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Giorgio Trinchieri

Cancer and Inflammation Program, CCR, NCI, NIH

The role of the commensal microbiota in carcinogenesis and cancer therapy

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH
National Institutes of Health

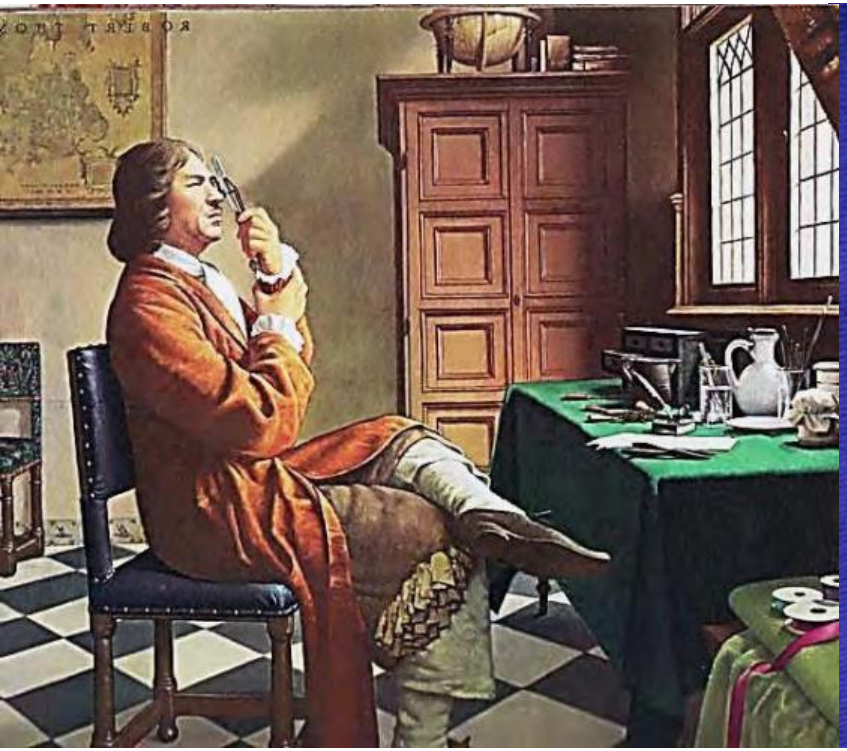
NATIONAL CANCER INSTITUTE

Center for Cancer Research

Disclosure

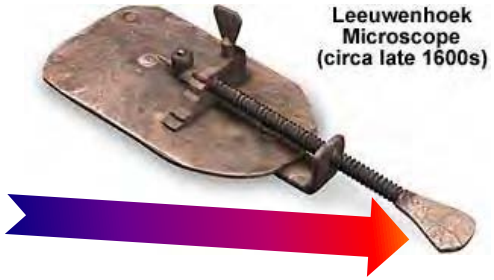
This presenter has no financial interest or other relationships with manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

1683: First observation of commensal microbes (the microbiota)

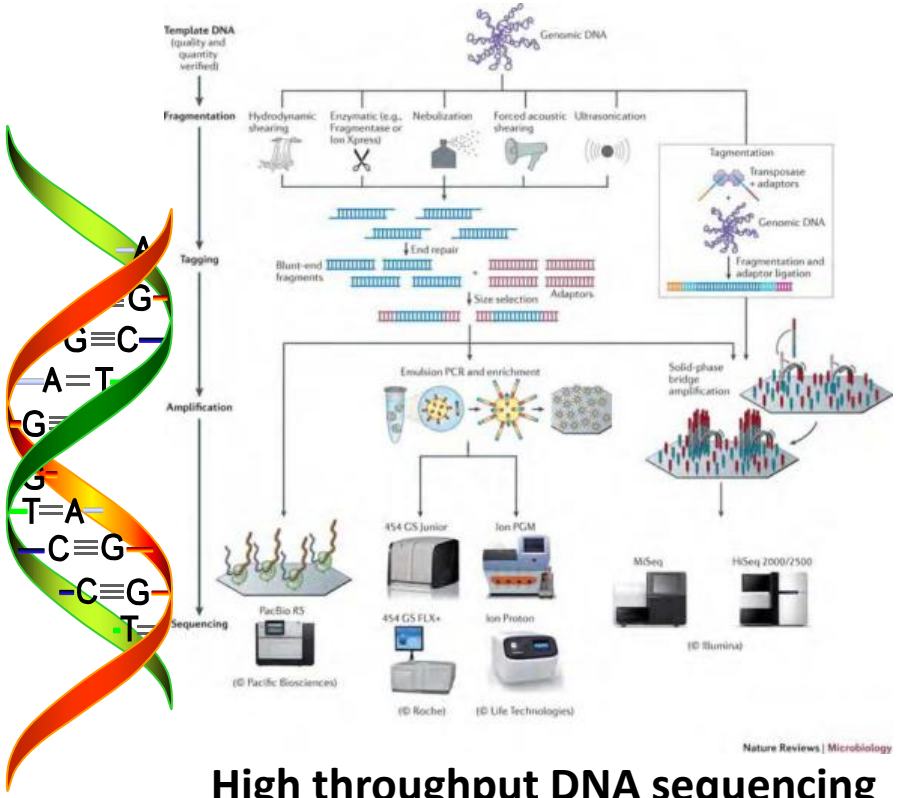


On September 17, 1683 Antonie van Leeuwenhoek wrote to the Royal Society in London about observations on the plaque between his own teeth with his homemade microscope:

"I then most always saw, with great wonder, that in the said matter there were many very little living animalcules, very prettily a-moving".

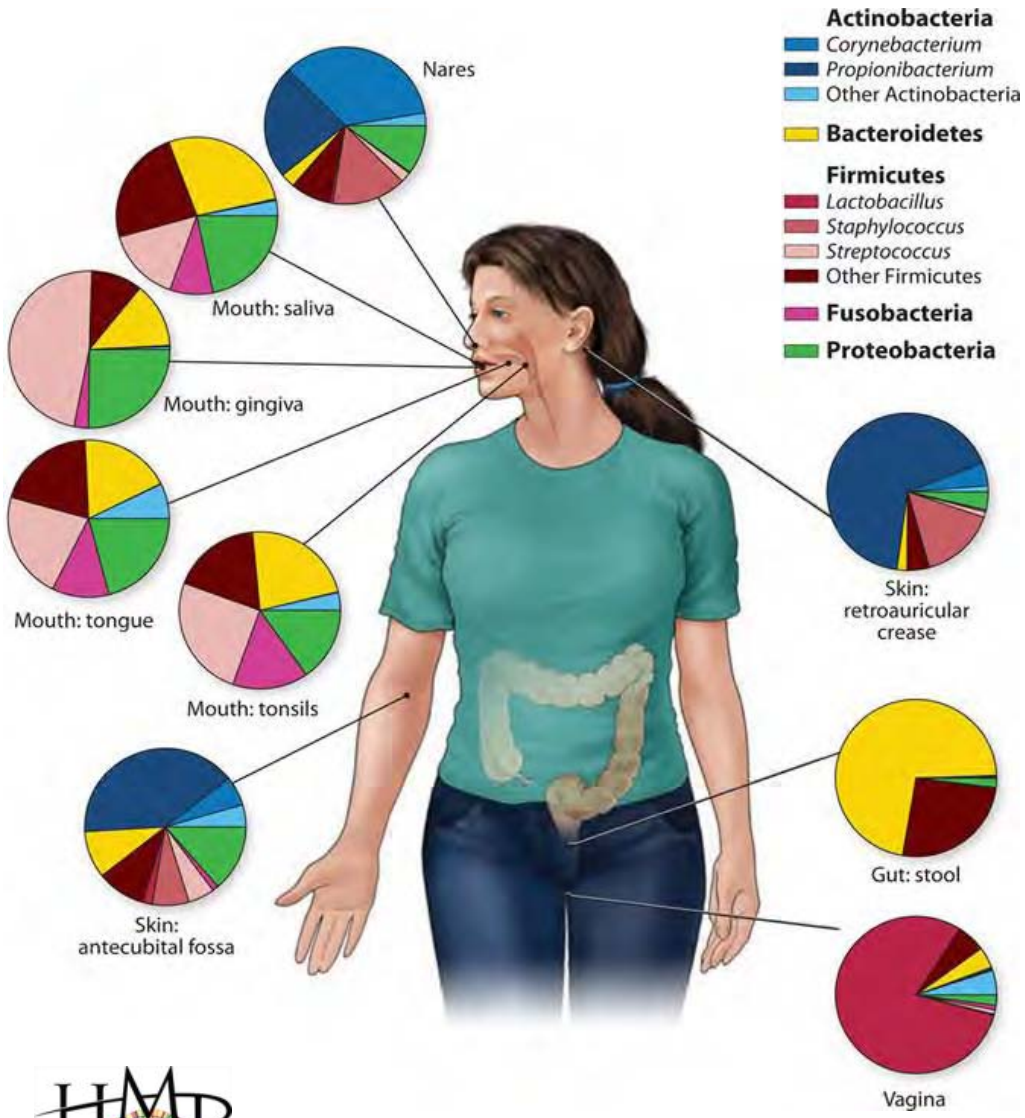


We can culture only a fraction of the bacterial species that live in our body



High throughput DNA sequencing

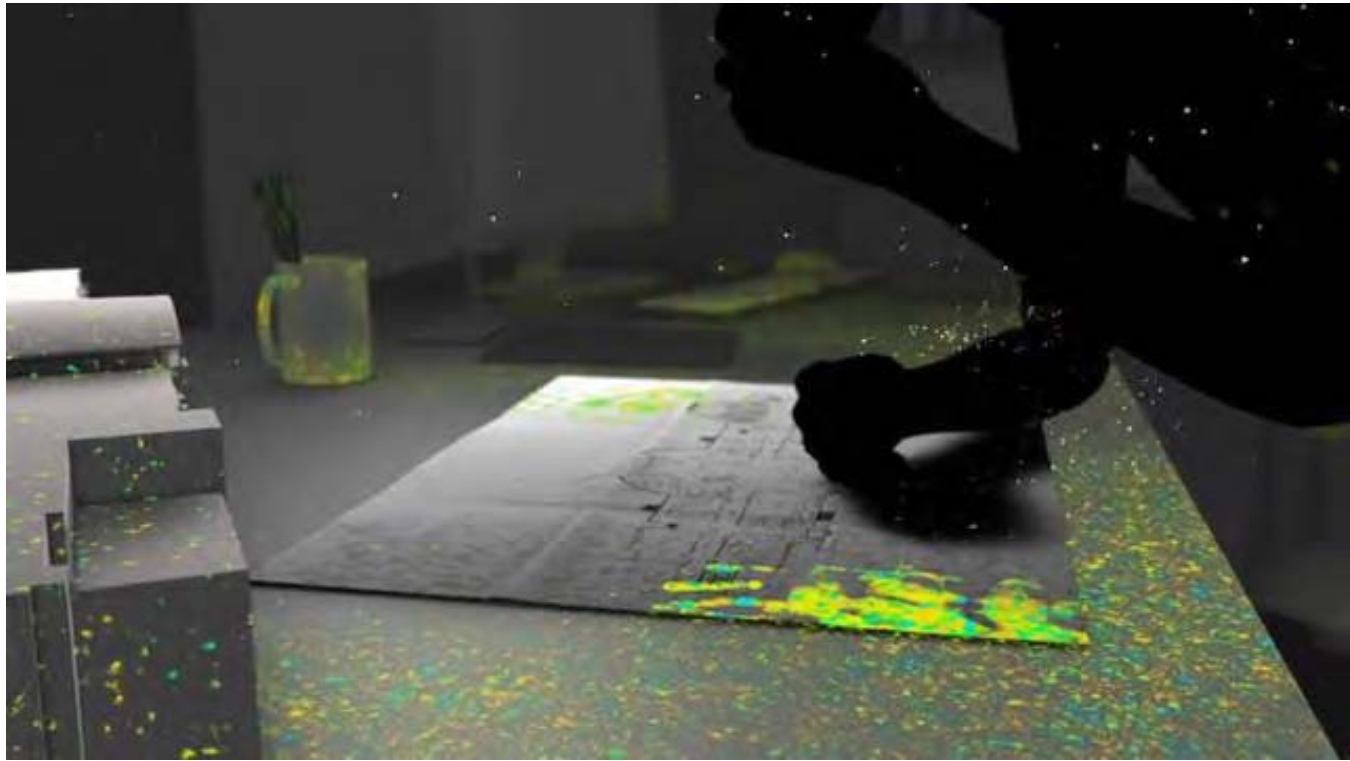
Humans have co-evolved with microbial partners



Human microbiome project

BioBE Center
Cameron Slayden Animator

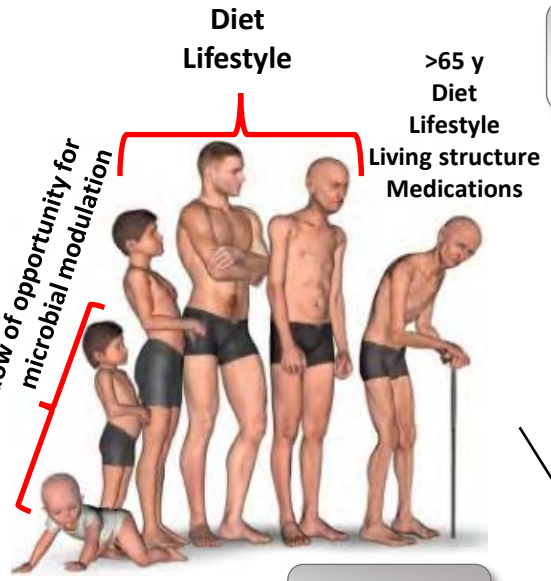
- We are a composite of species: bacteria, archea, protozoa, fungi, viruses, bacteriophages
- Commensal microorganisms
  - inhabit all barrier surfaces of our organism
  - are at least as numerous as human cells
  - their DNA (the microbiome) contains 100 times more genes than our 'own' human genome



Humans are metaorganisms composed of the large host (human) cells and commensal microbial cells

The commensal microbiota is indispensable for the survival of the metaorganism and the cross-talk between the host and its microbiota regulates many physiological functions.

Changes in our microbiota…



Age

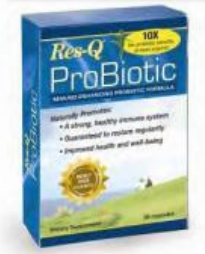
Geographical location

Lifestyle

Nutrition

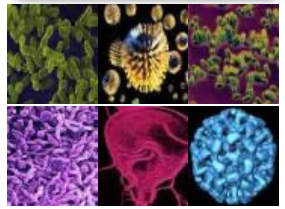
Hygiene

Probiotics

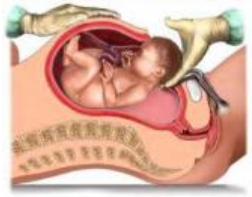


Antibiotics

Infections

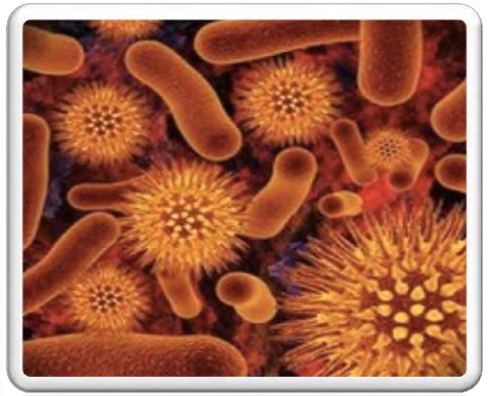


Mode of delivery



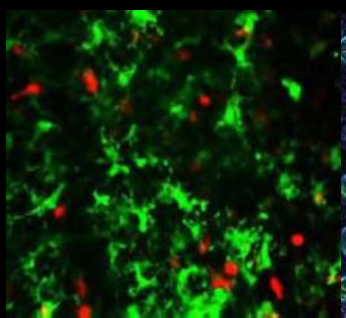
Host Genetics

(genetics accounts for between 1 to 8% of microbiota diversity)

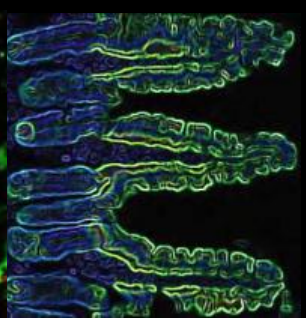


Dysbiosis: a microbiota imbalance that may be associated with illnesses

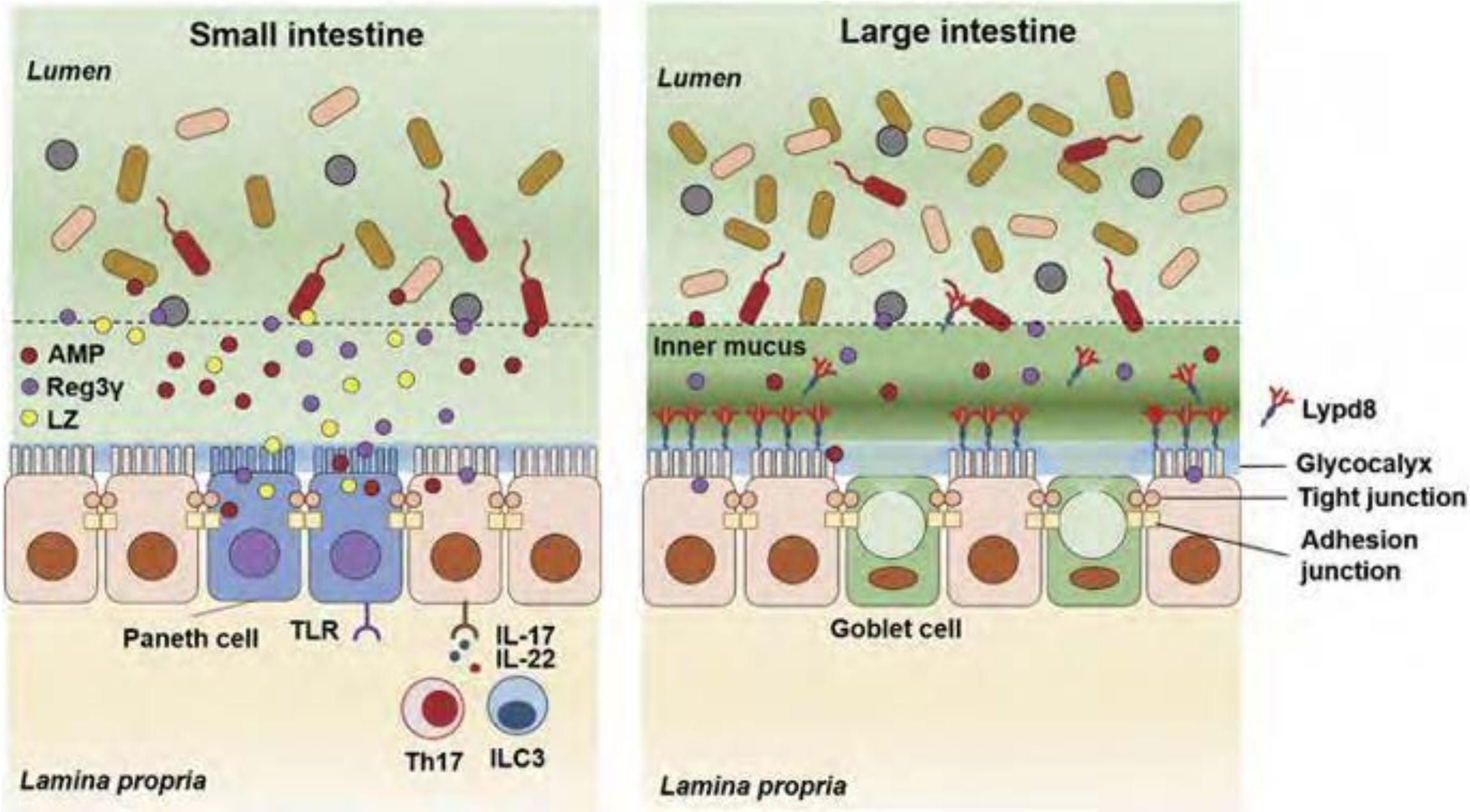
Lamina propria



Mucosa

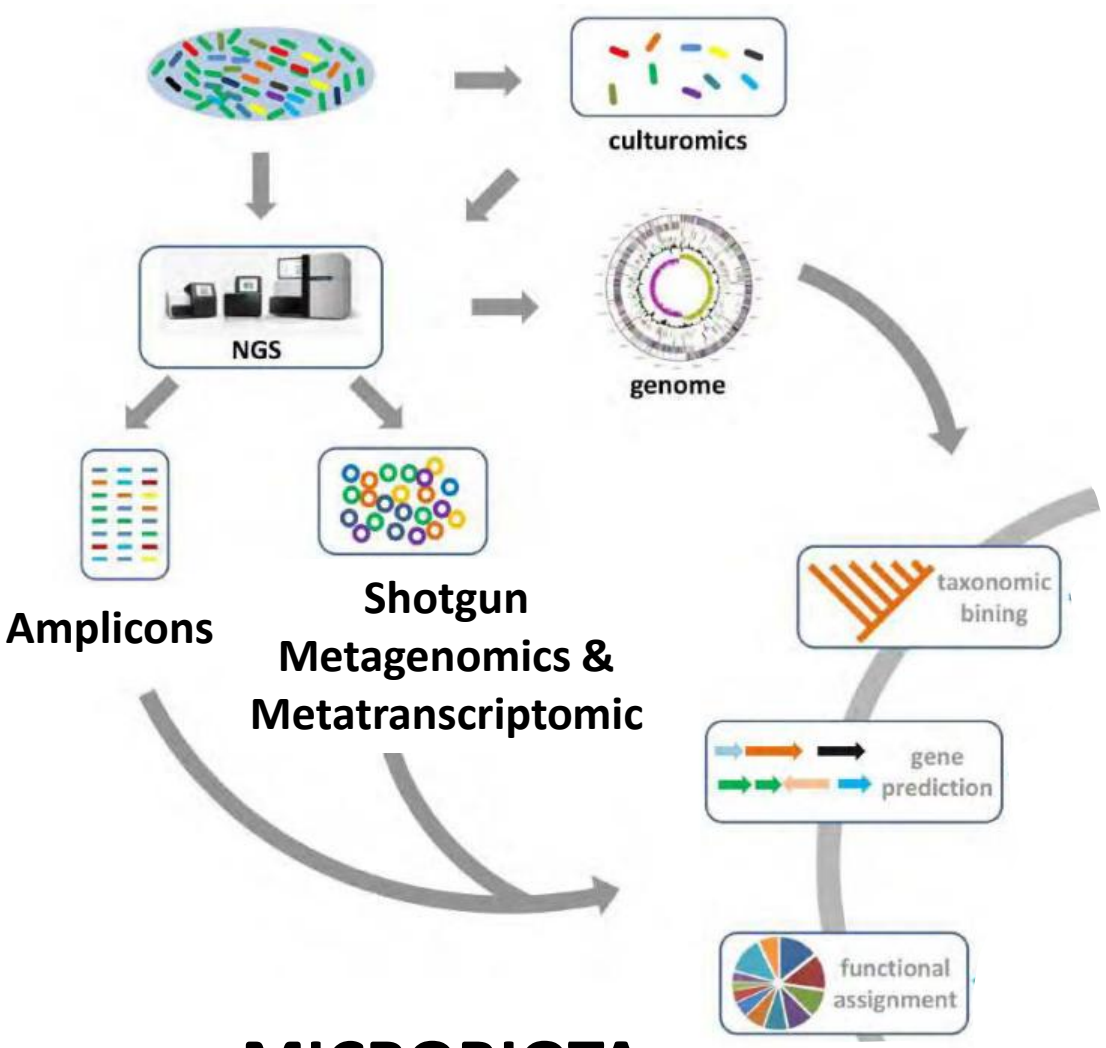


Microbiota


Small intestine
Lumen
AMP
Reg3γ
LZ
Paneth cell
TLR
IL-17
IL-22
Th17
ILC3
Lamina propria
Large intestine
Lumen
Inner mucus
Lypd8
Glycocalyx
Tight junction
Adhesion junction
Goblet cell
Lamina propria

Transkingdom Networks:
A Systems Biology Approach to Identify Causal Members of Host-Microbiota Interactions

Variable regions of the 16 rRNA gene



MICROBIOTA

HOST

Modified from: Ji B, Nielsen J. From next-generation sequencing to systematic modeling of the gut microbiome. Front Genet. 2015

'STEMIC
FFECTS

LOCAL
EFFECTS

Innate and adaptive skin immunity

Immune response to respiratory viruses, Allergy

Behavior and cognitive functions

Development of the immune system

Inflammatory bowel diseases

Nutrient absorption, Synthesis of Vitamins, Metabolism of bile and hormones, Fermentation of undigestable carbohydrates,

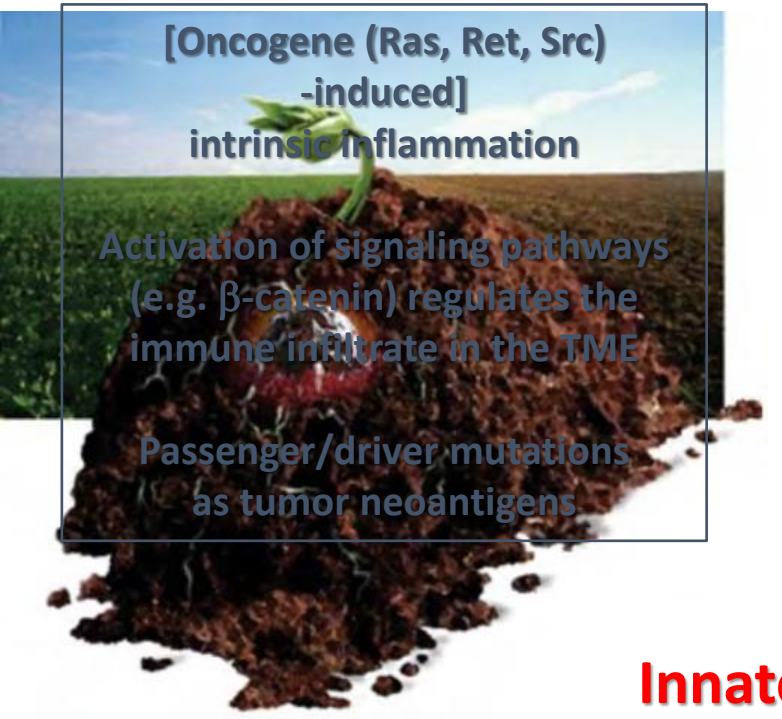
Barrier fortification, Mucosal Immunity

Metabolism
(Obesity, metabolic syndrome, insulin resistance)

Autoimmunity

Naik S, ..., Trinchieri G, Segre JA, Belkaid Y.
Compartmentalized control of skin immunity by resident commensals
Science. 2012;337:1115-9

Cancer as a disease of the human metaorganism



Seed and soil

TUMOR CELLS
(cancer genetics)

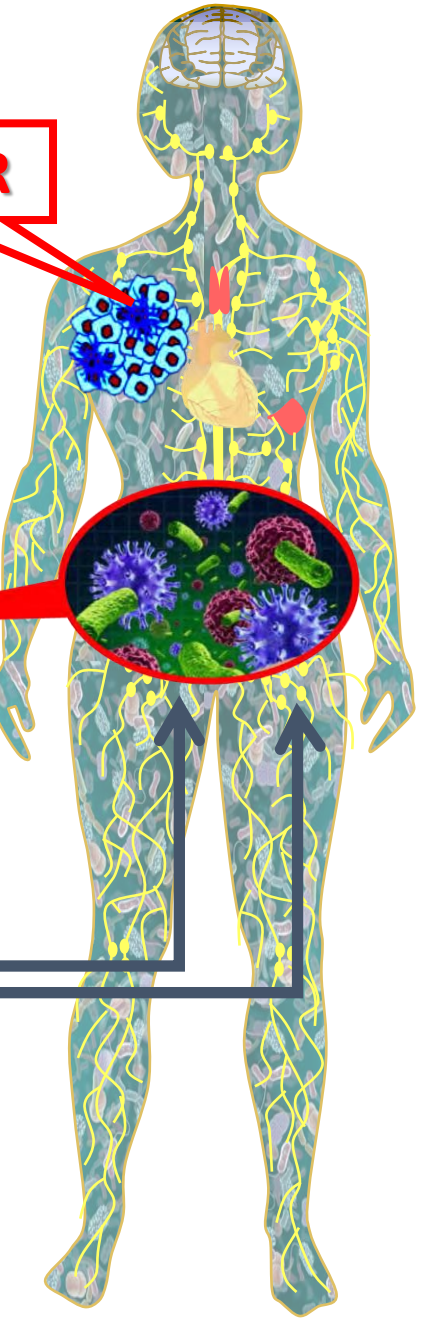
Genetic and epigenetic control of oncogenes and tumor suppressor gene expression

Tumor microenvironment

Inflammation

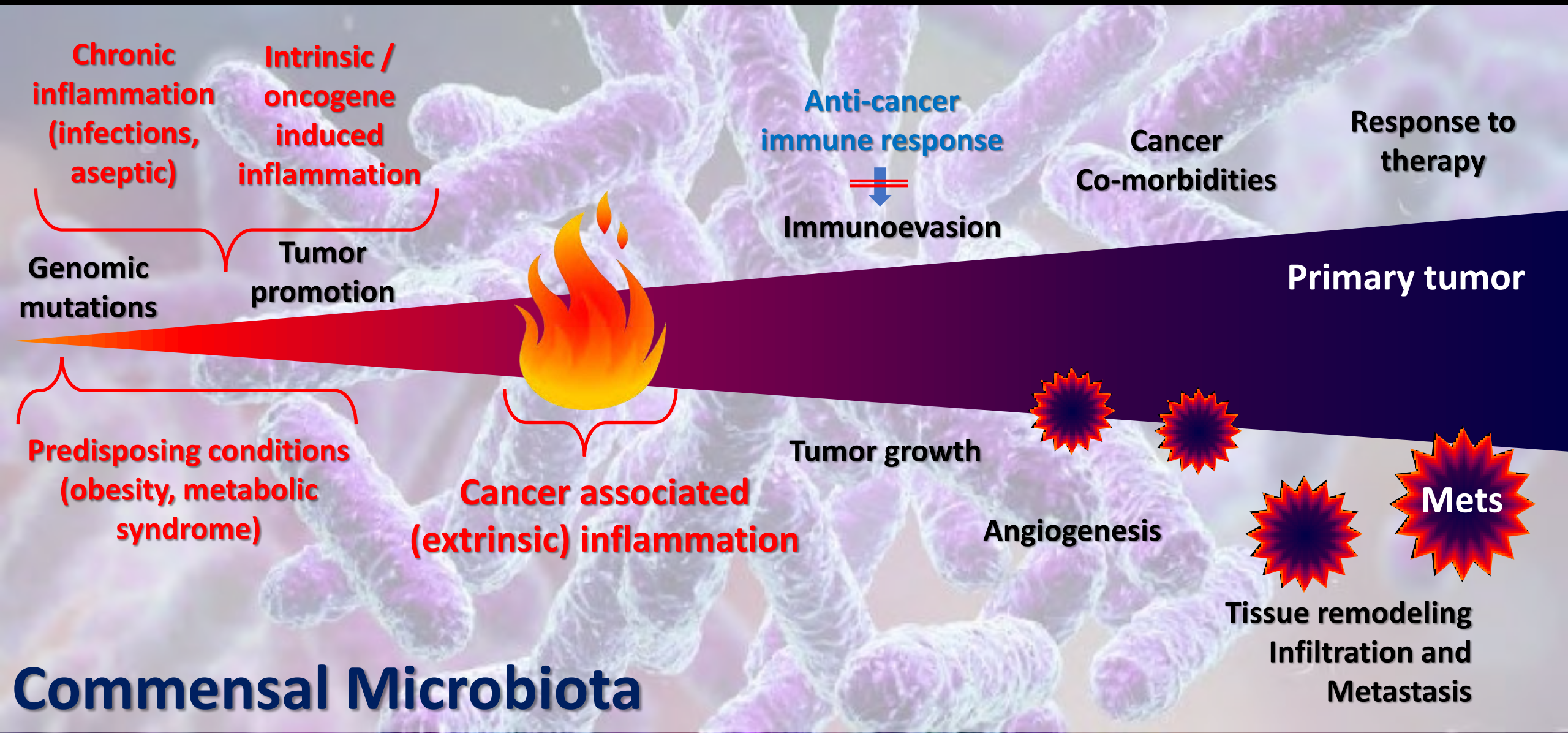
Innate and adaptive immune response

Host genetics < **Environmental and lifestyle factors**



Commensal Microbiota

Cancer, Inflammation & the Microbiota



Rous Sarcoma Virus

Rous Sarcoma Virus induces tumors in adult birds at the site of injection or injury but not in sterile embryos even if the cells in the embryo express the Src viral oncogene and show a transformed phenotype when cultured *in vitro*.

Bissell MJ, Hines WC (2011) Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med 17: 320-9

Dolberg DS, Bissell MJ (1984) Inability of Rous sarcoma virus to cause sarcomas in the avian embryo. Nature 309: 552-6

Dolberg DS, Hollingsworth R, Hertle M, Bissell MJ (1985) Wounding and its role in RSV-mediated tumor formation. Science 230: 676-8

Local and distant effects of the microbiota on cancer

Stomach cancer
(*Helicobacter pylori*)
Colon rectal carcinoma
(*Escherichia coli*, *Fusobacterium* spp. enterotoxigenic *Bacteroides fragilis*, *Streptococcus gallolyticus*)
Gallbladder carcinoma
(*Salmonella enterica* Thyphi)

Cancer at epithelial barrier surfaces

Cancer at sterile sites

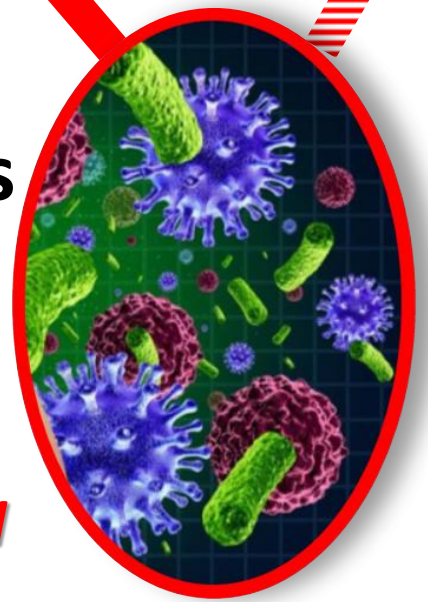
Systemic effects

Malt lymphoma
Hepatocellular carcinoma
Mammary carcinoma
Thymic lymphoma
Sarcoma
Ovarian Cancer

Pancreatic cancer
Lung cancer
CRC metastases

Inactivation of chemotherapeutic drugs (gemcitabine)
Either immunosuppression or immune activation

Local effects



Intratumoral bacteria

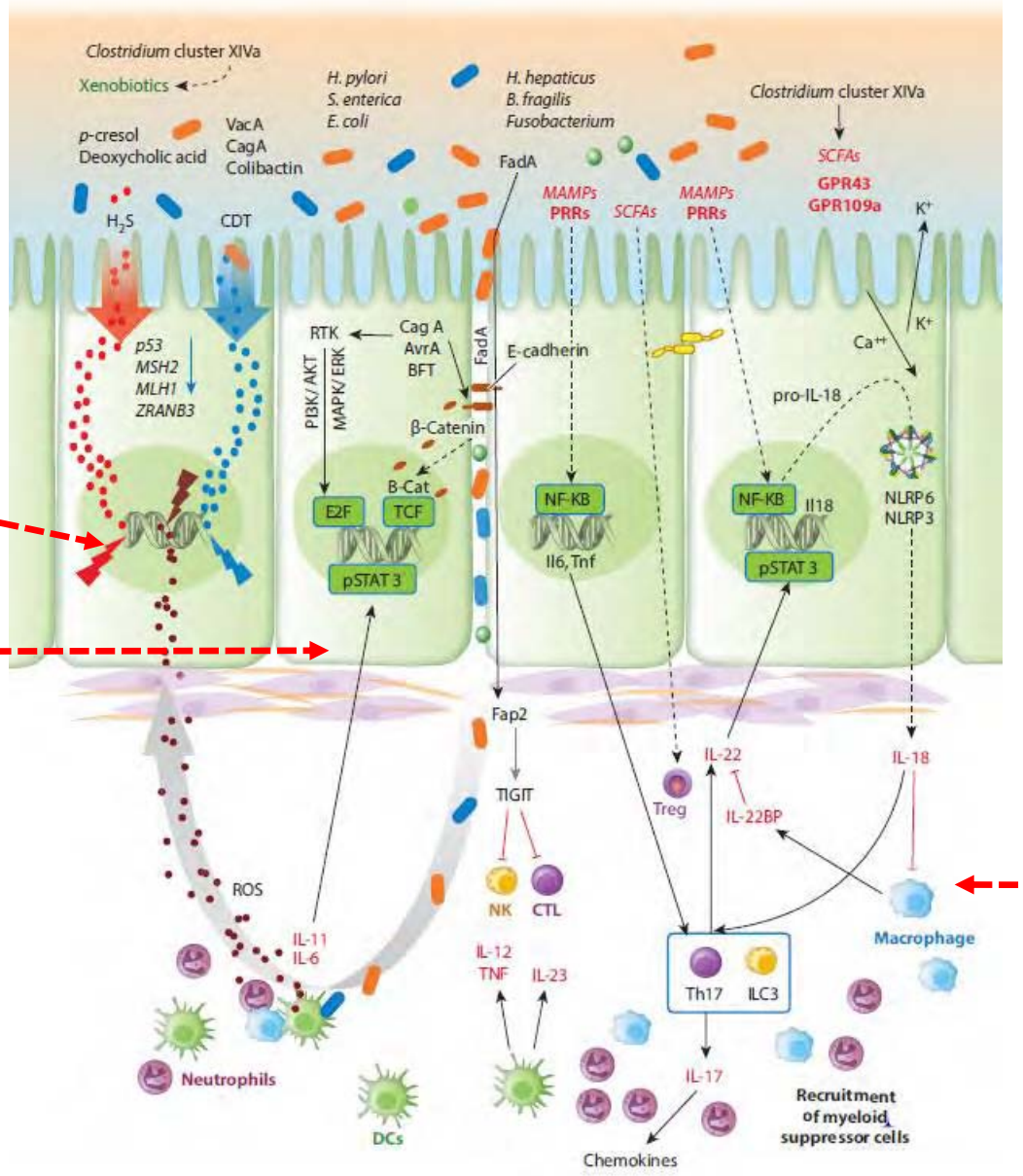
(Gut) Commensal Microbiota

Effectiveness and Toxicity of Chemotherapy and Immunotherapy against sterile tumors

The microbiota affects cancer cell genetic stability and proliferative pathways as well as inflammation and immunity in the tumor microenvironment

Genetic stability (DNA damage, DNA repair)

Proliferative pathways

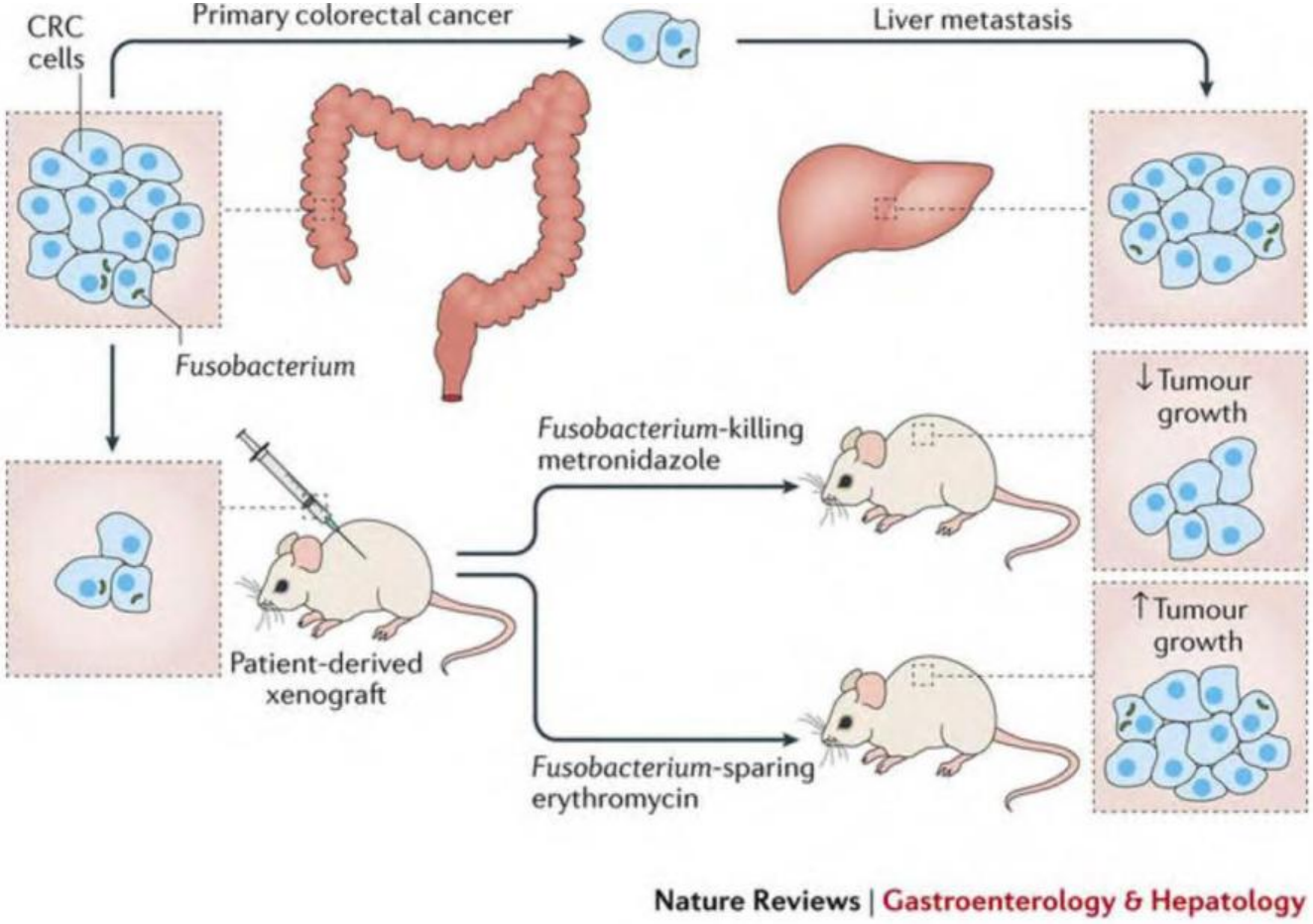


Inflammation and immunity

Dzutsev A, Badger JH, Perez-Chanona E, Roy S, Salcedo R, Smith CK, Trinchieri G.
Microbes and Cancer
Annual Rev Immunol. 2017

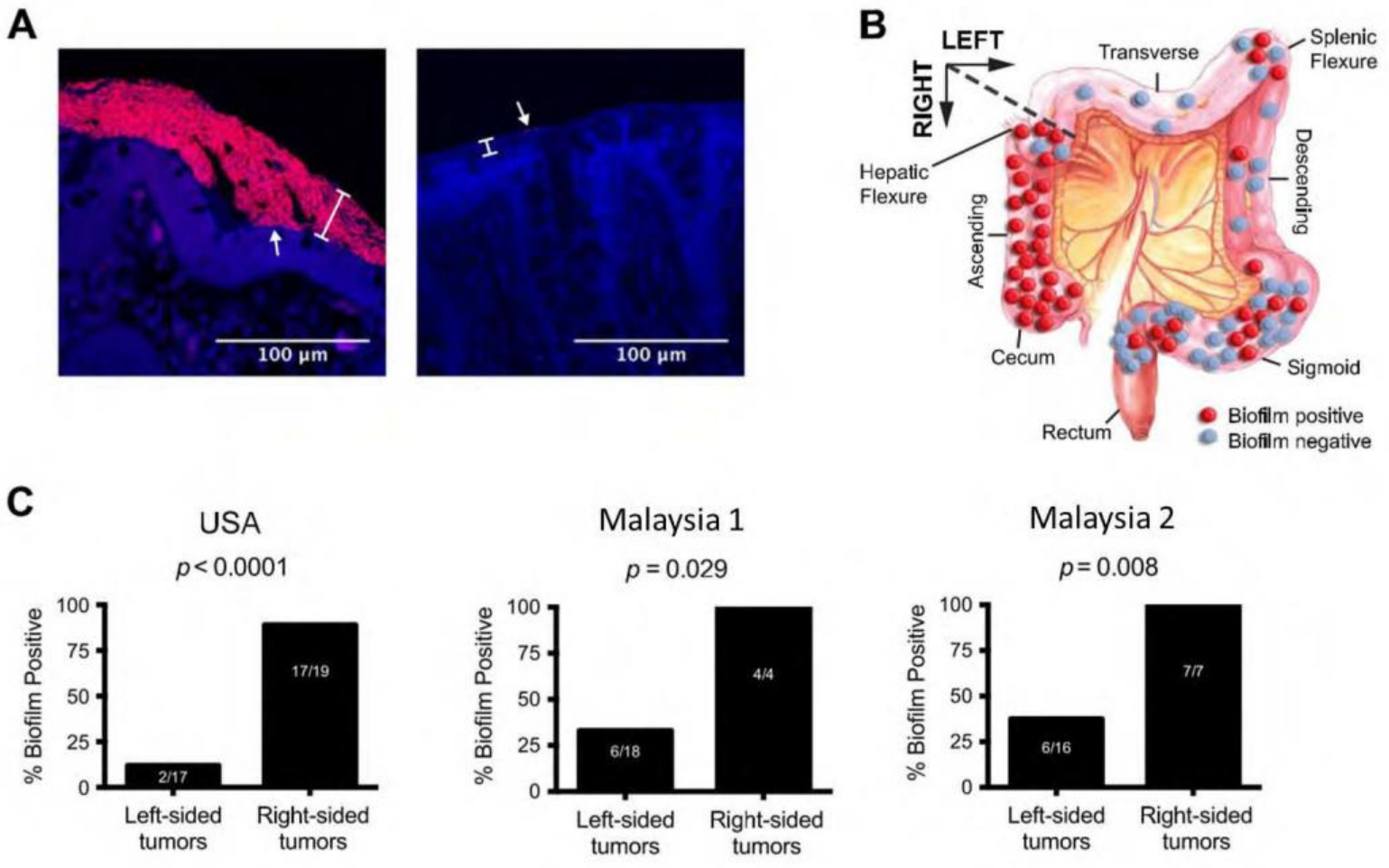
Fusobacterium nucleatum **is present at higher frequency in the colon of CRC patients and particularly in the tumor area where it may form microfilms.**

- **activation of E-cadherin–β-catenin signalling via the adhesion protein FadA**
- **establishment of a pro-tumorigenic inflammatory microenvironment**
- **inhibition of antitumour immunity via the Fap2–TIGIT (T-cell immunoreceptor with Ig and ITIM domains)**
- **upregulation of microRNA-21 to enhance cancer cell proliferation and invasion**
- **stimulation of cancer cell aut**



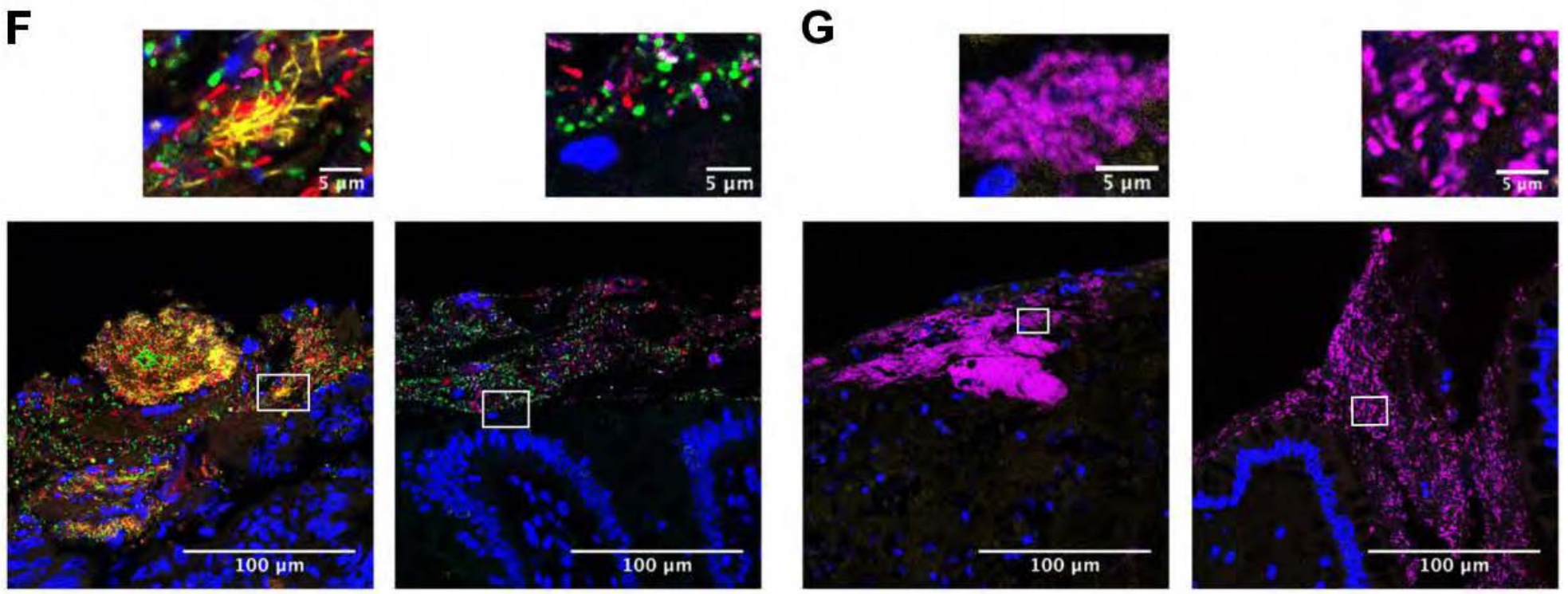
Bullman, S. *et al*. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science* 35 1443–1448 (2017)

Colorectal carcinoma are enriched for biofilms harboring symbionts with capacity for tumorigenesis



Drewes JL, White JR, Dejea CM, Fathi P, Iyadorai T, Vadivelu J, Roslani AC, Wick EC, Mongodin EF, Loke MF, Thulasi K, Gan HM, Goh KL, Chong HY, Kumar S, Wanyiri JW, Sears CL. 2017. High-resolution bacterial 16S rRNA gene profile meta-analysis and biofilm status reveal common colorectal cancer consortia. *NPJ Biofilms Microbiomes 3: 34*

Colorectal carcinoma are enriched for biofilms harboring symbionts with capacity for tumorigenesis

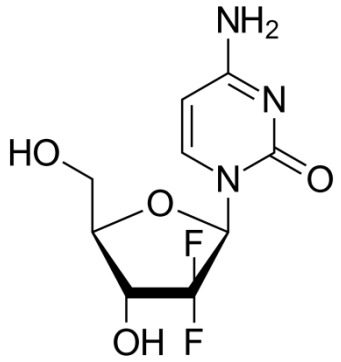


Biofilm-positive samples were stained with DAPI (blue) and probes against four bacterial membership groups:
Fusobacterium (yellow), Bacteroidetes (green), Lachnospiraceae (red), and Proteobacteria (magenta).

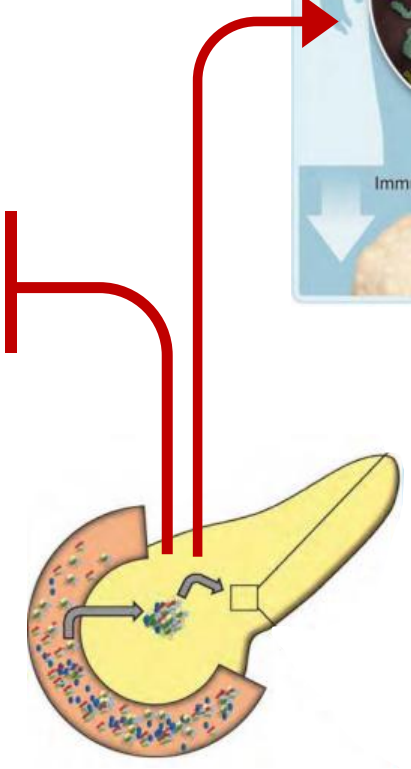
Drewes JL, White JR, Dejea CM, Fathi P, Iyadorai T, Vadivelu J, Roslani AC, Wick EC, Mongodin EF, Loke MF, Thulasi K, Gan HM, Goh KL, Chong HY, Kumar S, Wanyiri JW, Sears CL. 2017. High-resolution bacterial 16S rRNA gene profile meta-analysis and biofilm status reveal common colorectal cancer consortia. ***NPJ Biofilms Microbiomes 3: 34***

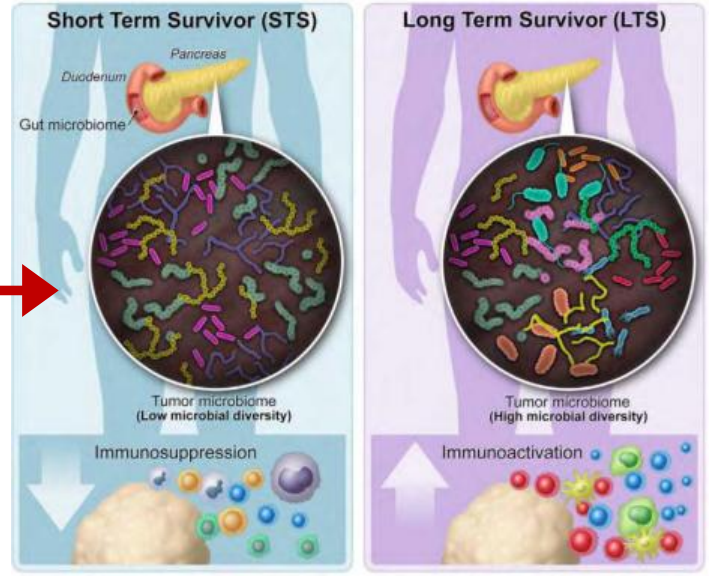
Intratumoral bacteria: Pancreatic Ductal Adenocarcinoma (PDA)

Intratumor bacteria, primarily Gammaproteobacteria, inactivate the chemotherapeutic drug gemcitabine by expressing the enzyme cytidine deaminase.



Geller, L. T., … R. Straussman. 2017.
Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine.
Science 357: 1156-1160.





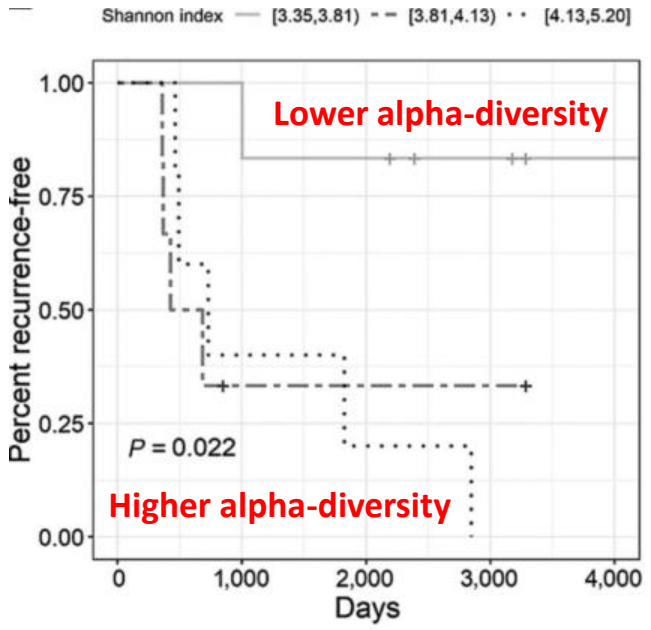
- PDAC long-term survivors display high tumor microbial diversity and immunoactivation
- A PDAC tumoral microbiome signature predicts PDAC long-term survival
- The gut microbiome modulates the PDAC tumor microbiome landscape
- Fecal microbial transplants can modulate tumors immunosuppression and growth

Riquelme, … F. McAllister. 2019.
Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes.
Cell 178: 795-806.e712.

Pushalkar, S., M. ….. G. Miller. 2018.
The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression.
Cancer discovery 8: 403-416.

- Intratumor microbiome drives suppressive monocytic cellular differentiation in pancreatic cancer via selective Toll-like receptor ligation leading to T-cell anergy
- Targeting the microbiome protects against oncogenesis, reverses intratumoral immune tolerance, and enables efficacy for checkpoint-based immunotherapy

Intratumoral bacteria: Lung Microbiota and Cancer

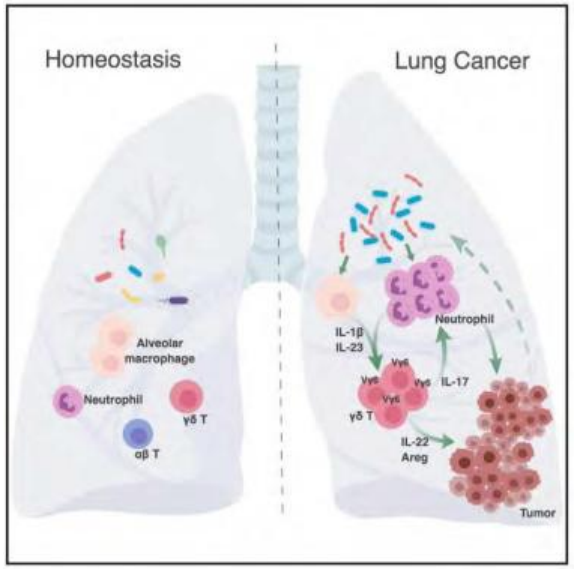


- Higher microbiome α-diversity in normal lung tissue (but not tumor tissue) of NSCLC patients was associated with reduce disease-free survival
- The presence of Koribacteraceae was associated with increased survival, whereas greater abundance of families Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae were associated with reduced survival

Peters, B. A., … J. Ahn. 2019.
The Microbiome in Lung Cancer Tissue and Recurrence-Free Survival.
Cancer Epidemiol Biomarkers Prev 28: 731-740.

- This study of 142 lung cancer patients and 33 healthy control showed both microbiome-gene and microbiome-exposure interactions in lung cancer tissue.
- Specifically, squamous cell carcinoma harboring TP53 mutations, which can impair epithelial function, have a unique bacterial consortium that in smoking-associated tumors shows higher relative abundance of certain species such as *Acidovorax*.

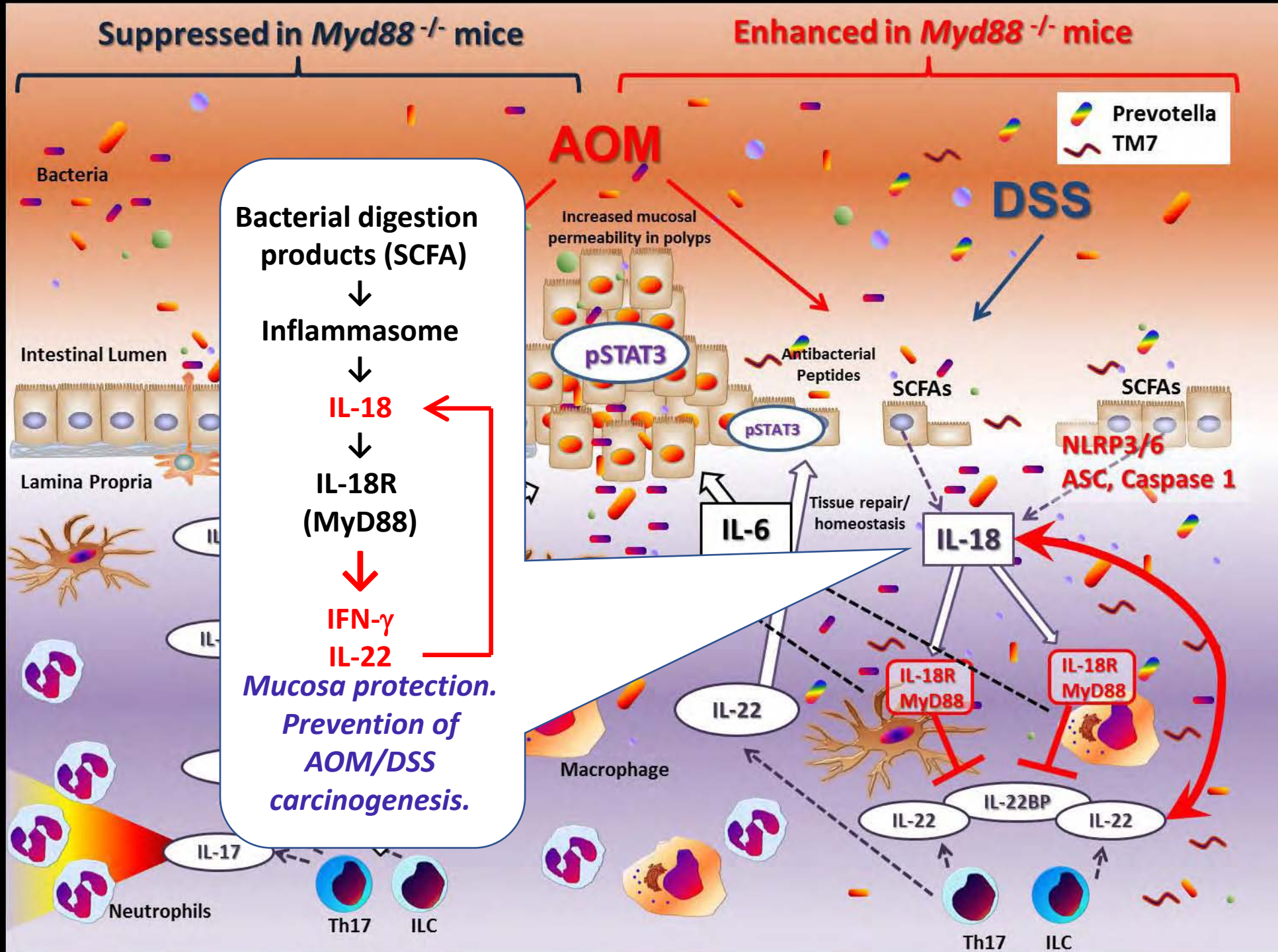
Greathouse, K. L., …C. C. Harris. 2018.
Interaction between the microbiome and TP53 in human lung cancer.
Genome biology 19: 123.



- Depletion of commensal microbiota suppresses lung adenocarcinoma development induced in mice by Kras mutation and p53 loss
- Lung cancer development is associated with local dysbiosis and inflammation
- Microbiota drive proliferation and activation of Vγ6+Vδ1+ T cells in lung cancer
- γδ T cells promote neutrophil infiltration and tumor cell proliferation

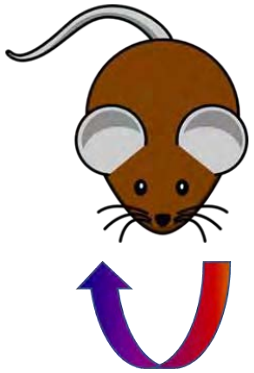
Jin, C., …T. Jacks. 2019.
Commensal Microbiota Promote Lung Cancer Development via gammadelta T Cells. Cell 176: 998-1013.e1016.

Microbiota-host interaction in colon carcinogenesis



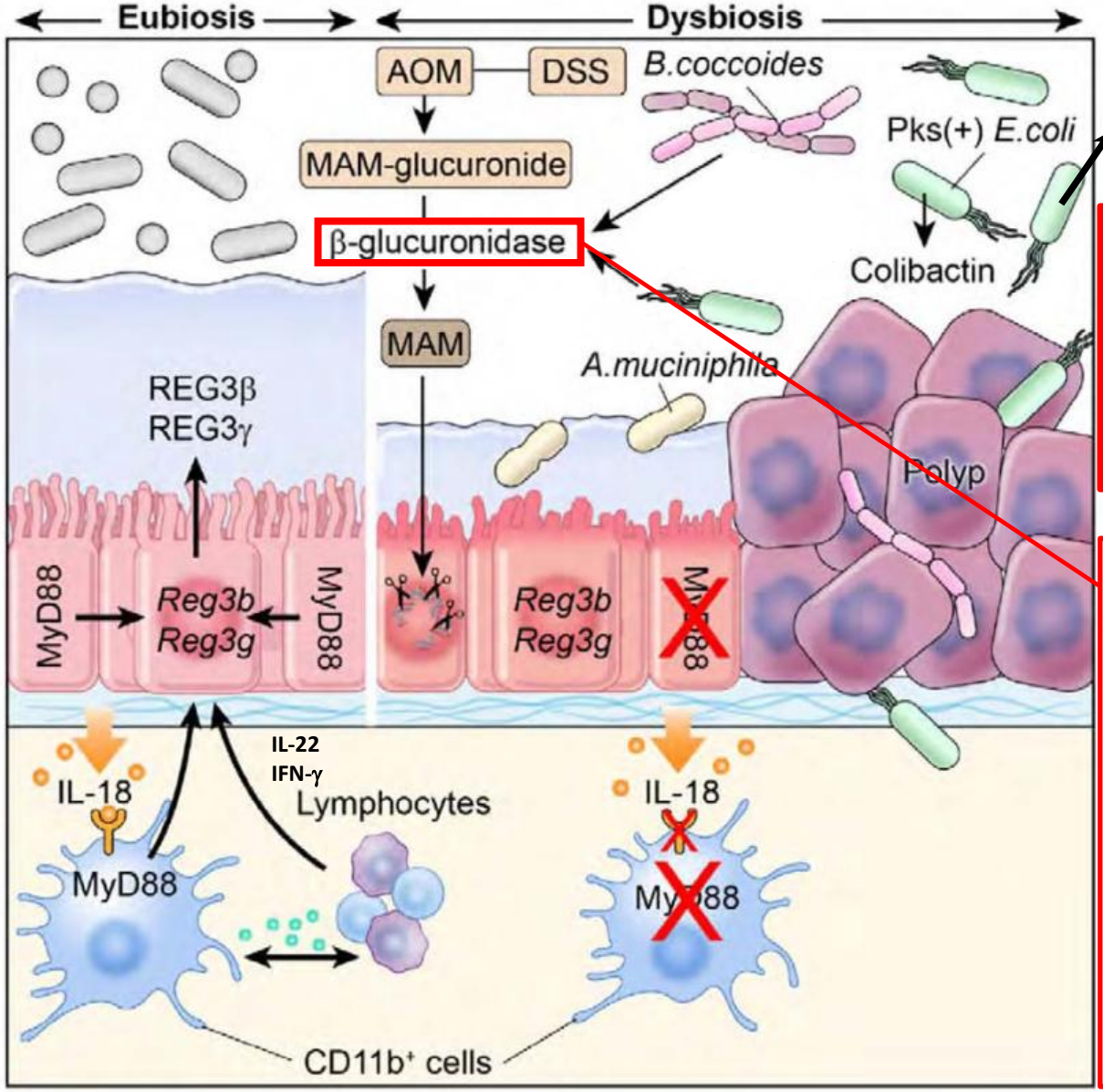
Lack of IL-18R signaling in CD11b$^+$ myeloid cells induces a transmissible dysbiosis that affects both tumor initiation and promotion

Myd88 or *IL18r* deficiency in myeloid cells



Transmissible Bacterial Dysbiosis

Susceptibility to colon carcinogenesis (AOM/DSS)

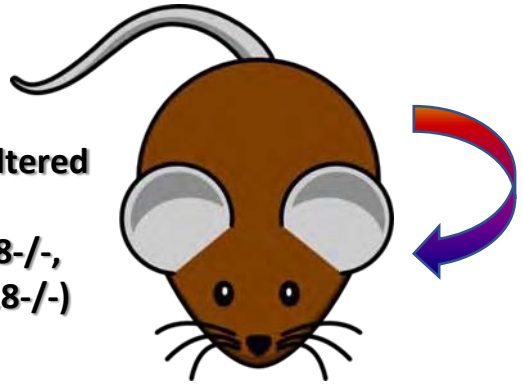


Bacterial antibiotics (Colicin from O7H7 *E. coli* and lantibiotic from *B. coccoides*) may play a role in the dominance of the transmissible dysbiosis into wild type mice

Bacterial β-glucuronidase is responsible for reactivation of other carcinogens such as the environmental pollutant benzopyrene and the food-borne carcinogen 2-amino-3-methylimidazo[4,5-f]quinoline, is a biomarker for colon cancer and is responsible for the intestinal toxicity of the drug Irinotecan

Host genetics may affect the mouse phenotype by modifying the composition of the microbiota

Genetically altered mouse
(e.g. MyD88-/-, TLR5-/-, IL-18-/-)



Phenotype
(e.g. spontaneous colitis, susceptibility to inducer of colitis and carcinogenesis, tumor growth, response to anti-cancer therapy, response to vaccination)

Bacterial Dysbiosis

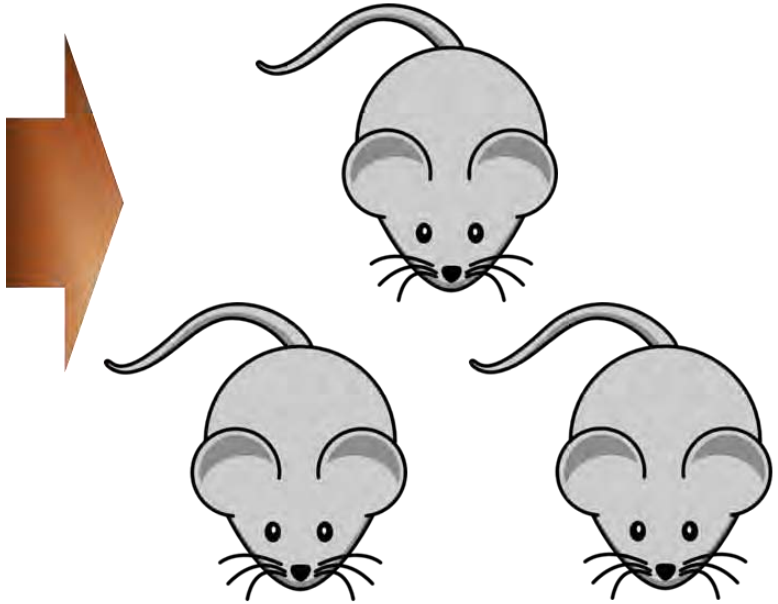
Virus infection
(e.g. norovirus)

Reactivation of endogenous retroviruses (ERVs) (lymphomas, mouse)
or
Pro-inflammatory ERV transcript
(humans)

Mycosis → Oral and esophageal carcinogenesis
(humans and mouse)

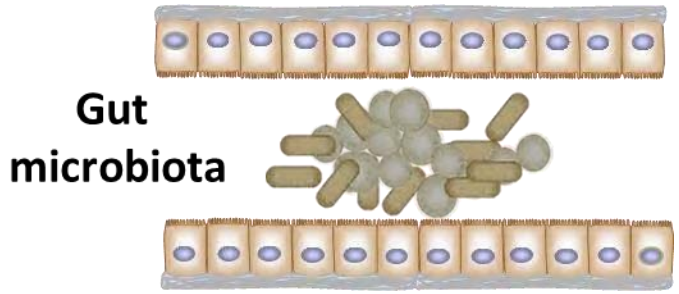
Protozoan parasites
(e.g. *Trichomonas muris*)
Protozoan viruses

Wild type mice
(co-housed, fecal transplant, fostering)

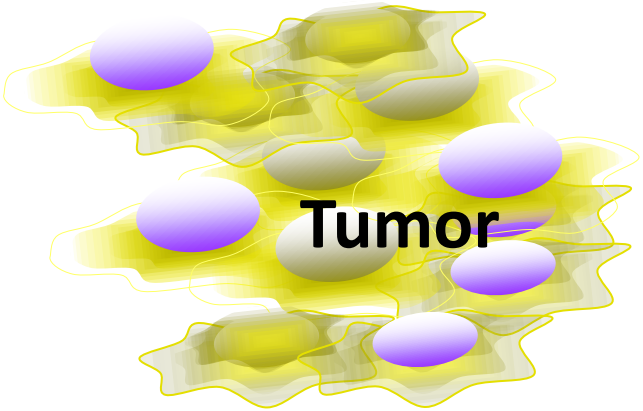


No phenotype
Partial phenotype
Full phenotype

Is the response to cancer therapy regulated by the commensal bacteria?



Cancer Immunotherapy & Chemotherapy

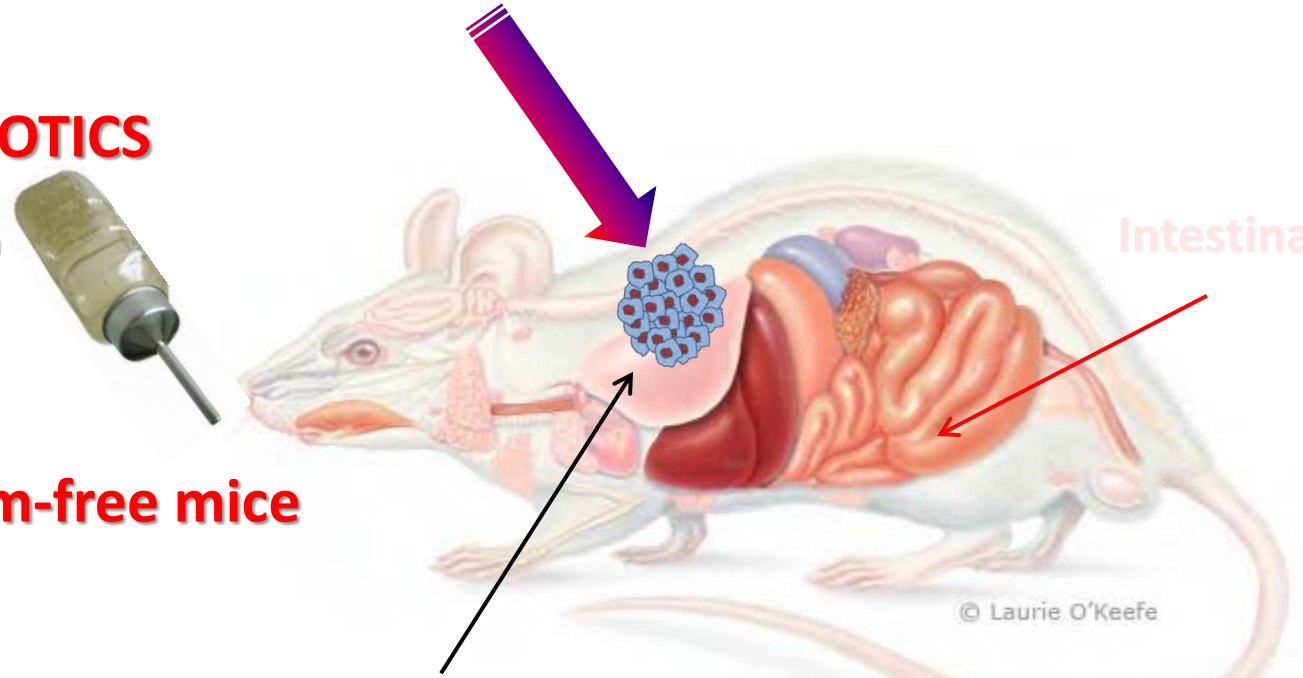


Is the response to cancer therapy regulated by commensal bacteria?

Systemic anti-IL-10R + Intratumor CpG-OGN immunotherapy
Platinum compound (oxaliplatin, cisplatin) chemotherapy

ANTIBIOTICS

Neomycin
Vancomycin
Imipenem



or Germ-free mice

Sterile subcutaneous transplanted tumor

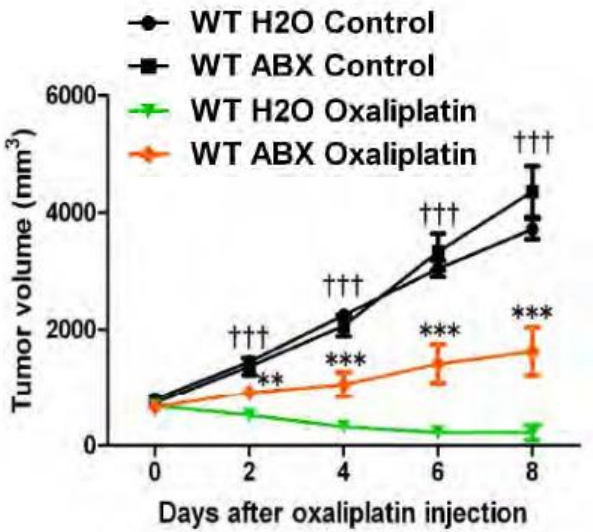
Noriho Iida, Amiran Dzutsev, C. Andrew Stewart, …… Giorgio Trinchieri, Romina S. Goldszmid
Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment
Science, 2013; 342:967-70

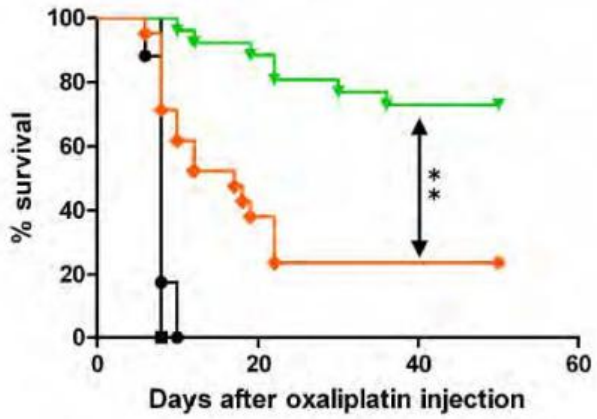
Antibiotics (ABX) suppress the anti-tumor effect of immune and chemo therapy

Anti-IL-10R/CpG

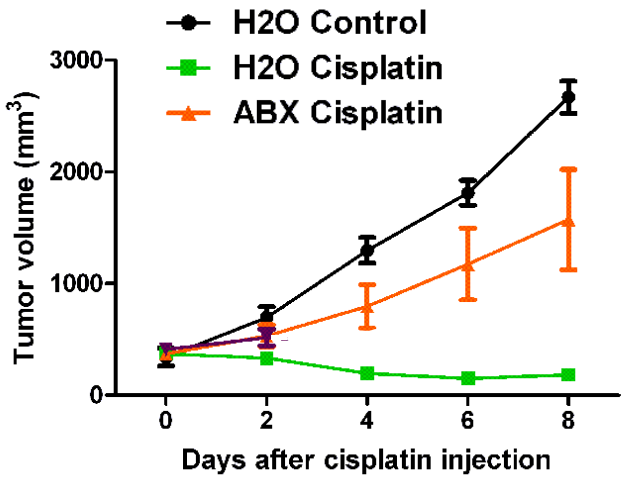
MC38 subcutaneous tumor

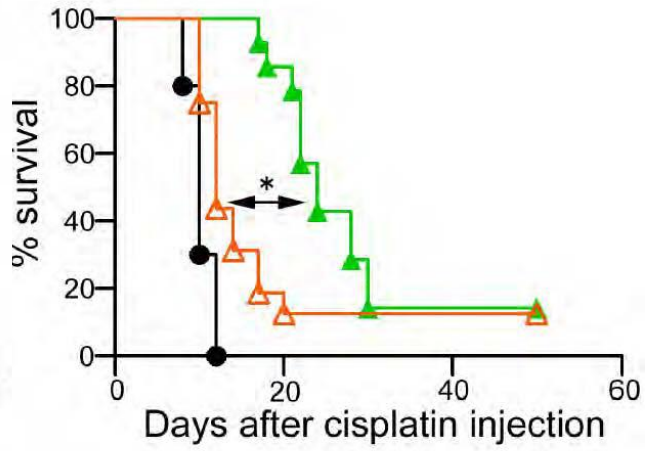
Oxaliplatin





Cisplatin

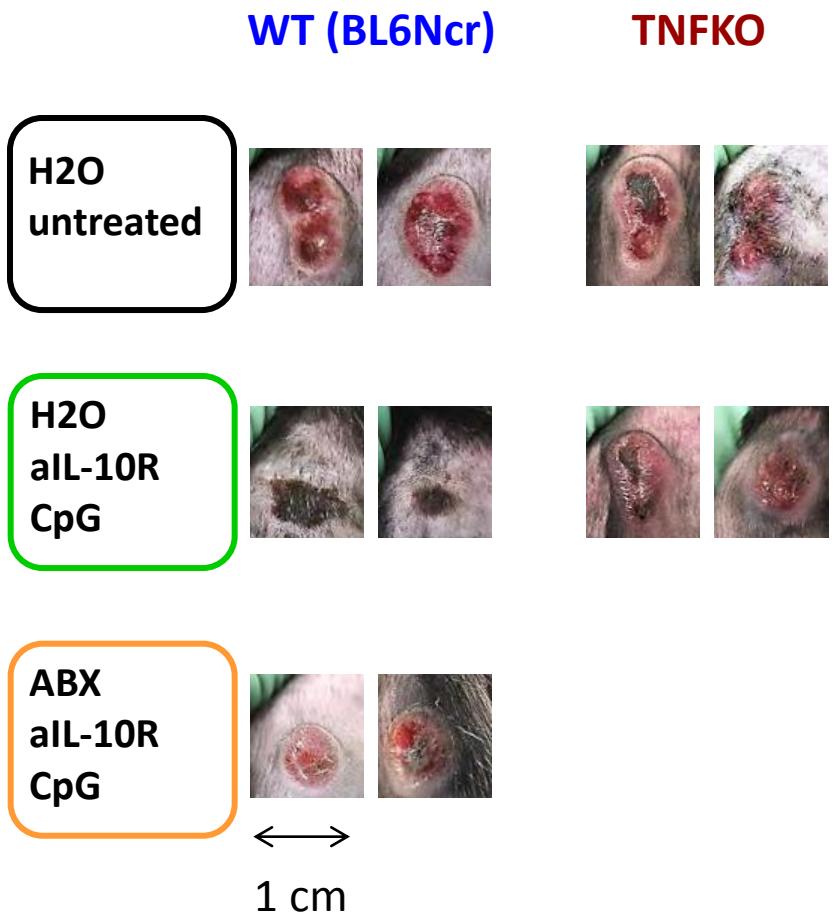




EL4 subcutaneous tumor

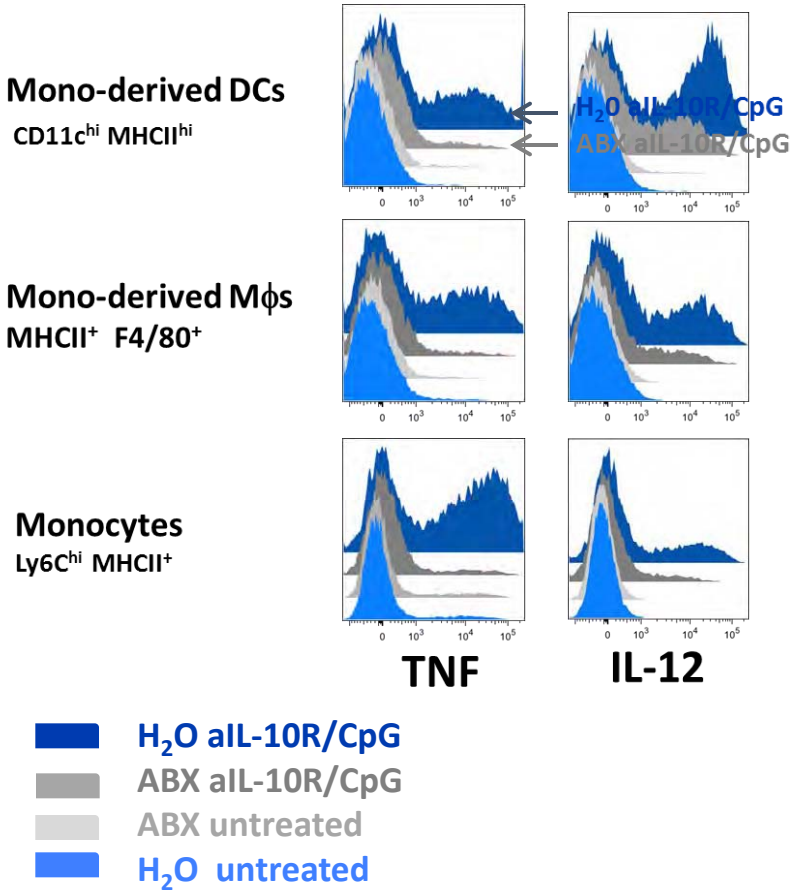
Iida N, Dzutsev A, Stewart CA, ……..Belkaid Y, Trinchieri G, Goldszmid RS. 2013. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science 342: 967-70*

Antibiotics (ABX) suppress TNF-mediated early necrosis of the tumor and decrease inflammatory cytokine production following anti-IL-10R/CpG



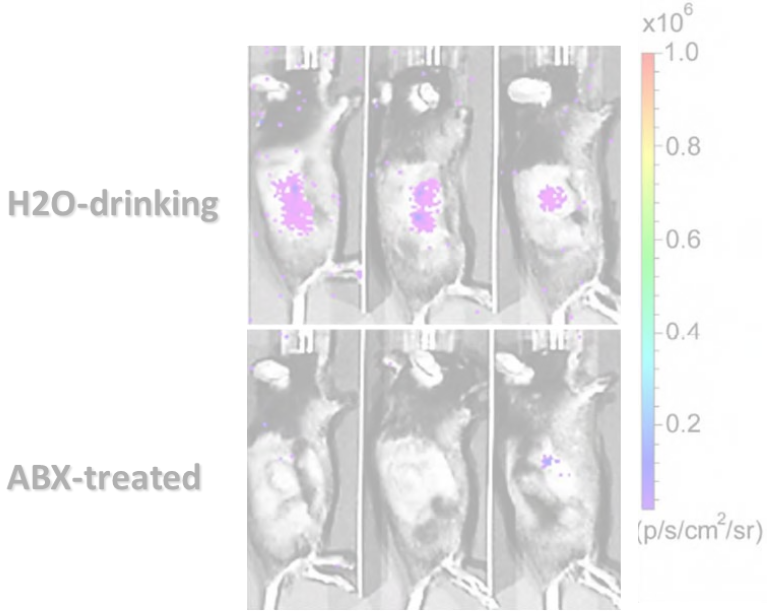
MC38 tumor, 72 h after CpG treatment

ABX decrease TNF and IL-12 production by tumor-infiltrating myeloid cells following aIL-10R/CpG



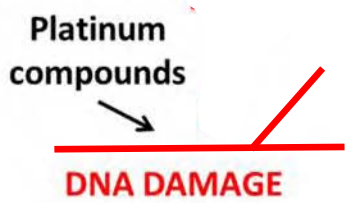
ABX impair oxaliplatin therapy by preventing production of ROS from NOX2 + myeloid cells that is required for DNA damage after formation of platinum DNA adducts

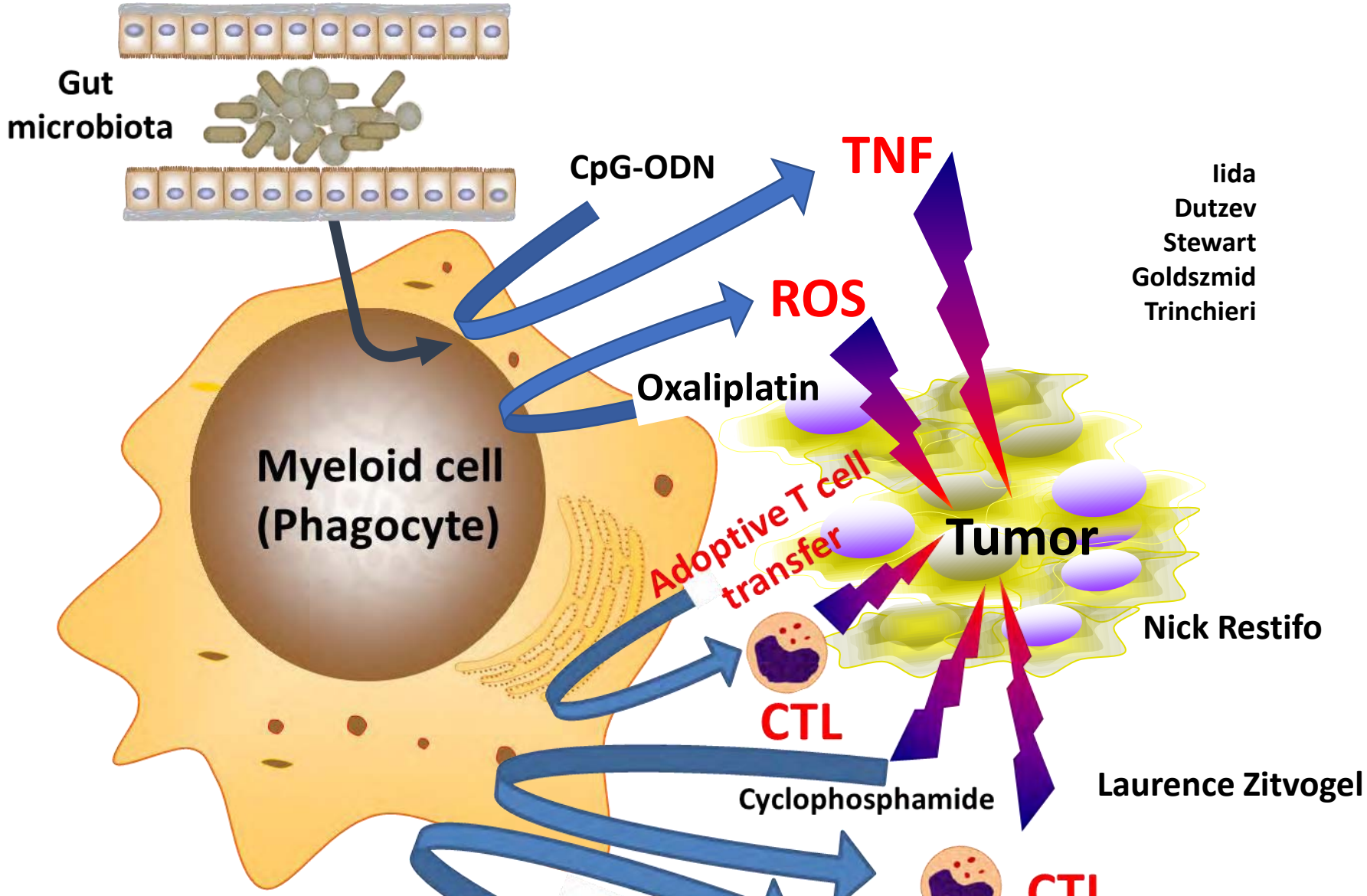
Oxaliplatin induces ROS production in tumors of control but not ABX-treated mice



Oxaliplatin-induced
L-012 Bioluminescence (ROS)

- EL4 tumors-bearing B6 mice were treated with 10mg/kg oxaliplatin
- ROS-induced bioluminescence using the L-012 probe was analyzed 24 hours after oxaliplatin injection





The composition of the (gut) mi me determines the efficacy of cancer the ining infiltrating myeloid cells in dis umors

Melanoma

Science REPORTS

Cite as: V. Gopalakrishnan *et al.*, *Science* 10.1126/science.aan4236 (2017)

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Ruminococcaceae
Clostridiales
Faecalibacterium prausnitzii

Lung and renal cancer

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Akkermansia muciniphila
Alistipes spp

Melanoma

Science

CANCER IMMUNOTHERAPY

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

Vyara Matson,[1]* Jessica Fessler,[1]* Riyue Bao,[2,3]* Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4]†

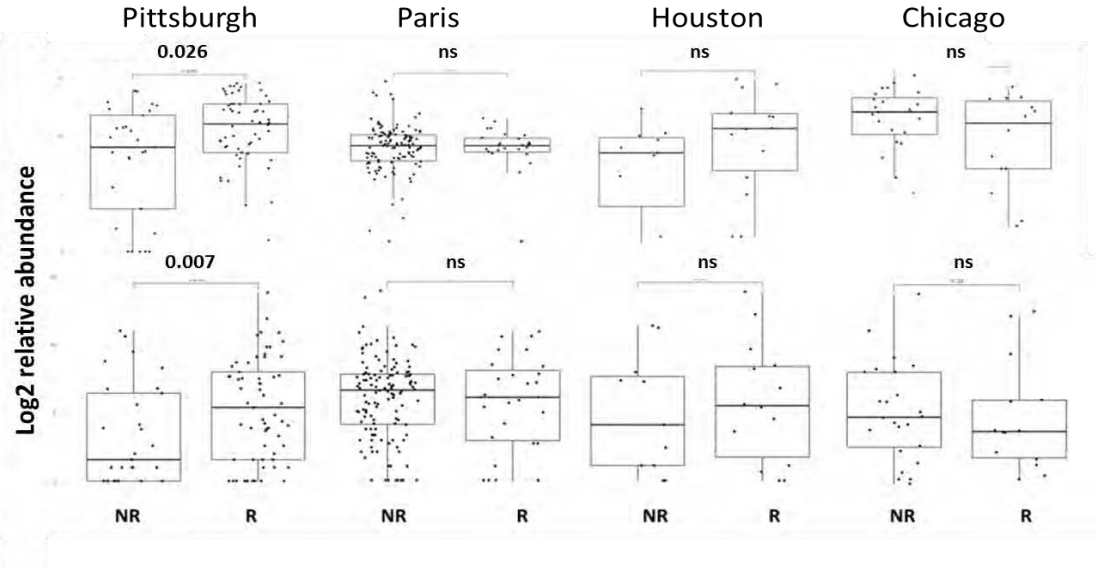
Bifidobacterium longum
Collinsella aerofaciens
Enterococcus faecium.

Anti-PD1 treated melanoma patients
Hassane Zarour, Diwakar Davar and John Kirkwood
Melanoma and Skin Cancer program, U. Pittsburgh

p=0.007 Bacteroides_nordii |L2FC= −2.7
p=0.012 Prevotella_ihumii |L2FC= −2.6
p=0.026 Alistipes_senegalensis |L2FC= −2.1
p=0.021 Collinsella_intestinalis |L2FC= −3.5
p=0.033 Alistipes_Unclassified |L2FC= −2.6
p=0.039 Johnsonella_ignava |L2FC= −2.7
p=0.049 c__Gammaproteobacteria |L2FC= −2.2

Alistipes senegalensis

Bacteriodes nordii



Science

Melanoma

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Science

Lung and renal cancer

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Science

Melanoma

CANCER IMMUNOTHERAPY

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Grocery s
natural dis
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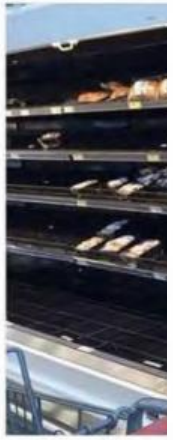


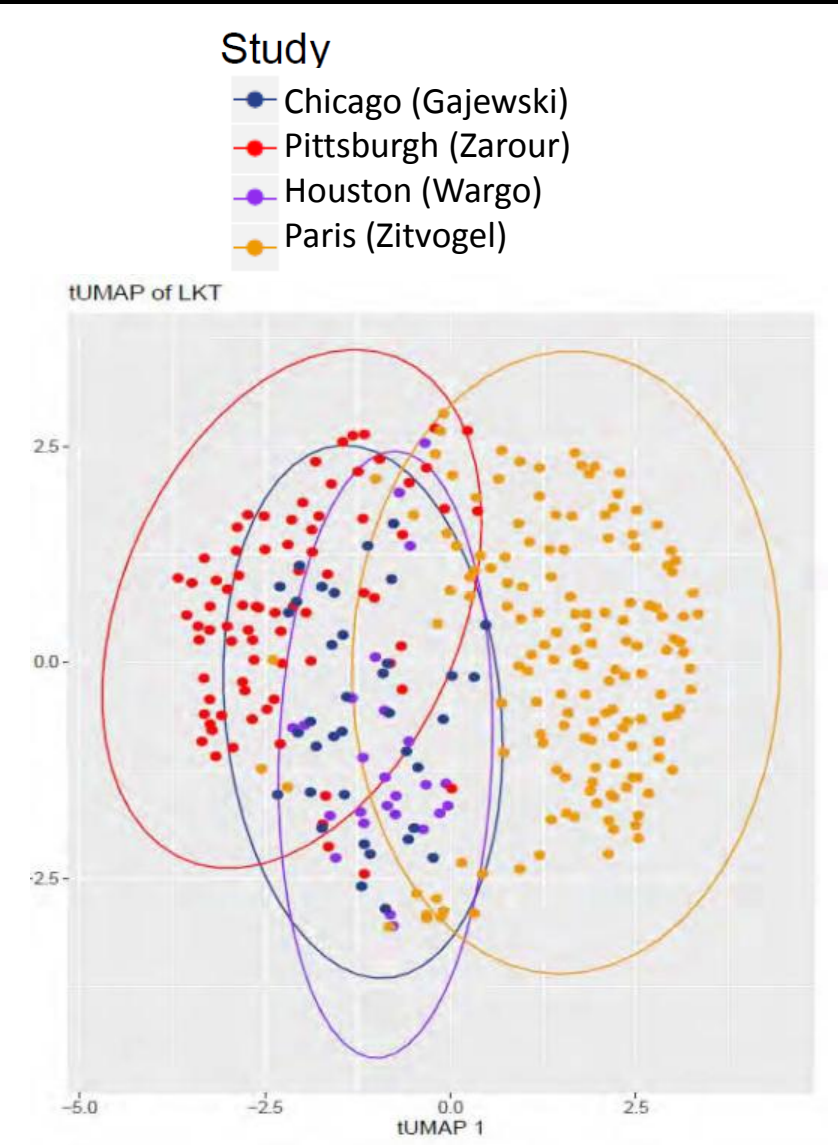
ARTICLE | NATURE | VOL 555 | 8 MARCH 2018

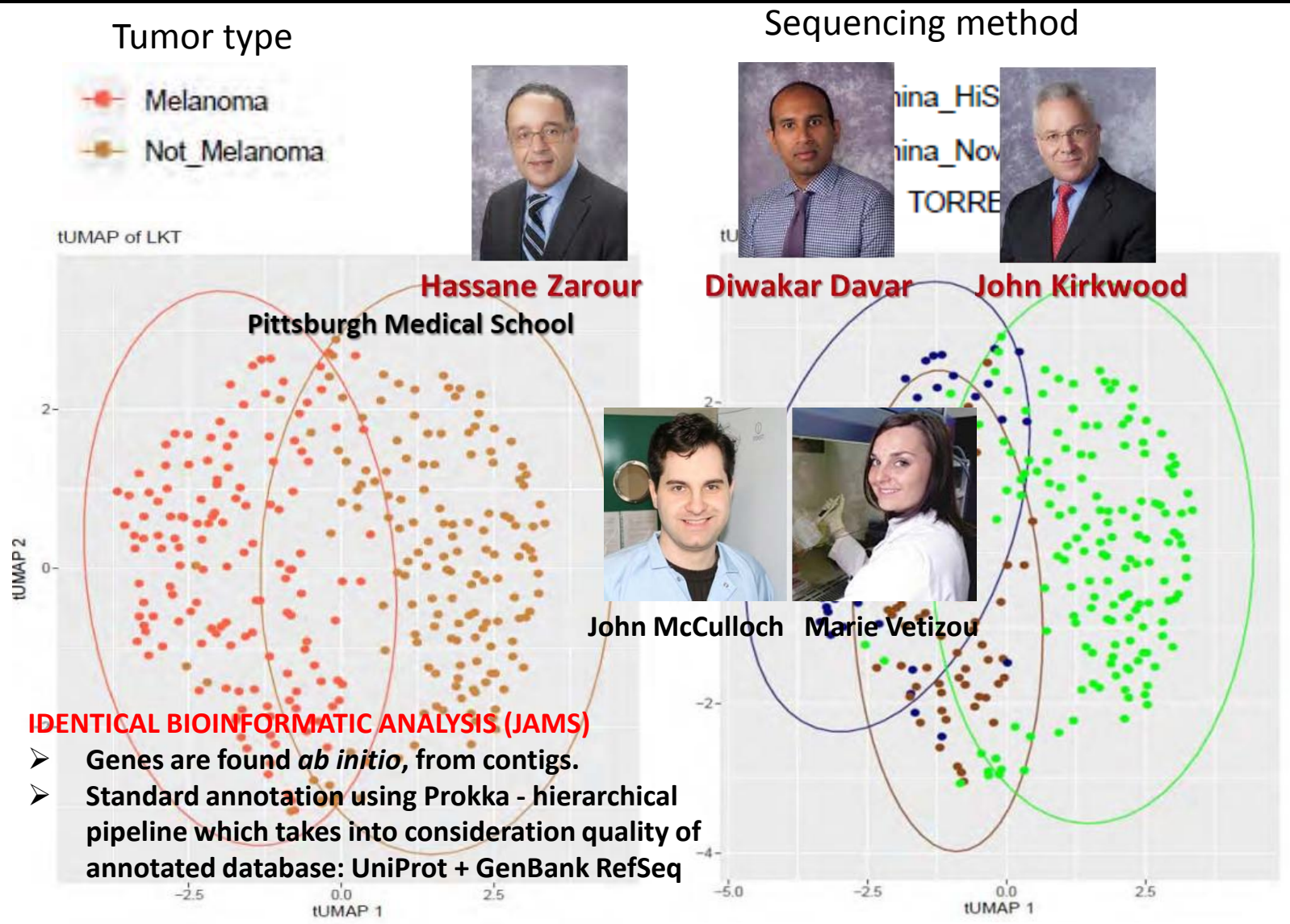
doi:10.1038/nature25973

Environment dominates over host genetics in shaping human gut microbiota

Daphna Rothschild[1,2]*, Omer Weissbrod[1,2]*, Elad Barkan[1,2]*, Alexander Kurilshikov[3], Tal Korem[1,2], David Zeevi[1,2], Paul I. Costea[1,2], Anastasia Godneva[1,2], Iris N. Kalka[1,2], Noam Bar[1,2], Smadar Shilo[1,2], Dar Lador[1,2], Arnau Vich Vila[3,4], Niv Zmora[5,6,7], Meirav Pevsner-Fischer[5], David Israeli[8], Noa Kosower[1,2], Gal Malka[1,2], Bat Chen Wolf[1,2], Tali Avnit-Sagi[1,2], Maya Lotan-Pompan[1,2], Adina Weinberger[1,2], Zamir Halpern[7,9], Shai Carmi[10], Jingyuan Fu[3,11], Cisca Wijmenga[3,12], Alexandra Zhernakova[3], Eran Elinav[5]§ & Eran Segal[1,2]§

Microbiota taxonomic identification in cancer patients may be affected by geography, disease and sequencing technology





Hassane Zarour

Pittsburgh Medical School

Sequencing method

Diwakar Davar

John Kirkwood

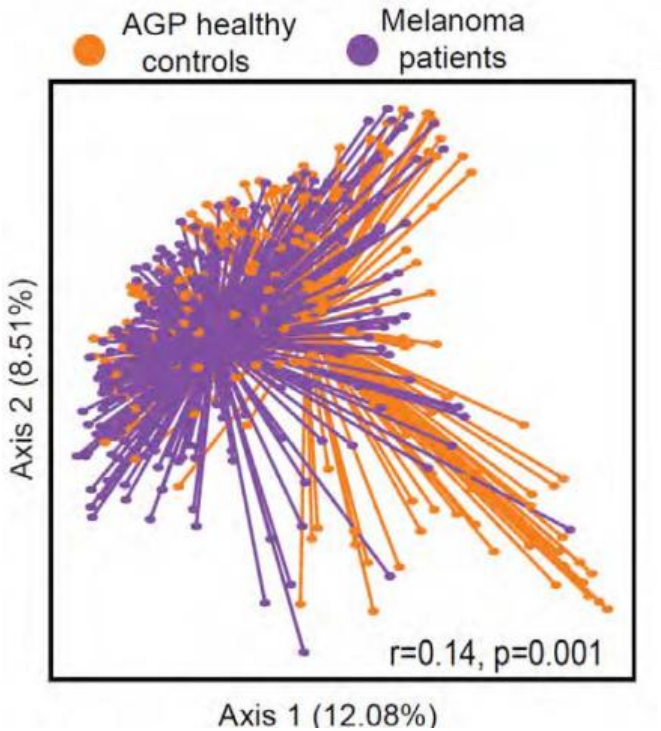
John McCulloch

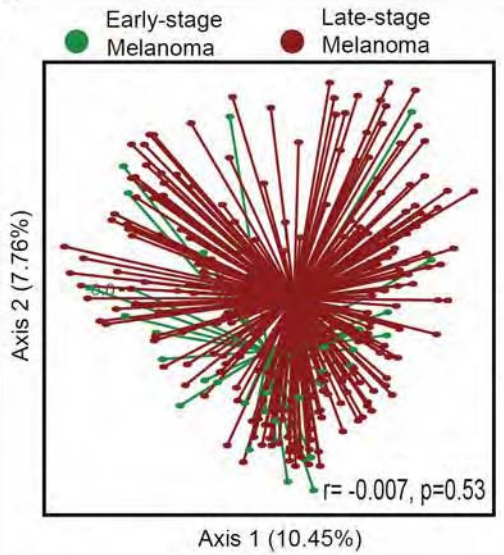
Marie Vetizou

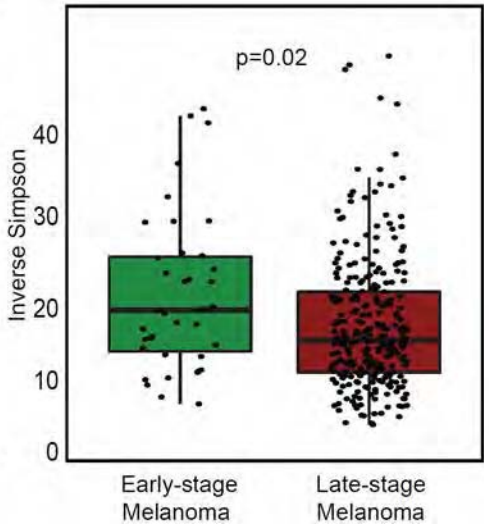
IDENTICAL BIOINFORMATIC ANALYSIS (JAMS)

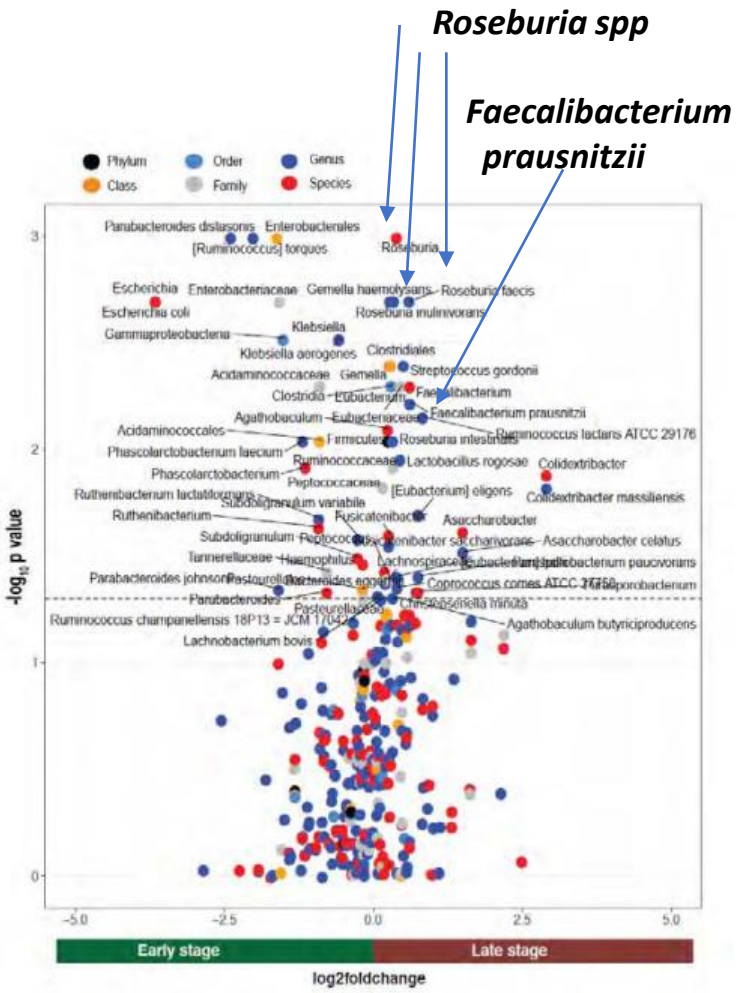
- **Genes are found *ab initio*, from contigs.**
- **Standard annotation using Prokka - hierarchical pipeline which takes into consideration quality of annotated database: UniProt + GenBank RefSeq**

Melanoma patients have different microbiota composition than healthy donors and both alpha and beta diversity change with disease progression



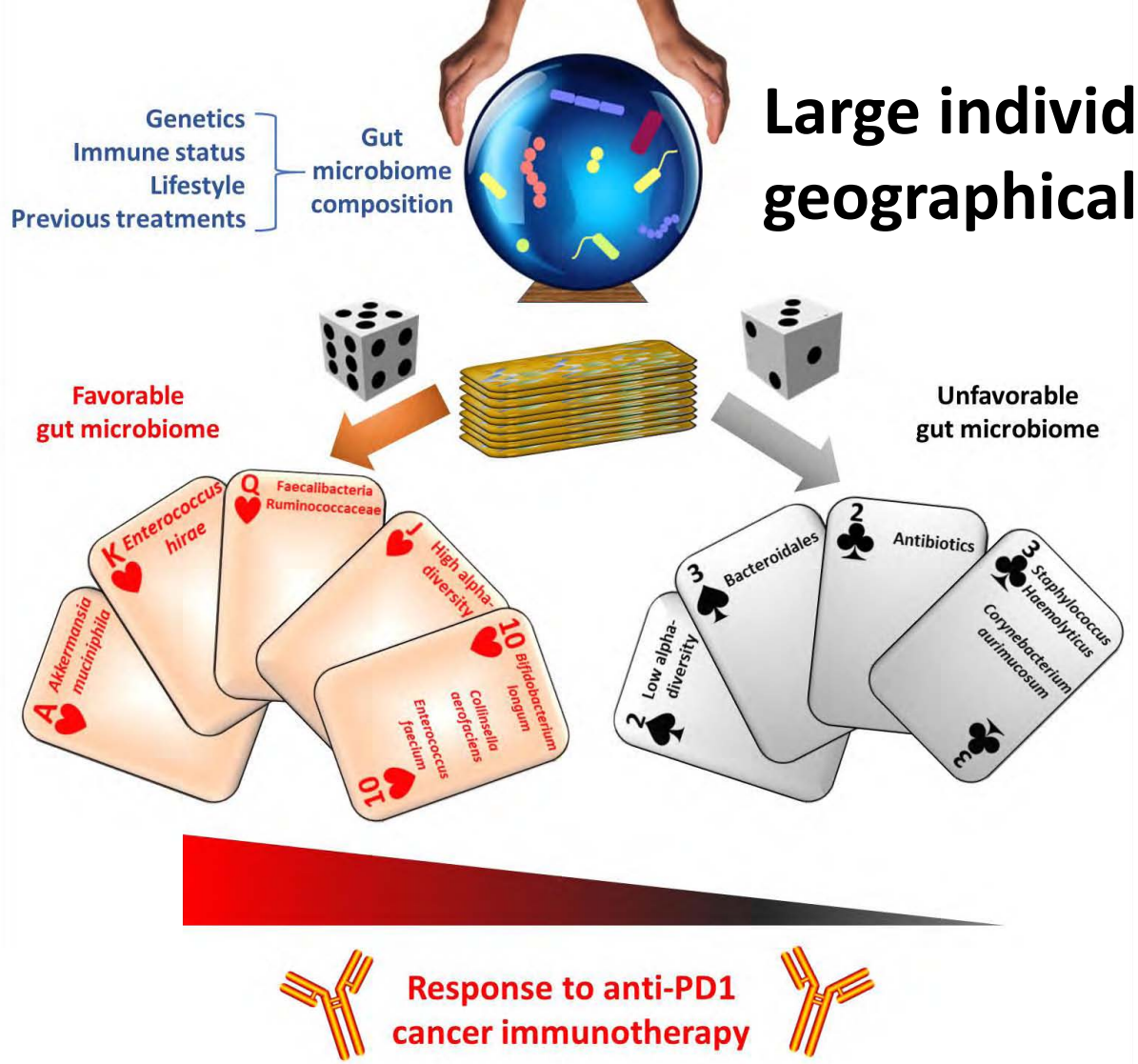






Spencer, C., McQuade, J.L., Vetizou, M. ……
McCulloch, J. …….
Trinchieri, G., Daniel-McDouglas C., Wargo, J.
Submitted

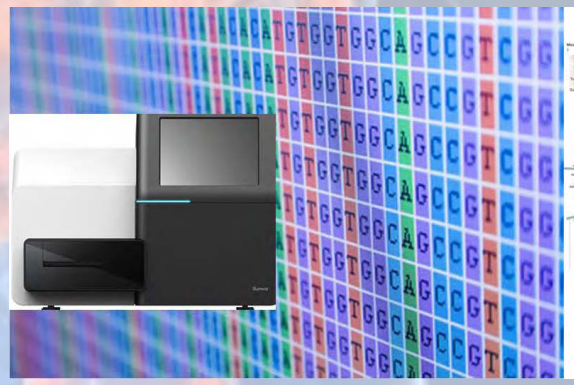
Large individual and geographical diversity

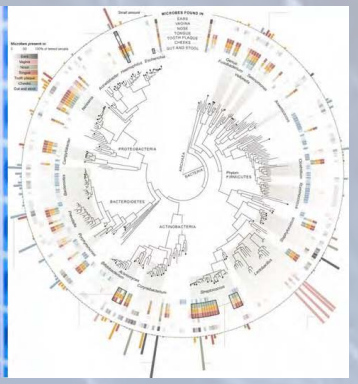


Mouse and, in part, clinical studies have established an important modulating role of the gut microbiome composition on the immune-checkpoint inhibition cancer therapy

Marie Vetizou

Microbiota analysis



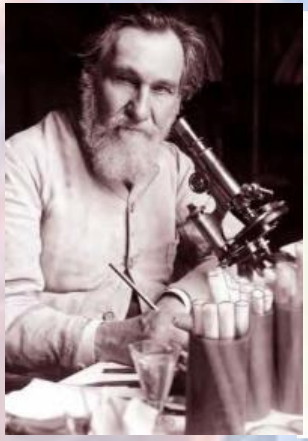


Antonie van Leeuwenhoek, 1683:
First observation of commensal microbes

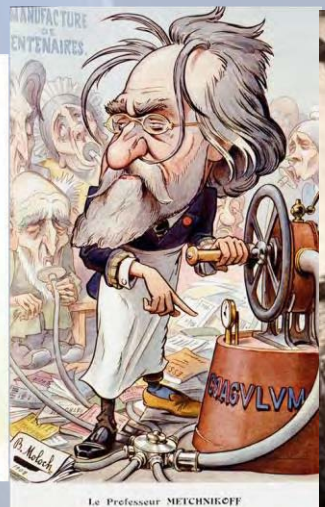
CAN WE TARGET THE MICROBIOME TO IMPROVE THERAPY RESPONSE?

Targeting the microbiota

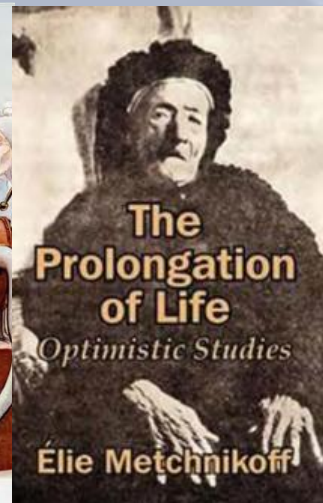
- Diet
- Antibiotics
- Probiotics
- Prebiotics
- Fecal transplant
- Oral formulation of bacteria or their spores



'LE FERMENT' APPARATUS
BY METCHNIKOFF, C1910



Le Professeur METCHNIKOFF



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Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,3] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,3] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,3] Marine Fidelle,[1,2,3] Caroline Flament,[1,2,3] Vichnou Poirier-Colame,[1,2,3] Paule Opolon,[5] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[16] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[8,21,22] Bernard Escudier,[1,14,22] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,2,3] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28]* Laurence Zitvogel[1,2,3,16]*

Akkermansia muciniphila

Alistipes spp

Melanoma

CANCER IMMUNOTHERAPY

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

Vyara Matson,[1]* Jessica Fessler,[1]* Riyue Bao,[2,3]* Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4]†

Bifidobacterium longum

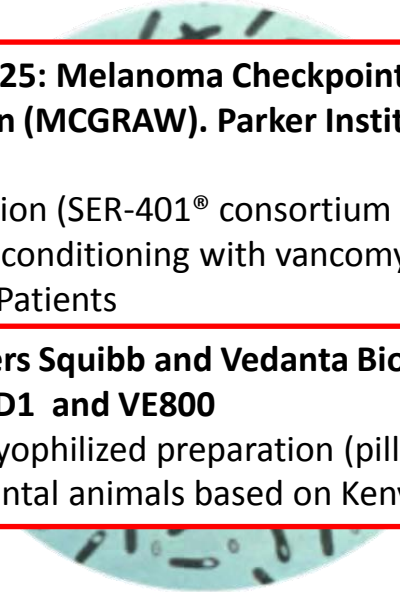
Collinsella aerofaciens

Enterococcus faecium

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

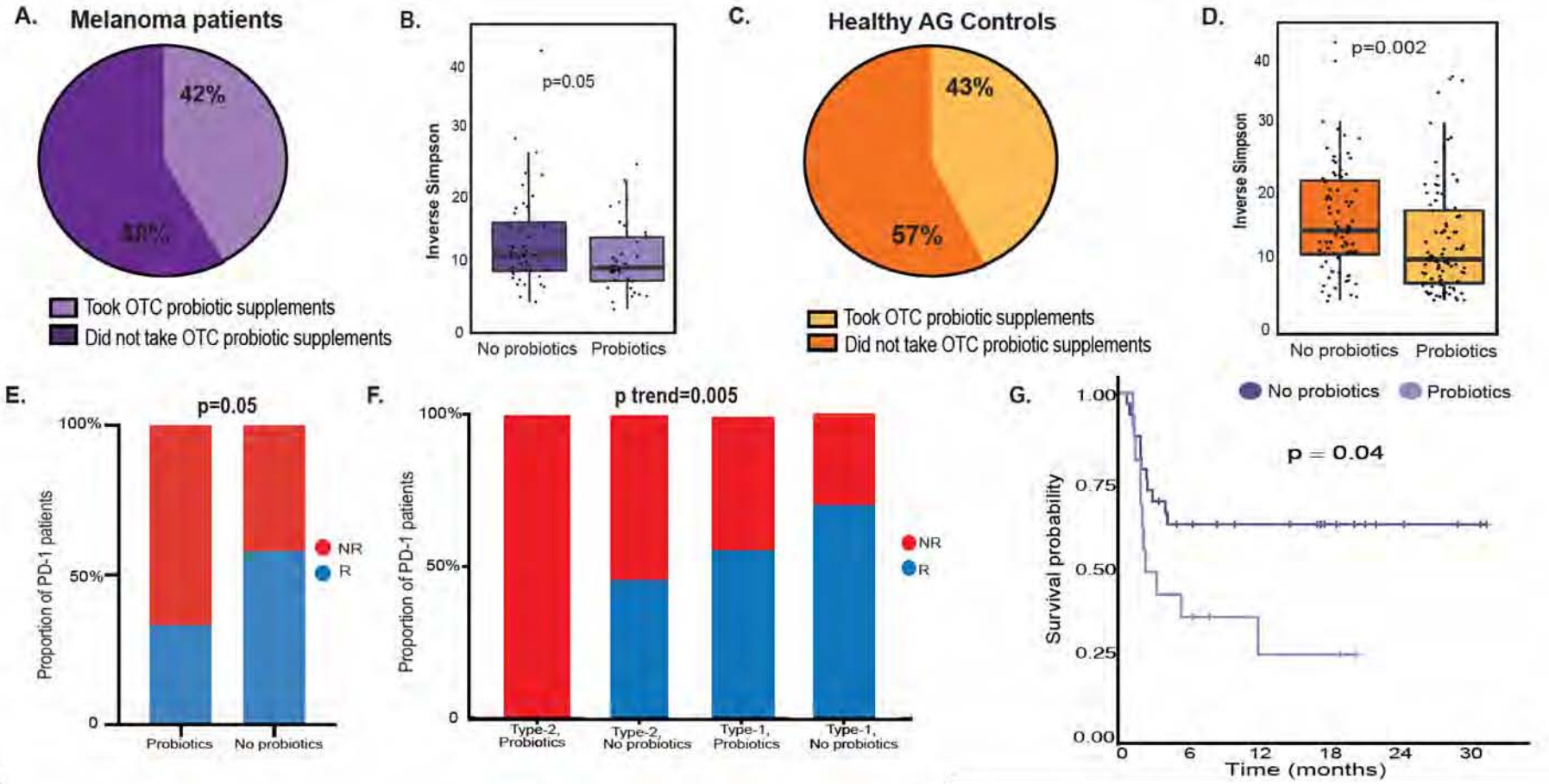
VE800 is a lyophilized preparation (pills) of 8 bacterial strains in experimental animals based on Kenya Honda work

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

Associations of OTC probiotic use with features of the gut microbiome and response to melanoma therapy



Spencer, C.
McQuade, J.L.
Vetizou, M.
……
McCulloch, J.
…….
Trinchieri, G.
Daniel-McDouglas C.
Wargo, J.
Submitted

Spencer, C., McQuade, J.L., Vetizou, M. ……
McCulloch, J. …….
Trinchieri, G., Daniel-McDouglas C., Wargo, J.
Submitted

Science

Lung and renal cancer

REPORTS

Cite as: V. Gopalakrishnan *et al.*, *Science* 10.1126/science.aan4236 (2017)

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

V. Gopalakrishnan,[1,2]* C. N. Spencer,[1,2]* L. Nezi,[2]* A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[2] P. A. Prieto,[1]† D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[3] A. P. Cogdill,[1,2] L. Zhao,[2] C. W. Hudgens,[4] D. S. Hutchinson,[2] T. Manzo,[3] M. Petaccia de Macedo,[6]‡ T. Cotechini,[6] T. Kumar,[3] W. S. Chen,[3] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[6]§ E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[13] S. Shelburne,[2,13] L. M. Vence,[5] P. C. Okhuysen,[13] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1]|| L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[9] Z. A. Cooper,[1,9]¶ P. A. Futreal,[3] C. R. Daniel,[6,9] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff[6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[2]‡ J. A. Wargo,[1,2]‡**

Ruminococcaceae

Clostridiales

Faecalibacterium prausnitzii

Science

Melanoma

REPORTS

Cite as: B. Routy *et al.*, *Science* 10.1126/science.aan3706 (2017)

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

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Akkermansia muciniphila

Alistipes spp

Science

Melanoma

CANCER IMMUNOTHERAPY

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

Vyara Matson,[1]* Jessica Fessler,[1]* Riyue Bao,[2,3]* Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4]†

Bifidobacterium longum

Collinsella aerofaciens

Enterococcus faecium

Fecal microbiome transplant (FMT)

NCT03341143: Fecal Microbiota Transplant (FMT) in Melanoma Patients. University of Pittsburgh

12 anti-PD1 refractory patients have been transplanted with the fecal microbiome from responsive patients and treated again with pembrolizumab®:

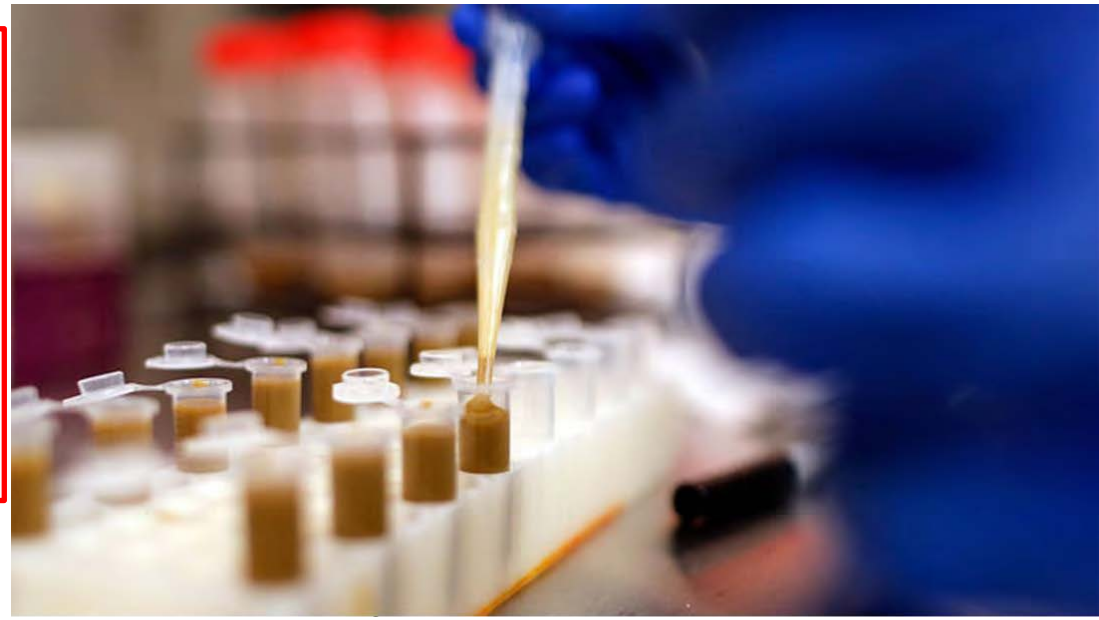
Enrolled: 12; Evaluable: 8
Best Response: 1 PR, 1 CR, 5 SD, 1 PD
Current Response: 1 PR, 1 CR, 2 SD, 4 PD

We are working with the University of Pittsburgh by characterizing the changes in microbiota composition in the transplanted patients by metagenomic analysis and testing the transplanted microbiomes in gnotobiotic mice in conventional conditions or following diet alterations.

NCT03353402: Fecal Microbiota Transplantation (FMT) in Metastatic Melanoma Patients Who Failed Immunotherapy. Sheba Medical Center Tel HaShomer, Israel

NCT03341143: Fecal Microbiota Transplant (FMT) in Melanoma Patients. University of Pittsburgh

NCT03772899: Fecal Microbial Transplantation in Combination With Immunotherapy in Melanoma Patients (MIMic). Lawson Health Research Institute, London, CA



Fecal transplants could help patients on cancer immunotherapy drugs

By Jocelyn Kaiser | Apr. 5, 2019 , 1:45 PM

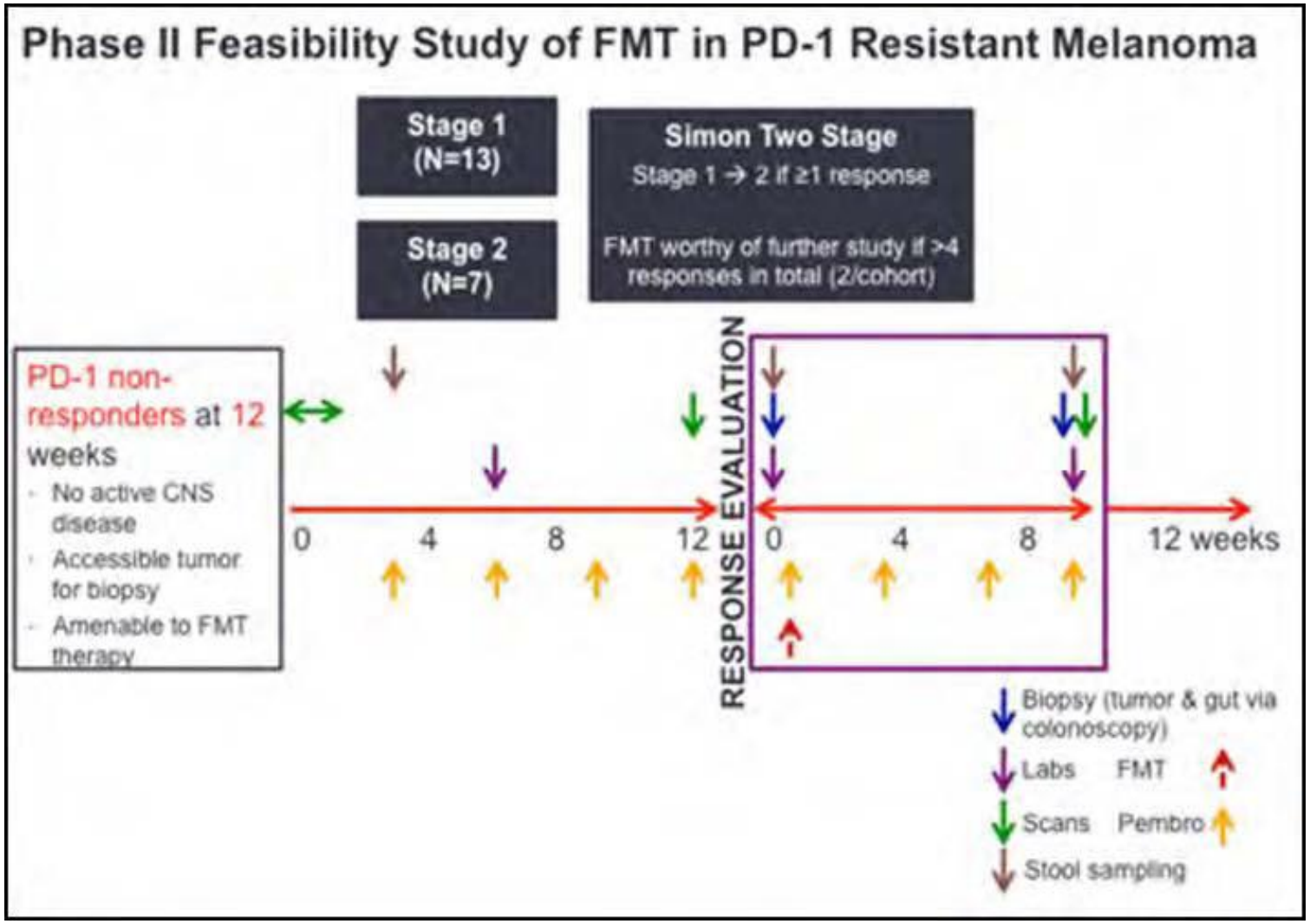
Science

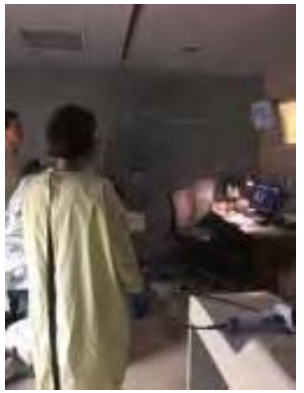
AACR April 2019 General Meeting

Patient 1: PR (7 months)
Patient 2: PD
Patient 3: PR (2 months), PD

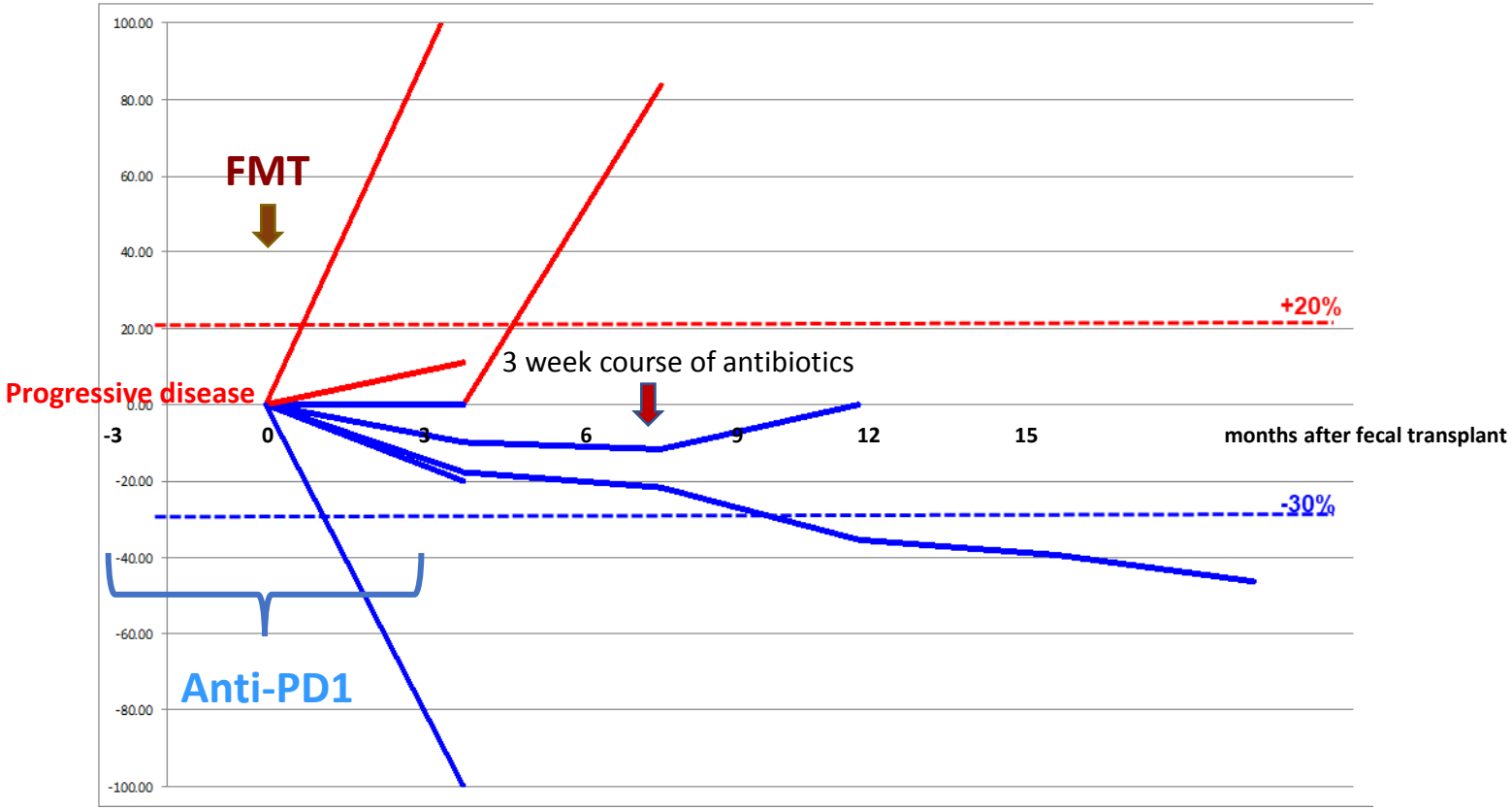
Gal Markel and Ben Boursi
Sheba Medical Center in Ramat Gan, Israel

NCT03341143: Fecal Microbiota Transplant (FMT) in Melanoma Patients. University of Pittsburgh





NCT03341143: Fecal Microbiota Transplant (FMT) in anti-PD1 refractory Melanoma Patients. University of Pittsburgh



Enrolled: 12; Evaluable: 8

Best Response: 1 PR, 1 CR, 5 SD, 1 PD

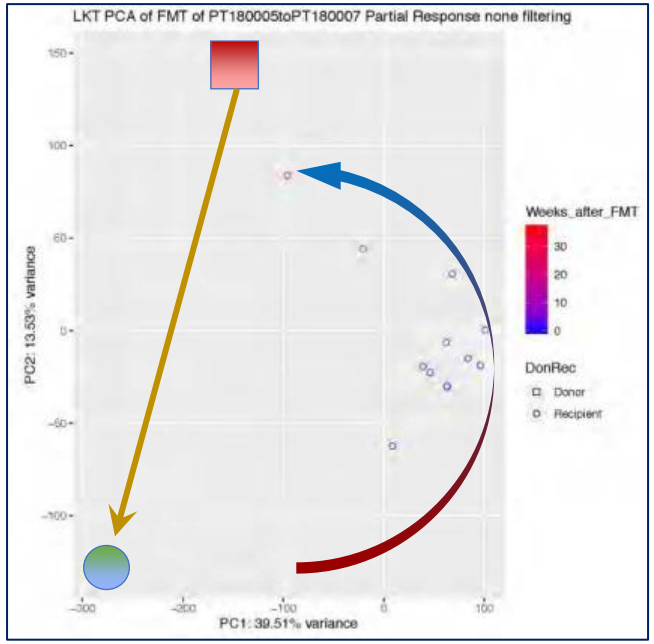
Current Response: 1 PR, 1 CR, 2 SD, 4 PD

NCT03341143: Fecal Microbiota Transplant (FMT) in Melanoma Patients. Metagenomic analysis of microbiome in donors and recipients

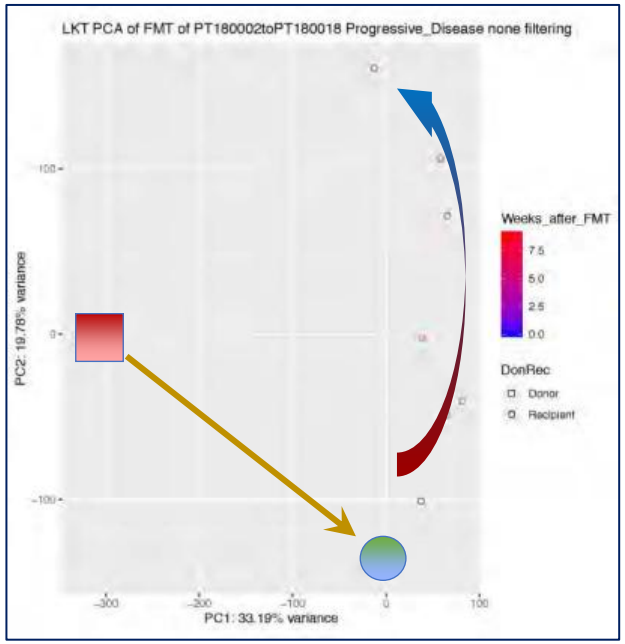
Donor

Recipient

FMT: PT180005toPT180007
Response: Partial Response



FMT: PT180002 to PT180018
Response: Progressive Disease

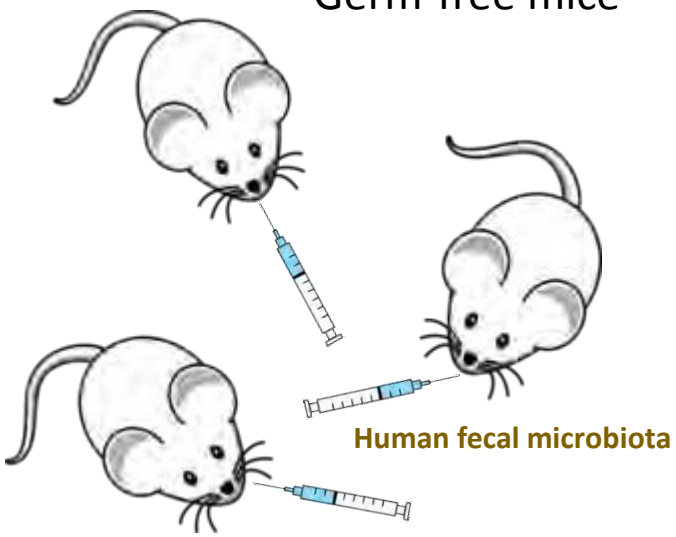


Donor

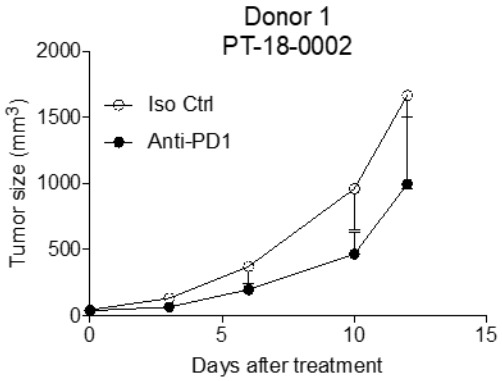
Recipient

John McCulloch **Marie Vetizou**

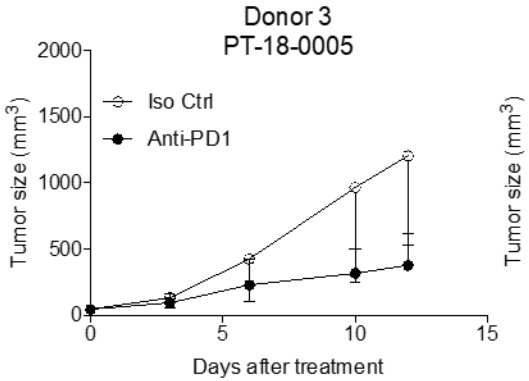
NCT03341143: Fecal Microbiota Transplant (FMT) in Melanoma Patients. Testing FMT donors in gnotobiotic mice



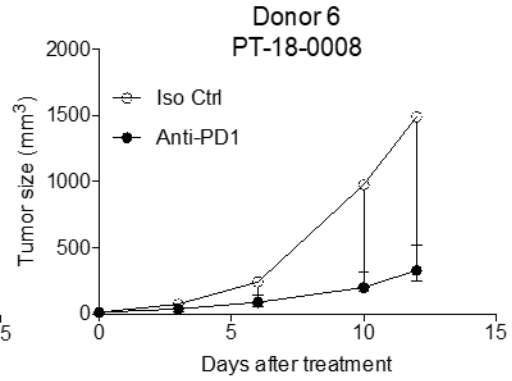
Responder patients as FMT donors



2 recipients:
-PD (PT-18-0017)
-SD to PD (PT-18-0018)

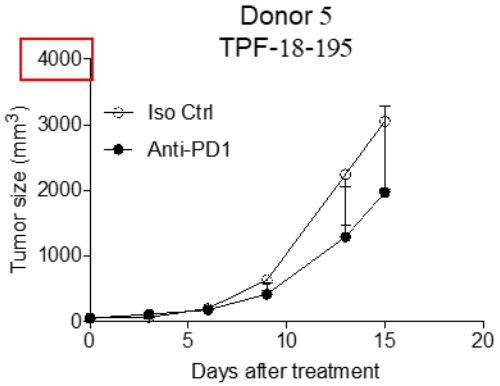


2 recipients:
-SD to PR (PT-18-0007)
-PD (PT-19-0001)



4 recipients:
-SD to PD (PT-18-0033)
-SD to SD (PT-18-0034)
-pending (PT-18-0009)
-pending (PT-18-0010)

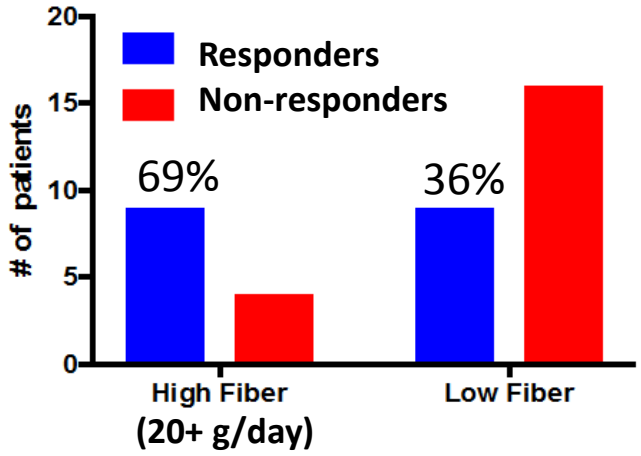
Non-responder patient as FMT donors



Marie Vetizou

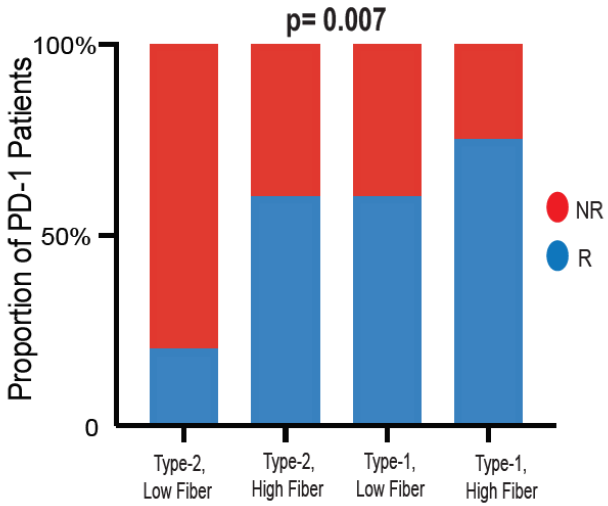
Effect of dietary fiber intake on anti-PD1 Response

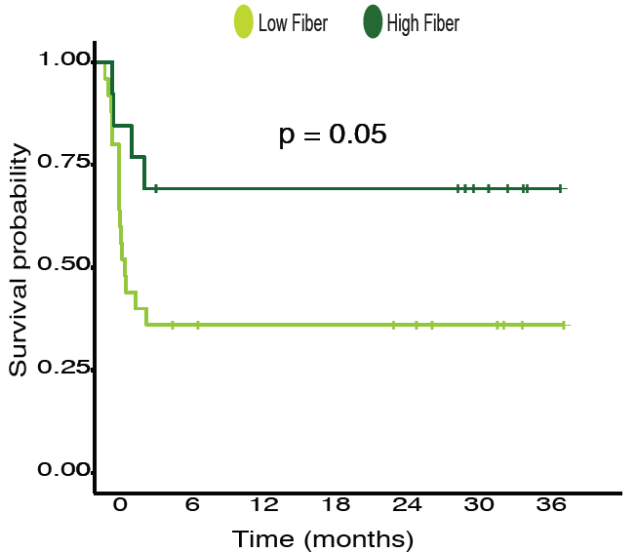
Effect of high/low fiber diet on anti-PD1 response in melanoma patients



(20+ g/day)

p=0.05 OR: 1.02-26.25
(McQuade, SMR 2018)





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McQuade, J.L.
Vetizou, M.
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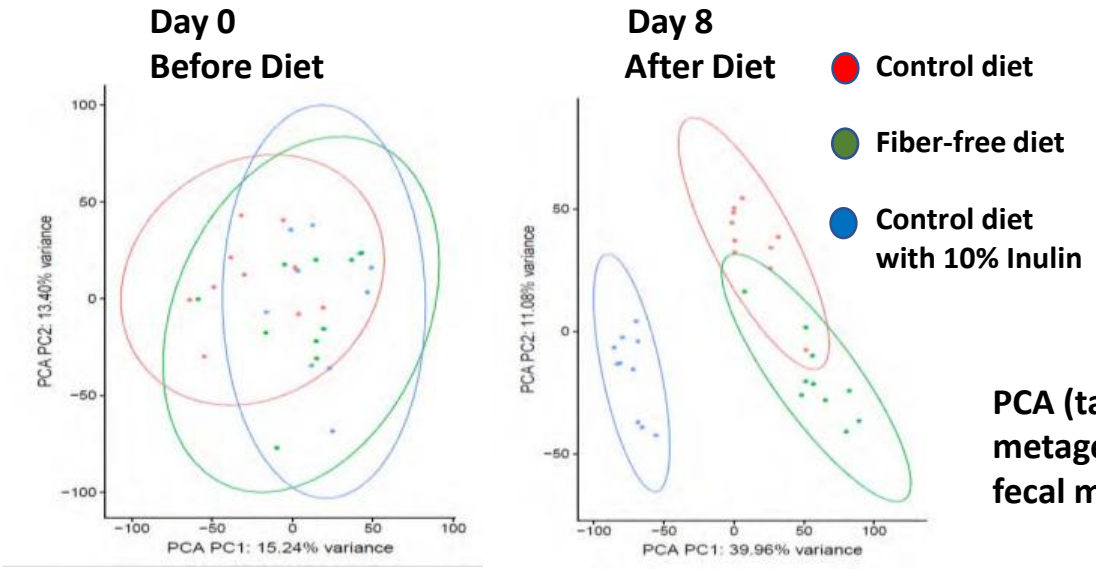
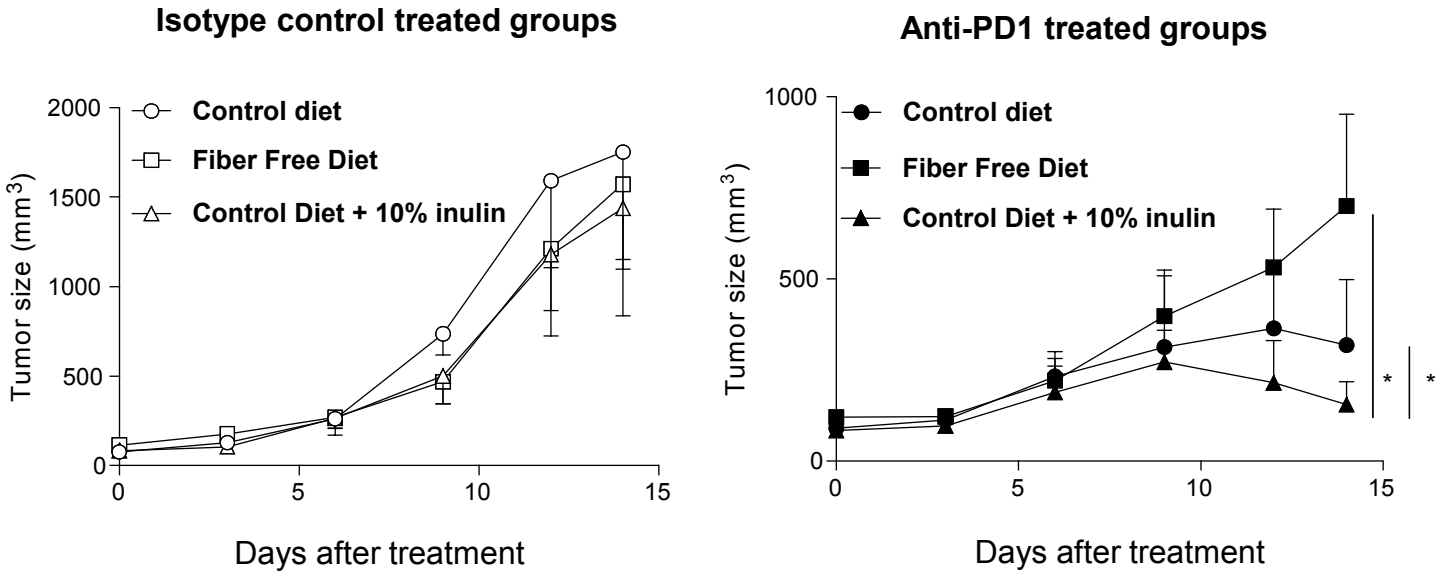
McCulloch, J.
…….
Trinchieri, G.
Daniel-McDouglas C.
Wargo, J.
Submitted

Effect of dietary fiber intake on anti-PD1 Response

Marie Vetizou



PCA (taxonomic) of shotgun metagenomic sequencing of fecal microbiota



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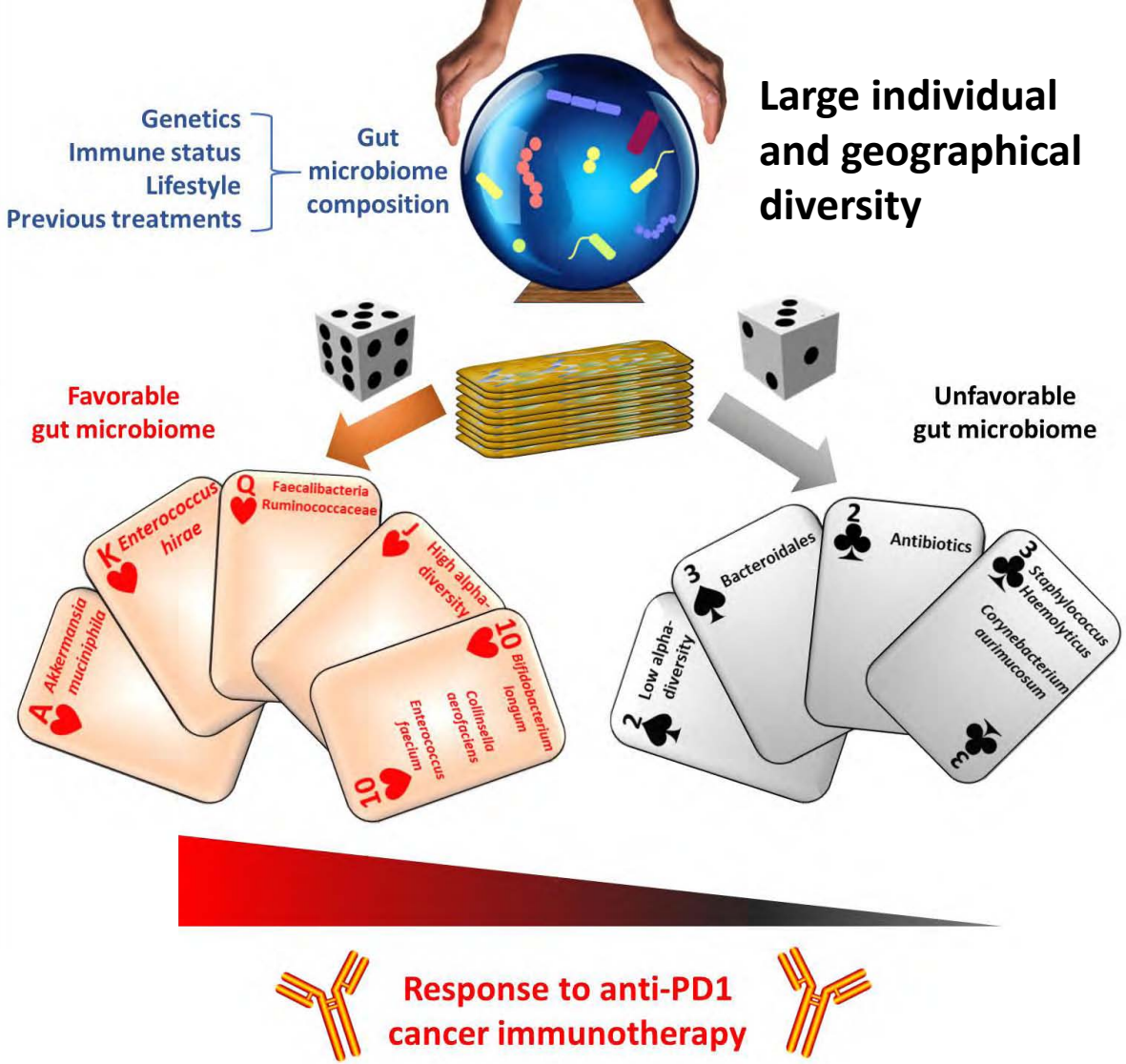


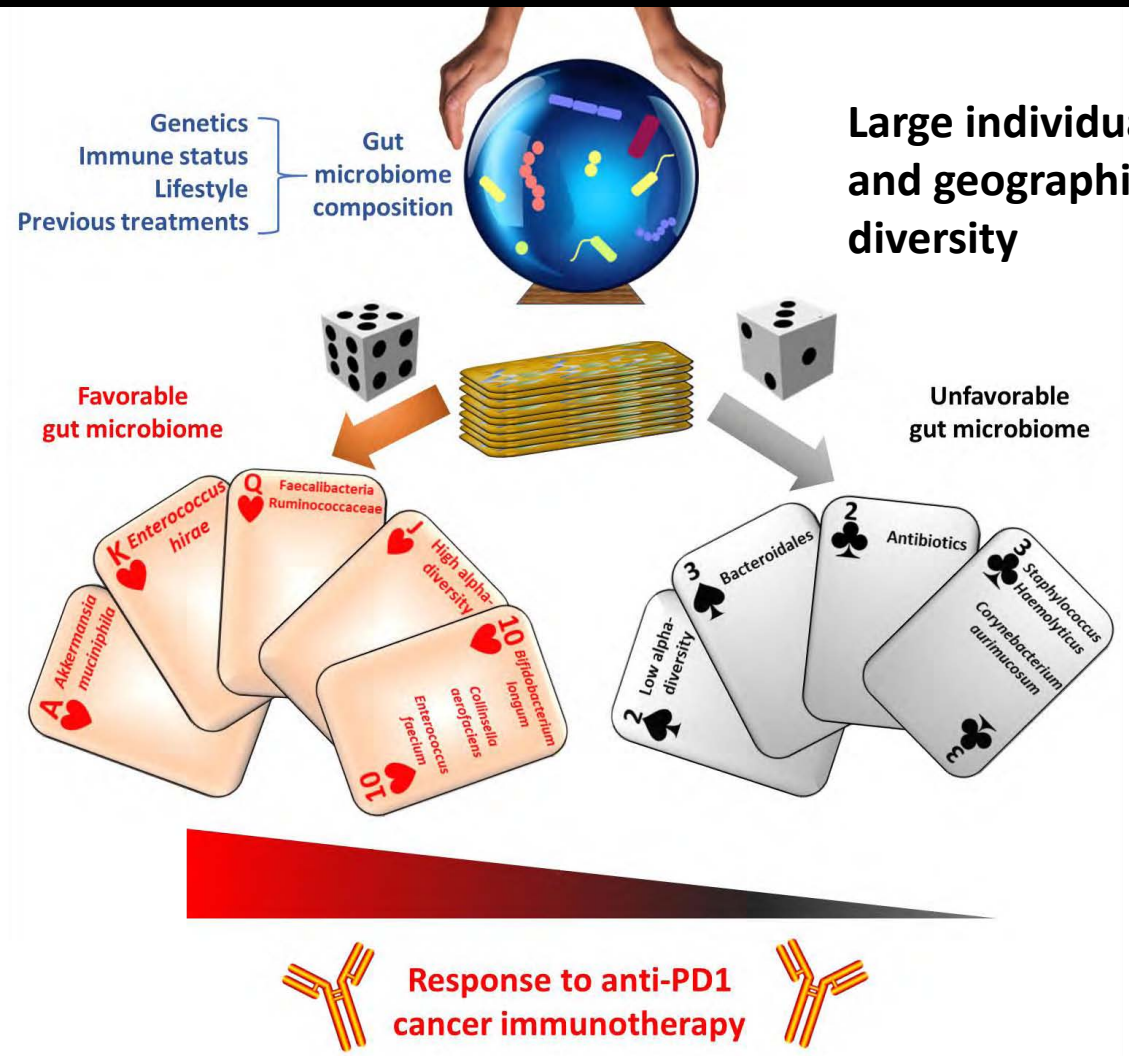
Mouse and, in part, clinical studies have established an important modulating role of the gut microbiome composition on the immune-checkpoint inhibition cancer therapy

Scene from Federico Fellini's "E la nave va" (1983)

IT IS LIKE WATCHING A FELLINI'S MOVIE:
SOMETHING CLEARLY IMPORTANT IS HAPPENING
BUT IT IS NOT CLEAR WHAT IT IS

John McCulloch

PAST



Large individual and geographical diversity

Mouse and, in part, clinical studies have established an important modulating role of the gut microbiome composition on the immune-checkpoint inhibition cancer therapy

PROGRESS/GOALS

- ✓ **Discovery of reliable microbiome-related biomarkers for prediction of response and stratification of patients**
- ✓ **Identification of favorable microbiomes for fecal transfer from responder patients or healthy donors**
- ✓ **Identification of consortia of commensal bacteria that favor a clinical response**
- ✓ **Identification of perturbations (diet, prebiotics, etc.) able to induce or maintain a favorable microbiome composition**
- ✓ **Identification and therapeutic use of bacterial metabolites enhancing anti-tumor immunity**
- ✓ **Targeting molecular pathways by which the host-microbiome cross-talk enhance the anti-cancer response**

Cancer therapy

Noriho Iida
Amiran Dzutsev
Andy Charles Stewart
Romina Goldszmid

Hassane Zarour
Diwakar Davar
John Kirkwood

Pittsburgh Medical School

Christine Spencer
Jennifer McQuade
Carrie Daniel-MacDougall
Jennifer Wargo

MD Anderson CC

Dysbiosis & mouse genetics

Amiran Dzutsev
Ton Sales
Indira Rao

Prepartum ABX

Stephanie Prescott

Ivan Vujkovic-Cvijin
Yasmine Belkaid

NIAID, Bethesda, MD

Stephan Rosshart
Barbara Rehermann

NIDDK, Bethesda

Chemotherapy toxicity & cachexia

Soumen Roy
Rodrigo Das Neves
Carolyne Smith
Raquel Costa
Bathai Edwards

Chi-Ping Day
Glenn Merlino

CCR, NCI, Bethesda

Colon carcinogenesis

Rosalba Salcedo
Ernesto Perez-Chanona
Jonathan Badger
John McCulloch

Anti-PD1 therapy

Marie Vetizou (CRI Fellow)
John McCulloch
Jonathan Badger
Amiran Dzutsev

Colm O'hUigin
Jane Yuan
Vishal Thovarai
Richard Rodrigues

Microbiota Facility,
Cancer and Inflammation Program
CCR, NCI, Bethesda, MD

Simone Difilippantonio
Misty Hawes

Gnotobiotic facility
LASP. LEIDOS
FNLCR, Frederick, MD

Cancer and Inflammation Program, CCR, NCI, Bethesda and Frederick, MD

Sharon Bargo
Pramita Chatterjee
Ren Ming Dai
April Huang
Loretta Smith
Megan Karwan

Final scene from Federico Fellini's "E la nave va" (1983)