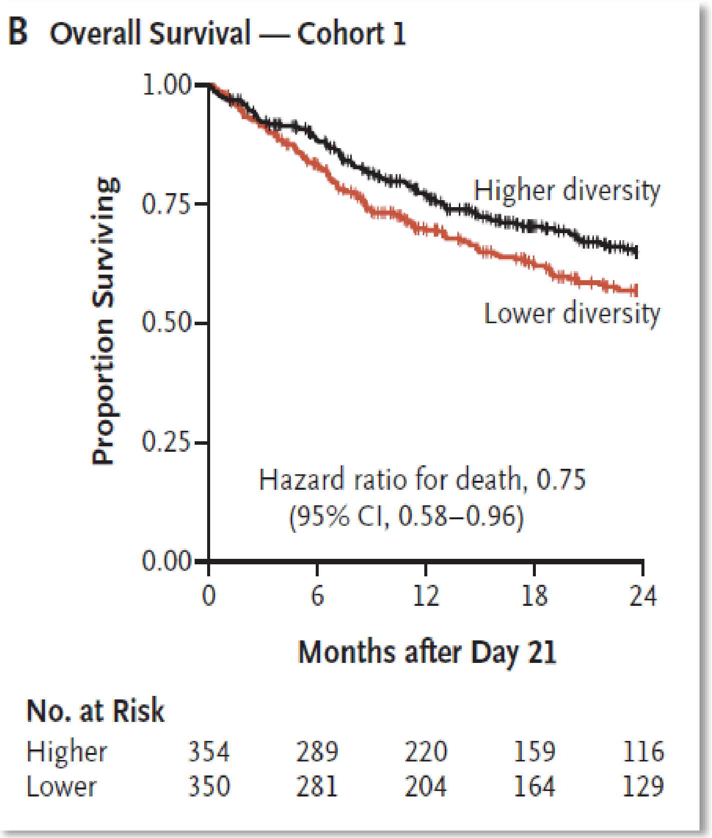


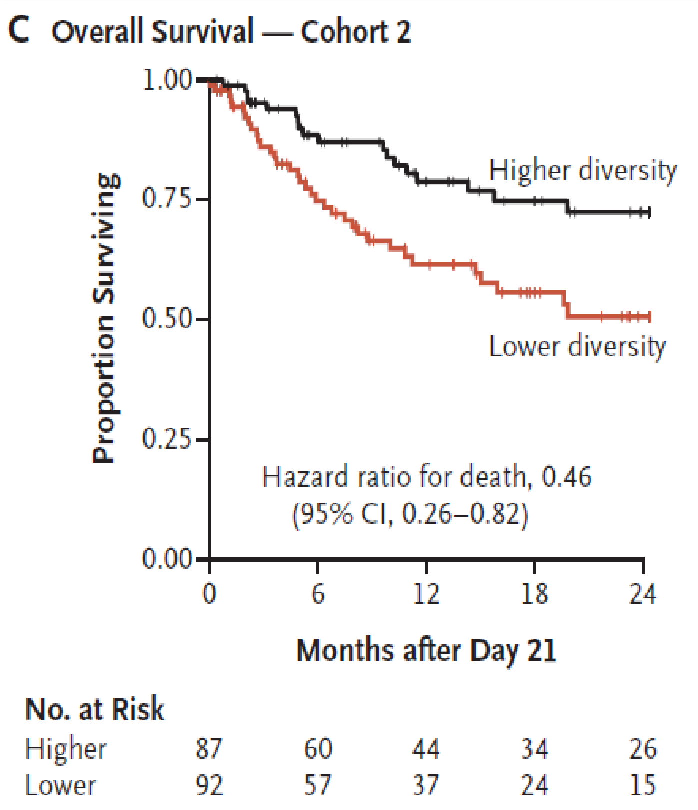


N=541 patients admitted for allo-HCT with a 2-year follow-up

Peled JU, et al. J Clin Oncol 2017 May 20;35(15):1650-1659

Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation



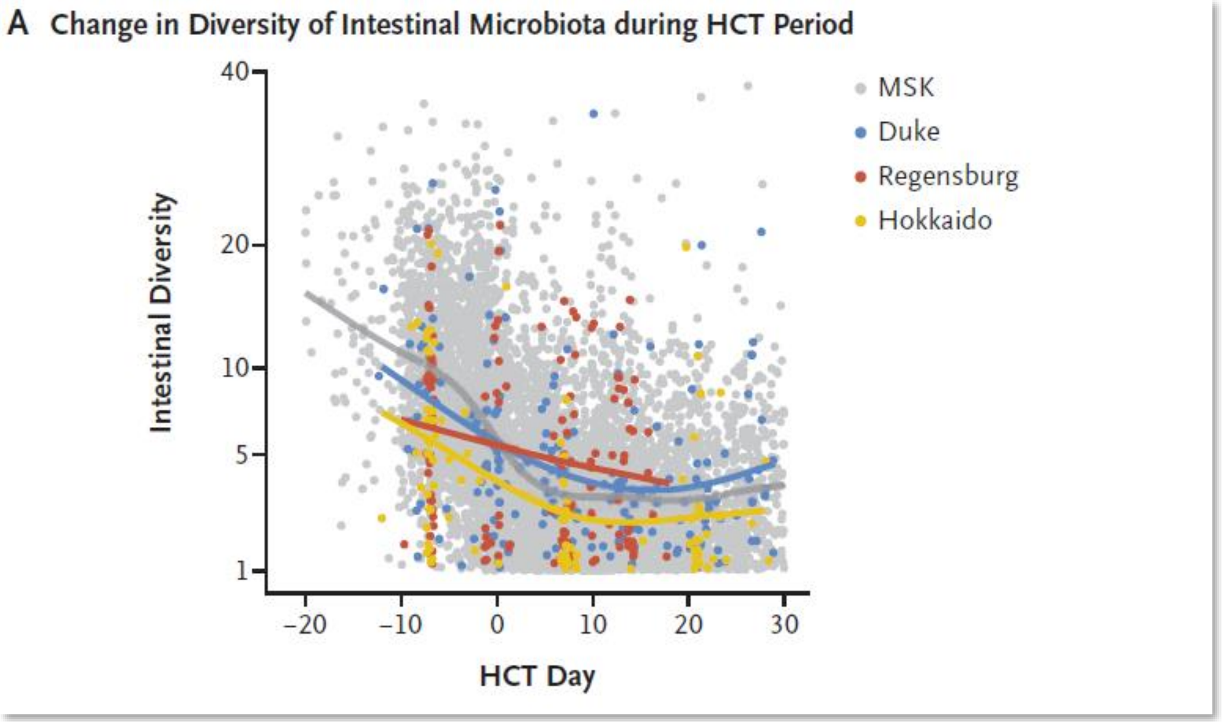


- Higher diversity of intestinal microbiota was associated with a lower risk of death in independent cohorts
- Subgroup analyses identified an association between lower intestinal diversity and higher risks of transplantation-related death and death attributable to graft-versus-host disease
- Baseline samples obtained before transplantation already showed evidence of microbiome disruption, and lower diversity before transplantation was associated with poor survival

Peled JU, et al. N Engl J Med . 2020 Feb 27;382(9):822-834

Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation

- ☐ Observational study, including 8767 fecal samples obtained from 1362 patients undergoing allogeneic hematopoietic-cell transplantation at the four centers
- ☐ The microbiota composition of fecal samples was profiled by means of 16S ribosomal RNA gene sequencing

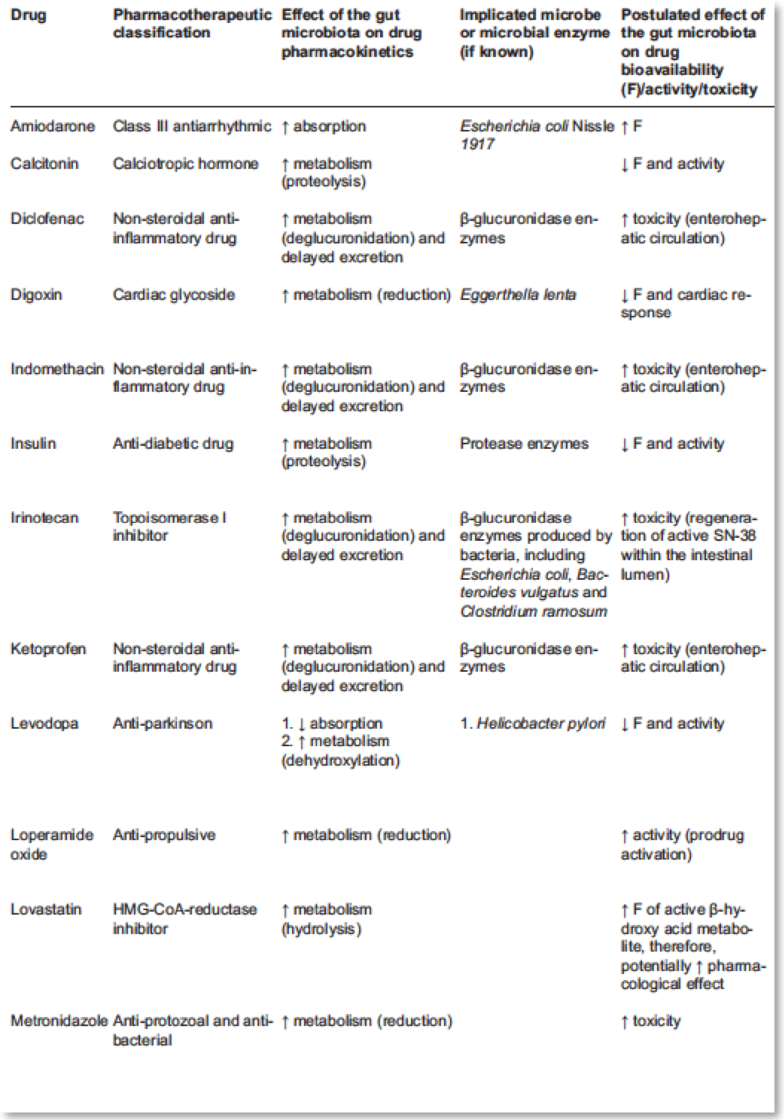


Patterns of microbiota disruption characterized by loss of diversity and domination by single taxa

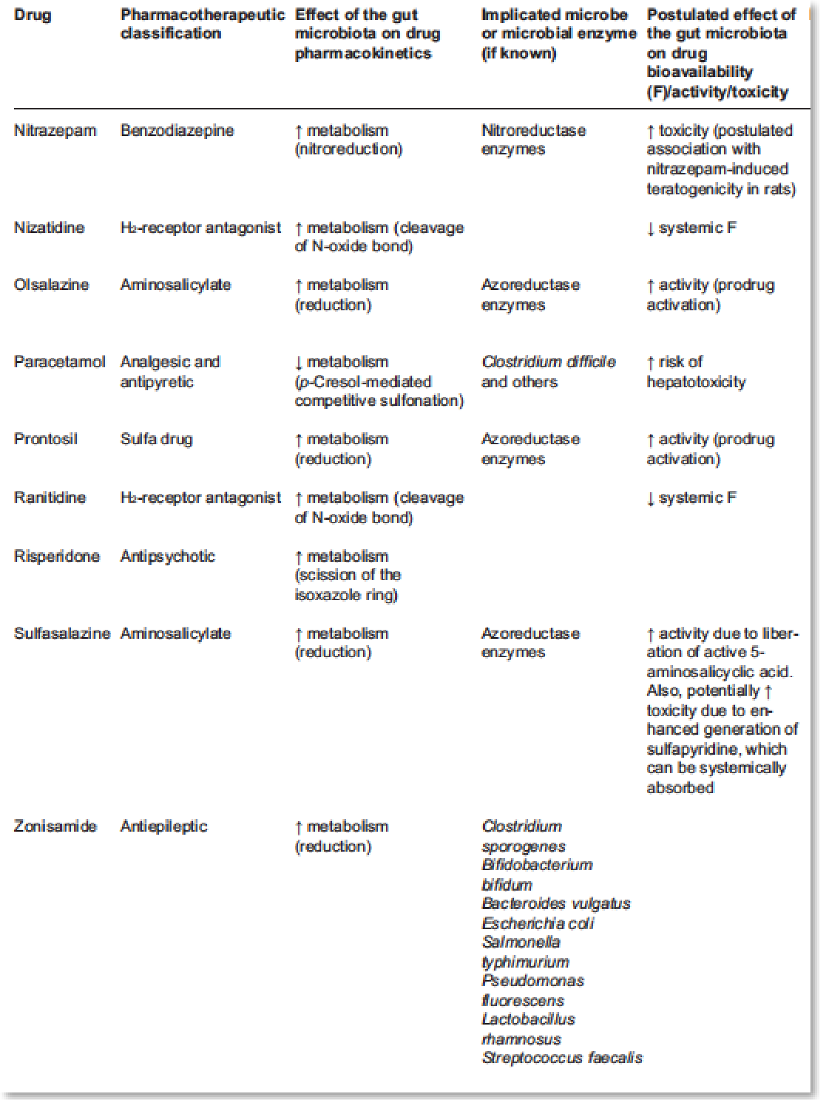
Peled JU, et al. N Engl J Med . 2020 Feb 27;382(9):822-834

Therapeutic approaches

Microbiome-drugs interaction



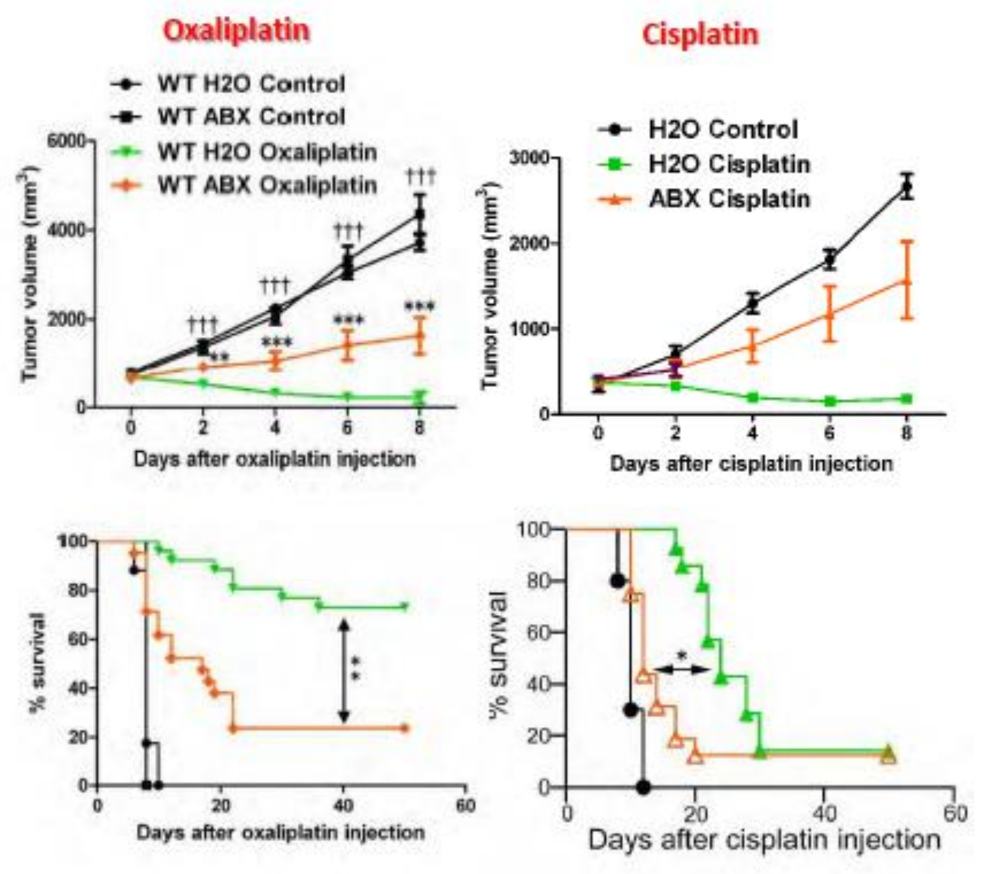
Drug	Pharmacotherapeutic classification	Effect of the gut microbiota on drug pharmacokinetics	Implicated microbe or microbial enzyme (if known)	Postulated effect of the gut microbiota on drug bioavailability (F)/activity/toxicity
Amiodarone	Class III antiarrhythmic	↑ absorption	*Escherichia coli* Nissle *1917*	↑ F
Calcitonin	Calciotropic hormone	↑ metabolism (proteolysis)		↓ F and activity
Diclofenac	Non-steroidal anti-inflammatory drug	↑ metabolism (deglucuronidation) and delayed excretion	β-glucuronidase enzymes	↑ toxicity (enterohepatic circulation)
Digoxin	Cardiac glycoside	↑ metabolism (reduction)	*Eggerthella lenta*	↓ F and cardiac response
Indomethacin	Non-steroidal anti-inflammatory drug	↑ metabolism (deglucuronidation) and delayed excretion	β-glucuronidase enzymes	↑ toxicity (enterohepatic circulation)
Insulin	Anti-diabetic drug	↑ metabolism (proteolysis)	Protease enzymes	↓ F and activity
Irinotecan	Topoisomerase I inhibitor	↑ metabolism (deglucuronidation) and delayed excretion	β-glucuronidase enzymes produced by bacteria, including *Escherichia coli, Bacteroides vulgatus* and *Clostridium ramosum*	↑ toxicity (regeneration of active SN-38 within the intestinal lumen)
Ketoprofen	Non-steroidal anti-inflammatory drug	↑ metabolism (deglucuronidation) and delayed excretion	β-glucuronidase enzymes	↑ toxicity (enterohepatic circulation)
Levodopa	Anti-parkinson	1. ↓ absorption 2. ↑ metabolism (dehydroxylation)	1. *Helicobacter pylori*	↓ F and activity
Loperamide oxide	Anti-propulsive	↑ metabolism (reduction)		↑ activity (prodrug activation)
Lovastatin	HMG-CoA-reductase inhibitor	↑ metabolism (hydrolysis)		↑ F of active β-hydroxy acid metabolite, therefore, potentially ↑ pharmacological effect
Metronidazole	Anti-protozoal and antibacterial	↑ metabolism (reduction)		↑ toxicity



Drug	Pharmacotherapeutic classification	Effect of the gut microbiota on drug pharmacokinetics	Implicated microbe or microbial enzyme (if known)	Postulated effect of the gut microbiota on drug bioavailability (F)/activity/toxicity
Nitrazepam	Benzodiazepine	↑ metabolism (nitroreduction)	Nitroreductase enzymes	↑ toxicity (postulated association with nitrazepam-induced teratogenicity in rats)
Nizatidine	H_2-receptor antagonist	↑ metabolism (cleavage of N-oxide bond)		↓ systemic F
Olsalazine	Aminosalicylate	↑ metabolism (reduction)	Azoreductase enzymes	↑ activity (prodrug activation)
Paracetamol	Analgesic and antipyretic	↓ metabolism (*p*-Cresol-mediated competitive sulfonation)	*Clostridium difficile* and others	↑ risk of hepatotoxicity
Prontosil	Sulfa drug	↑ metabolism (reduction)	Azoreductase enzymes	↑ activity (prodrug activation)
Ranitidine	H_2-receptor antagonist	↑ metabolism (cleavage of N-oxide bond)		↓ systemic F
Risperidone	Antipsychotic	↑ metabolism (scission of the isoxazole ring)		
Sulfasalazine	Aminosalicylate	↑ metabolism (reduction)	Azoreductase enzymes	↑ activity due to liberation of active 5-aminosalicyclic acid. Also, potentially ↑ toxicity due to enhanced generation of sulfapyridine, which can be systemically absorbed
Zonisamide	Antiepileptic	↑ metabolism (reduction)	*Clostridium sporogenes* *Bifidobacterium bifidum* *Bacteroides vulgatus* *Escherichia coli* *Salmonella typhimurium* *Pseudomonas fluorescens* *Lactobacillus rhamnosus* *Streptococcus faecalis*	

Enright EF, YJBM 2016

Antibiotics



EL4 subcutaneous tumor

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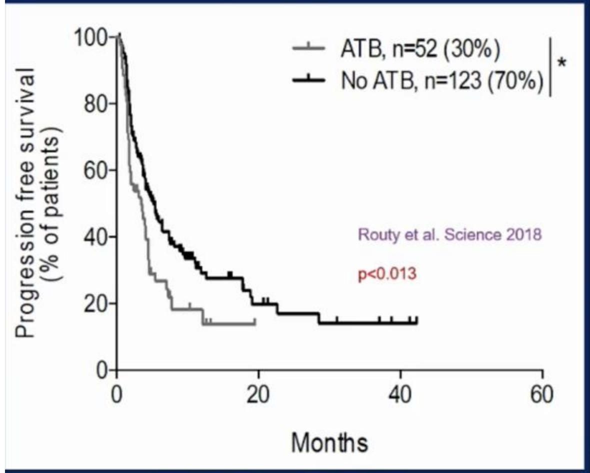
Science. 2013 November 22; 342(6161): 967–970. doi:10.1126/science.1240527.

Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment

Noriho Iida[1,*], Amiran Dzutsev[1,2,*], C. Andrew Stewart[1,*], Loretta Smith[1], Nicolas Bouladoux[3], Rebecca A. Weingarten[4], Daniel A. Molina[5], Rosalba Salcedo[1], Timothy Back[1], Sarah Cramer[1], Ren-Ming Dai[1,2], Hiu Kiu[1], Marco Cardone[1], Shruti Naik[3], Anil K. Patri[6], Ena Wang[7], Francesco M. Marincola[7,8], Karen M. Frank[4], Yasmine Belkaid[3], Giorgio Trinchieri[1,†,‡], Romina S. Goldszmid[1,†,‡]

META-ANALYSIS: DELETERIOUS EFFECTS OF ANTIBIOTICS FOR THE CLINICAL BENEFIT OF IMMUNE CHECKPOINT INHIBITORS.

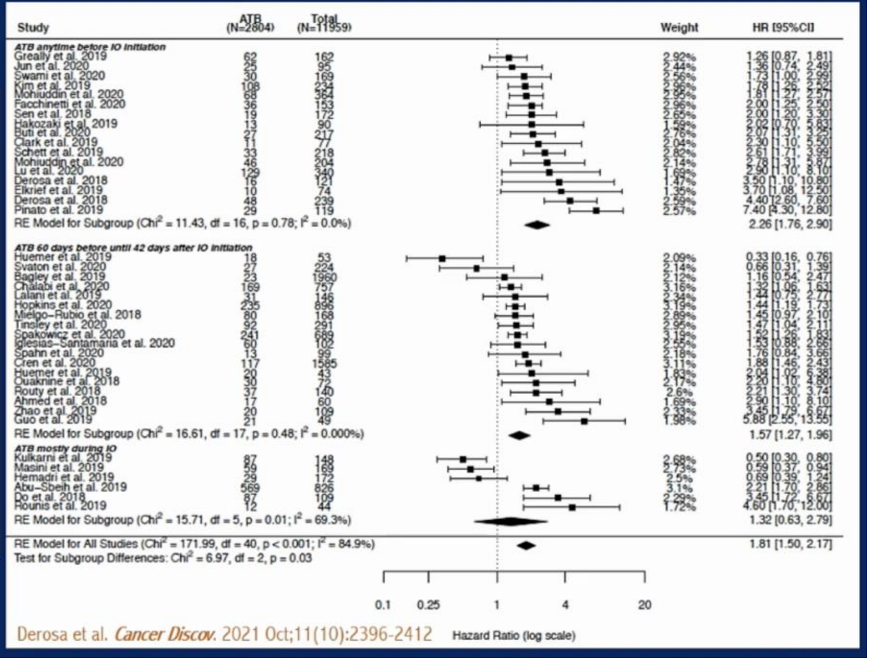
ATB:antibiotics



Routy et al. Science 2018

p<0.013

Routy et al; Science, Oct 27, 2017.
Median PFS ATB: 3.5 months
Median PFS No ATB: 5.2 months



Study	ATB (N=2804)	Total (N=11959)	Weight	HR [95%CI]
ATB anytime before IO initiation				
Greally et al. 2019	62	162	2.92%	1.26 [0.87, 1.81]
Jun et al. 2020	25	95	2.44%	1.36 [0.74, 2.49]
Swami et al. 2020	30	169	2.56%	1.73 [1.00, 2.99]
Kim et al. 2019	108	234	2.96%	1.78 [1.26, 2.52]
Mohiuddin et al. 2020	68	364	2.95%	1.81 [1.27, 2.57]
Facchinetti et al. 2020	36	153	2.96%	2.00 [1.25, 2.50]
Sen et al. 2018	19	172	2.65%	2.00 [1.20, 3.30]
Hakozaki et al. 2019	13	90	1.59%	2.02 [0.70, 5.83]
Buti et al. 2020	27	217	2.76%	2.07 [1.31, 3.25]
Clark et al. 2019	11	77	2.04%	2.30 [1.10, 5.50]
Schett et al. 2019	33	218	2.82%	2.61 [1.71, 3.99]
Mohiuddin et al. 2020	46	204	2.14%	2.78 [1.31, 5.87]
Lu et al. 2020	129	340	1.69%	2.90 [1.10, 8.10]
Derosa et al. 2018	16	121	1.47%	3.50 [1.10, 10.80]
Elkrief et al. 2019	10	74	1.35%	3.70 [1.08, 12.50]
Derosa et al. 2018	48	239	2.59%	4.40 [2.60, 7.60]
Pinato et al. 2019	29	119	2.57%	7.40 [4.30, 12.80]
RE Model for Subgroup ($Chi^2 = 11.43$, df = 16, p = 0.78; $I^2 = 0.0\%$)				2.26 [1.76, 2.90]
ATB 60 days before until 42 days after IO initiation				
Huemer et al. 2019	18	53	2.09%	0.33 [0.16, 0.76]
Svaton et al. 2020	27	224	2.14%	0.66 [0.31, 1.39]
Bagley et al. 2019	23	1960	2.12%	1.16 [0.54, 2.47]
Chalabi et al. 2020	169	757	3.16%	1.32 [1.06, 1.63]
Lalani et al. 2019	31	146	2.34%	1.44 [0.75, 2.77]
Hopkins et al. 2020	235	896	3.19%	1.44 [1.19, 1.73]
Mielgo–Rubio et al. 2018	80	168	2.89%	1.45 [0.97, 2.10]
Tinsley et al. 2020	92	291	2.95%	1.47 [1.04, 2.11]
Spakowicz et al. 2020	241	689	3.19%	1.52 [1.26, 1.83]
Iglesias–Santamaria et al. 2020	60	102	2.55%	1.53 [0.88, 2.66]
Spahn et al. 2020	13	99	2.18%	1.76 [0.84, 3.66]
Cren et al. 2020	117	1585	3.11%	1.88 [1.46, 2.43]
Huemer et al. 2019	20	43	1.83%	2.04 [1.02, 6.38]
Ouaknine et al. 2018	30	72	2.17%	2.20 [1.10, 4.80]
Routy et al. 2018	37	140	2.6%	2.21 [1.30, 3.74]
Ahmed et al. 2018	17	60	1.69%	2.90 [1.10, 8.10]
Zhao et al. 2019	20	109	2.33%	3.45 [1.79, 6.67]
Guo et al. 2019	21	49	1.98%	5.88 [2.55, 13.55]
RE Model for Subgroup ($Chi^2 = 16.61$, df = 17, p = 0.48; $I^2 = 0.000\%$)				1.57 [1.27, 1.96]
ATB mostly during IO				
Kulkarni et al. 2019	87	148	2.68%	0.50 [0.30, 0.80]
Masini et al. 2019	59	169	2.73%	0.59 [0.37, 0.94]
Hemadri et al. 2019	29	172	2.5%	0.69 [0.39, 1.24]
Abu–Sbeih et al. 2019	569	826	3.1%	2.21 [1.70, 2.86]
Do et al. 2018	87	109	2.29%	3.45 [1.72, 6.67]
Rounis et al. 2019	12	44	1.72%	4.60 [1.70, 12.00]
RE Model for Subgroup ($Chi^2 = 15.71$, df = 5, p = 0.01; $I^2 = 69.3\%$)				1.32 [0.63, 2.79]
RE Model for All Studies ($Chi^2 = 171.99$, df = 40, p < 0.001; $I^2 = 84.9\%$)				1.81 [1.50, 2.17]
Test for Subgroup Differences: $Chi^2 = 6.97$, df = 2, p = 0.03				

Derosa et al. *Cancer Discov.* 2021 Oct;11(10):2396-2412

ATB NOT ONLY COMPROMISE THE EFFICACY OF IMMUNE CHECKPOINT INHIBITORS

but also that of

- CAR-T CELL THERAPY

(Smith M. et al. Nat. Med. Apr 2022, Stein-Thoeringer CK et al. Nat. Med. March 2023)

- HEMATOPOIETIC STEM CELL TRANSPLANTATION

(Peled JU et al. N. Engl. J. Med. 382, 822–834 (2020)).

Gut microbiome correlates of response and toxicity following anti-CD19 CAR T cell therapy

Melody Smith[1,2,3,4], Anqi Dai[1,26], Guido Ghilardi[5,6,26], Kimberly V. Amelsberg[5,6], Sean M. Devlin[7], Raymone Pajarillo[5,6], John B. Slingerland[1], Silvia Beghi[8], Pamela S. Herrera[1,9], Paul Giardina[1], Annelie Clurman[1], Emmanuel Dwomoh[1], Gabriel Armijo[1], Antonio L. C. Gomes[1], Eric R. Littmann[10], Jonas Schluter[11], Emily Fontana[12], Ying Taur[13], Jae H. Park[2,3,14], Maria Lia Palomba[2,3,15], Elizabeth Halton[3,16], Josel Ruiz[1], Tania Jain[17], Martina Pennisi[18], Aishat Olaide Afuye[1], Miguel-Angel Perales[1,2], Craig W. Freyer[19], Alfred Garfall[5], Shannon Gier[5], Sunita Nasta[5,20], Daniel Landsburg[5,20], James Gerson[5,20], Jakub Svoboda[5,20], Justin Cross[21], Elise A. Chong[5,6,20], Sergio Giralt[1,2], Saar I. Gill[5,6], Isabelle Riviere[2,22], David L. Porter[5,6], Stephen J. Schuster[5,6,20], Michel Sadelain[22], Noelle Frey[5,6], Renier J. Brentjens[2,3,14,22], Carl H. June[5,23], Eric G. Pamer[10], Jonathan U. Peled[1,2], Andrea Facciabene[5,8,24,27] ✉, Marcel R. M. van den Brink[1,25,27] ✉ and Marco Ruella[5,6,20,27] ✉

nature medicine

Article

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A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy

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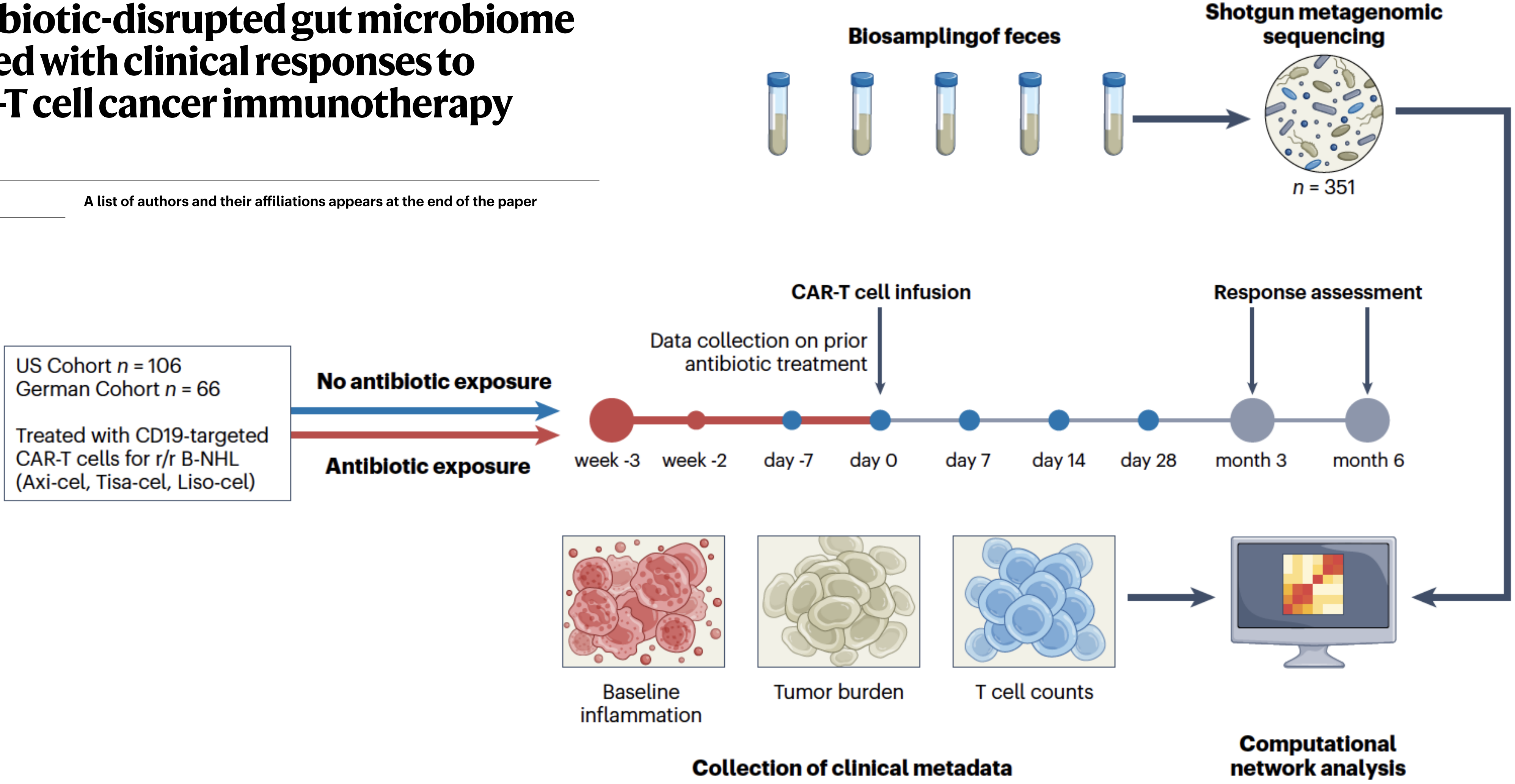
A list of authors and their affiliations appears at the end of the paper



US Cohort $n = 106$
German Cohort $n = 66$

Treated with CD19-targeted CAR-T cells for r/r B-NHL (Axi-cel, Tisa-cel, Liso-cel)

No antibiotic exposure

Antibiotic exposure

Biosamplingof feces

Shotgun metagenomic sequencing

$n = 351$

CAR-T cell infusion

Data collection on prior antibiotic treatment

Response assessment

week -3, week -2, day -7, day 0, day 7, day 14, day 28, month 3, month 6

Baseline inflammation

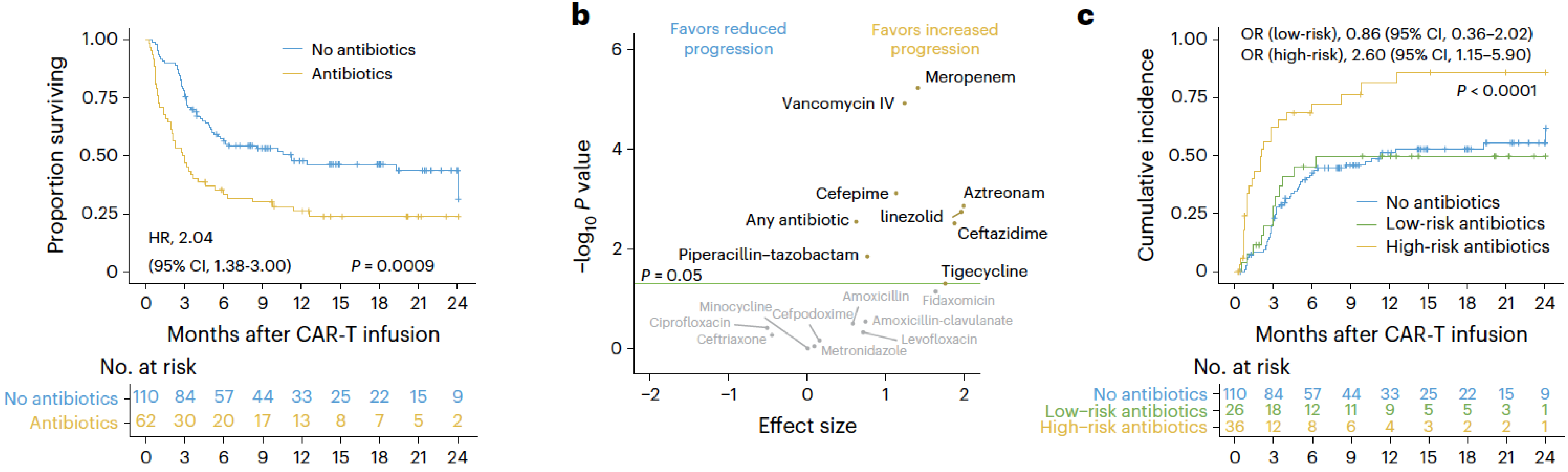
Tumor burden

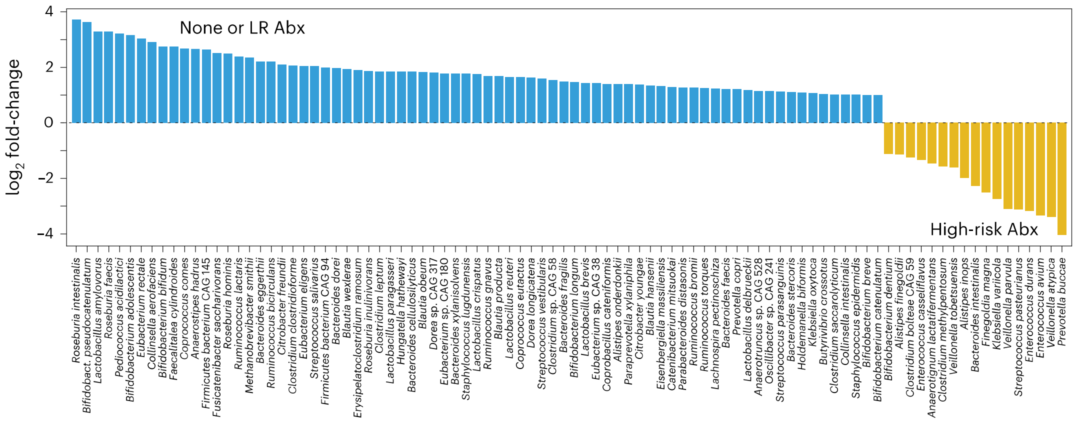
T cell counts

Collection of clinical metadata

Computational network analysis

Stein-Thoeringer, C.K., et al. Nat Med (2023). https://doi.org/10.1038/s41591-023-02234-6


Proportion surviving
1.00
0.75
0.50
0.25
0
No antibiotics
Antibiotics
HR, 2.04
(95% CI, 1.38-3.00)
P = 0.0009
0
3
6
9
12
15
18
21
24
Months after CAR-T infusion
No. at risk
No antibiotics 110 84 57 44 33 25 22 15 9
Antibiotics 62 30 20 17 13 8 7 5 2
b
Favors reduced progression
Favors increased progression
−log10 P value
6
4
2
0
Meropenem
Vancomycin IV
Cefepime
Aztreonam
Any antibiotic
linezolid
Ceftazidime
Piperacillin–tazobactam
Tigecycline
P = 0.05
Amoxicillin
Fidaxomicin
Minocycline
Cefpodoxime
Ciprofloxacin
Amoxicillin–clavulanate
Ceftriaxone
Levofloxacin
Metronidazole
−2
−1
0
1
2
Effect size
c
Cumulative incidence
OR (low-risk), 0.86 (95% CI, 0.36–2.02)
OR (high-risk), 2.60 (95% CI, 1.15–5.90)
P < 0.0001
No antibiotics
Low-risk antibiotics
High-risk antibiotics
Months after CAR-T infusion
No. at risk
No antibiotics 110 84 57 44 33 25 22 15 9
Low-risk antibiotics 26 18 12 11 9 5 5 3 1
High-risk antibiotics 36 12 8 6 4 3 2 2 1


log2 fold-change
4
2
0
-2
-4
None or LR Abx
High-risk Abx
Roseburia intestinalis
Bifidobact. pseudocatenulatum
Lactobacillus amylovorus
Roseburia faecis
Pediococcus acidilactici
Bifidobacterium adolescentis
Eubacterium rectale
Collinsella aerofaciens
Bifidobacterium bifidum
Faecalitalea cylindroides
Coprococcus comes
Anaerostipes hadrus
Firmicutes bacterium CAG 145
Fusicatenibacter saccharivorans
Roseburia hominis
Ruminococcus lactaris
Methanobrevibacter smithii
Bacteroides eggerthii
Ruminococcus bicirculans
Citrobacter freundii
Clostridium clostridioforme
Eubacterium eligens
Streptococcus salivarius
Firmicutes bacterium CAG 94
Bacteroides dorei
Blautia wexlerae
Erysipelatoclostridium ramosum
Roseburia inulinivorans
Clostridium leptum
Lactobacillus paragasseri
Hungatella hathewayi
Bacteroides cellulosilyticus
Blautia obeum
Dorea sp. CAG 317
Eubacterium sp. CAG 180
Bacteroides xylanisolvens
Staphylococcus lugdunensis
Lactobacillus crispatus
Ruminococcus gnavus
Blautia producta
Lactobacillus reuteri
Coprococcus eutactus
Dorea longicatena
Streptococcus vestibularis
Clostridium sp. CAG 58
Bacteroides fragilis
Bifidobacterium longum
Lactobacillus brevis
Eubacterium sp. CAG 38
Coprobacillus cateniformis
Alistipes onderdonkii
Paraprevotella xylaniphila
Citrobacter youngae
Blautia hansenii
Eisenbergiella massiliensis
Catenibacterium mitsuokai
Parabacteroides distasonis
Ruminococcus bromii
Ruminococcus torques
Lachnospira pectinoschiza
Bacteroides faecis
Prevotella copri
Lactobacillus delbrueckii
Anaerotruncus sp. CAG 528
Oscillibacter sp. CAG 241
Streptococcus parasanguinis
Bacteroides stercoris
Holdemanella biformis
Klebsiella oxytoca
Butyrivibrio crossotus
Clostridium saccharolyticum
Collinsella intestinalis
Staphylococcus epidermidis
Bifidobacterium breve
Bifidobacterium catenulatum
Bifidobacterium dentium
Alistipes finegoldii
Clostridium bolteae CAG 59
Enterococcus casseliflavus
Anaerotignum lactatifermentans
Clostridium methylpentosum
Veillonella tobetsuensis
Alistipes inops
Bacteroides intestinalis
Finegoldia magna
Klebsiella variicola
Veillonella parvula
Streptococcus pasteurianus
Enterococcus durans
Enterococcus avium
Veillonella atypica
Prevotella buccae

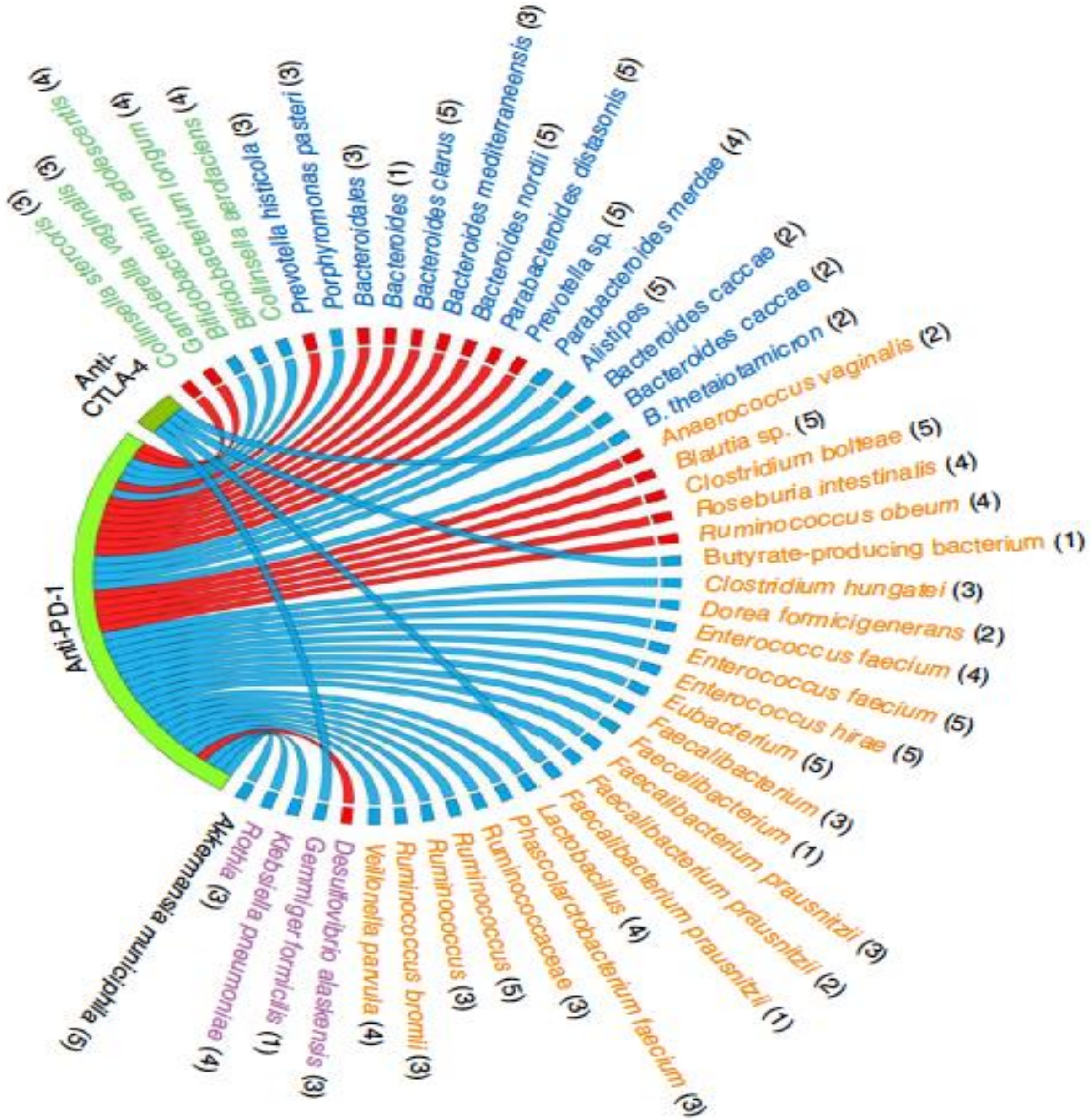
Gut microbiome may predict response to ICIs in epithelial cancers

Bacterial phyla involved:

- 🟩 Actinobacteria
- 🟦 Bacteroidetes
- 🟧 Firmicutes
- 🟪 Proteobacteria
- ⬛ Verrucomicrobia

Association with response:

- 🟦 Enriched in responders
- 🟥 Enriched in nonresponders



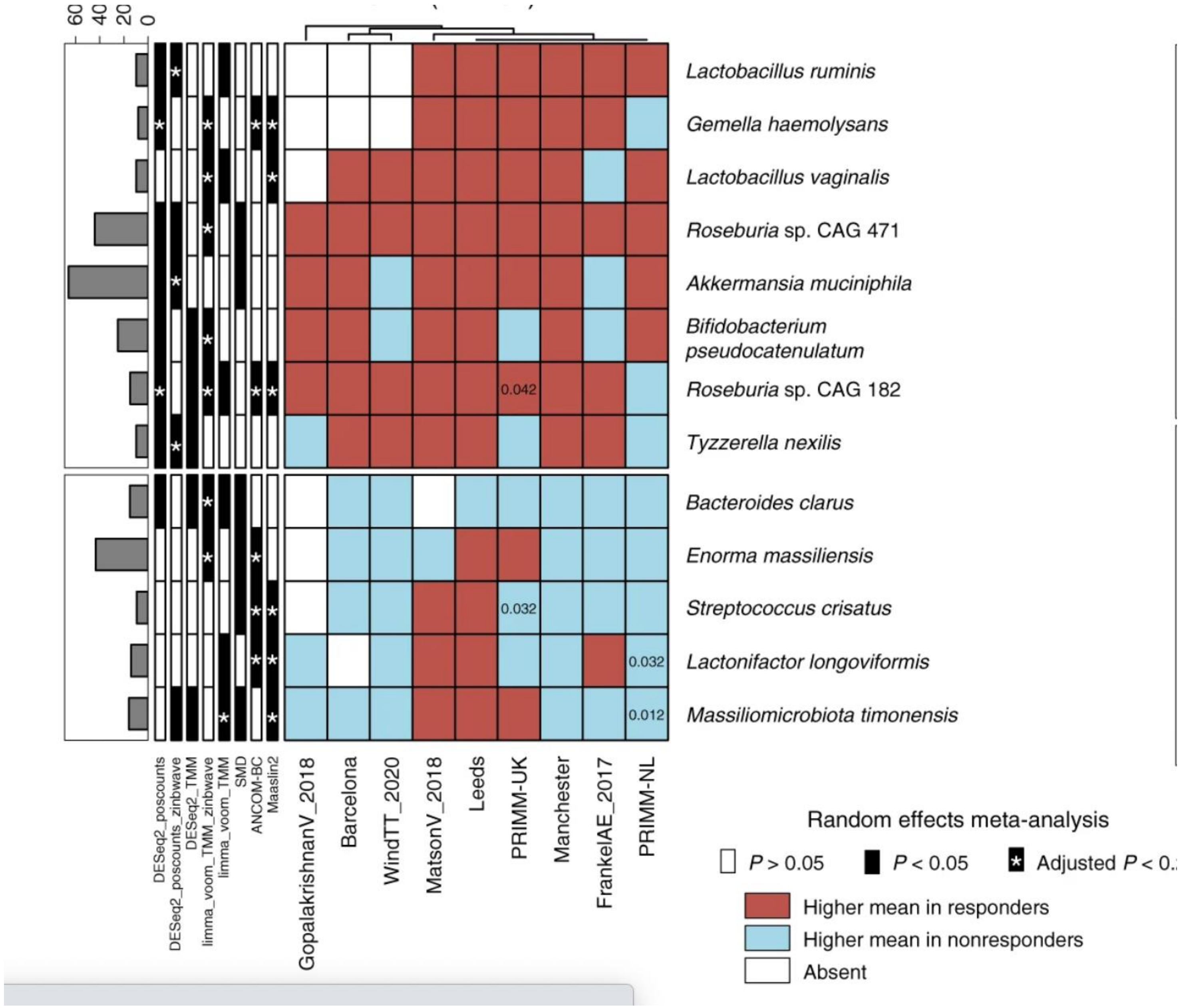
Ma et al, Frontiers Micro 2019; Routy et al, Science 2018; Gopalakrishnan et al, Science 2017

A microbial panel can predict response to ICI in melanoma

WGS of of stool samples collected before ICI initiation in 312 patients with melanoma from different cohorts

- A panel of species, including *Bifidobacterium pseudocatenulatum*, *Roseburia* spp. and *Akkermansia muciniphila*, associated with responders was identified

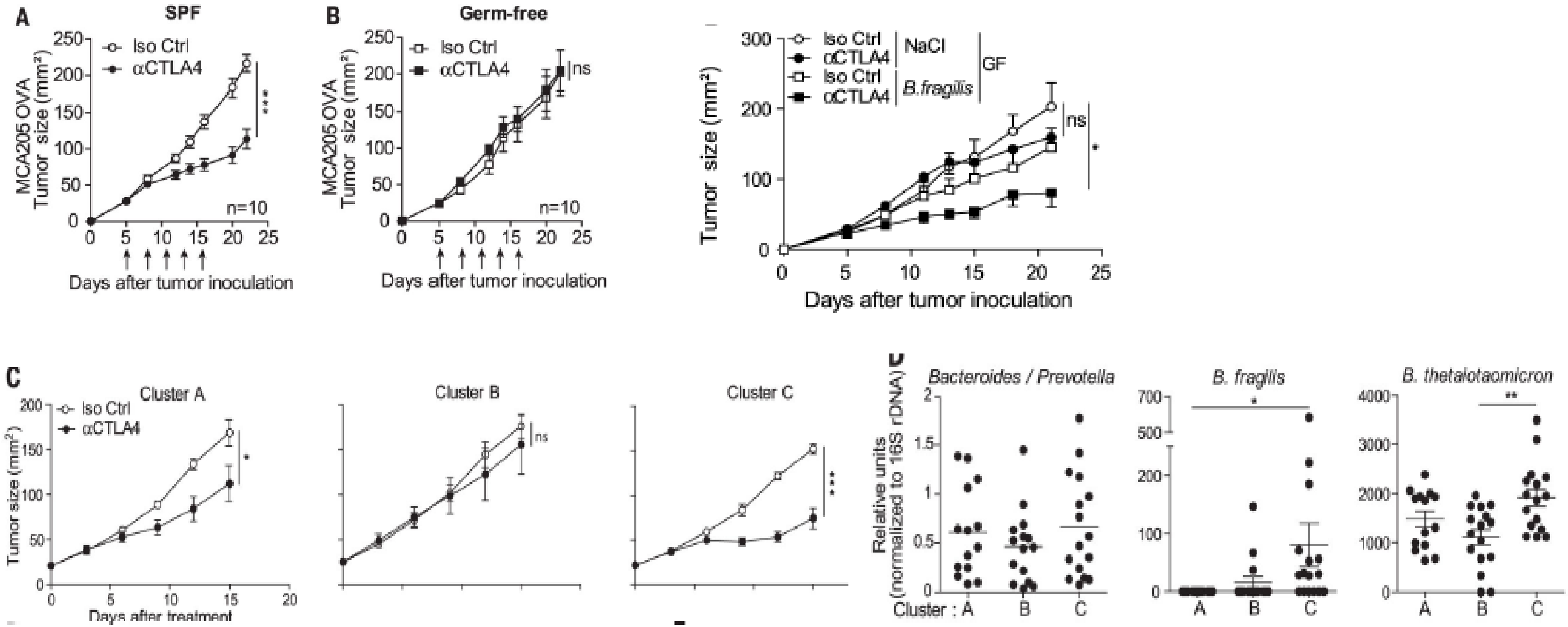
No single species could be regarded as a fully consistent biomarker across studies



Lee et al – Nat Med 2022

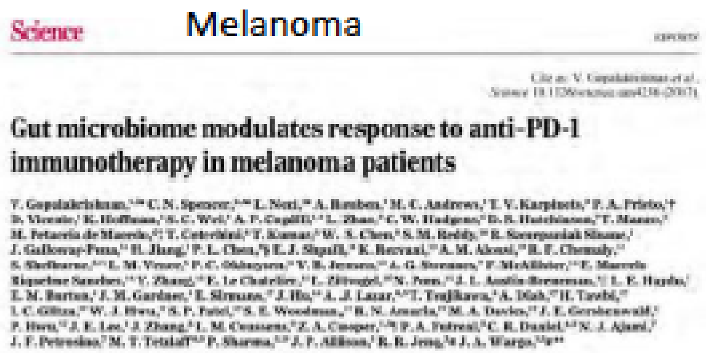
Anti-CTLA4 (Ipilimumab)

Effetto positivo: *Bacteroides (B.fragiis)* migliora la risposta all'anti CTLA4 *(topo e pazienti di melanoma)*



Vetizou M, Science 2015

Anti-PD1



Science

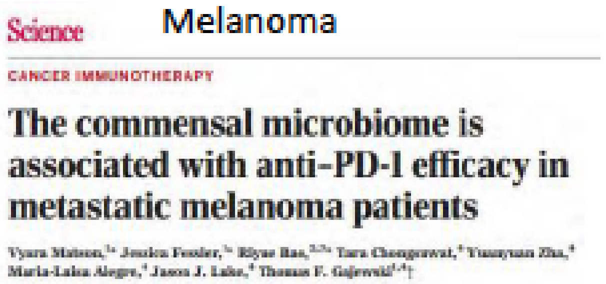
Melanoma

Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients

Ruminococcaceae

Clostridiales

Faecalibacterium prausnitzii



Science

Melanoma

CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients

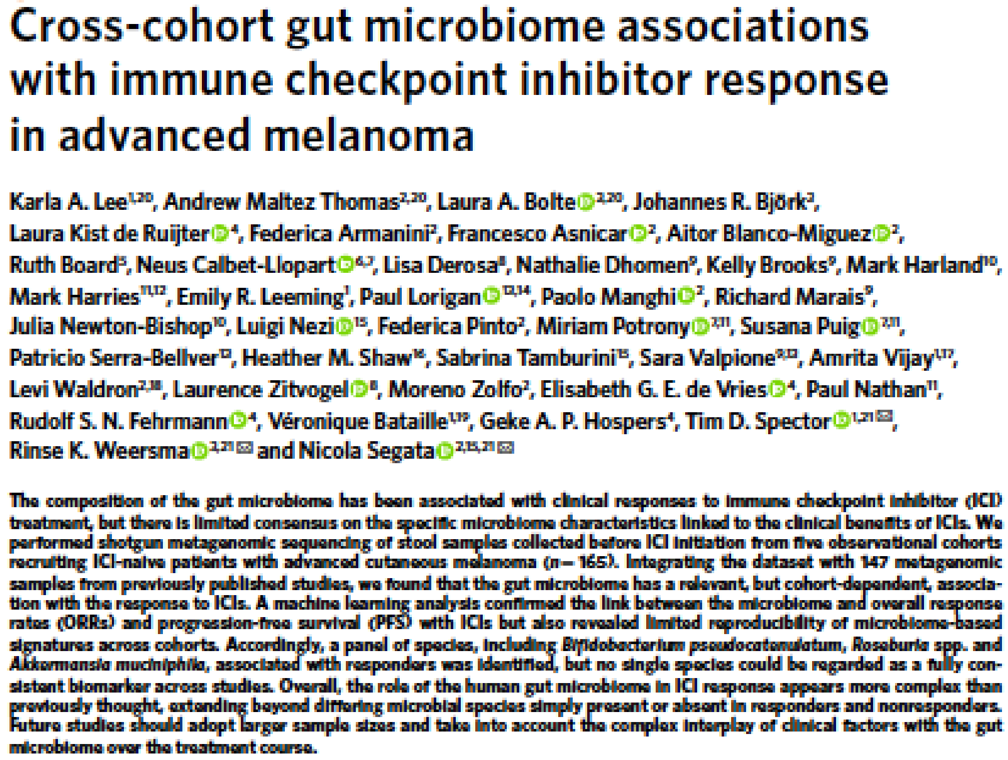
Bifidobacterium longum

Collinsella aerofaciens

Enterococcus faecium.

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

John A. McCulloch[1,7], Diwakar Davar[2,7], Richard R. Rodrigues[1,2,7], Jonathan H. Badger[1], Jennifer R. Fang[4], Alicia M. Cole[4], Ascharya K. Balaji[4], Marie Vetizou[4], Stephanie M. Prescott[4], Miriam R. Fernandes[4], Raquel G. F. Costa[4], Wuxing Yuan[1,2], Rosalba Salcedo[4], Erol Bahadiroglu[4], Soumen Roy[4], Richelle N. DeBlasio[2], Robert M. Morrison[2], Joe-Marc Chauvin[2], Quanquan Ding[2], Bochra Zidi[2], Ava Lowin[2], Saranya Chakka[2], Wentao Gao[2], Ornella Pagliano[2], Scarlett J. Ernst[2], Amy Rose[2], Nolan K. Newman[3], Andrey Morgun[3], Hassane M. Zarour[2,6,8] ✉, Giorgio Trinchieri[4,8] ✉ and Amiran K. Dzutsev[4,8] ✉

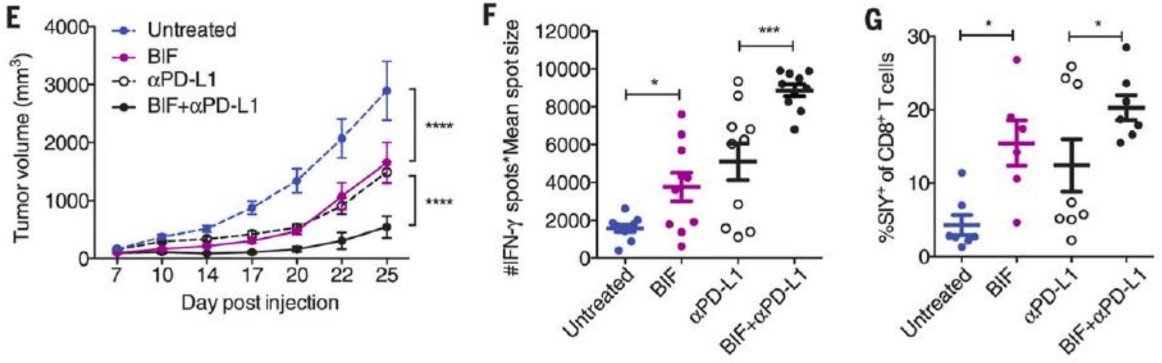


OPEN

Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma

Karla A. Lee[1,20], Andrew Maltez Thomas[2,20], Laura A. Bolte[2,20], Johannes R. Björk[2], Laura Kist de Ruijter[4], Federica Armanini[2], Francesco Asnicar[2], Aitor Blanco-Miguez[2], Ruth Board[5], Neus Calbet-Llopart[6,7], Lisa Derosa[8], Nathalie Dhomen[9], Kelly Brooks[9], Mark Harland[10], Mark Harries[11,12], Emily R. Leeming[1], Paul Lorigan[13,14], Paolo Manghi[2], Richard Marais[9], Julia Newton-Bishop[10], Luigi Nezi[15], Federica Pinto[2], Miriam Potrony[7,11], Susana Puig[7,11], Patricio Serra-Bellver[13], Heather M. Shaw[16], Sabrina Tamburini[15], Sara Valpione[9,13], Amrita Vijay[1,17], Levi Waldron[2,18], Laurence Zitvogel[8], Moreno Zolfo[2], Elisabeth G. E. de Vries[4], Paul Nathan[11], Rudolf S. N. Fehrmann[4], Véronique Bataille[1,19], Geke A. P. Hospers[4], Tim D. Spector[1,21] ✉, Rinse K. Weersma[2,21] ✉ and Nicola Segata[2,15,21] ✉

The composition of the gut microbiome has been associated with clinical responses to immune checkpoint inhibitor (ICI) treatment, but there is limited consensus on the specific microbiome characteristics linked to the clinical benefits of ICIs. We performed shotgun metagenomic sequencing of stool samples collected before ICI initiation from five observational cohorts recruiting ICI-naive patients with advanced cutaneous melanoma ($n = 165$). Integrating the dataset with 147 metagenomic samples from previously published studies, we found that the gut microbiome has a relevant, but cohort-dependent, association with the response to ICIs. A machine learning analysis confirmed the link between the microbiome and overall response rates (ORRs) and progression-free survival (PFS) with ICIs but also revealed limited reproducibility of microbiome-based signatures across cohorts. Accordingly, a panel of species, including *Bifidobacterium pseudocatenulatum*, *Roseburia* spp. and *Akkermansia muciniphila*, associated with responders was identified, but no single species could be regarded as a fully consistent biomarker across studies. Overall, the role of the human gut microbiome in ICI response appears more complex than previously thought, extending beyond differing microbial species simply present or absent in responders and nonresponders. Future studies should adopt larger sample sizes and take into account the complex interplay of clinical factors with the gut microbiome over the treatment course.



Silvan A, Science 2015

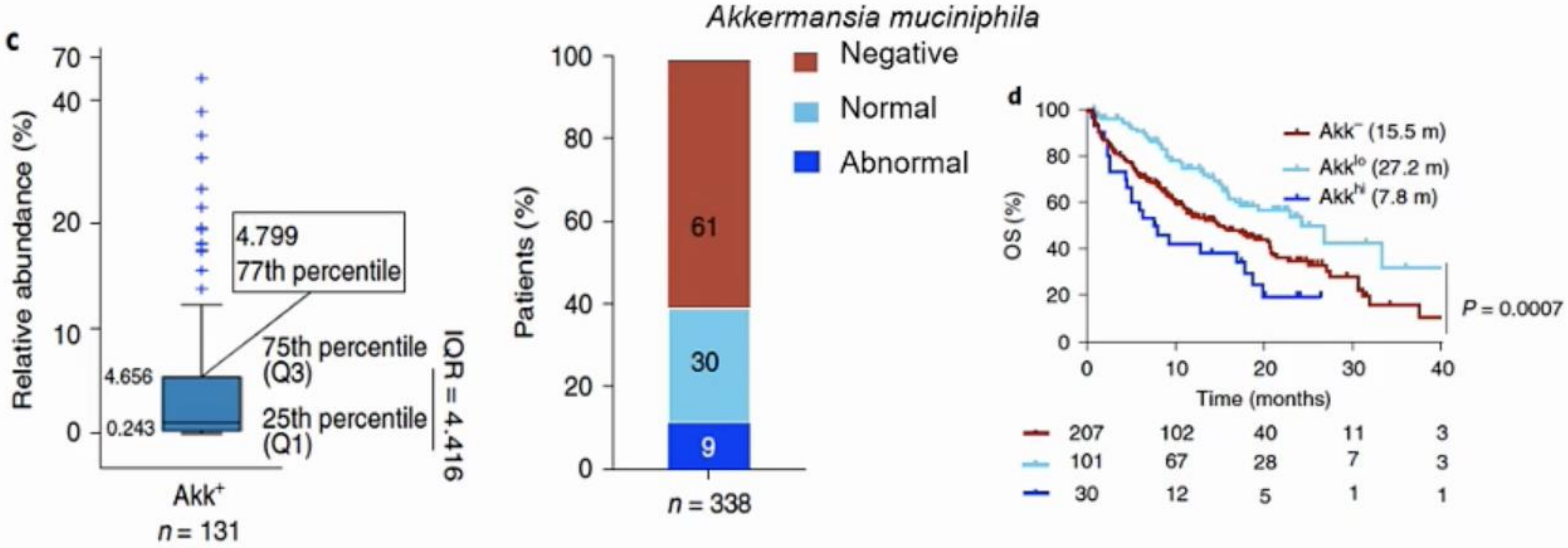
Akkermansia abundance as a predictor> tools development

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01655-5

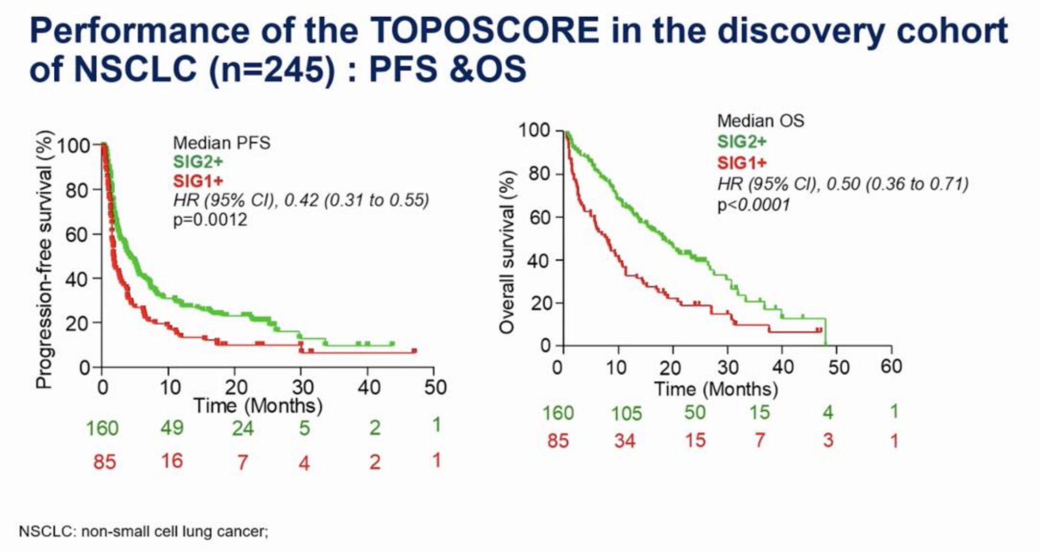
Check for updates

Intestinal *Akkermansia muciniphila* predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer

Lisa Derosa[1,2,3,4,35], Bertrand Routy[5,6,35], Andrew Maltez Thomas[7,8,35], Valerio Iebba[9],

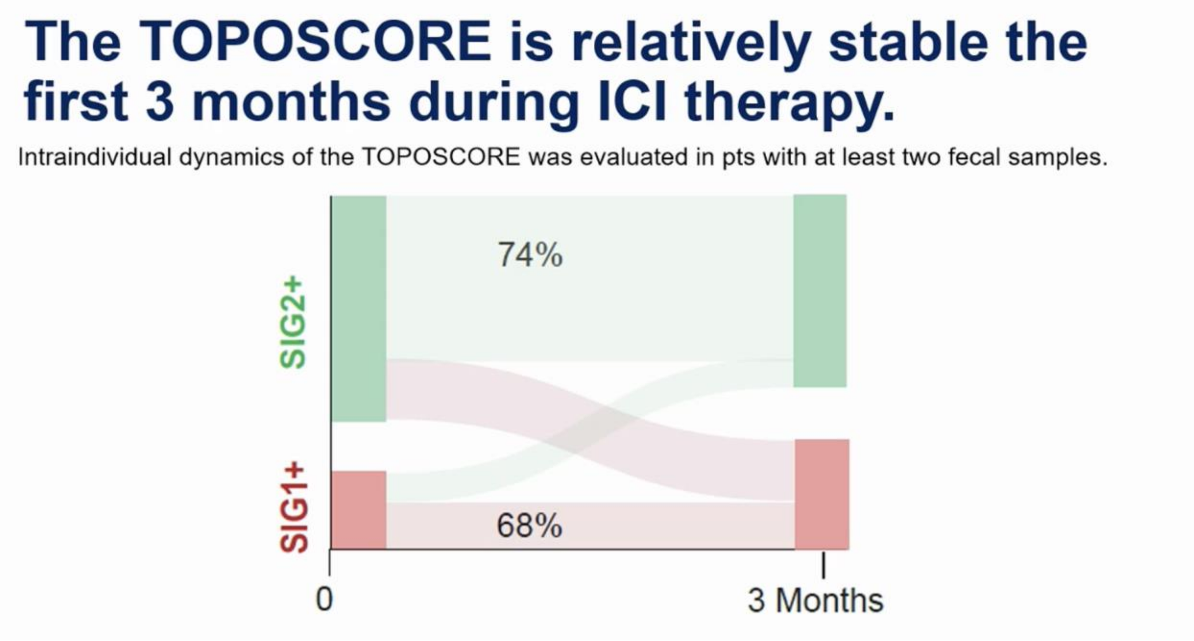


Derosa et al. Nat Med 2022



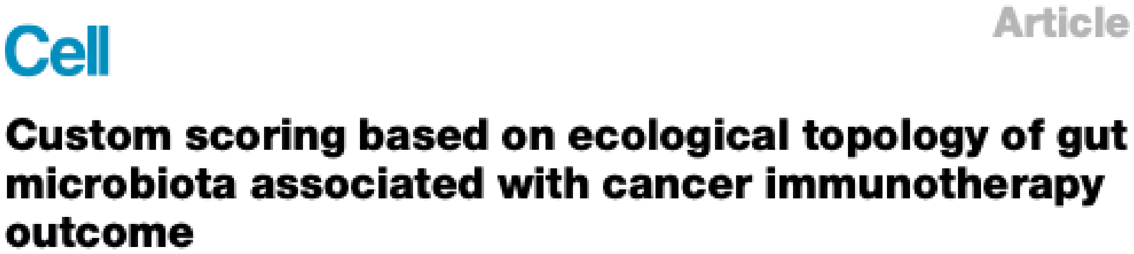
Performance of the TOPOSCORE in the discovery cohort of NSCLC (n=245) : PFS &OS

NSCLC: non-small cell lung cancer;



The TOPOSCORE is relatively stable the first 3 months during ICI therapy.

Intraindividual dynamics of the TOPOSCORE was evaluated in pts with at least two fecal samples.



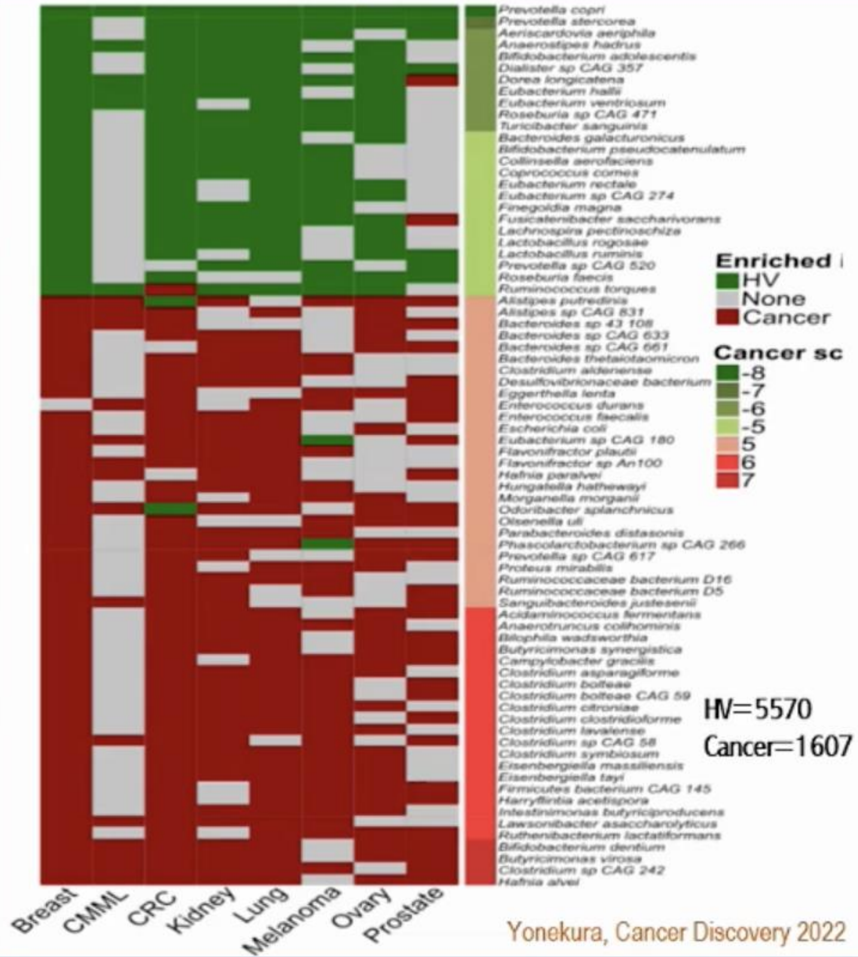
Cell

Article

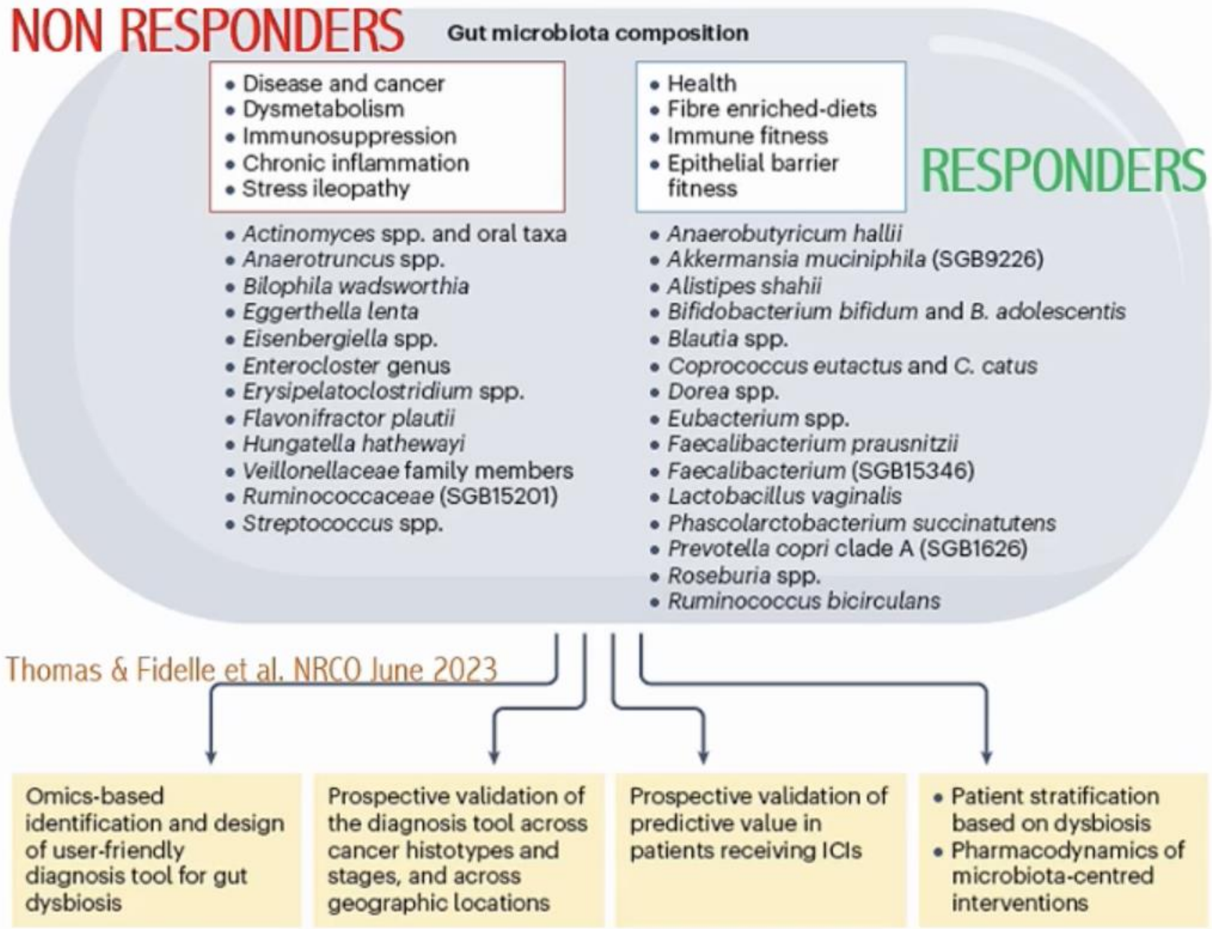
Custom scoring based on ecological topology of gut microbiota associated with cancer immunotherapy outcome

Derosa et al 2024

GUT DYSBIOSIS IN CANCER PATIENTS: Divergence between healthy volunteers and cancer patients and between responders or non responders to IO



Yonekura, Cancer Discovery 2022



NON RESPONDERS

Gut microbiota composition

- Disease and cancer
- Dysmetabolism
- Immunosuppression
- Chronic inflammation
- Stress ileopathy

- *Actinomyces* spp. and oral taxa
- *Anaerotruncus* spp.
- *Bilophila wadsworthia*
- *Eggerthella lenta*
- *Eisenbergiella* spp.
- *Enterocloster* genus
- *Erysipelatoclostridium* spp.
- *Flavonifractor plautii*
- *Hungatella hathewayi*
- *Veillonellaceae* family members
- *Ruminococcaceae* (SGB15201)
- *Streptococcus* spp.

RESPONDERS

- Health
- Fibre enriched-diets
- Immune fitness
- Epithelial barrier fitness

- *Anaerobutyricum hallii*
- *Akkermansia muciniphila* (SGB9226)
- *Alistipes shahii*
- *Bifidobacterium bifidum* and *B. adolescentis*
- *Blautia* spp.
- *Coprococcus eutactus* and *C. catus*
- *Dorea* spp.
- *Eubacterium* spp.
- *Faecalibacterium prausnitzii*
- *Faecalibacterium* (SGB15346)
- *Lactobacillus vaginalis*
- *Phascolarctobacterium succinatutens*
- *Prevotella copri* clade A (SGB1626)
- *Roseburia* spp.
- *Ruminococcus bicirculans*

Thomas & Fidelle et al. NRCO June 2023

Omics-based identification and design of user-friendly diagnosis tool for gut dysbiosis

Prospective validation of the diagnosis tool across cancer histotypes and stages, and across geographic locations

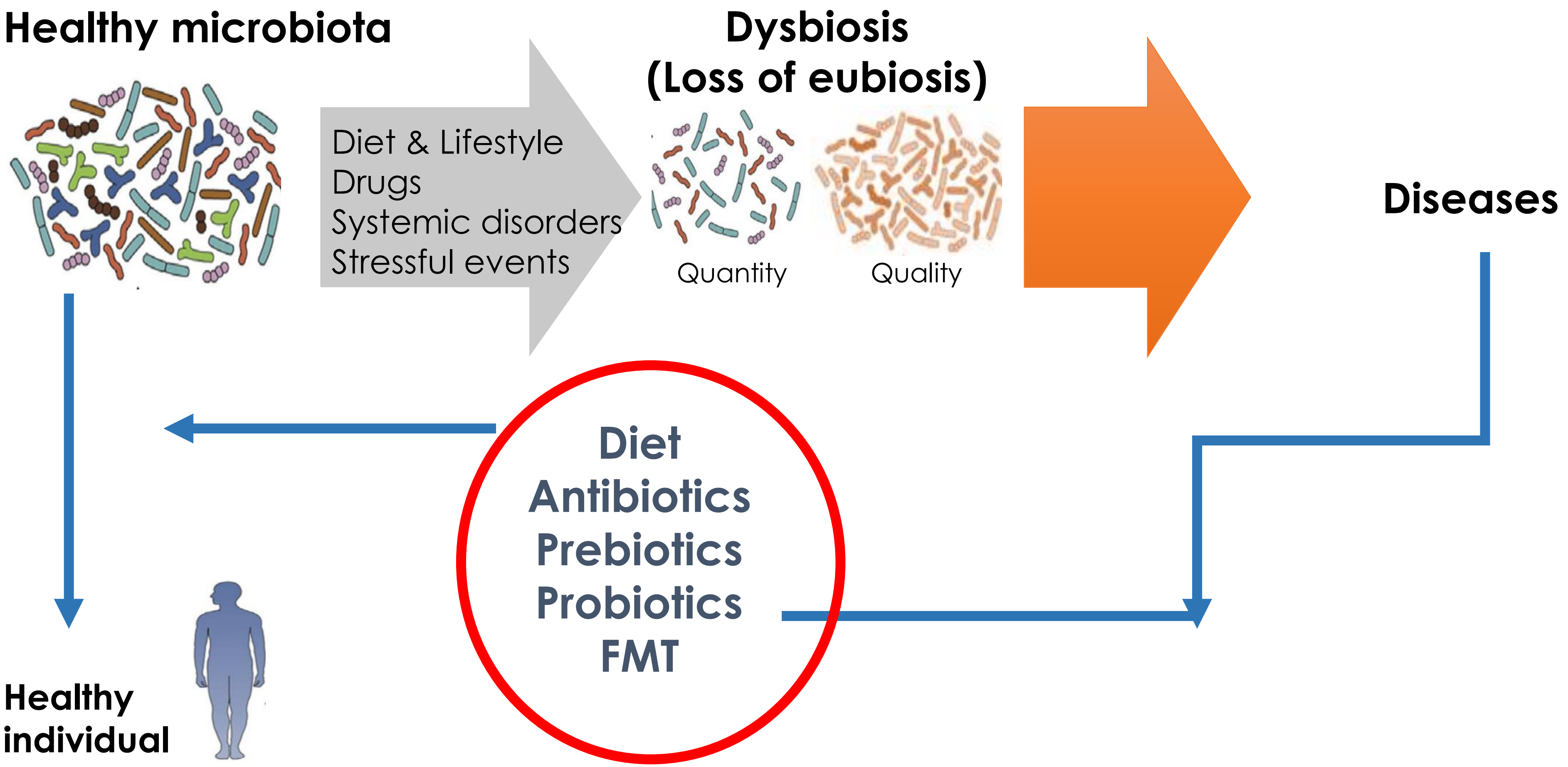
Prospective validation of predictive value in patients receiving ICIs

- Patient stratification based on dysbiosis
- Pharmacodynamics of microbiota-centred interventions

Is there room for exploiting the microbiome in clinical practice?

- Assess the risk of disease development/progression
- Assess the influence of microbiota on response to treatments
- **Therapeutic reasons**

Rationale of Microbiota Modulation



Healthy microbiota

Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

Dysbiosis
(Loss of eubiosis)

Quantity

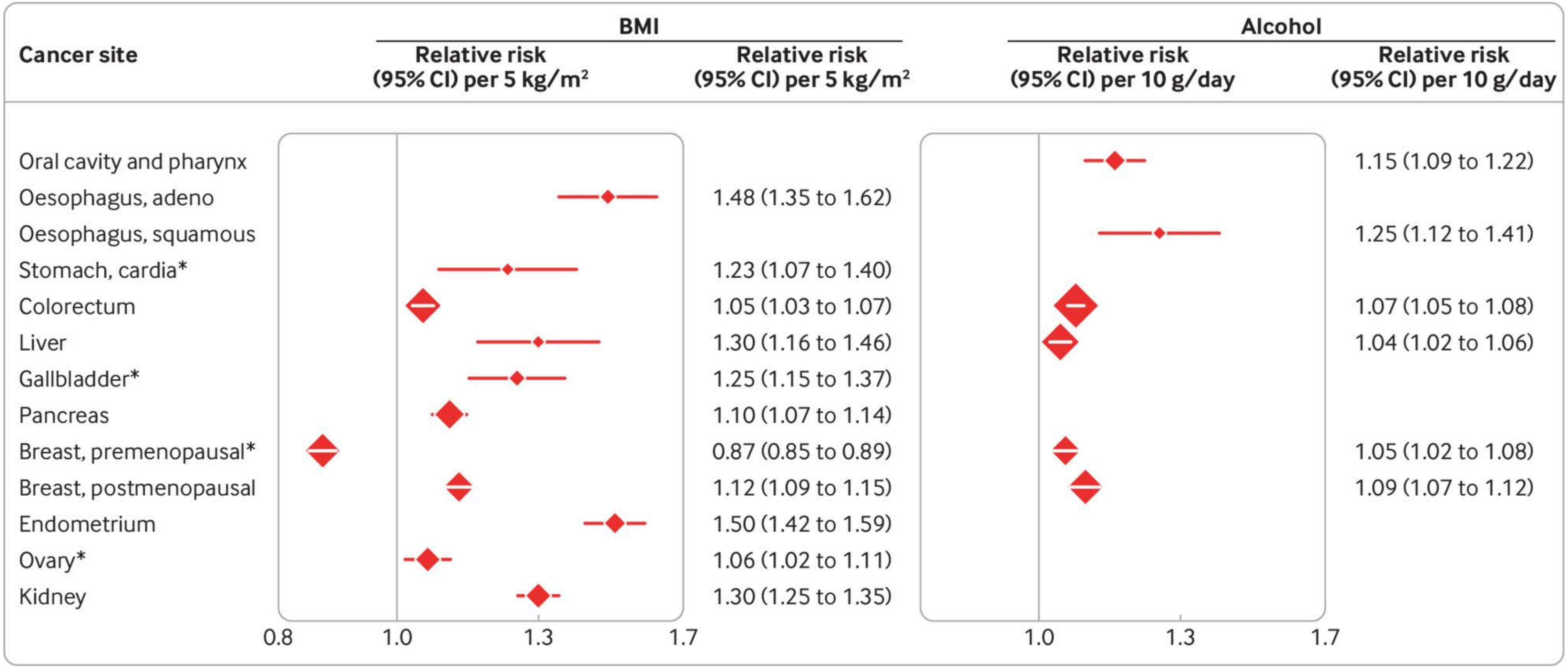
Quality

Diseases

Diet
Antibiotics
Prebiotics
Probiotics
FMT

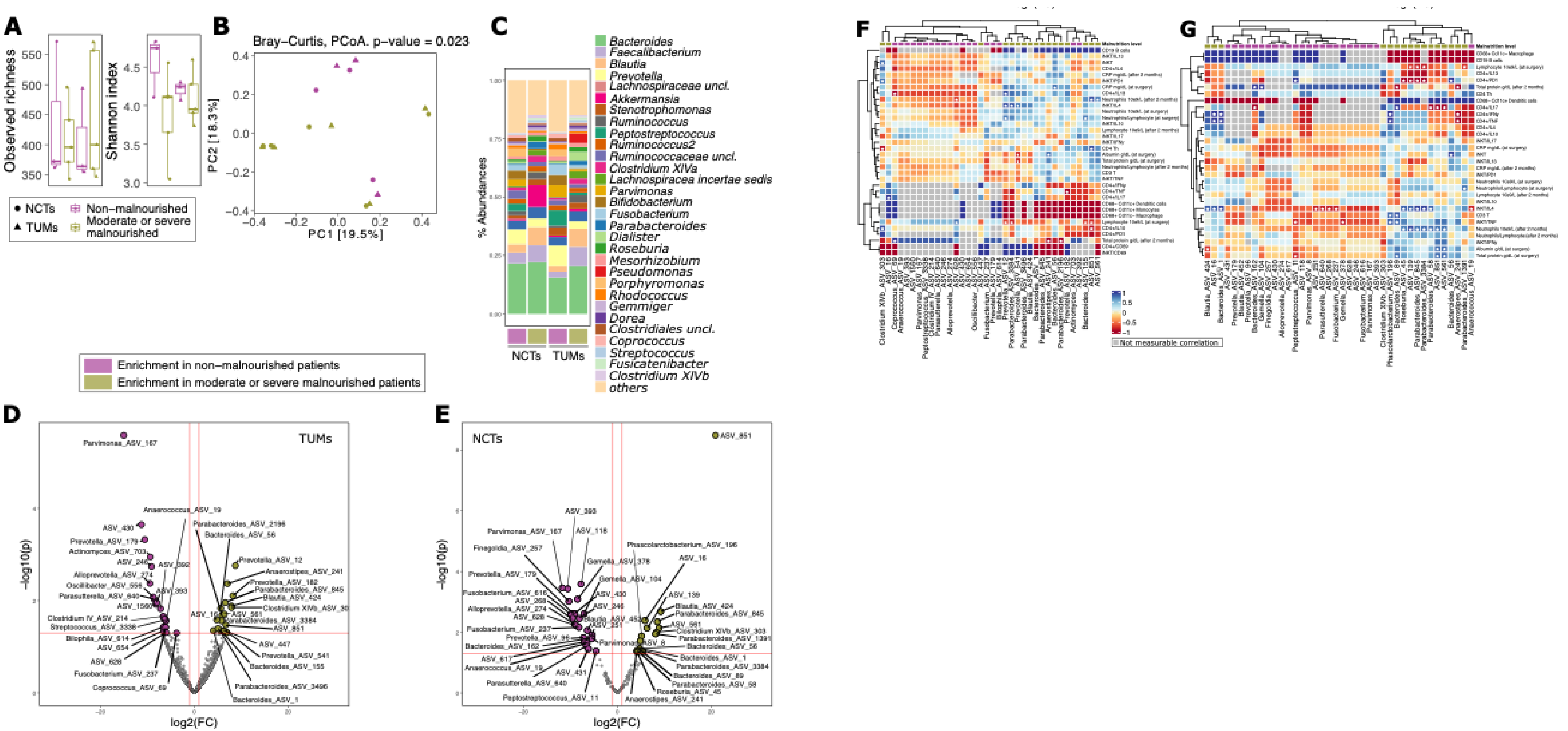
Healthy individual

Diet



Cancer site	BMI		Alcohol	
	Relative risk (95% CI) per 5 kg/m^2	Relative risk (95% CI) per 5 kg/m^2	Relative risk (95% CI) per 10 g/day	Relative risk (95% CI) per 10 g/day
Oral cavity and pharynx				1.15 (1.09 to 1.22)
Oesophagus, adeno		1.48 (1.35 to 1.62)		
Oesophagus, squamous				1.25 (1.12 to 1.41)
Stomach, cardia*		1.23 (1.07 to 1.40)		
Colorectum		1.05 (1.03 to 1.07)		1.07 (1.05 to 1.08)
Liver		1.30 (1.16 to 1.46)		1.04 (1.02 to 1.06)
Gallbladder*		1.25 (1.15 to 1.37)		
Pancreas		1.10 (1.07 to 1.14)		
Breast, premenopausal*		0.87 (0.85 to 0.89)		1.05 (1.02 to 1.08)
Breast, postmenopausal		1.12 (1.09 to 1.15)		1.09 (1.07 to 1.12)
Endometrium		1.50 (1.42 to 1.59)		
Ovary*		1.06 (1.02 to 1.11)		
Kidney		1.30 (1.25 to 1.35)		

Malnutrition in CRC patients



Perillo et al under revision

Prevent or treat cancer

Gastrointestinal tumor
- Colorectal cancer

Non-gastrointestinal tumor
- Liver cancer
- Pancreatic cancer
- Breast cancer
- Lung cancer

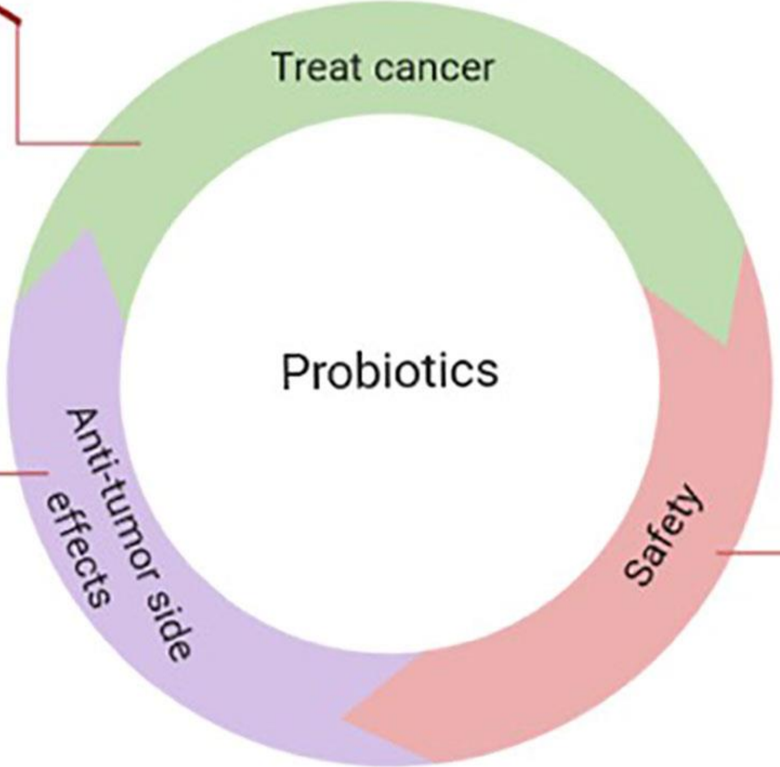
Improve side effects of anti-tumor treatment

Intestinal mucosal damage
- Diarrhea

Oral mucosal damage
- Mucositis

Systemic inflammation
- Graft-versus-host disease

Other inflammation reaction



Adverse effect of probiotics

Gastrointestinal reaction
- Diarrhea
- Bloating

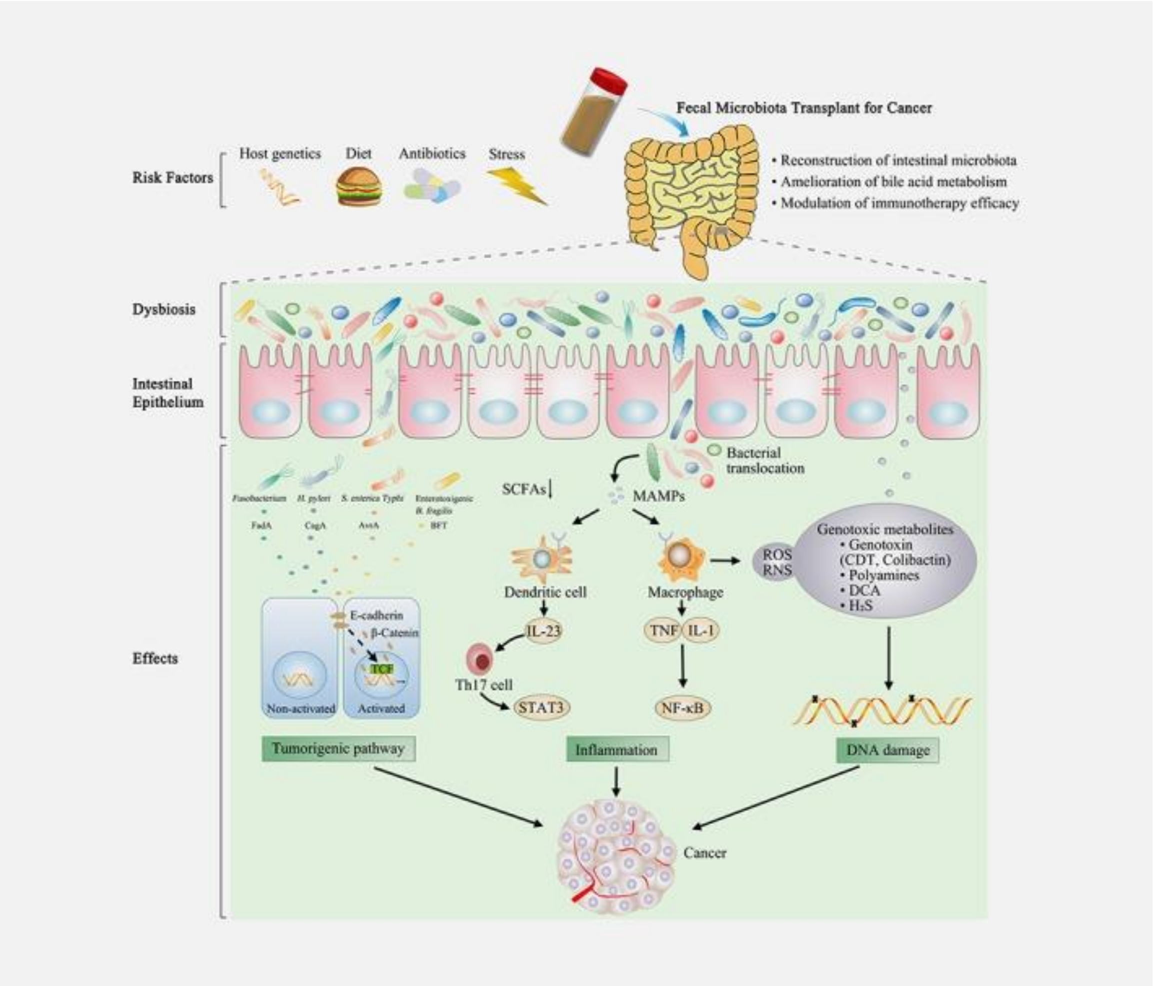
Infection
- Bacteremia
- Fungemia
- Endocarditis

Gene transfer
- Antibiotic resistance

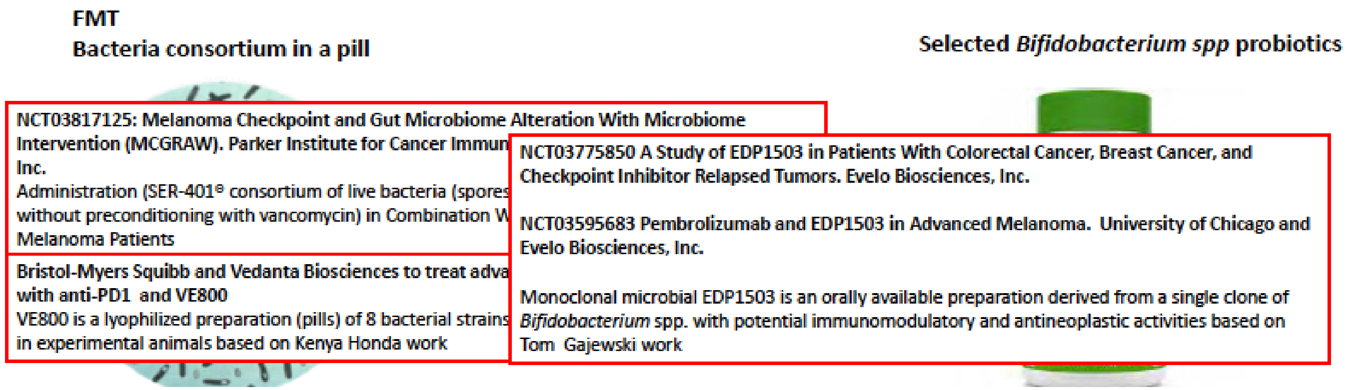
Skin
- Rash
- Acne

Susceptible population
- Infant
- The elder
- Hospitalized people
- Immunodeficiency patient

FMT (trapianto di microbiota fecale)



- Melanoma, RC, NSLLC, CAR-T
- complications
  - C.difficile
  - Mucosite da radioterapia
  - GVHD



FMT
Bacteria consortium in a pill

Selected *Bifidobacterium spp* probiotics

NCT03817125: Melanoma Checkpoint and Gut Microbiome Alteration With Microbiome Intervention (MCGRAW). Parker Institute for Cancer Immun
Inc.
Administration (SER-401® consortium of live bacteria (spores
without preconditioning with vancomycin) in Combination W
Melanoma Patients

Bristol-Myers Squibb and Vedanta Biosciences to treat adva
with anti-PD1 and VE800
VE800 is a lyophilized preparation (pills) of 8 bacterial strains
in experimental animals based on Kenya Honda work

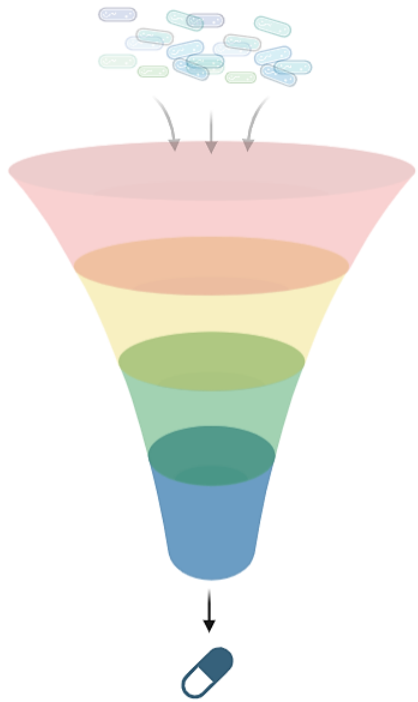
NCT03775850 A Study of EDP1503 in Patients With Colorectal Cancer, Breast Cancer, and Checkpoint Inhibitor Relapsed Tumors. Evelo Biosciences, Inc.

NCT03595683 Pembrolizumab and EDP1503 in Advanced Melanoma. University of Chicago and Evelo Biosciences, Inc.

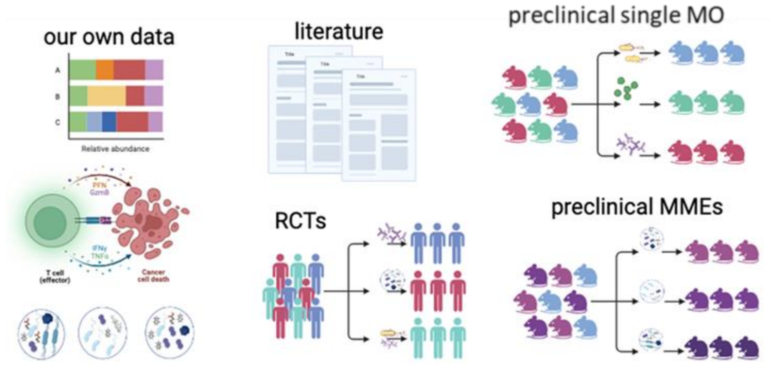
Monoclonal microbial EDP1503 is an orally available preparation derived from a single clone of *Bifidobacterium* spp. with potential immunomodulatory and antineoplastic activities based on Tom Gajewski work

The goal

To generate **microbial consortia capable of** enhancing **iNKT cells' cytotoxic functions**.

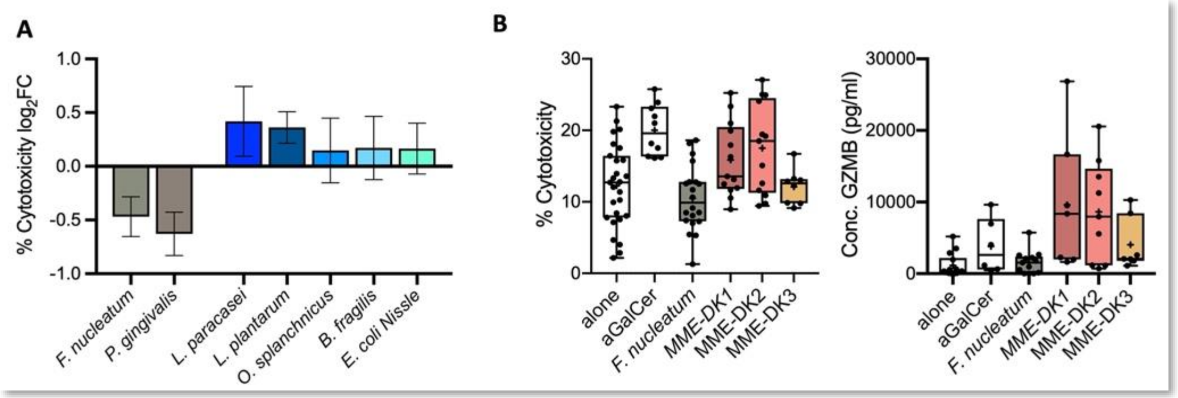


The approach



→ Classifier

The results



Open questions

- Variability in the sampling, sequencing, analysis

Consensus microbiome

- frequency of sampling/analysis

- Other variables (es: diet, age, lifestyle, drugs, sex)

- Other microbiome components (es , fungi, virus?)

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REVIEW · Volume 10, Issue 2, P154-167, February 2025

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International consensus statement on microbiome testing in clinical practice

Serena Porcari, MD [a,d] · Benjamin H Mullish, MD [g,h] · Francesco Asnicar, PhD [i] · Prof Siew C Ng, MD [j,k,l] · Prof Liping Zhao, PhD [n] · Richard Hansen, MD [o] · et al. Show more

nature microbiology

Review article

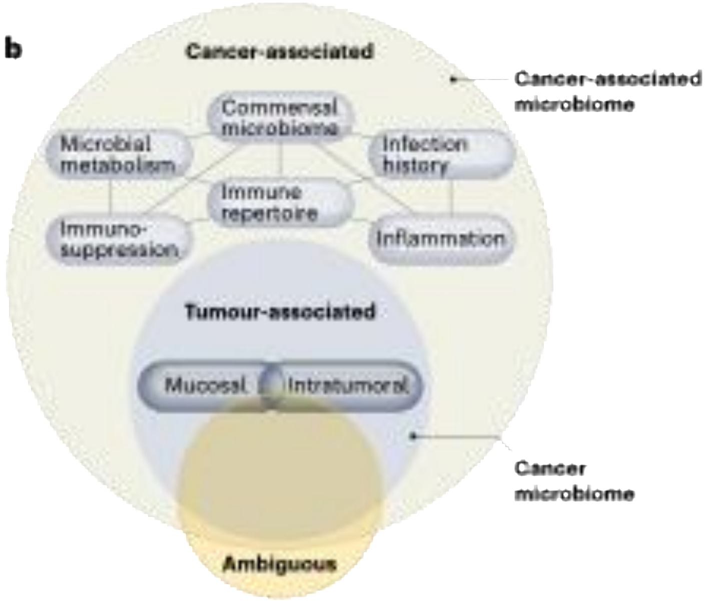
https://doi.org/10.1038/s41564-025-02103-7

The multi-kingdom cancer microbiome

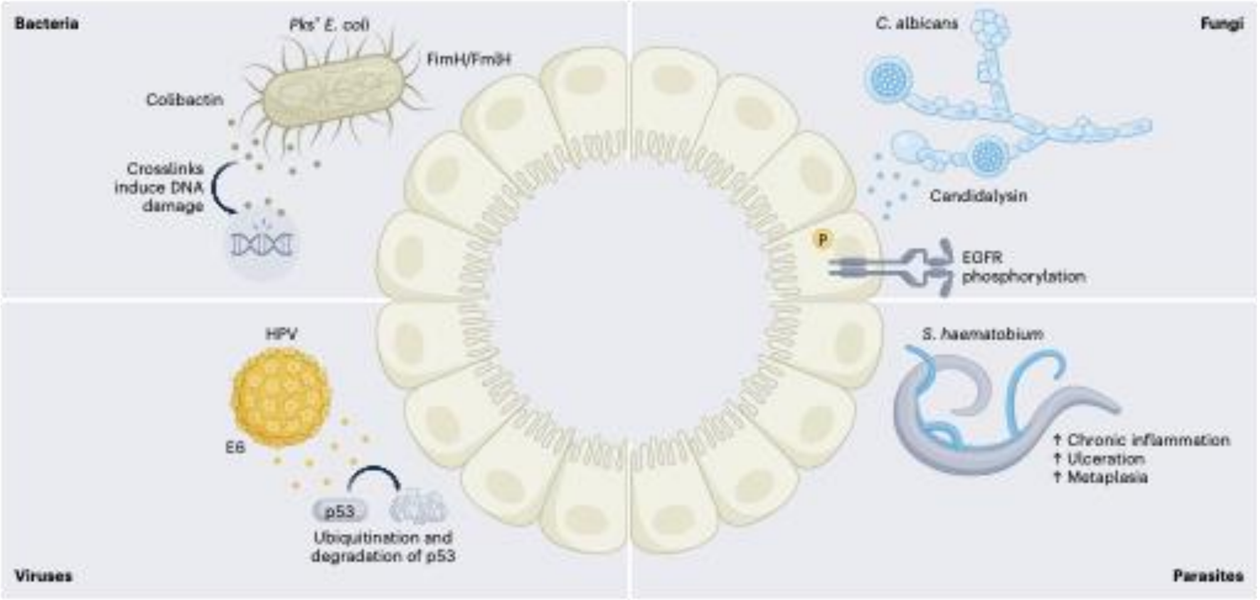
Received: 6 May 2024

Accepted: 28 July 2025

Anders B. Dohlman [1], Xiangyu Pan [2,3], Laurence Zitvogel [4,5,6,7] &
Iliyan D. Iliev [2,3,8,9]



	Viruses	Parasites	Bacteria	Fungi
Head and neck	HPV (oral)[a][15,53] EBV (nasal)[a][15]		*F. nucleatum*[187]	Candida[21,22]
Oesophageal			*F. nucleatum*[65,188]	Cladosporium[100] Candida[21,22,100]
Stomach	EBV[a][15,33,189]		*H. pylori*[a][10,35,41,42] *S. anginosis*[41,42]	Candida[21,22]
Large intestine			*F. nucleatum*[162,163] Enterotoxigenic *B. fragilis*[15,26,74,190] *pks*$^+$ *E. coli*[25,26,34,75,191] *Parvimonas micra*[192,193] *C. jejuni*[77] *Peptostreptococcus anaerobius*[78,79,194]	Candida[21,22]
Skin	KSHV[a][15,195] MCPyV[15,196]			
Brain	JCV[a][196–198]			
Lung			*C. pneumoniae*[66]	*Aspergillus*[199] *Blastomyces*[21,22]
Liver	HBV[a]/HCV[a][15,200]			
Bile duct		*O. viverrini*[a][15,47,48] *C. sinensis*[a][15,47,48]		
Gallbladder			*S. typhi*[85]	
Pancreas				*Malassezia*[201]
Bladder		*S. haematobium*[a][15,47,48]		
Cervical	HPV[a][8,15,53]			



UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Facciotti Lab, BTBS
Alberto Baeri
Elena Oriani
Paola Pinco
Georgia Lattanzi
Federica Perillo
Angelica Diaz-Basabe

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Mucosal Immunology&microbiota
Chiara Amoroso
Yvanna Honcharyuk
Bruna Caridi
Francesco Strati
Alessandro Fumagalli
Oriana Ramponi
Paola Maragno

Sistema Sanitario Regione Lombardia

Gastroenterology Unit
Prof. Flavio Caprioli
Daniele Noviello
Simone Conforti
Piazza N, Marinoni B
Clorinda Ciafardini
Sara Comparetti

Surgery Unit
Prof. Luigi Boni
CRC: Baldari, Cassinotti, Carrara, Costa
IBD: Botti, Oreggia, Prati

UNIVERSITAS STUDIORUM MEDIOLANENSIS

Pathological Anatomy Unit
Prof. Stefano Ferrero
Gianluca Lopez

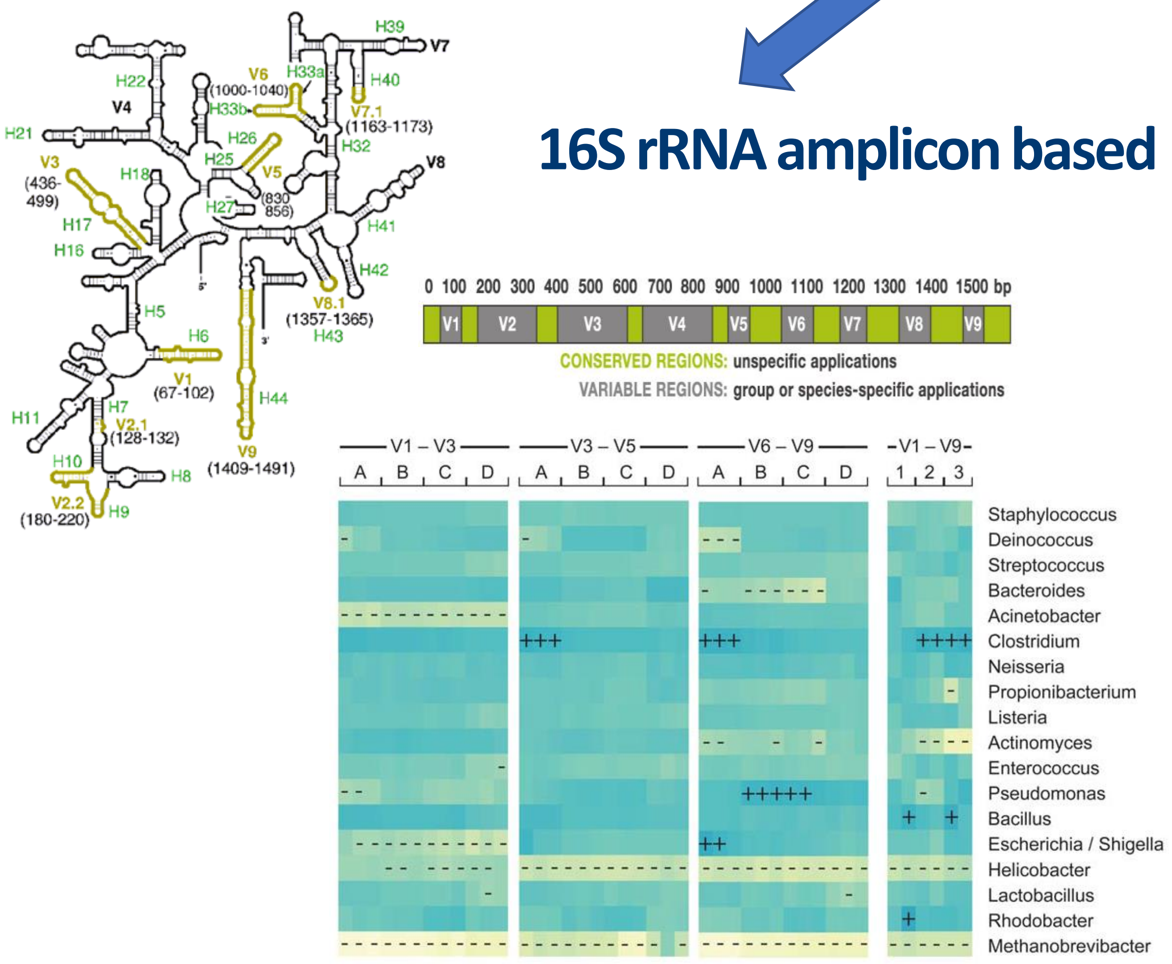
Medical Oncology Unit
Barbara Galassi

Flow cytometry
Laura Porretta
Federico Colombo
Elena Trombetta

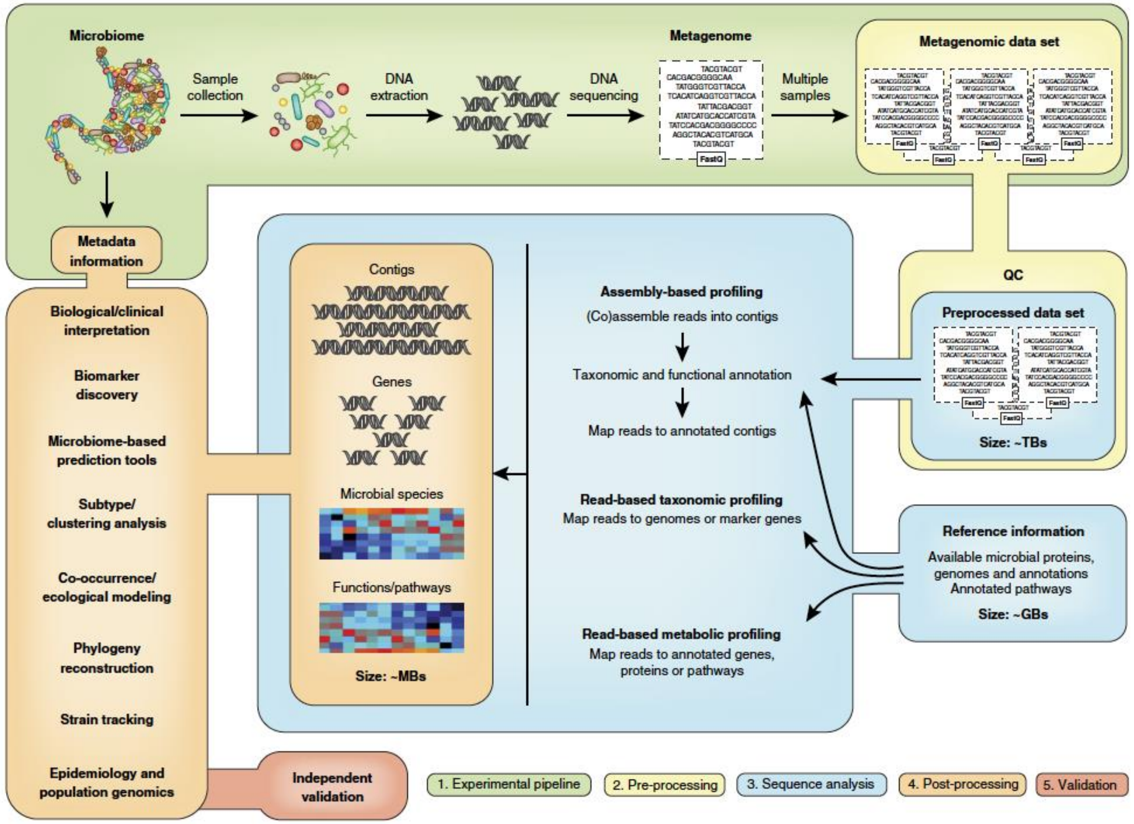
AIRC
EACR European Association for Cancer Resea
Recovery And Resilience Plan
#NEXTGENERATIONITALIA
Ministero della Salute
MUR Ministero dell'Università e della Ricerca

Metodi di sequenziamento

16S rRNA amplicon based



Whole genome shotgun (WGS)



Microbiome

Sample collection

DNA extraction

DNA sequencing

Metagenome

Multiple samples

Metagenomic data set

Metadata information

Biological/clinical interpretation

Biomarker discovery

Microbiome-based prediction tools

Subtype/ clustering analysis

Co-occurrence/ ecological modeling

Phylogeny reconstruction

Strain tracking

Epidemiology and population genomics

Independent validation

Contigs

Genes

Microbial species

Functions/pathways

Size: ~MBs

Assembly-based profiling

(Co)assemble reads into contigs

Taxonomic and functional annotation

Map reads to annotated contigs

Read-based taxonomic profiling

Map reads to genomes or marker genes

Read-based metabolic profiling

Map reads to annotated genes, proteins or pathways

QC

Preprocessed data set

Size: ~TBs

Reference information

Available microbial proteins, genomes and annotations
Annotated pathways

Size: ~GBs

1. Experimental pipeline
2. Pre-processing
3. Sequence analysis
4. Post-processing
5. Validation