



Therapeutic effect of microbiome in lung cancer

2018. 2. 10

이상훈

CONTENT TITLE



1. Definition
2. Previous studies
3. Results
4. 연구계획

Microbiota? Microbiome?

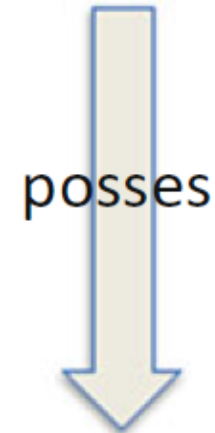
“ Microbiota ”

total collection of organisms of a geographic region or a time period

“Microbiome”

collection of the genomes of the microbes

Microbiota
(all present microbes)



Microbiom
(all present genes)

Microbiota? Microbiome?

- Even the lung, thought to be sterile part, now considered to be colonized.
- Human-associated microbiota: at least 40,000 strains in 1800 genera.
- Microbiota(1–2kg) vs Brain(1.5kg)
- 2004.04.14 Human genome sequencing complete
- 2008, Human Microbiome Project
“ characterization of the human microbiome and analysis of its role in human health and disease ”

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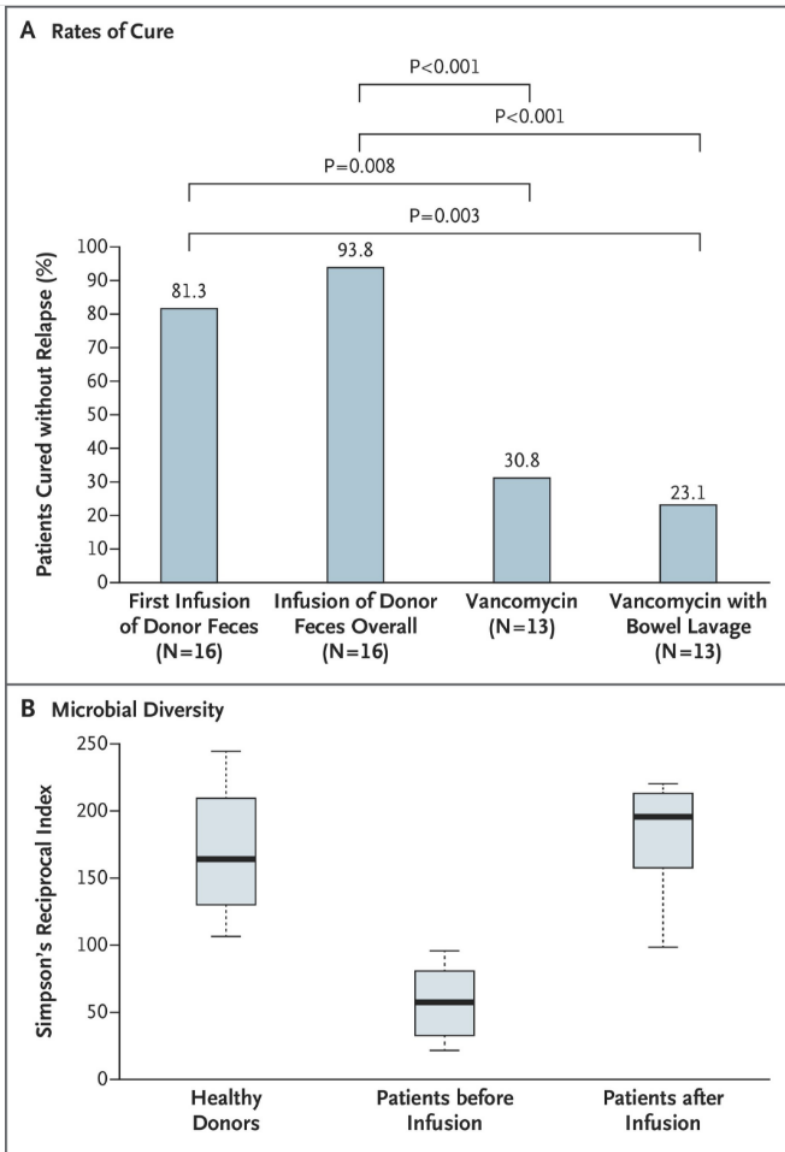
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- [Association of Oral Microbiome With Risk for Incident Head and Neck Squamous Cell Cancer.](#)
- 1. Hayes RB, Ahn J, Fan X, Peters BA, Ma Y, Yang L, Agalliu I, Burk RD, Ganly I, Purdue MP, Freedman ND, Gapstur SM, Pei Z.
JAMA Oncol. 2018 Jan 11. doi: 10.1001/jamaoncol.2017.4777. [Epub ahead of print]
PMID: 29327043
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- Recurrent *C. difficile*
- Fecal transplantation

Els van Nood et al *N Engl J Med* 2013;368:407-15.

THE LANCET

Vol 341

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ARTICLES

An international association between *Helicobacter pylori* infection and gastric cancer

THE EUROGAST STUDY GROUP

JOURNAL OF PATHOLOGY
J. Pathol. **189**: 12–19 (1999)

HUMAN PAPILLOMAVIRUS IS A NECESSARY CAUSE OF INVASIVE CERVICAL CANCER WORLDWIDE

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MICROBE	SITE OF CANCER
<i>Helicobacter pylori</i>	Stomach
Hepatitis B virus (HBV)	Liver
Hepatitis C virus (HCV)	
<i>Opisthorchis viverrini</i>	
<i>Clonorchis sinensis</i>	
Human papillomavirus (HPV)	Cervix Vagina Vulva Anus Penis Oropharynx
Epstein-Barr virus (EBV)	Nasopharynx Non-Hodgkin lymphoma Hodgkin lymphoma
Kaposi sarcoma-associated herpesvirus (KSHV or HHV8)	Kaposi sarcoma Primary effusion lymphoma
Human T-cell lymphotropic virus type 1 (HTLV-1)	Adult T-cell lymphoma
<i>Schistosoma haematobium</i>	Bladder

- **Table. Microbes Designated as Class 1 (Carcinogens) by the International Agency for Research on Cancer (IARC)**

- The human body harbors enormous numbers of microbiota that influence cancer susceptibility, in part through their prodigious metabolic capacity and their profound influence on immune cell function. **Microbial pathogens drive tumorigenesis in 15% to 20% of cancer cases.** Although association studies cannot distinguish whether changes in microbiota are causes or effects of cancer, **a causative role is supported** by rigorously controlled preclinical studies using gnotobiotic mouse models colonized with one or more specific bacteria. These studies demonstrate that **microbiota can alter cancer susceptibility and progression by diverse mechanisms**, such as modulating inflammation, inducing DNA damage, and producing metabolites involved in oncogenesis or tumor suppression....By incorporating **probiotics** as **adjuvants for checkpoint immunotherapy** or by designing small molecules that target microbial enzymes, microbiota can be harnessed to improve cancer care.

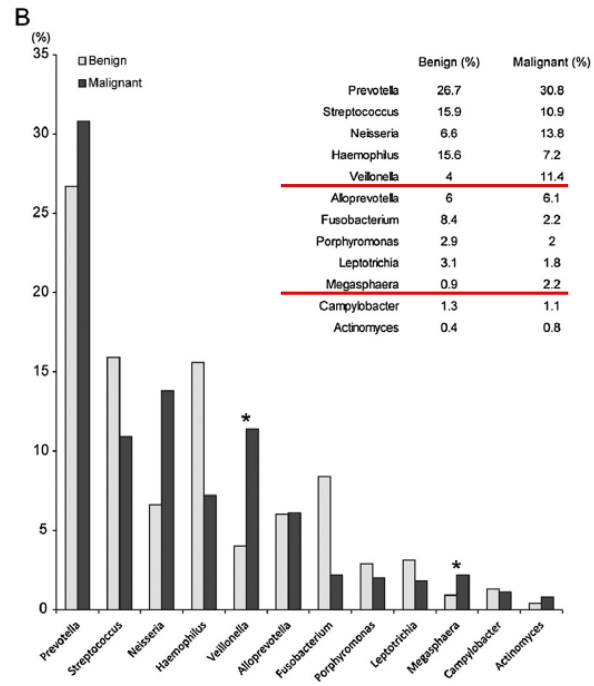
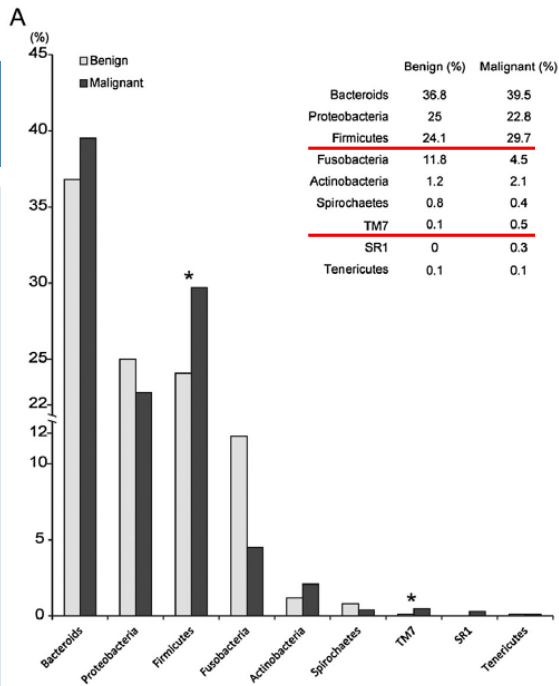
A Sample of Published Metagenomic Studies Analyzing Cases and Controls

TYPE OF CANCER	SAMPLING MATERIAL AND SITE	CONCLUSION	FINDINGS			REFERENCE
			ENRICHED IN CASES	REDUCED IN CASES	ENRICHED IN CONTROLS	
Colorectal adenoma	Mucosal adherent bacteria	Higher diversity and richness in cases compared with controls	Proteobacteria, <i>Dorea</i> spp., <i>Faecalibacterium</i> spp.	Bacteroidetes, <i>Coprococcus</i> spp.		Shen 2010 ⁴¹
Colorectal adenoma	Mucosal adherent bacteria	Higher diversity and richness in cases compared with controls; similar evenness	30 Genera, including: <i>Acidovorax</i> , <i>Aquabacterium</i> , <i>Cloacibacterium</i> , <i>Helicobacter</i> , <i>Lactococcus</i> , <i>Lactobacillus</i> , <i>Pseudomonas</i>		<i>Streptococcus</i>	Sanapareddy 2012 ⁴²
Colorectal adenoma	Preneoplastic colon polyps from African American patients	No statistically significant differences	Slight increases in Proteobacteria (<i>K. pneumoniae</i> , <i>E. coli</i>), Verrucomicrobia, Firmicutes	<i>Bacteroides</i>	Slightly higher abundance of <i>Oscillospira guillermondii</i> , <i>Subdoligranulum</i>	Brim 2013 ⁴³
Colorectal adenoma	Adenomatous tissues		<i>Bifidobacterium</i> sp, Eubacteria			Nugent 2014 ⁴⁴
Colorectal tubular adenoma, adenocarcinoma	Mucosal adherent bacteria	Dysbiosis in cases compared with healthy controls	<i>Fusobacterium nucleatum</i> , <i>Enterobacteriaceae</i> , <i>Methanobrevibacter</i> (Archaea, Methanobacteriales)			Mira-Pascual 2015 ⁴⁵
Colorectal adenoma, carcinoma	Feces	Progressive dysbiosis concurrent with progressive disease	ADENOMA: <i>Blautia</i> , <i>Ruminococcus</i> , <i>Clostridium</i> , <i>Lachnospiraceae</i> ; CARCINOMA: <i>Fusobacterium</i> , <i>Bacteroides</i> , <i>Phascolarctobacterium</i> , <i>Porphyromonas</i>			Zackular 2014 ⁴⁶
Colorectal adenoma	Feces	No significant differences; underpowered study confounded by antibiotics treatment	Proteobacteria, TM7			Goedert 2015 ⁴⁷
Colorectal carcinoma	Mucosal tissues	Increased abundance of <i>Fusobacterium</i>	<i>F. nucleatum</i> , <i>F. mortiferum</i> , <i>F. necrophorum</i>	Bacteroidetes, Firmicutes		Kostic 2012 ⁴⁸
Colorectal Adenoma	Feces	Compositional shifts occur in adenomatous tissues that correlate with alterations in bacterial metabolism	<i>Bilophila</i> , <i>Desulfovibrio</i> , <i>Mogibacterium</i> , Bacteroidetes. <i>Streptococcus</i> , <i>Veillonella</i> , <i>Mogibacterium</i> , and <i>Sutterella</i> predict presence of adenomatous polyps			Hale 2017 ⁴⁹
Colorectal polyps, carcinoma	Fecal and mucosal samples, from tumor and tumor-adjacent regions	Mucosal microbiota differs in cases and controls, particularly if lesion is proximal or distal; fecal and mucosal microbiota differ in CRC; analyses suggest that microbiota shifts are not secondary to the cancer	<i>Bacteroides</i> , <i>Roseburia</i> , <i>Ruminococcus</i> , <i>Oscillibacter</i> ; ORAL PATHOGENS: <i>Porphyromonas</i> , <i>Peptostreptococcus</i> , <i>Parvimonas</i> , <i>Fusobacterium</i> ; CLUSTERS OF COABUNDANCE GROUPS: Bacteroidetes cluster 2, Firmicutes cluster 2, pathogen cluster, Prevotella cluster	ON MUCOSA: Clusters of coabundance groups (Bacteroidetes duster 1, Firmicutes duster 1); IN FECES: Lachnospiraceae incertae sedis and Coprococcus		Flemer 2017 ⁵⁰

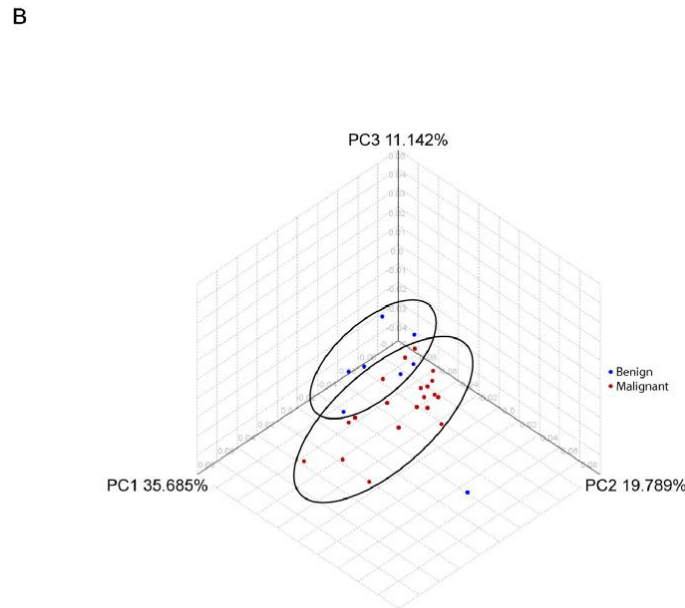
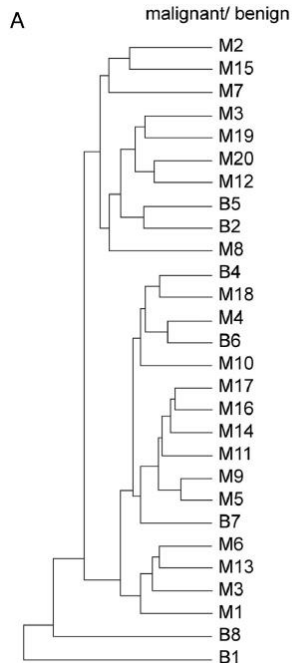
TYPE OF CANCER	SAMPLING MATERIAL AND SITE	CONCLUSION	FINDINGS			REFERENCE
			ENRICHED IN CASES	REDUCED IN CASES	ENRICHED IN CONTROLS	
Breast cancer	Tumor and adjacent normal breast tissue; healthy tissue from controls	Compositional differences between healthy controls and tumor-adjacent tissue from patients; similar compositional profiles between tumor and tumor-adjacent normal tissue within the same patient; strains isolated from tumors induced DNA double strand breaks in vitro	<i>Bacillus</i> , <i>Enterobacteriaceae</i> , <i>Staphylococcus</i> , <i>Comamonadaceae</i> , unclassified <i>Bacteroidetes</i>	<i>Prevotella</i> , <i>Lactococcus</i> , <i>Corynebacterium</i> , <i>Streptococcus</i> , <i>Micrococcus</i>		Urbaniak 2016 ⁵¹
Breast cancer	NAF of survivors and healthy controls	No compositional differences on areolar skin; ductal microbiota are significantly different between survivors and healthy controls; microbiota profiles are similar for paired areolar and NAF from the same individual	<i>Alistipes</i>		Undclassified <i>Sphingomonadaceae</i> family member	Chan 2016 ⁵²

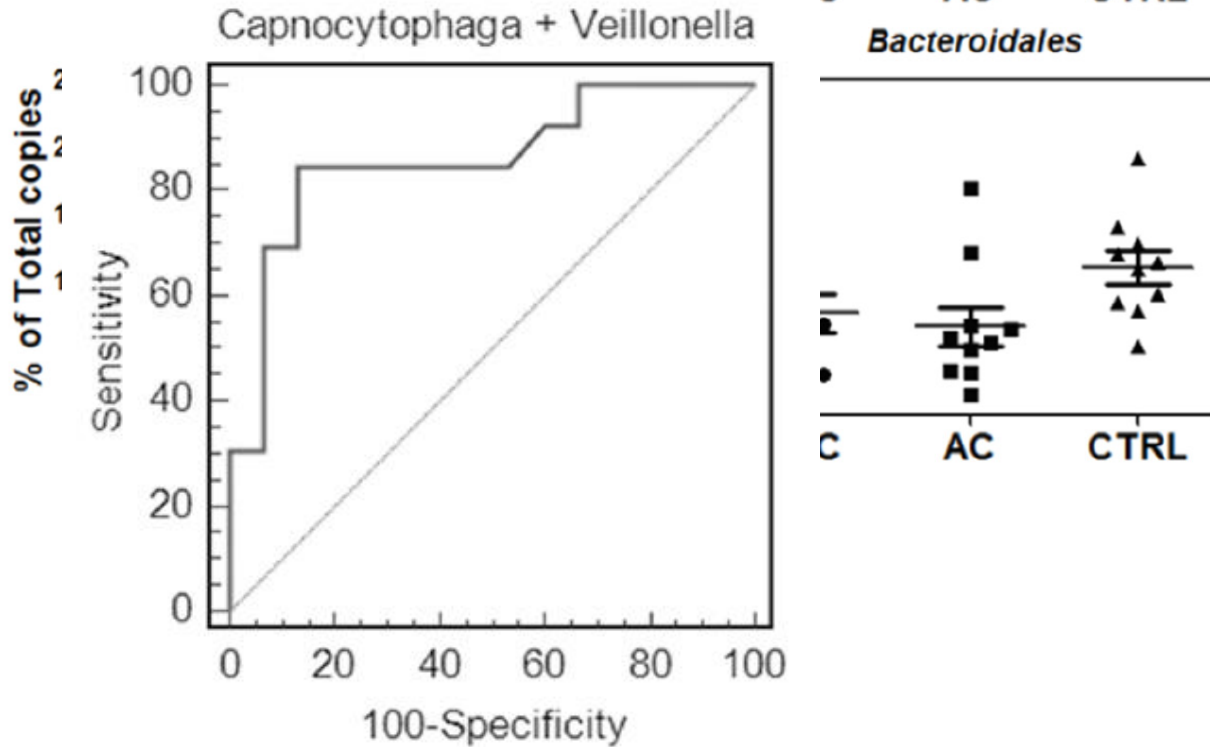
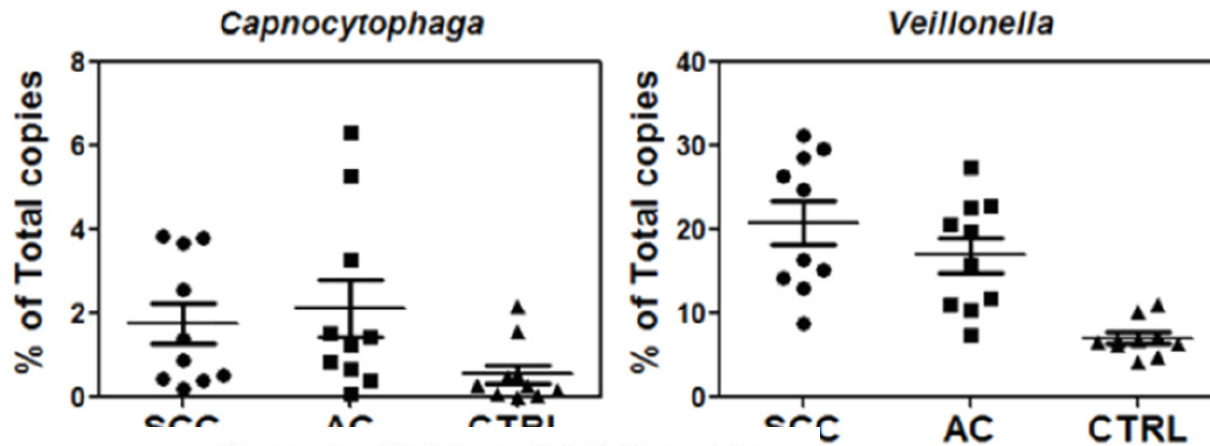
Microbiome in lung diseases

Medical condition	References	Differential taxa features*	Sample size	Sample type
Chronic Obstructive Pulmonary Disease	Kim et al. [23]	phyla: <i>Firmicutes</i> ↑ genera: <i>Ochrobactrum</i> ↑ <i>Stenotrophomonas</i> ↓ <i>Propionibacterium</i> ↓	26	lung tissue
	Sze et al. [24]	phyla: <i>Firmicutes</i> ↑ genera: <i>Lactobacillus</i> ↑	24	lung tissue
	Pragman et al. [25]	phyla: <i>Fusobacteria</i> ↑ genera: <i>Leptotrichia</i> ↑ <i>Fusobacterium</i> ↑	32	broncho alveolar lavage
	Millares et al. [26]	genera: <i>Pseudomonas</i> ↑ <i>Corynebacterium</i> ↑ <i>Moraxella</i> ↑	16	sputum
	Garcia-Nuñez et al. [27]	phyla: <i>Proteobacteria</i> ↑ <i>Firmicutes</i> ↑ <i>Actinobacteria</i> ↓ <i>Bacteroidetes</i> ↓	17	sputum
	Lee et al. [28]	phyla: <i>Bacteroidetes</i> ↑ <i>Firmicutes</i> ↑ <i>Fusobacteria</i> ↑ <i>Actinobacteria</i> ↑ <i>Proteobacteria</i> ↓	8	sputum
Cystic Fibrosis	Garcha et al. [29]	genera: <i>Prevotella</i> ↑ <i>Porphyromonas</i> ↑ <i>Veillonella</i> ↑ <i>Fusobacterium</i> ↑ <i>Streptococcus</i> ↑ stable: <i>H influenzae</i> ↑ exacerbation: <i>S pneumoniae</i> ↑ <i>M catarrhalis</i> ↑	134	sputum
	Carmody et al. [33]	genera: <i>Staphylococcus</i> ↑ <i>Burkholderia</i> ↑ <i>Streptococcus</i> ↑	4	sputum
	Fodor et al. [34]	genera: <i>Pseudomonas</i> ↑ <i>Burkholderia</i> ↑	23	sputum mouthwash
	Frayman et al. [35]	genera: <i>Staphylococcus</i> ↑ <i>Streptococcus</i> ↑ <i>Pseudomonas</i> ↑	95	broncho alveolar lavage
	Laguna et al. [36]	genera: <i>Streptococcus</i> ↑ <i>Burkholderia</i> ↑ <i>Prevotella</i> ↑ <i>Haemophilus</i> ↑ <i>Porphyromonas</i> , and <i>Veillonella</i> ↑	12	broncho alveolar lavage
	Feigelman et al. [37]	genera: <i>Pseudomonas</i> ↑ <i>Staphylococcus</i> ↑ <i>Stenotrophomonas</i> ↑ <i>Achromobacter</i> ↑	17	sputum
Asthma	Hilty et al. [22]	phyla: <i>Proteobacteria</i> ↑ genera: <i>Haemophilus</i> spp. ↑		bronchoscopy
	Marri et al. [44]	phyla: <i>Proteobacteria</i> ↑ <i>Firmicutes</i> ↓ <i>Actinobacteria</i> ↓	20	sputum
	Teo et al. [40]	phyla: <i>Proteobacteria</i> ↑ genera: <i>Streptococcus</i> ↑	234	nasopharyngeal
	Bisgaard et al. [39]	genera: <i>S. pneumoniae</i> ↑ <i>M. catarrhalis</i> ↑ <i>H. influenzae</i> ↑	321	hypopharyngeal
Idiopathic Pulmonary Fibrosis	Durack et al. [41]	genera: <i>Haemophilus</i> ↑ <i>Neisseria</i> ↑ <i>Fusobacterium</i> ↑ <i>Porphyromonas</i> ↑	42	bronchoscopy
	Molyneaux et al. [48]	genera: <i>Haemophilus</i> ↑ <i>Streptococcus</i> ↑ <i>Neisseria</i> ↑ <i>Veillonella</i> ↑	65	broncho alveolar lavage
	Han et al. [49]	genera: <i>Staphylococcus</i> ↑ <i>Streptococcus</i> ↑	55	broncho alveolar lavage
	Molyneaux et al. [47]	genera: <i>Streptococcus</i> ↑ <i>Prevotella</i> ↑ <i>Veillonella</i> ↑ <i>Haemophilus</i> ↑ <i>Pseudomonas</i> ↑	35	bronchoscopy



Lung mass
- Malignant (n=20)
- Benign (n=8)

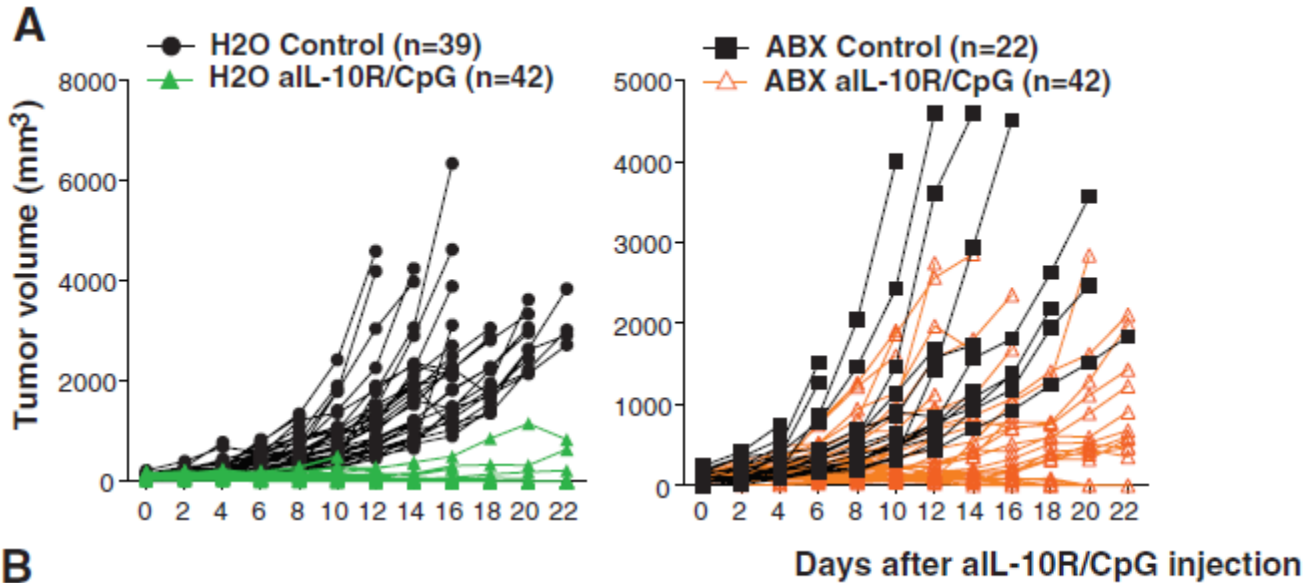




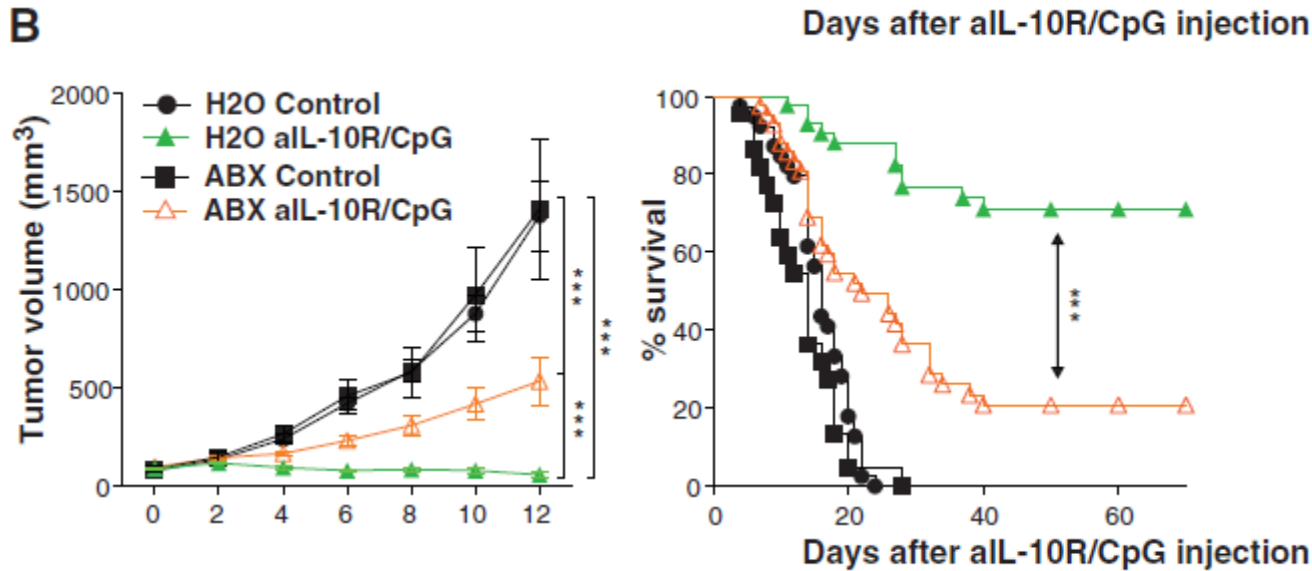
Salivary microbiota

- SCC (n=10)
- AC (n=10)
- Control (n=10)

Role of microbiome in cancer



ABX group (3wks)
 - vancomycin
 - imipenem
 - neomycin



Does the microbiome play a role in the effectiveness of colorectal cancer treatment?

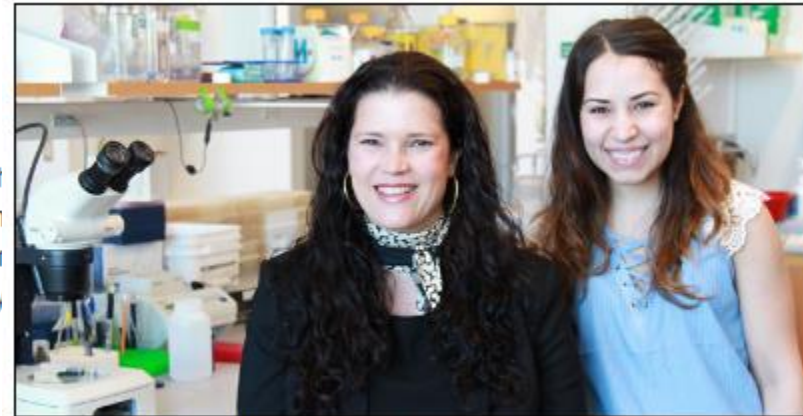
Connection between bacteria, chemotherapy discovered

Date: April 24, 2017

Source: University of Massachusetts Medical School

Summary: *C. elegans*, fed a diet of *E. coli* bacteria, are 100 times more sensitive to the chemotherapy drug floxuridine, commonly used to treat colon cancer, than different bacteria. These findings suggest that the bacteria residing in your tract may play an important role in your ability to respond to chemotherapy

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Marian Walhout, PhD, and Aurian Garcia Gonzalez

RELATED TOPICS

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- > Pharmacology
- > Personalized Medicine
- > Lung Cancer

Plants & Animals

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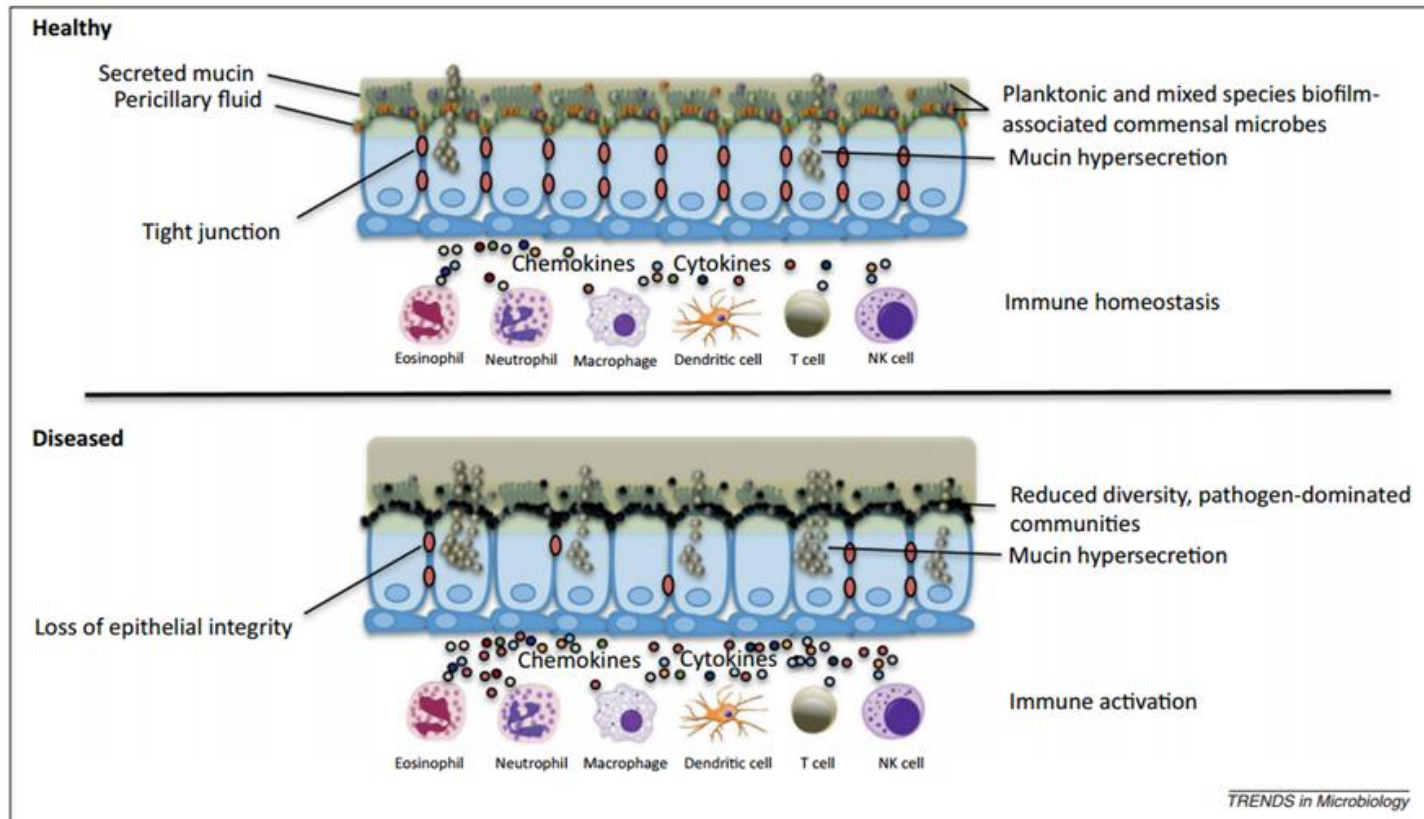
FULL STORY

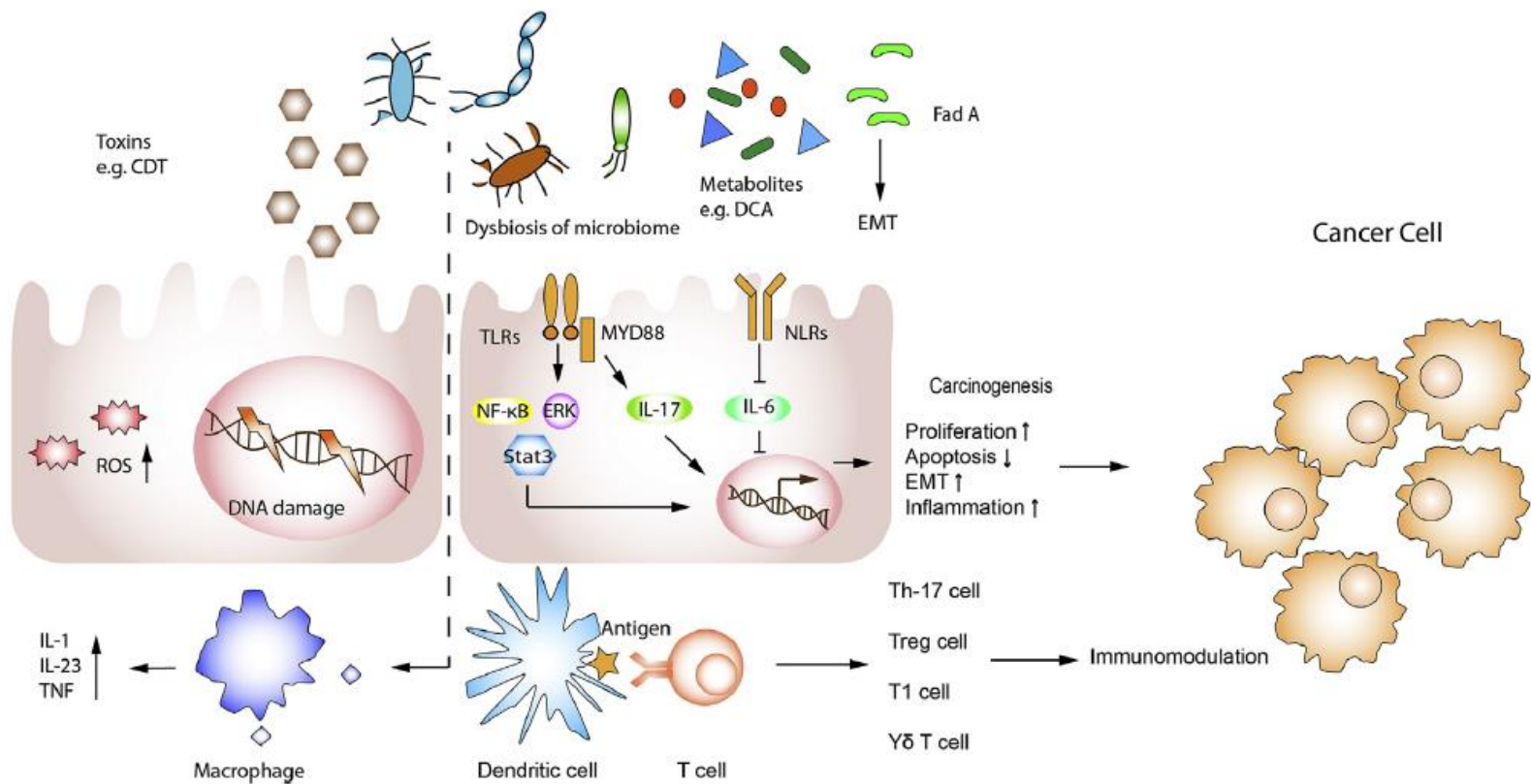
The bacteria residing in your digestive tract, or your gut microbiota, may play an important role in your ability to respond to chemotherapy drugs in the clinic, according to a new study by scientists at the University of Massachusetts Medical School. Published in *Cell*, the study by Marian Walhout, PhD, and colleagues show that when a common research model, the roundworm *Caenorhabditis elegans*, is fed a diet of *E. coli* bacteria, the worms were one hundred times more sensitive to the chemotherapy drug floxuridine (FUDR) than worms who were fed different bacteria. FUDR is a commonly used drug to treat colorectal cancer.

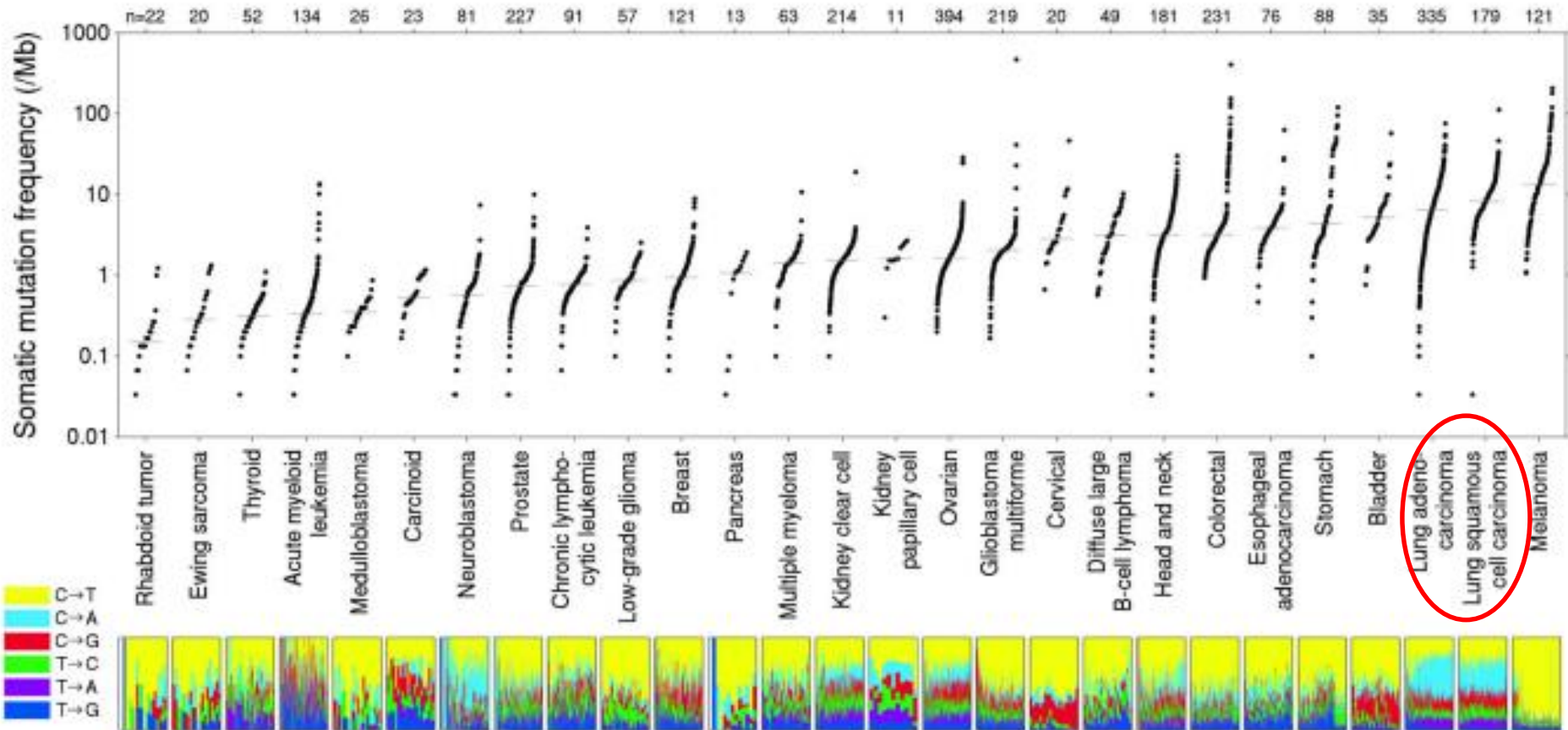
**Precision
medicine**

Garcia-Gonzalez et al., 2017, *Cell* 169, 431–441 April 20, 2017

Immunomodulatory effects of the microbiota in the lung







Lawrence et al. Nature. 2013 July 11; 499(7457): 214–218

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

Ayelet Sivan,^{1*} Leticia Corrales,^{1*} Nathaniel Hubert,² Jason B. Williams,¹ Keston Aquino-Michaels,³ Zachary M. Earley,² Franco W. Benyamin,¹ Yuk Man Lei,² Bana Jabri,² Maria-Luisa Alegre,² Eugene B. Chang,² Thomas F. Gajewski^{1,2†}

3 April 2015; accepted 21 October 2015
Published online 5 November 2015
10.1126/science.aad1329

- √ tumor microbiome therapy + tumor immunotherapy → synergistic effect
- √ Illumina 16S rRNA sequencing platform
- √ functional study using animal model

**B16-SIY
Melanoma model**



C57BL/6 mouse
(Jackson Laboratory-JAX)

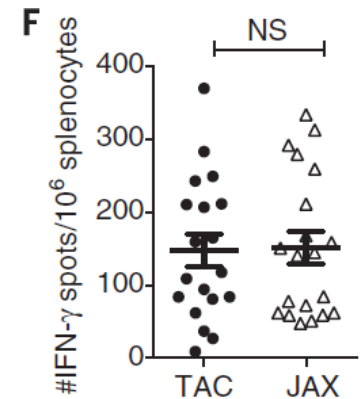
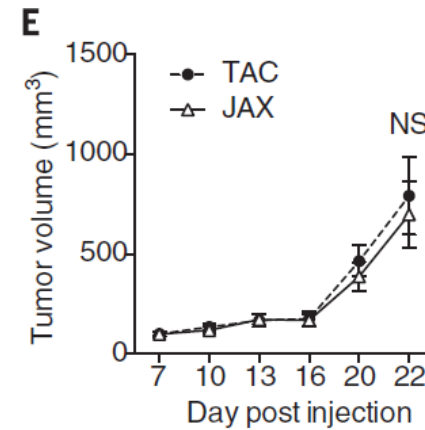
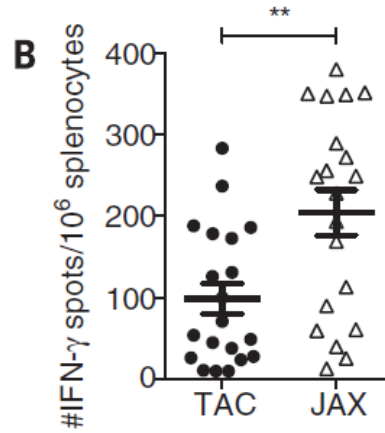
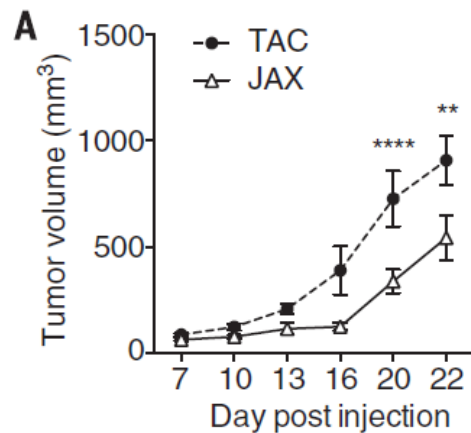


C57BL/6 mouse
(Taconic Farms-TAC)

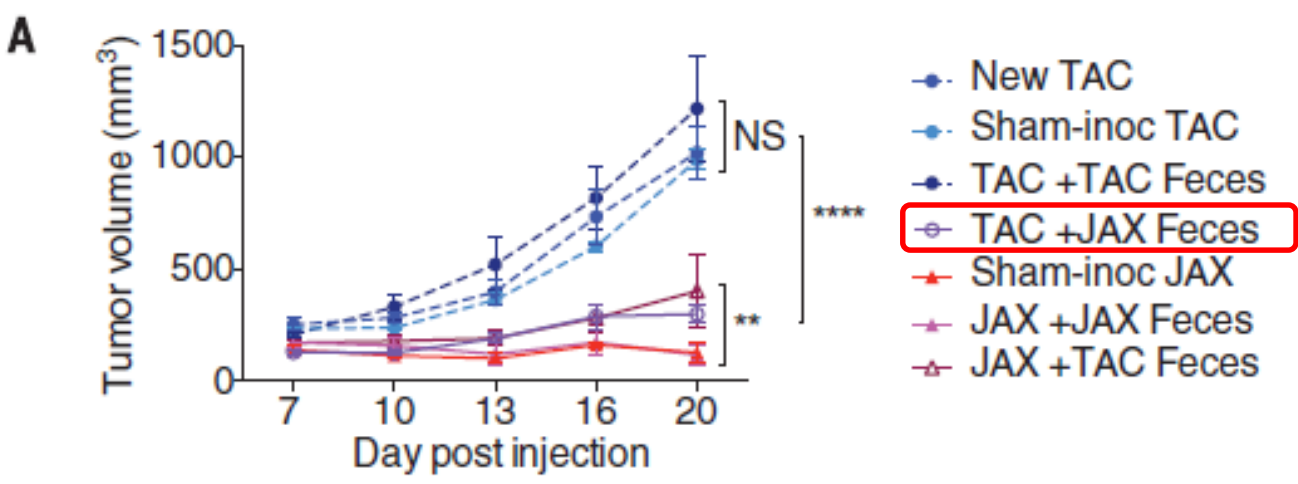
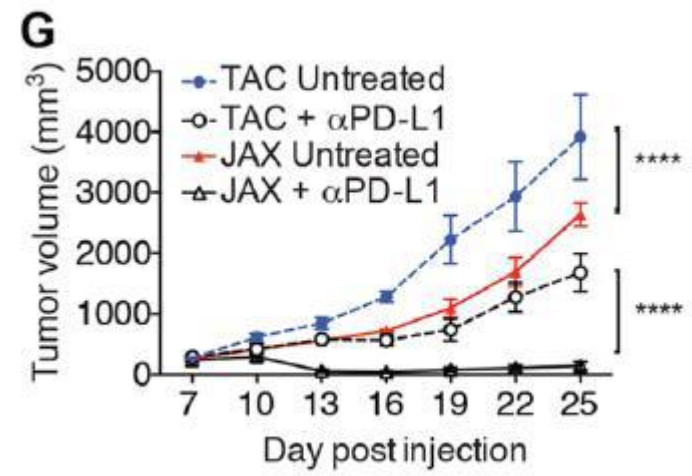
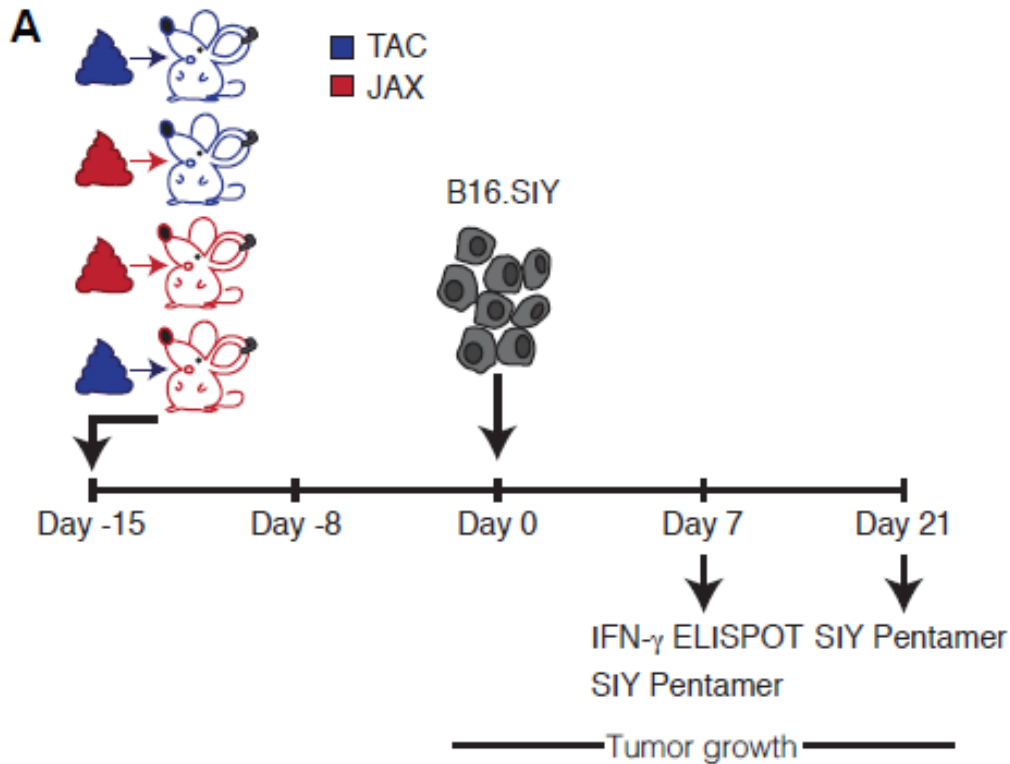
- genetically similar mouse
- differ in their commensal microbes (Ivanov et al., Cell, 2009)

Differences in melanoma outgrowth and tumor-specific immune responses

Cohoused for 3 weeks before tumor inoculation



Cohoused TAC and JAX mice appeared to acquire the **JAX phenotype**, which suggested that JAX mice may be colonized by **commensal microbes** that **dominantly facilitate antitumor immunity**

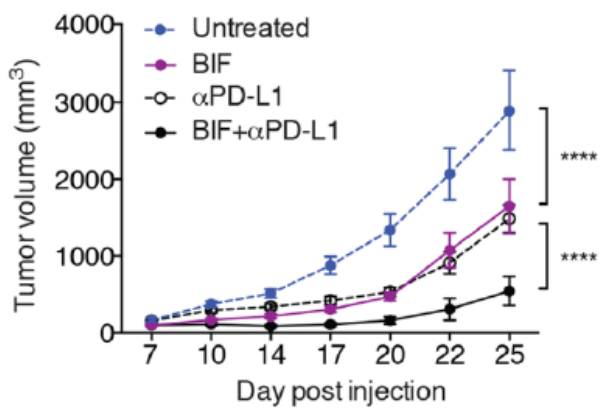


Specific bacteria associated with improved antitumor immune responses

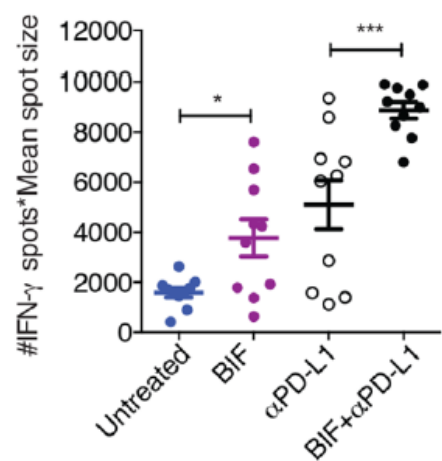
→ Fecal bacterial content analysis

Direct administration of **Bifidobacterium** to TAC recipients with established tumors improves tumor-specific immunity and response to α PD-L1 mAb therapy

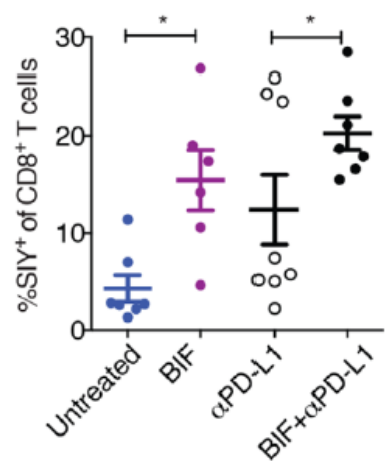
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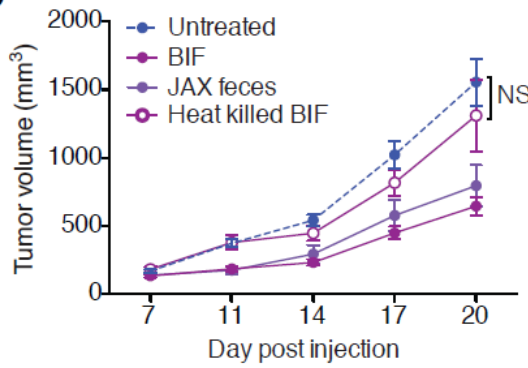
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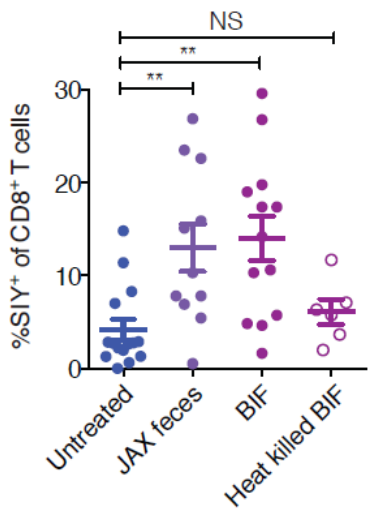
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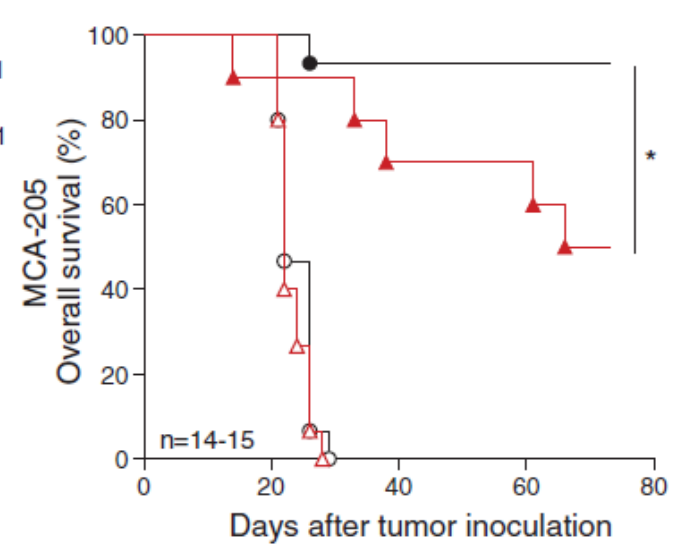
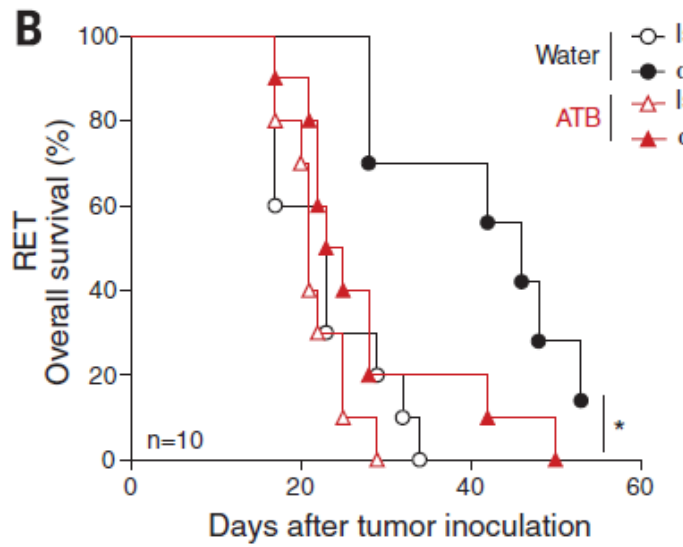
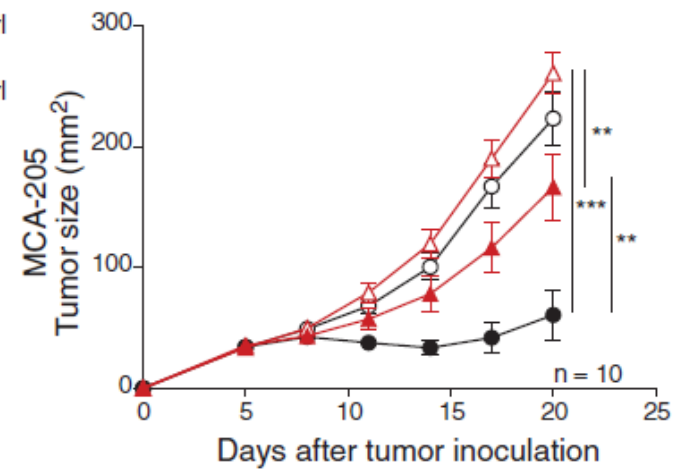
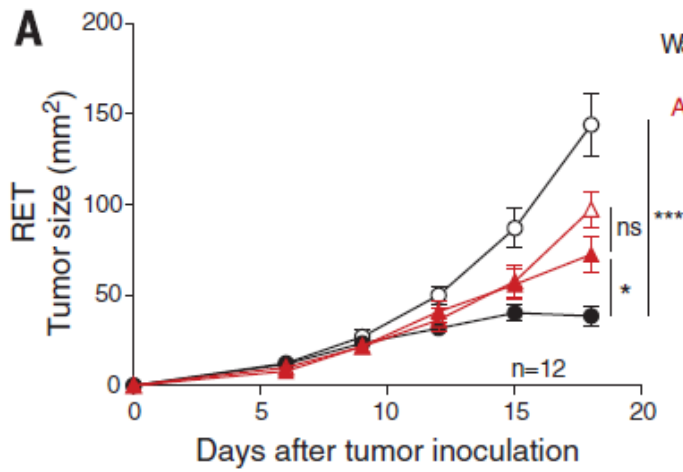
Heat inactivation

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

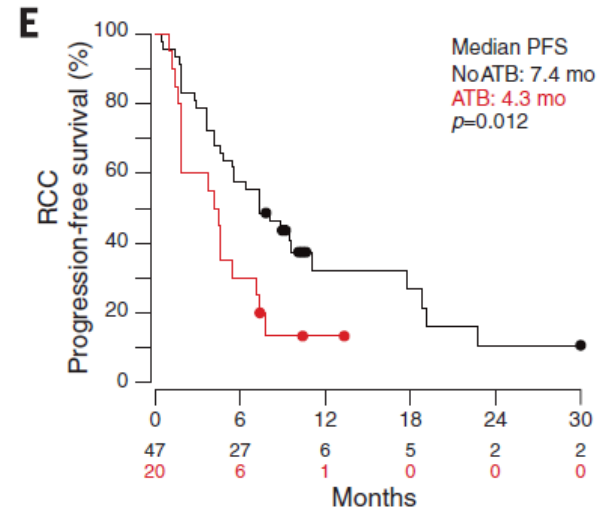
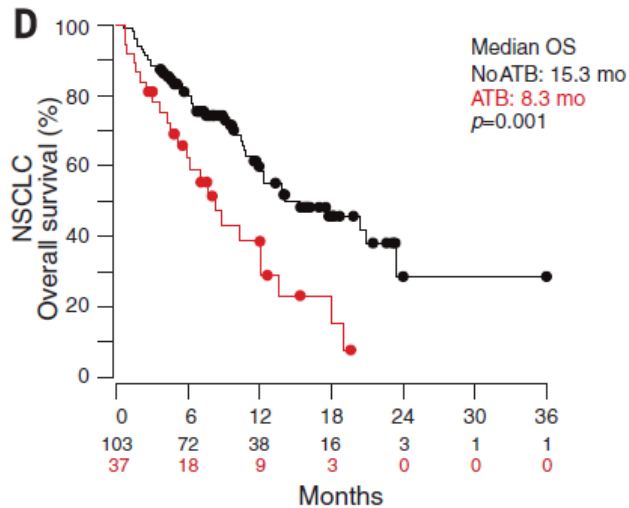
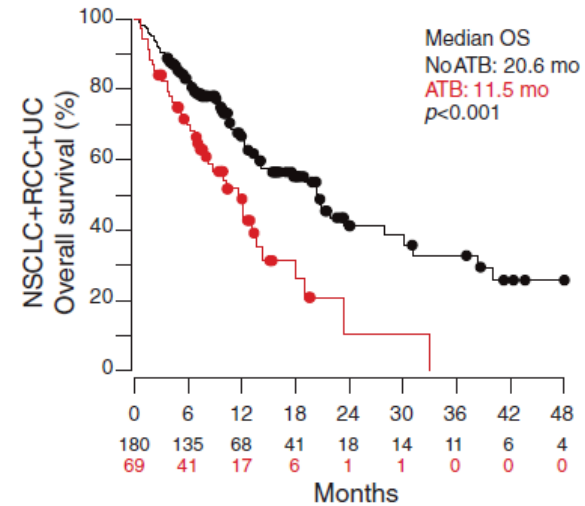
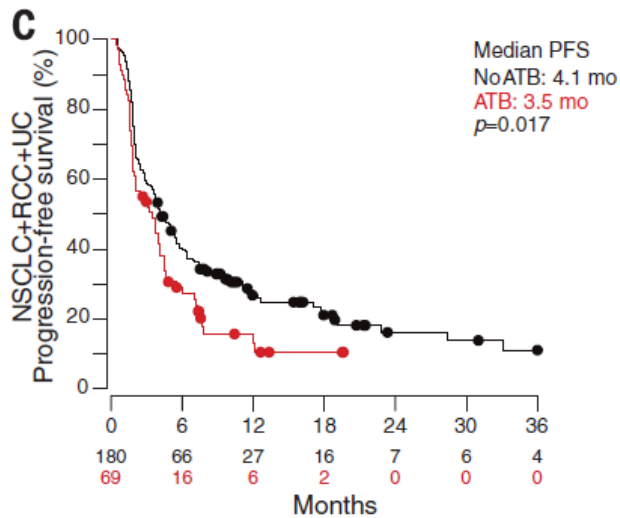
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Coureche Kaderbhai,¹⁶ Corentin Richard,¹⁶ Hira Rizvi,¹⁷ Florence Levenez,⁴
Nathalie Galleron,⁴ Benoit Quinquis,⁴ Nicolas Pons,⁴ Bernhard Ryffel,¹⁸
Véronique Minard-Colin,^{1,19} Patrick Gonin,^{1,20} Jean-Charles Soria,^{1,14} Eric Deutsch,^{1,13}
Yohann Loriot,^{1,3,14} François Ghiringhelli,¹⁶ Gérard Zalcman,¹⁵
François Goldwasser,^{9,21,22} Bernard Escudier,^{1,14,23} Matthew D. Hellmann,^{24,25}
Alexander Eggermont,^{1,2,14} Didier Raoult,²⁶ Laurence Albiges,^{1,3,14}
Guido Kroemer,^{8,9,10,11,12,27,28*} Laurence Zitvogel^{1,2,3,5*}

Routy *et al.*, *Science* **359**, 91–97 (2018) 5 January 2018

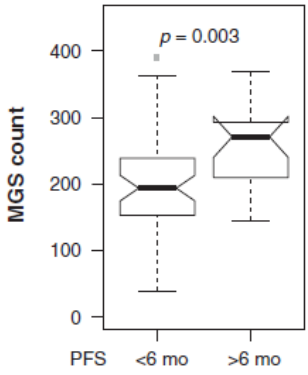
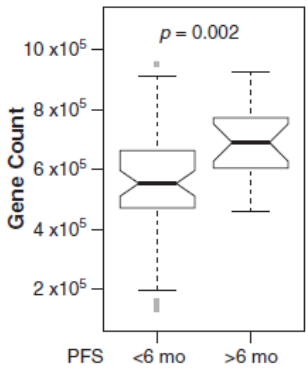
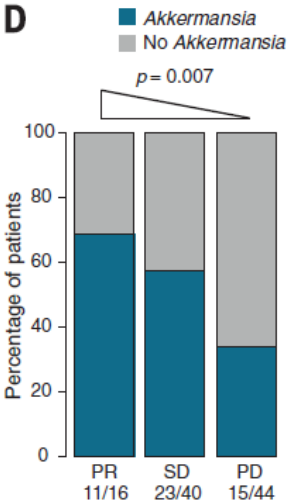
- √ Primary resistance to ICI – Abnormal gut microbiome (antibiotics)
- √ FMT from responder to ICI – ameliorated the antitumor effect of PD–1 blockade
- √ Akkermansia + FMT from nonresponder – restore the efficacy of PD–1 blockade



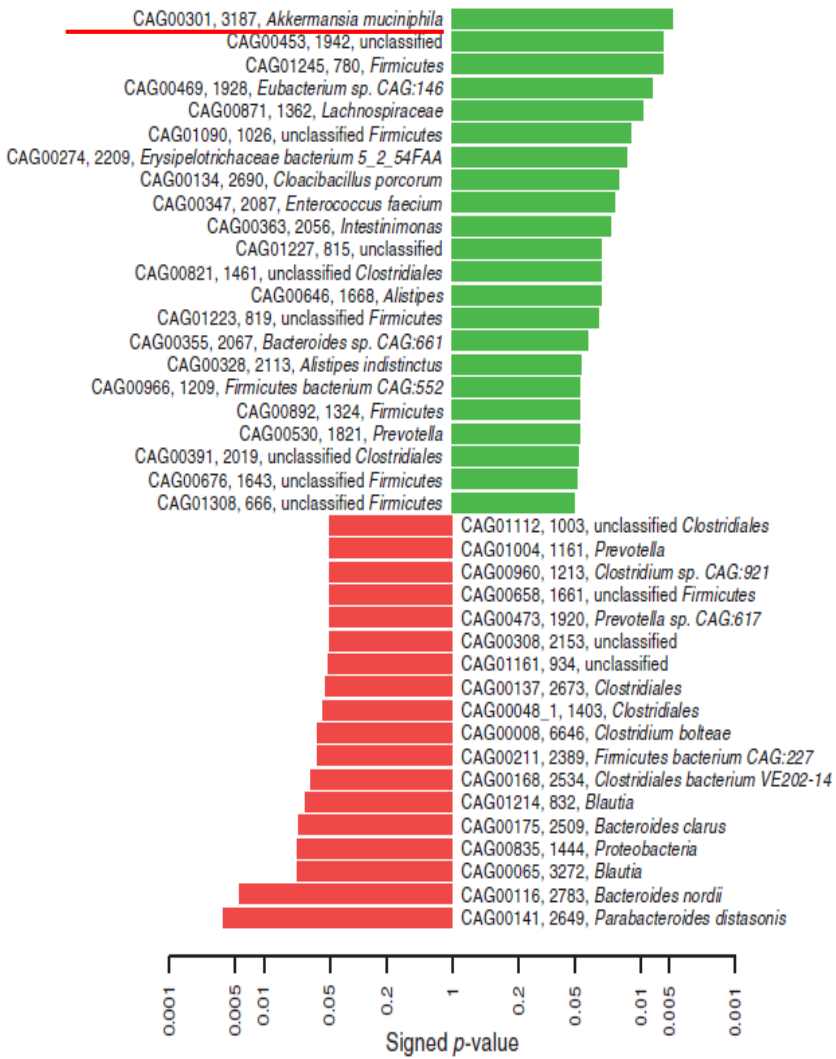
ATB - 2 weeks (ampicillin + colistin + streptomycin)



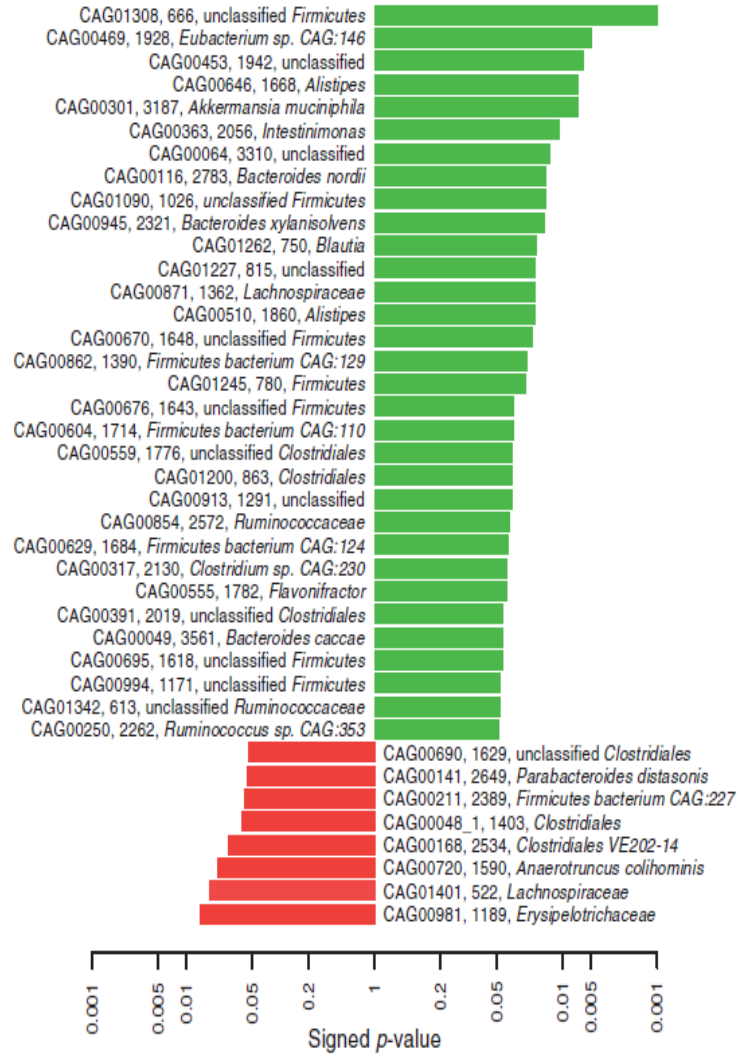
NSCLC (n=140), RCC (n=67), Urothelial carcinoma (n=42)
69(28%) – anti group
Dysbiosis might affect the therapeutic efficacy of ICIs ?

A**D****B**

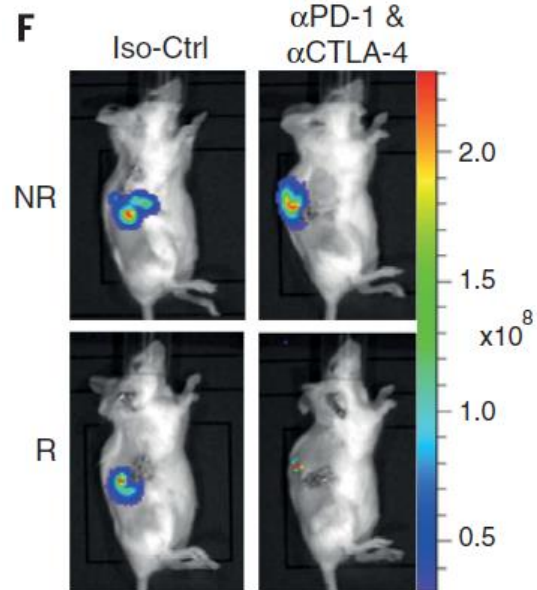
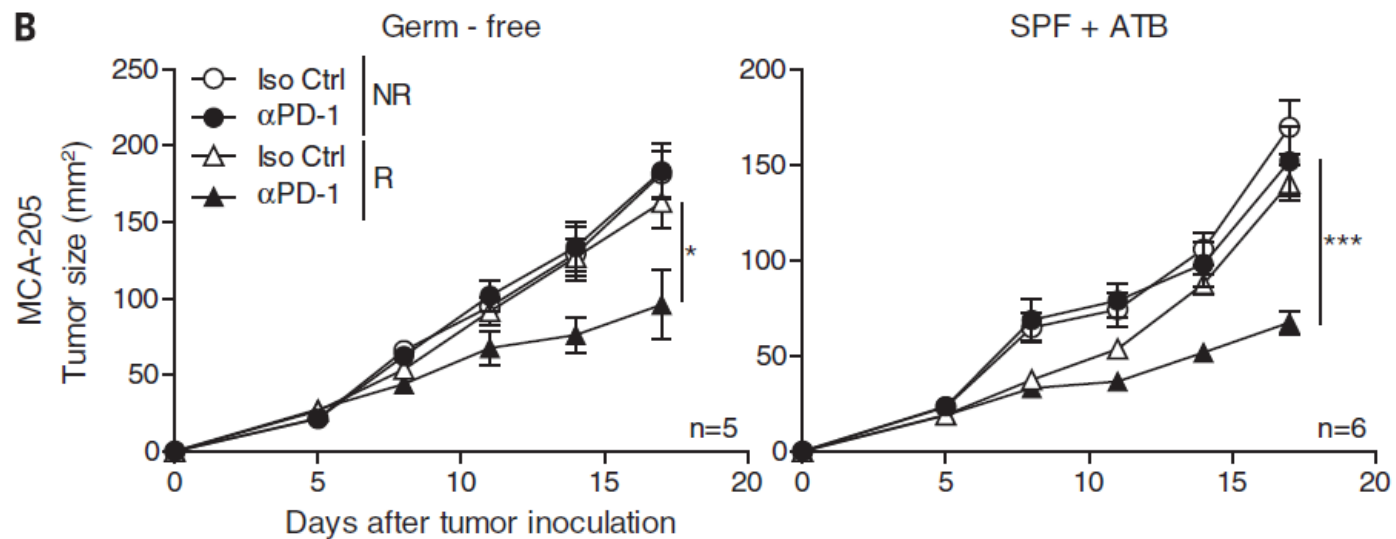
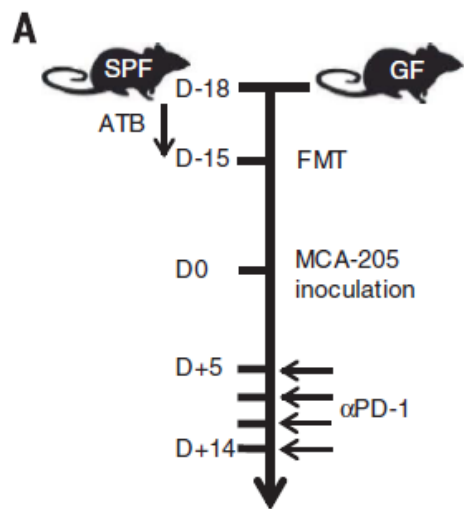
■ Enriched in R: Objective response (PR and SD)
■ Enriched in NR: Objective response (PD or death)

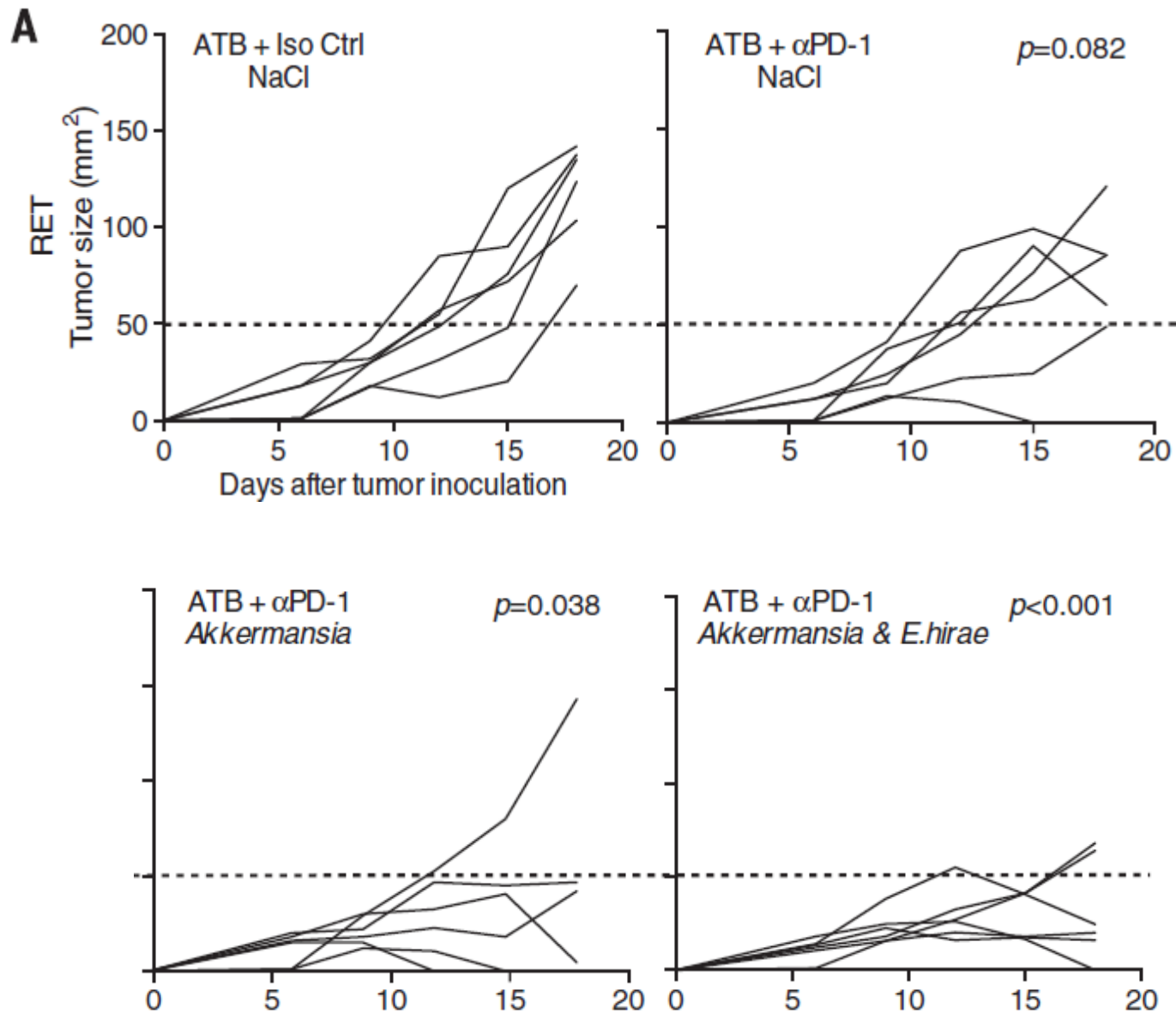
**C**

■ Enriched in patients PFS >3 mo
■ Enriched in patients PFS <3 mo

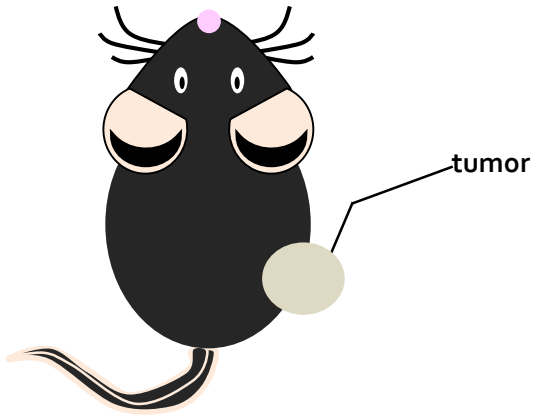


NSCLC (n=60), RCC (n=40)





IL12 및 B7 유전자치료와 Microbiome을 immuno-microbial therapy



C57BL/6

Cell : B16-F10 (melanoma cell line)

Bifidobacterium

YKL-IL12/mB7-1

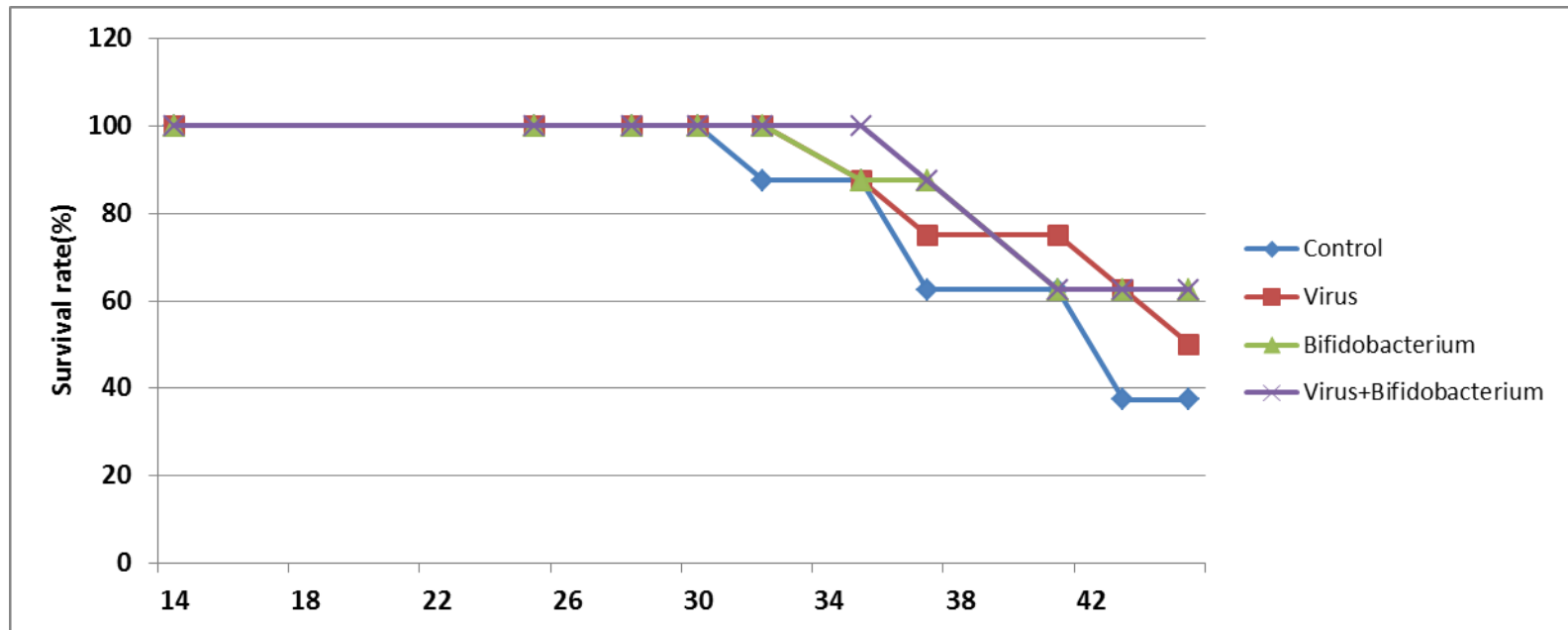
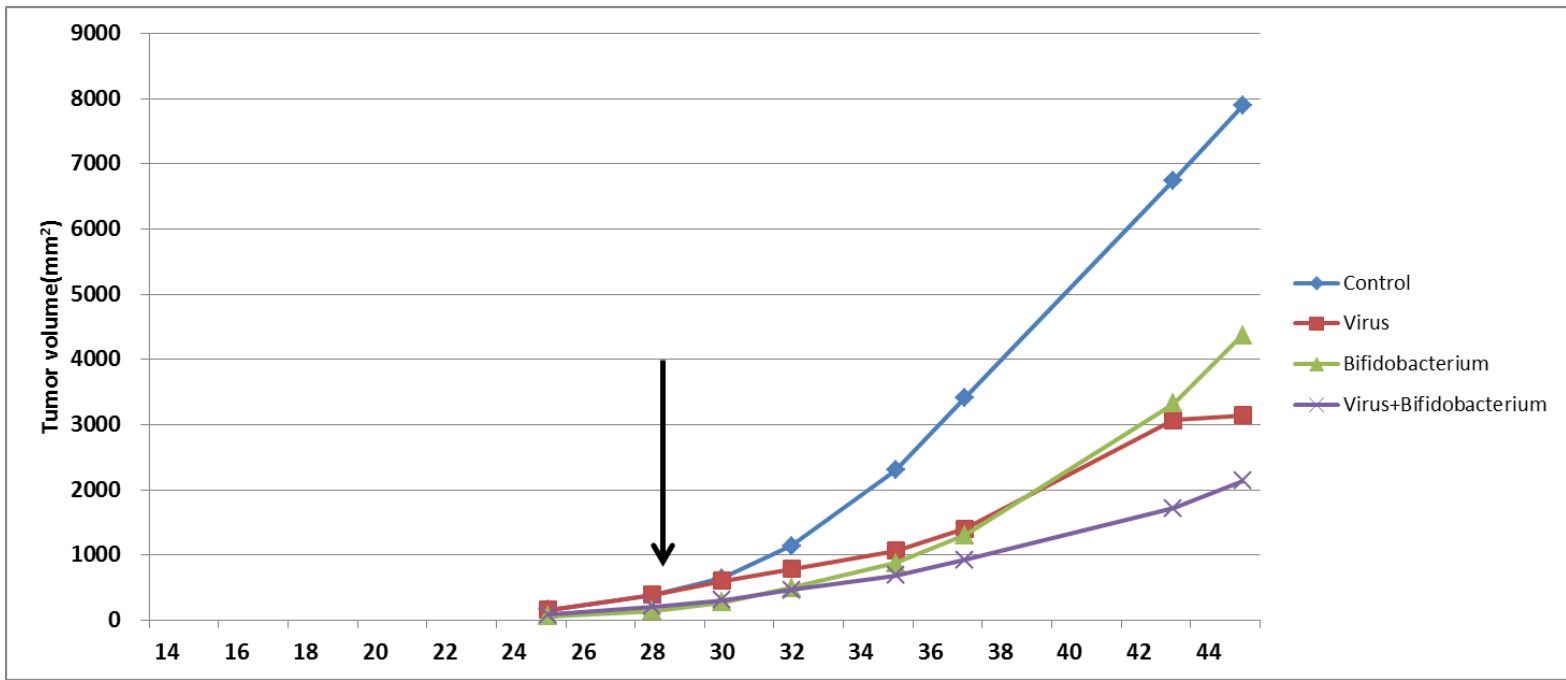
Group (n=10)

control

virus

Bifodobacterium

Bifi + virus





Control



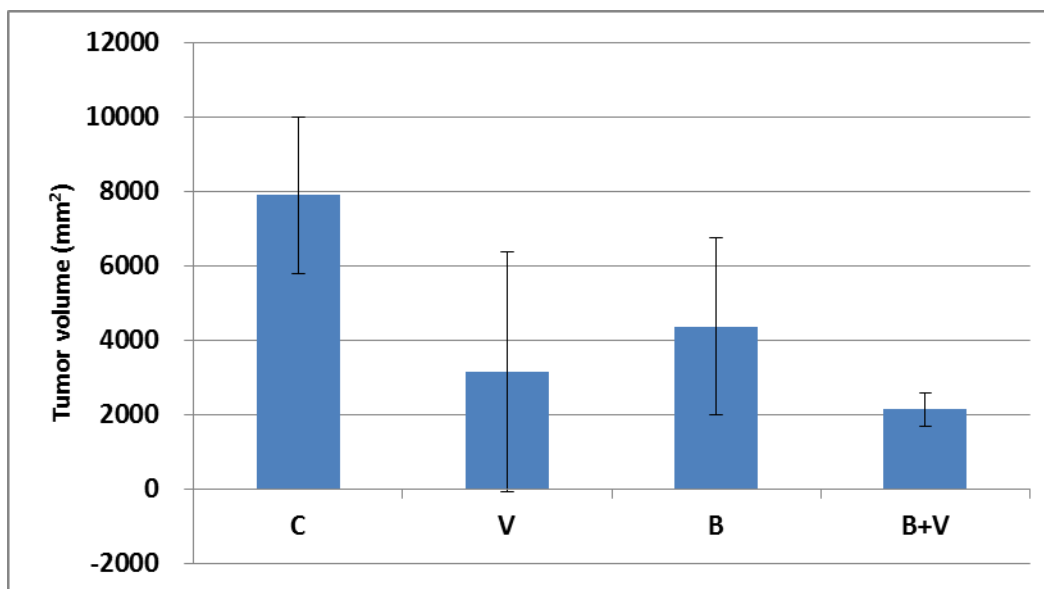
Virus



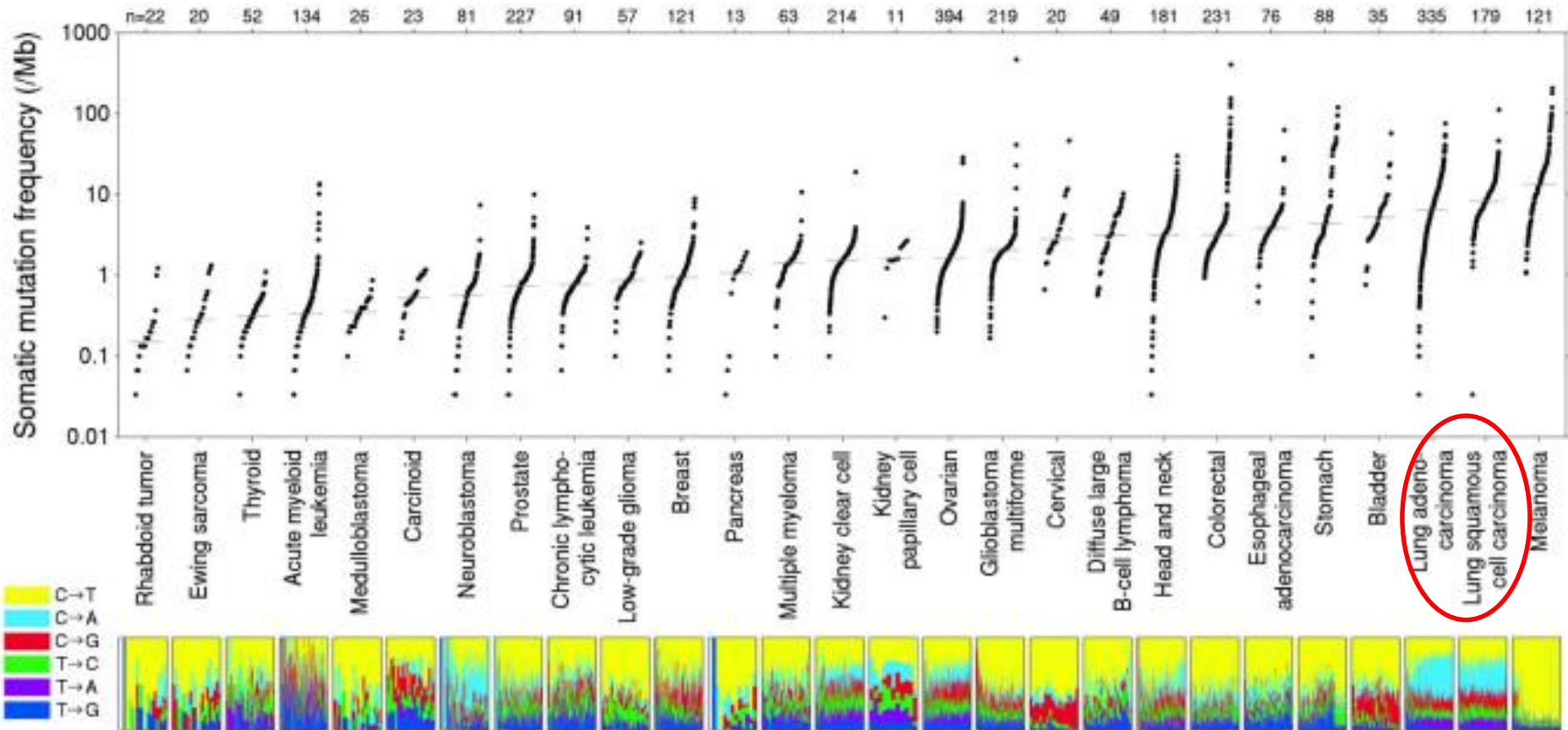
Bifidobacterium



**Bifidobacterium
+Virus**



44Day



Lawrence et al. Nature. 2013 July 11; 499(7457): 214–218

Human epigenetics and microbiome: the potential for a revolution in both research areas by integrative studies

It makes perfect sense that the host-associated **microbiome** may be the ultimate environmental trigger for **epigenetic processes**, because of its spatial location and ability to convert environmental and diet-derived compounds before they reach human cells.



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University of Arkansas, Fayetteville, USA
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Tel.: +1 479 575 6822
fgcarbon@uark.edu

연구계획

1. Lung cancer 환자에서 PD-L1 level 에 따른 microbiome 의 차이
2. Lung cancer 에서의 Immunotherapy 와 microbiome therapy 의 combination

Thank you