Προγράμματος Μεταπτυχιακών Σπουδών «Λοιμωξιολογία»
Αθήνα, 16 Μαρτίου 2021

# Μικροβιακή Χλωρίδα, από την Συμβίωση στην Παθογένεια

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Ιατρικό Τμήμα Δ.Π.Θ.

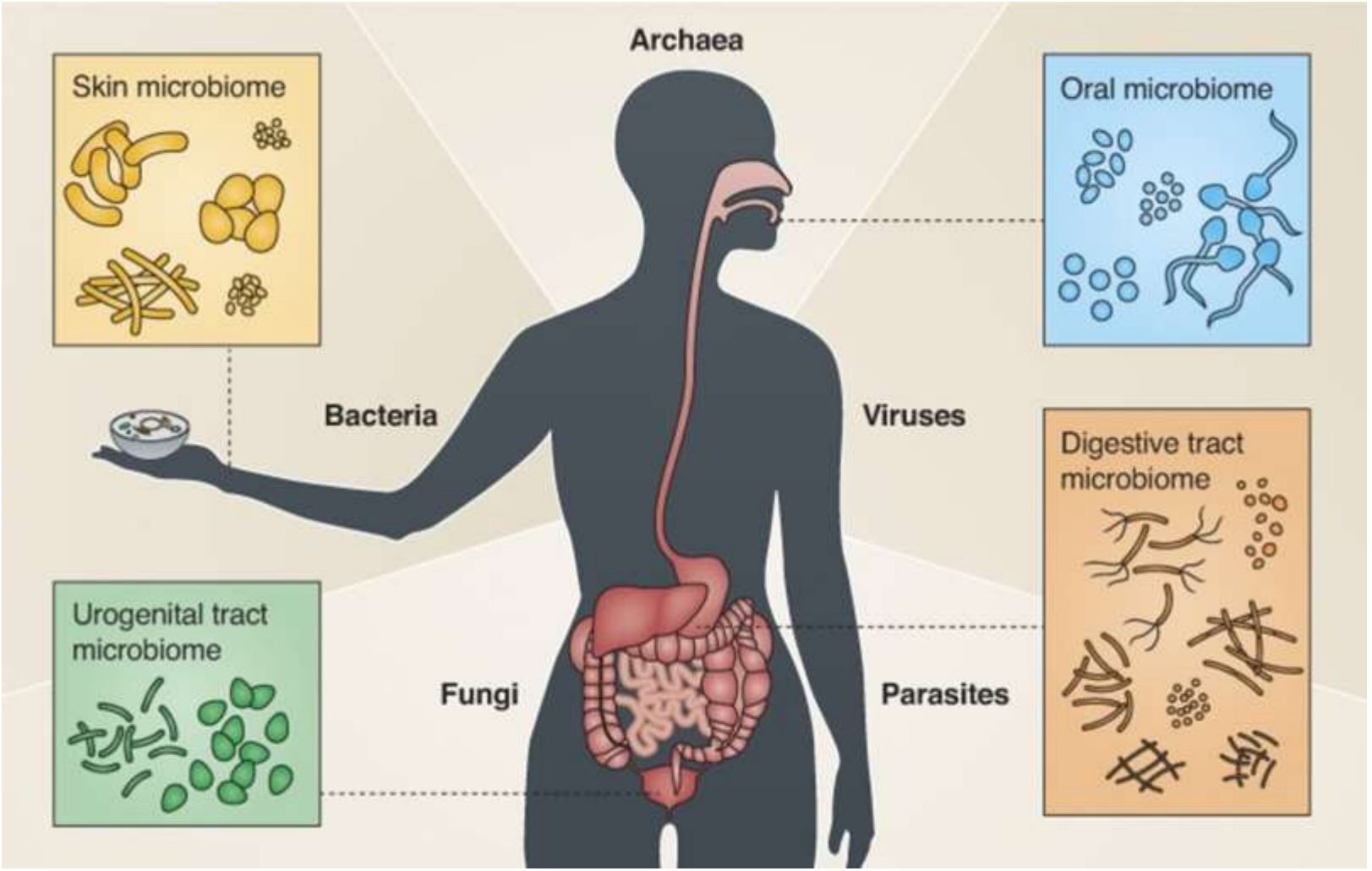
# Μικροβιακή χλωρίδα
# vs
# Μικροβίωμα

# Μικροβίωμα

- Το σύνολο του γενετικού υλικού (DNA) των μικροοργανισμών αποτελεί το **Μικροβίωμα**

- Όπως το σύνολο του γενετικού υλικού των κυττάρων μας αποτελεί το **Γονιδίωμα** μας

# Μικροβιακή Χλωρίδα



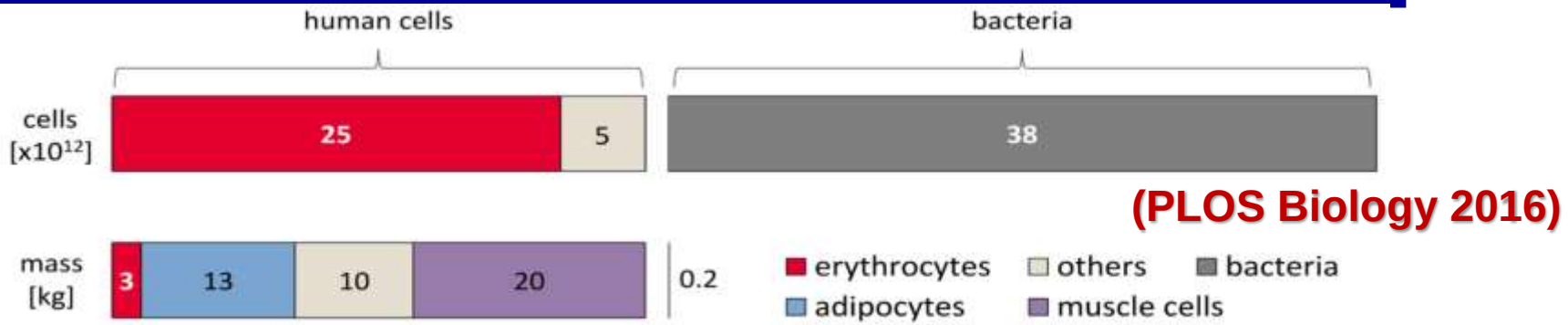

(Wendy S. Garrett. J Cell Biol. 2015;210:919-920)

# Μικροβιακή Χλωρίδα

- $10^{12}$ βακτήρια του σώματός μας (3% του σωματικού βάρους) > 10 Χ $10^{11}$ ανθρώπεια κύτταρα
- Βακτηριδιακά γονίδια (3,000,000) >100 Χ ανθρώπεια γονίδια (23,000) **(Costello et al Science. 2009)**

…more recent research estimates that to 3:1…

Nature 2016

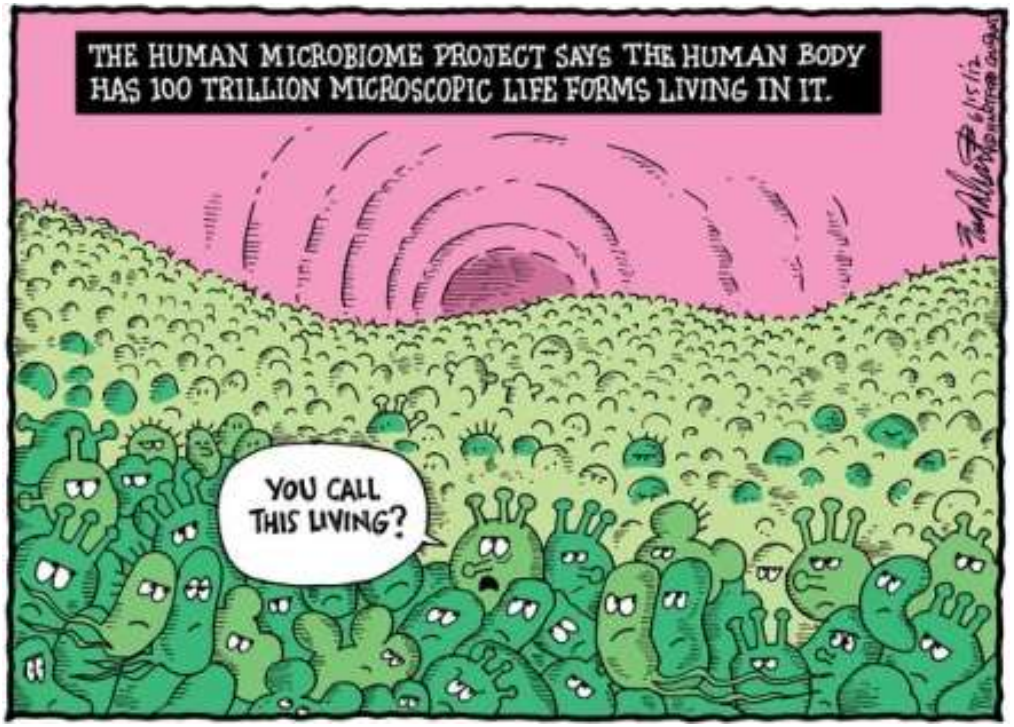



**(PLOS Biology 2016)**

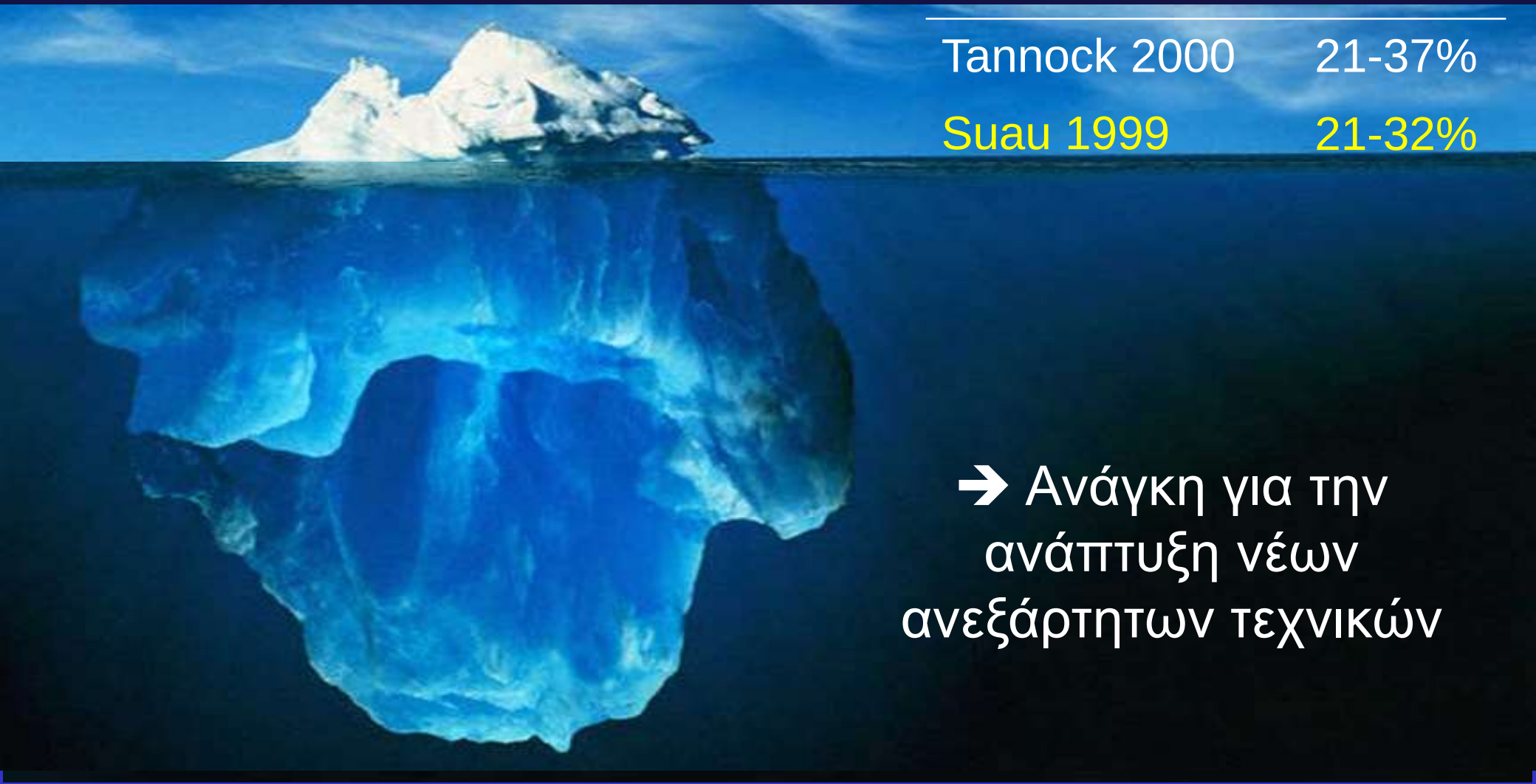
**Fig 3. Distribution of cell number and mass for different cell types in the human body (for a 70 kg adult man).** The upper bar displays the

# Μικροβιακή Χλωρίδα

- Υπάρχουν 100 τρισεκατομμύρια μικροοργανισμοί στο σώμα του ανθρώπου… 10 φορές περισσότερα από ανθρώπινα κύτταρα…..

# 70% των μικροοργανισμών της χλωρίδας μας παραμένουν “μη καλλιεργήσιμα”



| | cultivated fraction |
|---|---|
| Tannock 2000 | 21-37% |
| Suau 1999 | 21-32% |

➔ Ανάγκη για την ανάπτυξη νέων ανεξάρτητων τεχνικών

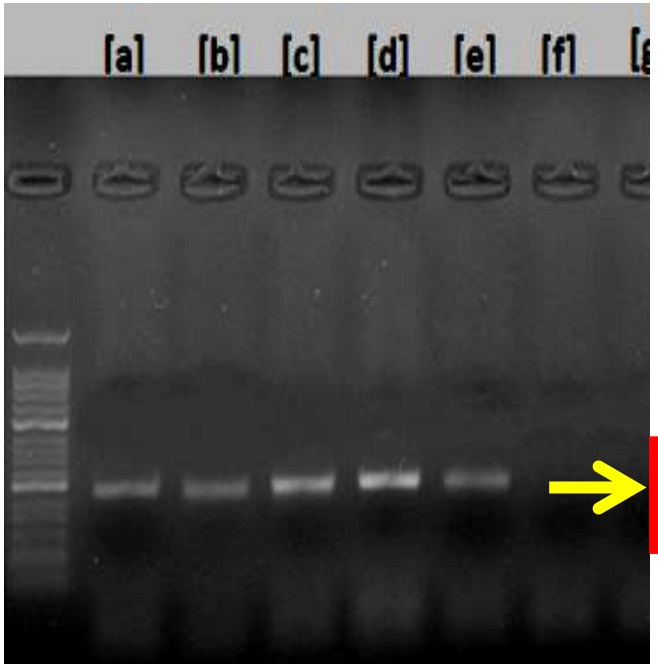
# Ανίχνευση μικροβιώματος

- Σήμερα η ανάπτυξη των τεχνικών της Μοριακής Ιατρικής μας δίνει την δυνατότητα να ξεπεράσουμε τα προβλήματα των καλλιεργειών.

- Όμως ακόμη η μη ταυτοποίηση του μικροβιώματος όλων των μικροοργανισμών παραμένει ένα μεγάλο ζήτημα.

# Ενίσχυση βακτηριδιακού DNA

- **Τιτλοδότηση (διαδοχικές**
- **αραιώσεις DNA κοπράνων)**




[a]: 164 ng/μl

[b]: 1.64 ng/μl

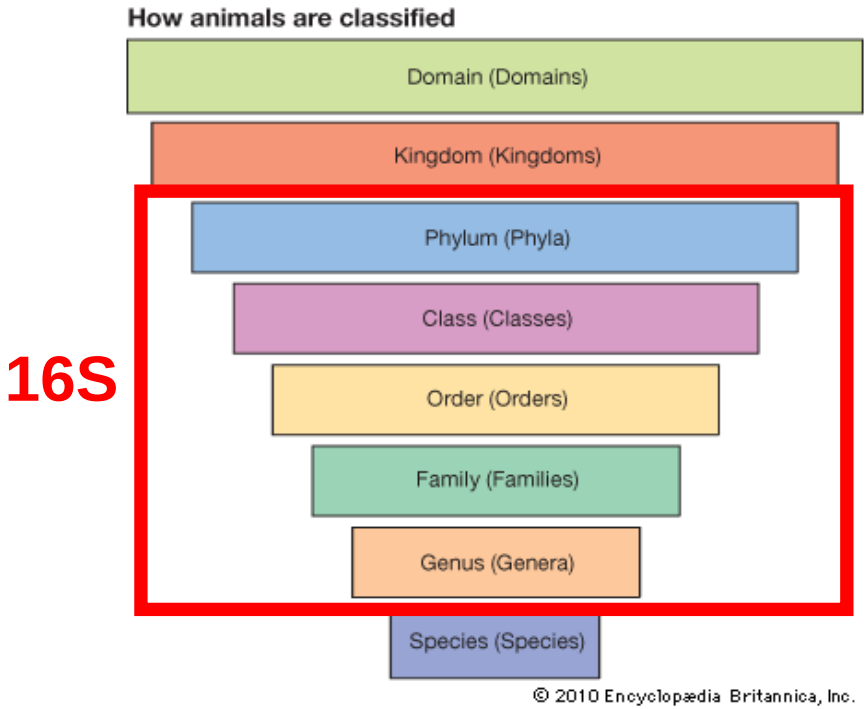
[c]: 164 pg/μl

[d]: 16,4 pg/μl

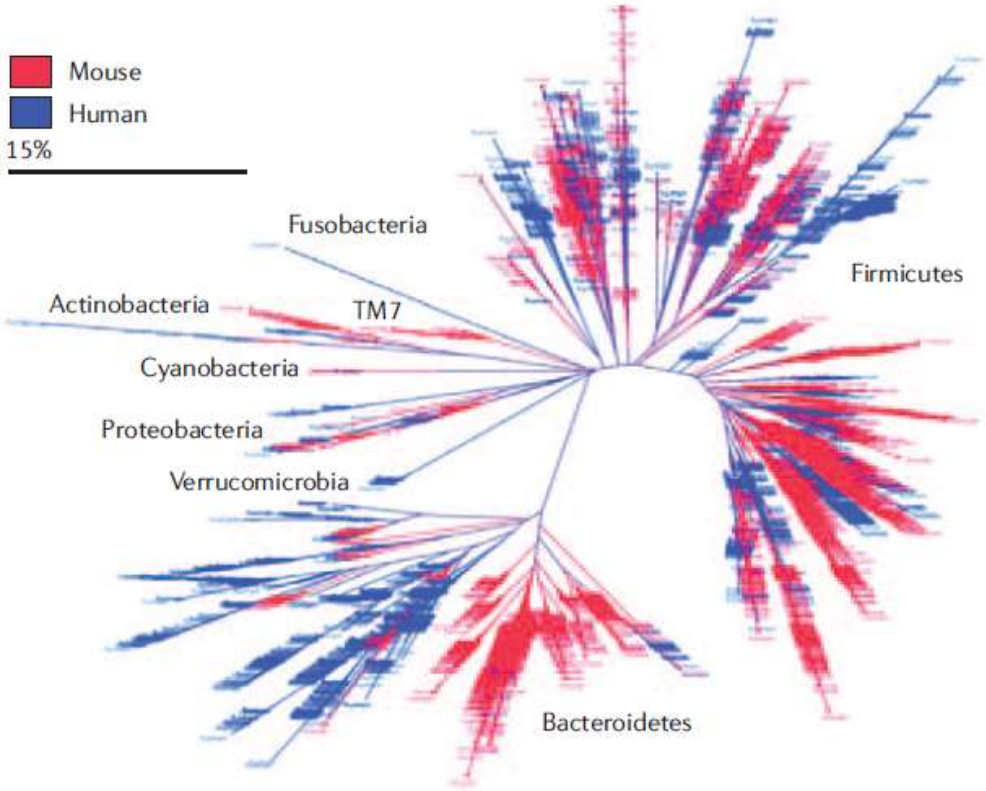
[e]: 1,64 pg/μl

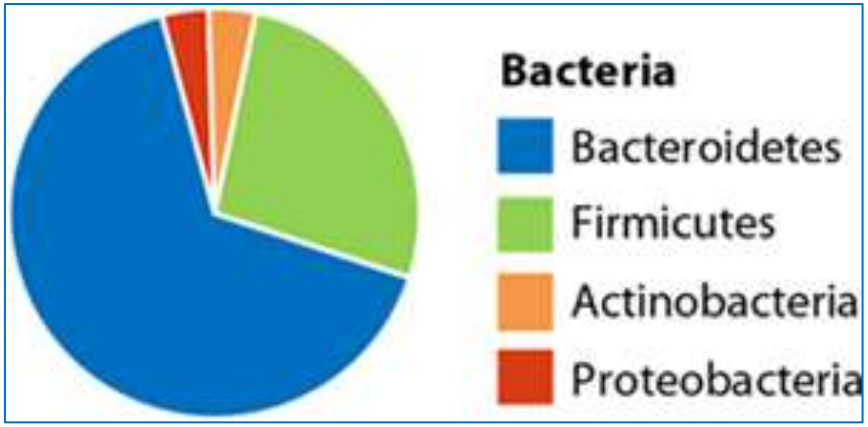
[f]: 164 fg/μl

- Και με τις πρόσφατες μεθόδους **γονοτύπησης του γονιδίου 16S** (μικρή ριβοσωμική υπομονάδα), φτάνουμε μέχρι διακριτικής ικανότητας ταυτοποίησης του γένους, αλλά όχι του είδους.
- Και αν θέλουμε μεγαλύτερη ανάλυση, μπορούμε να γονοτυπήσουμε όλο το μικροβιακό γενετικό υλικό με **shotgun sequencing.**



# Η σύνθεση του «φυσιολογικού» ανθρώπινου εντερικού μικροβιώματος




**Παθοβιωτικά (pathobionts)**

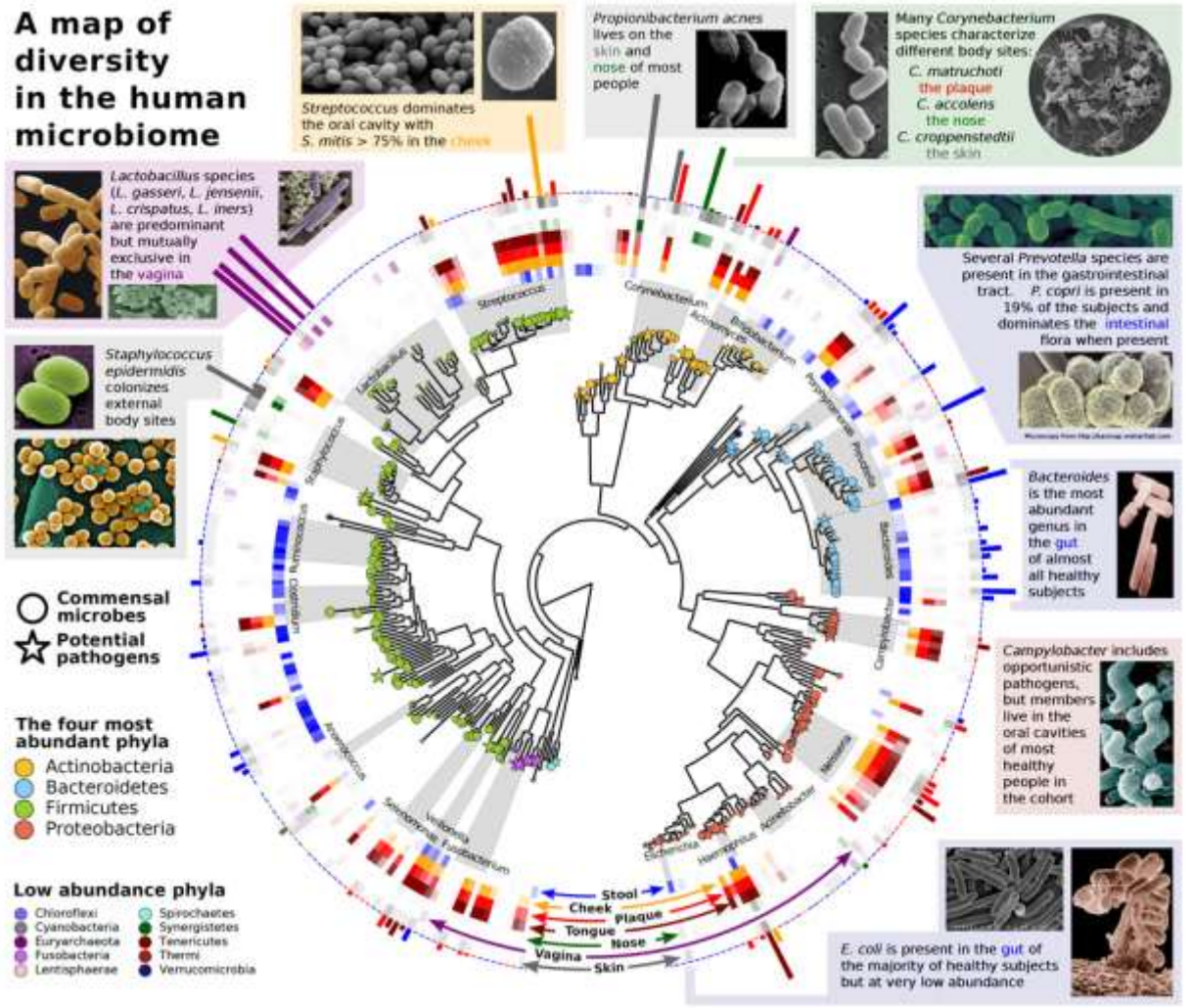
- Proteobacteria
- Actinobacteria

**Συμβιωτικά - αντιφλεγμονώδη**

- Firmicutes
- Bacteriodetes

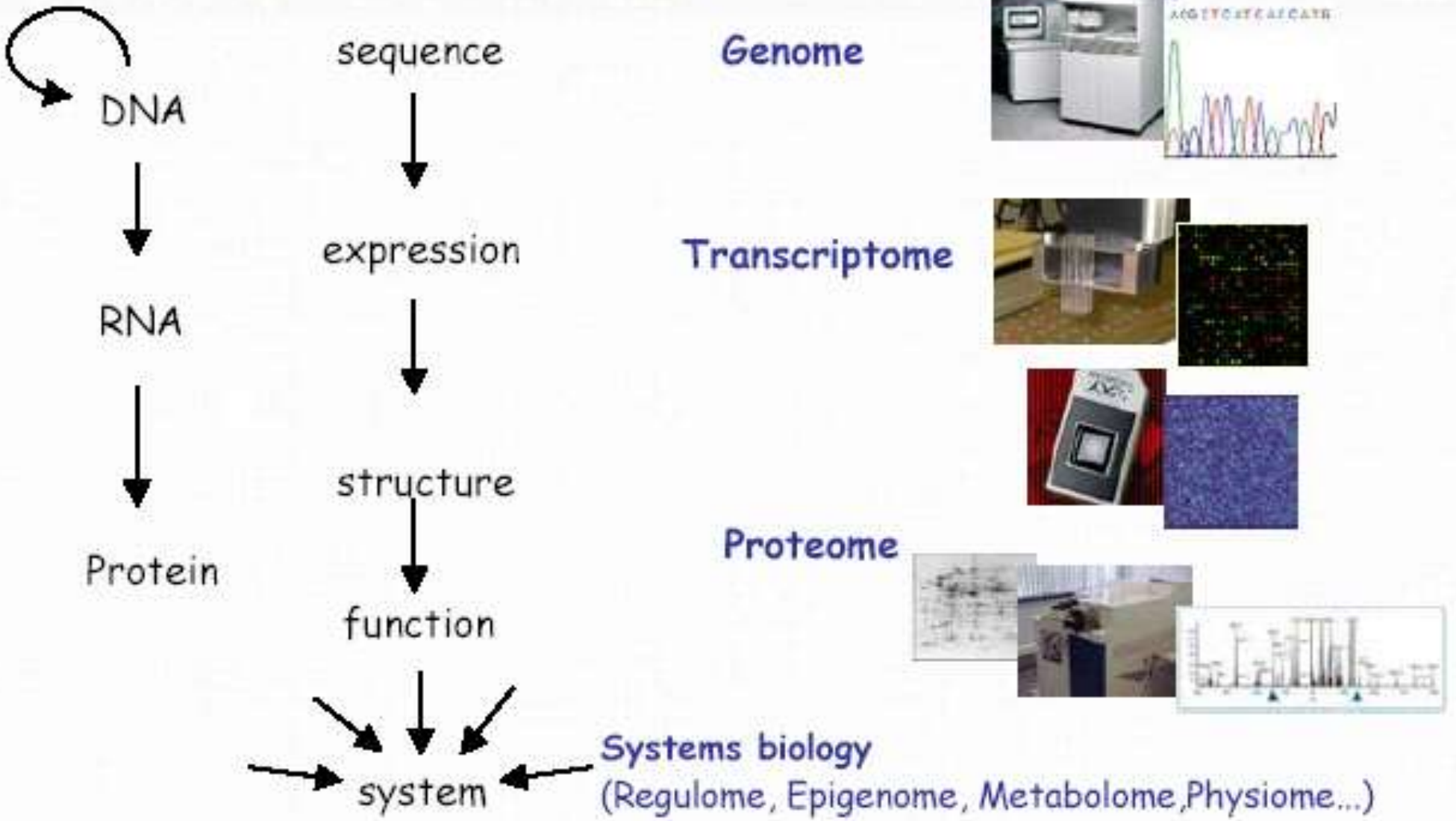
# Βιοπληροφορική

- Το **QIIME** είναι η gold standard πλατφόρμα ανάλυσης.
- Το **Calypso** είναι πιο πρόσφατη online πλατφόρμα.
- Το **STAMP** είναι software ανάλυσης.
- Το **PICRUSt** (*Phylogenetic Investigation of Comm by Reconstruction* of Unobserved States).



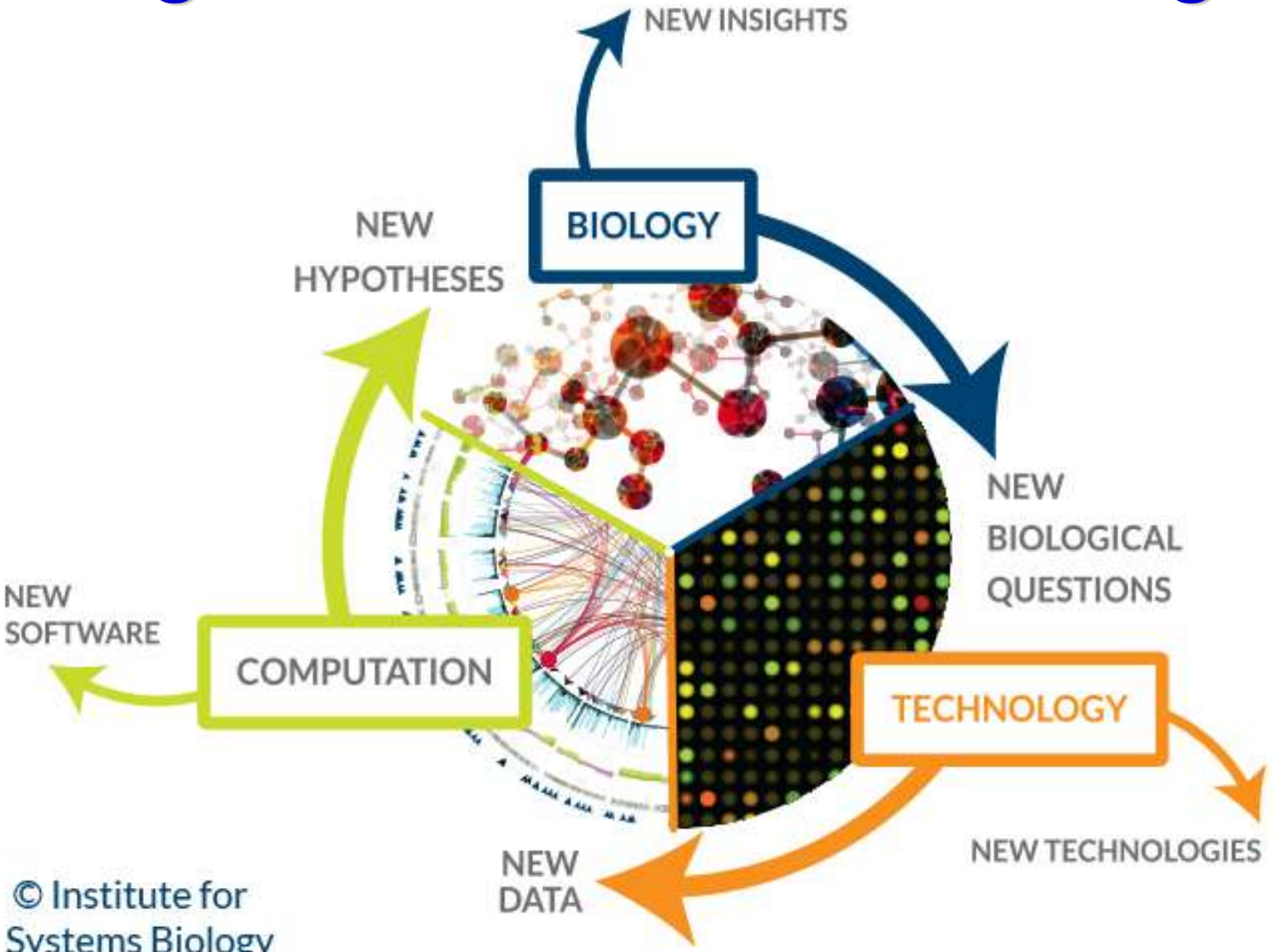

**(Morgan, et al. Trends Genet. 2013)**

# Biology as Information Science: in Large Scale!



# Bioinformatics:

## Transforming bio-information to knowledge



Journal of *Personalized Medicine*

MDPI

*Commentary*

# Personomics: The Missing Link in the Evolution from Precision Medicine to Personalized Medicine

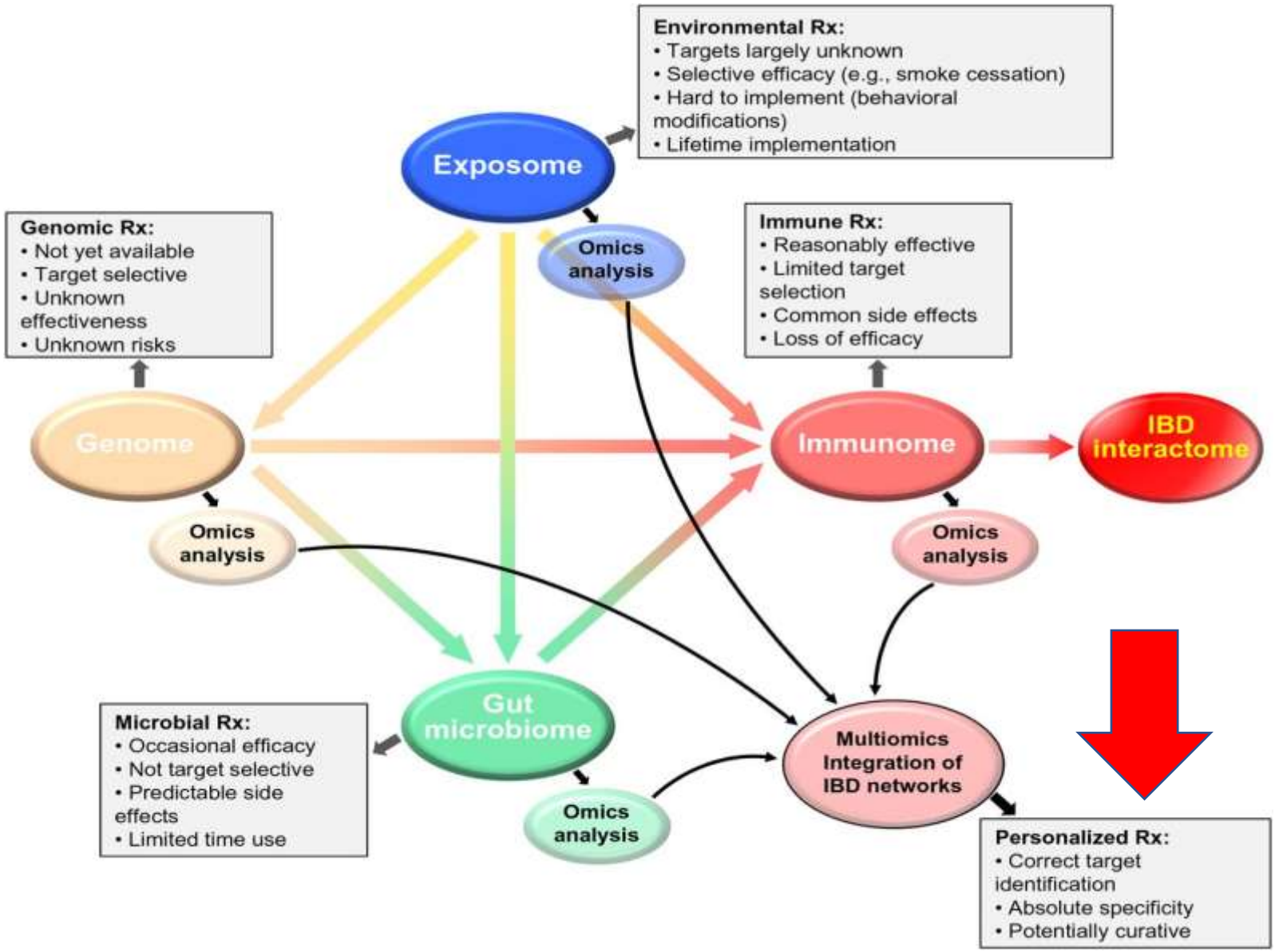
**Roy C. Ziegelstein**

Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; rziegel2@jhmi.edu;
Tel.: +1 410-955-8401

derived from knowing the patient as a person. These unique personal characteristics are defined by the tools of personalized medicine—personomics—which take into account an individual's personality, preferences, values, goals, health beliefs, social support network, financial resources, and unique life circumstances that affect how and when a given health condition will manifest in that person and how that condition will respond to treatment. In this paradigm, precision medicine may be considered a necessary step in the evolution of medical care to personalized medicine, with personomics as the missing link.

**(J. Pers. Med. 2017)**

# The concept of the IBD interactome



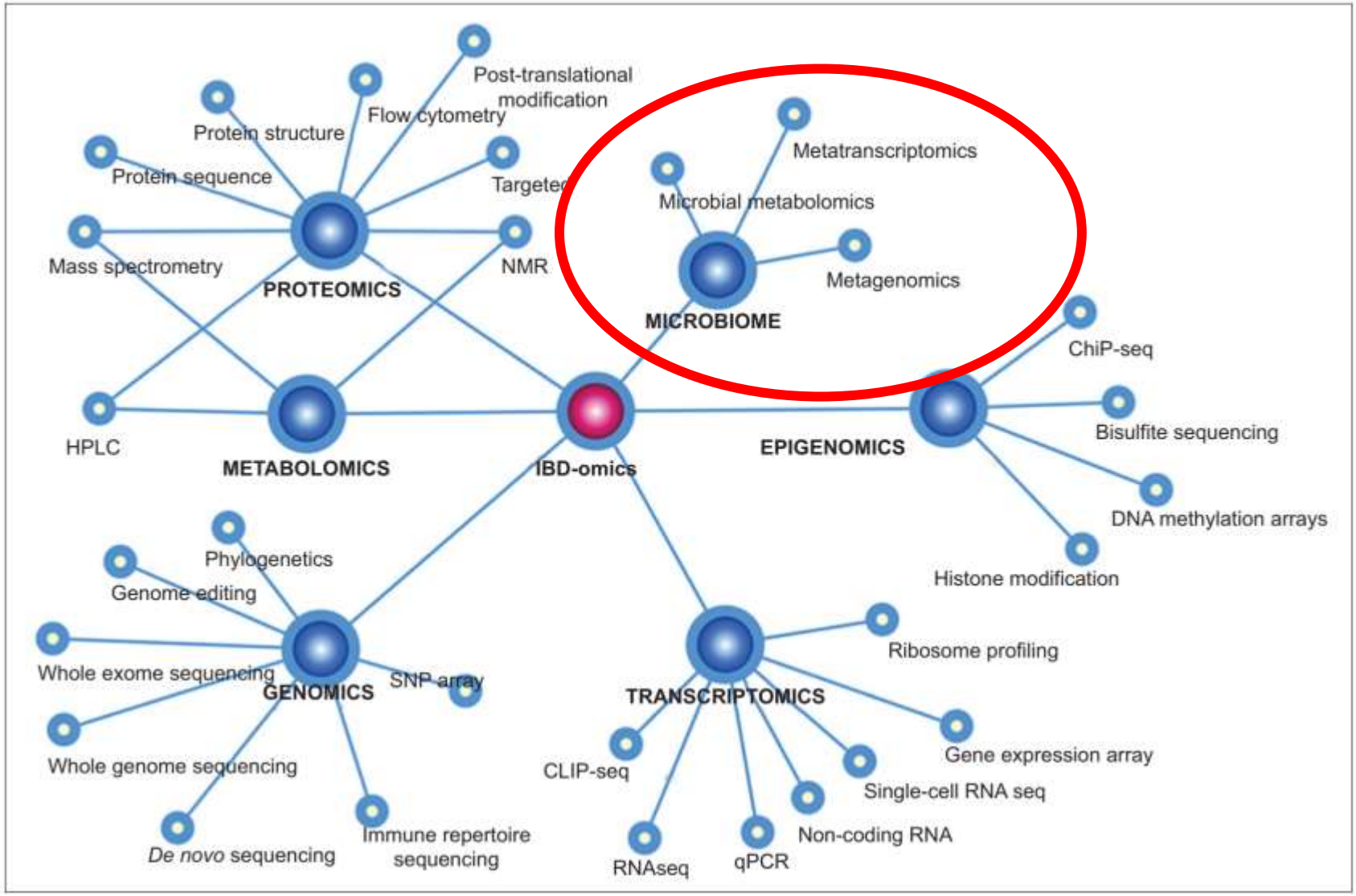

(Danese et al. *Gut* 2016)

# Systems biology in inflammatory bowel diseases: on the way to precision medicine

**(Annals of Gastroenterology 2019)**

**Nikolas Dovrolis, Eirini Filidou, George Kolios**

Democritus University of Thrace, Alexandroupolis, Greece



# Εντερική χλωρίδα του ανθρώπου

# GUT MICROBIOTA

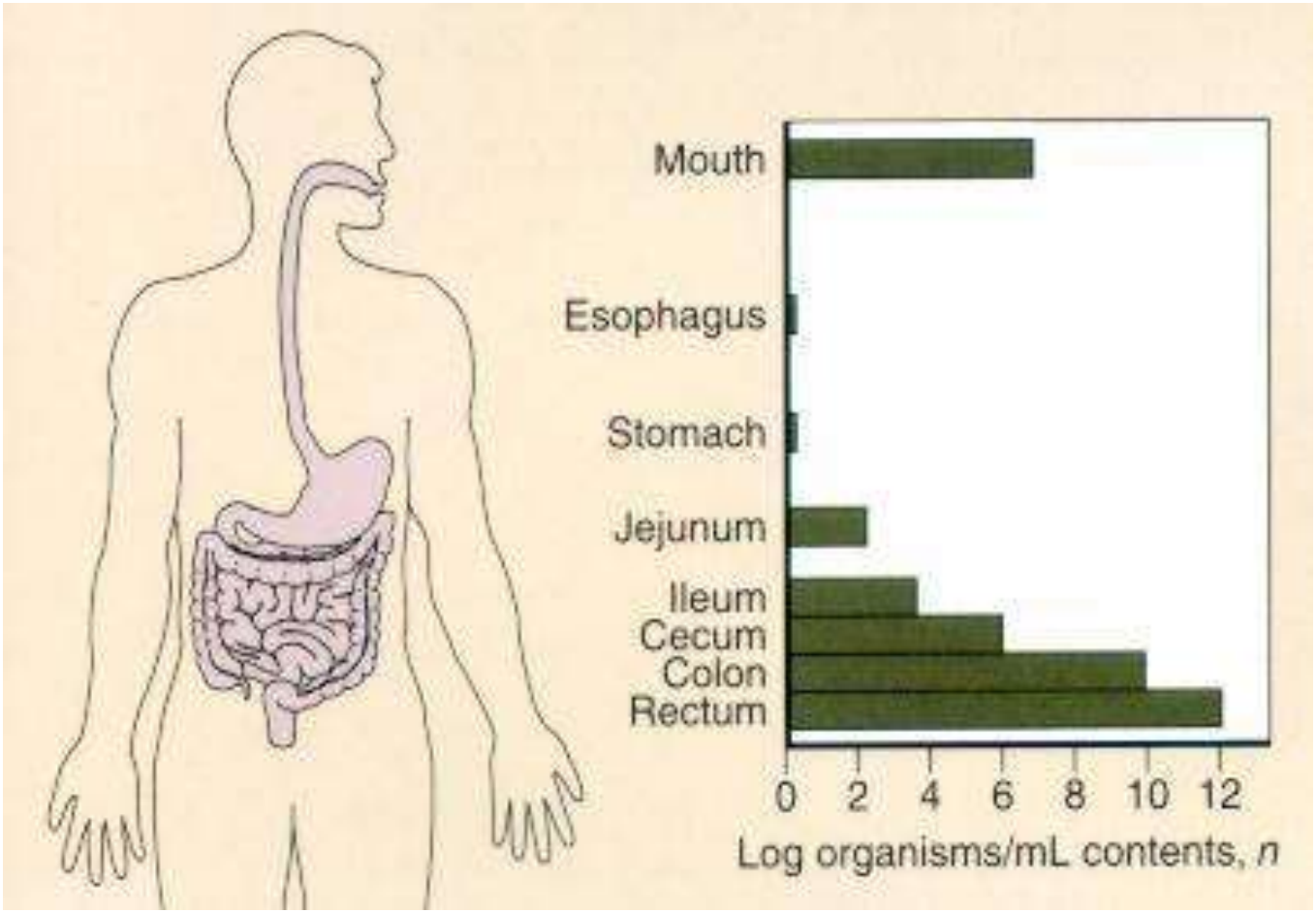
A huge quantity (hundreds of trillions) of bacteria and other microorganisms inhabit your intestines; they are key for your health and wellbeing.

The gastrointestinal TRACT SURFACE is as big as 2 TENNIS COURTS 400m²

95% of your bacteria is located in the GASTROINTESTINAL TRACT

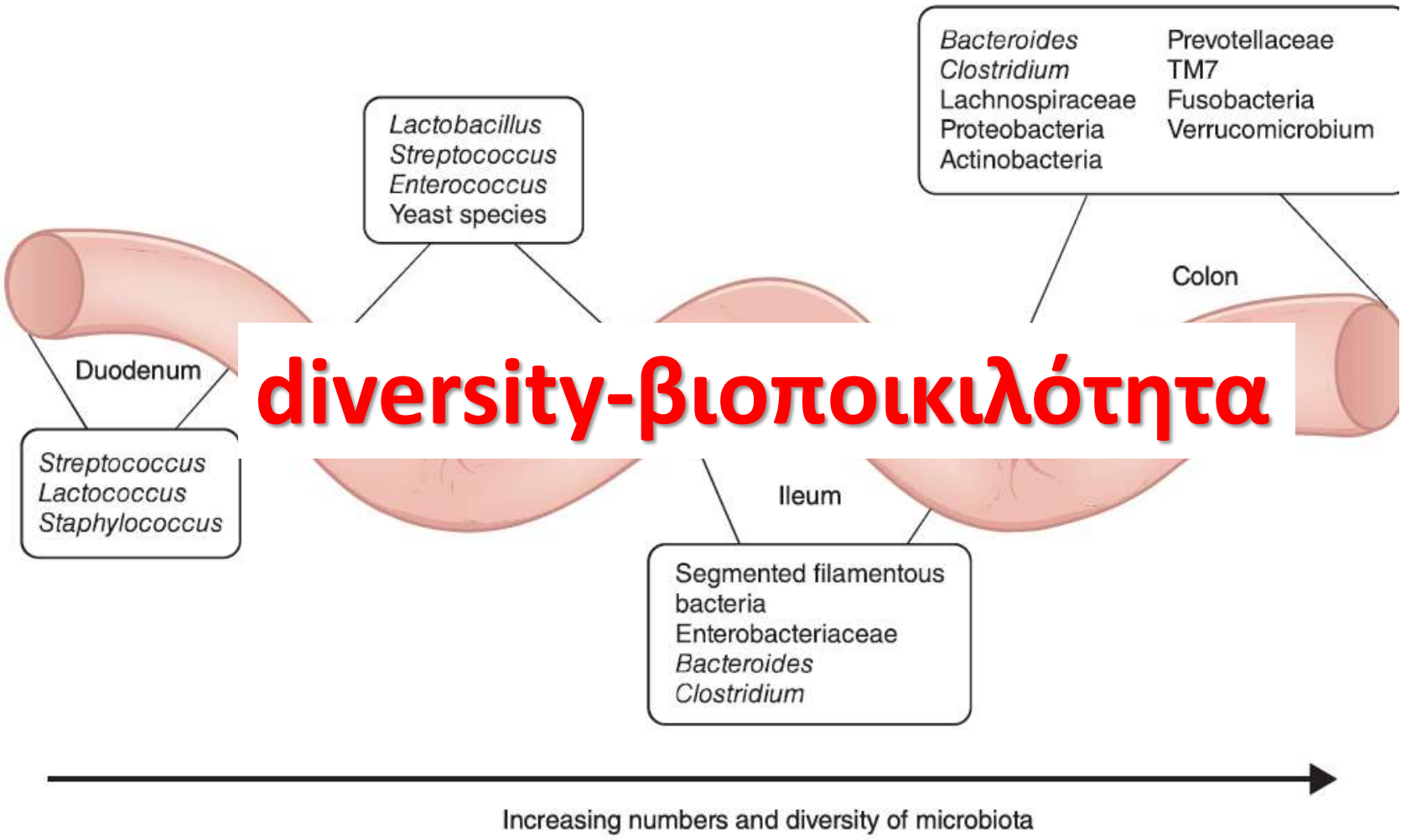
Gut microbiota´s WEIGHT can reach up to 1 to 2 Kg

# Φυσιολογική χλωρίδα του πεπτικού σωλήνα




(Laissue & Gebbers. *Curr Stud Hematol Blood Transfus* 1992)

# Φυσιολογική χλωρίδα του πεπτικού σωλήνα



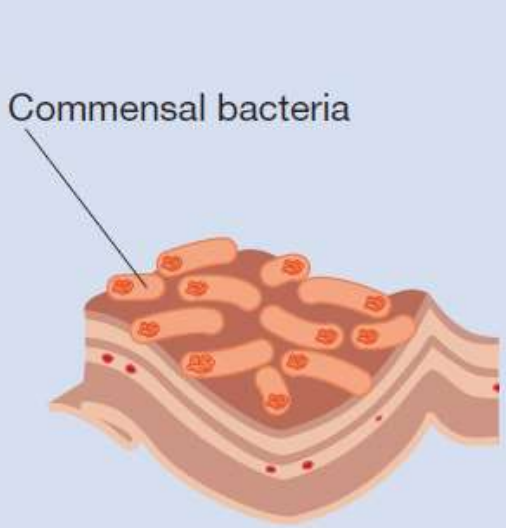

(Brown et al. Nature Immunol 2013)

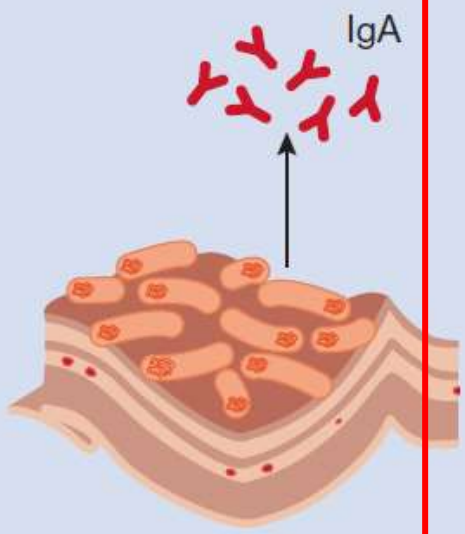
# Ο ρόλος της Εντερικής Χλωρίδας

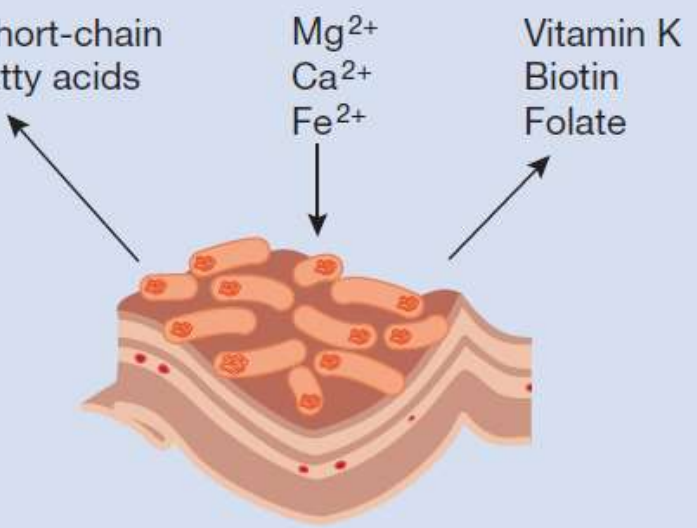
- Η εντερική χλωρίδα και ο εντερικός βλεννογόνος είναι δύο συμβιωτικοί οργανισμοί.
- **Που αναπτύχθηκαν παράλληλα μέσα στην εξελικτική πορεία**.
- Ο εντερικός αυλός παρέχει ευνοϊκές συνθήκες ανάπτυξης και θρεπτικά υλικά.
- Η χλωρίδα τροφικό/μεταβολικό ρόλο και προστασία από παθογόνους παράγοντες.

# Ο ρόλος της Φυσιολογικής Εντερικής Χλωρίδας

| Protective functions | Structural functions | Metabolic functions | |
|---|---|---|---|
| Pathogen displacement | Barrier fortification | Control IEC differentiation and proliferation | Ferment non-digestible dietary residue and endo-genous epithelial-derived mucus |
| Nutrient competition | Induction of IgA | Metabolize dietary carcinogens | Ion absorption |
| Receptor competition | Apical tightening of tight junctions | Synthesize vitamins e.g., biotin, folate | Salvage of energy |
| Production of anti-microbial factors e.g., bacteriocins, lactic acids | Immune system development | | |

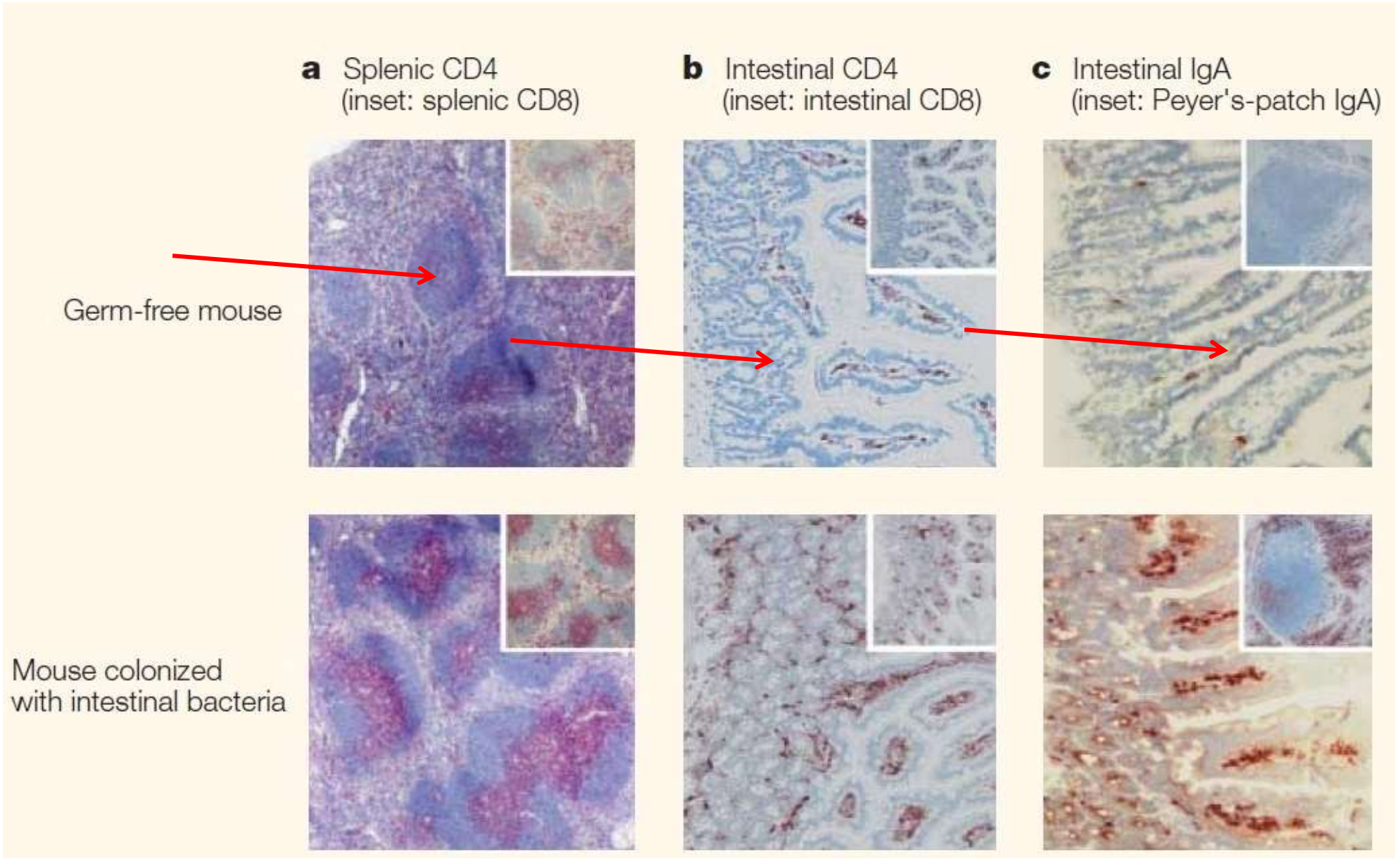



(O'Hara & Shanahan. EMBO reports 2006)

# Ανάπτυξη του βλεννογονίου ανοσολογικού συστήματος



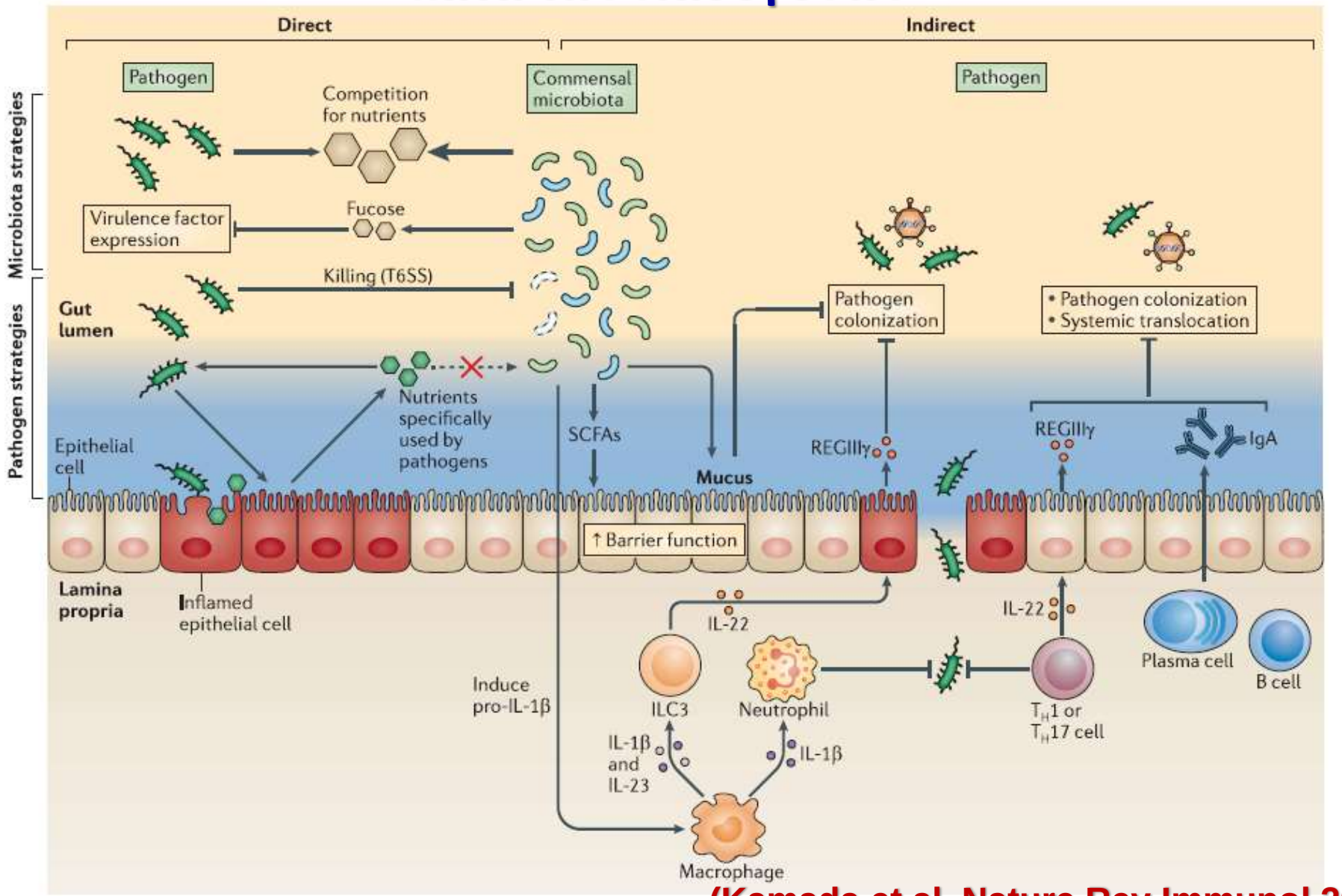

(Macpherson & Harris. Nature Reviews in Immunol 2004)

# Η τελική διαφοροποίηση των βλεννογονικών λεμφοκυττάρων επηρεάζεται απο την μικροχλωρίδα

| | |
|---|---|
| segmentous filamentous bacteria | *type 17 T helper (TH17) cells* |
| Clostridia | *Treg cells* |
| *Bacteroides fragilis* | *type 1 T helper (TH1) cells* |

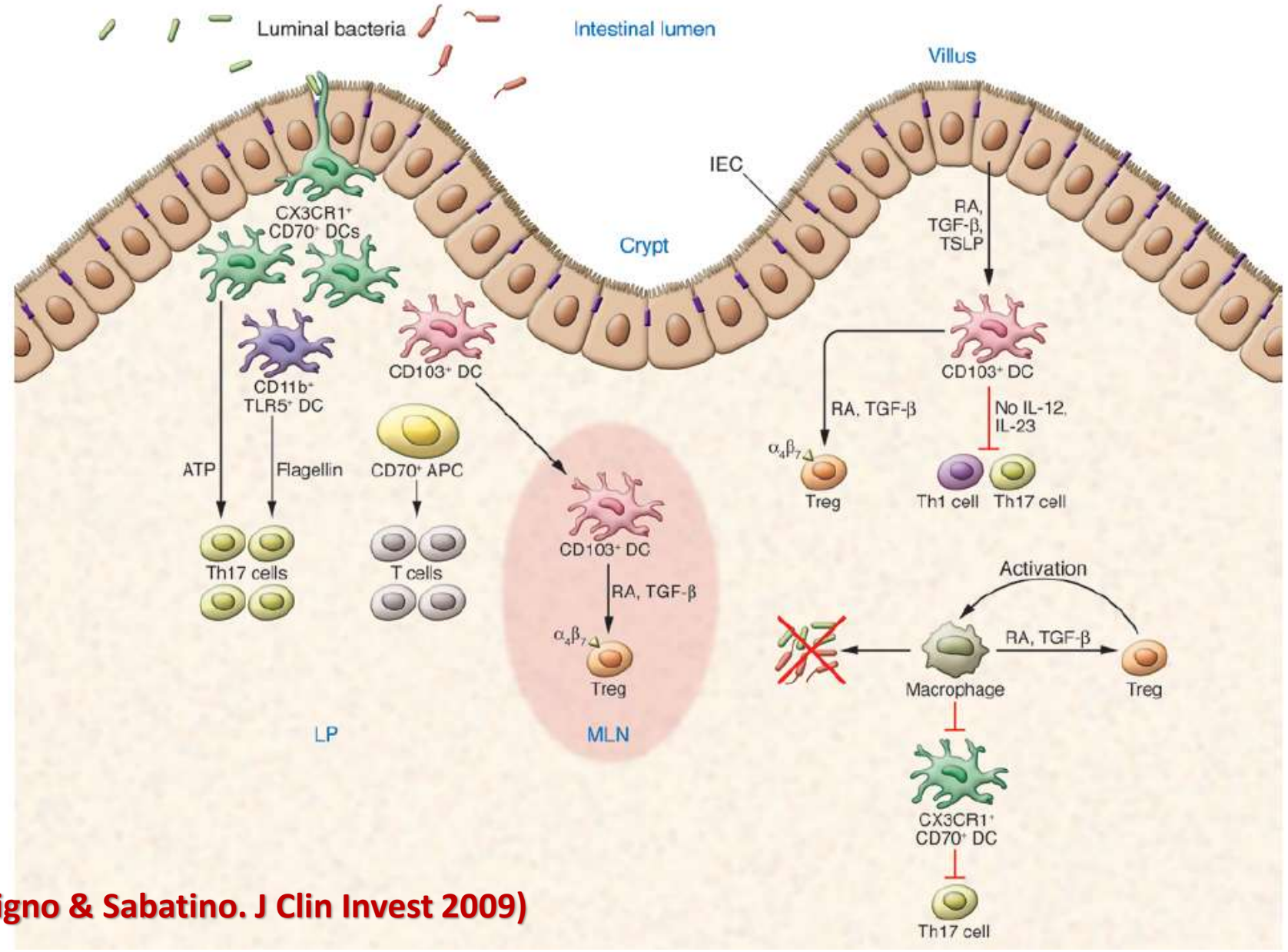
**Hooper, L. V., *Science 336, 1268–1273 (2012)***

# Έμμεση και άμεση συμβολή της χλωρίδας στην αντίσταση κατά των παθογόνων



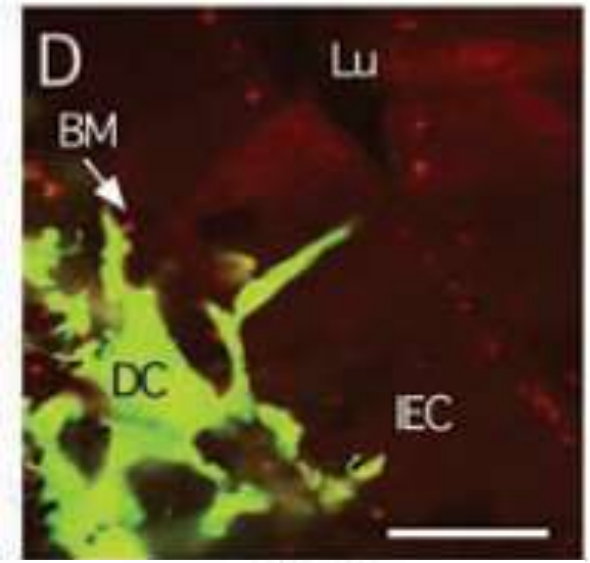

(Kamada et al. Nature Rev Immunol 2013)

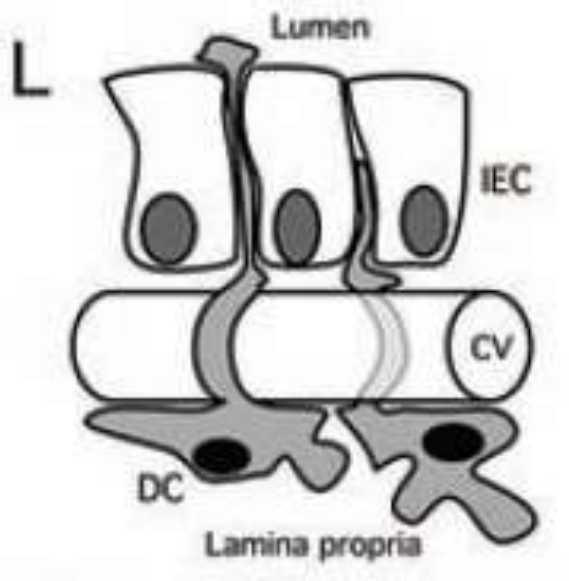
# Μηχανισμοί ανοχής



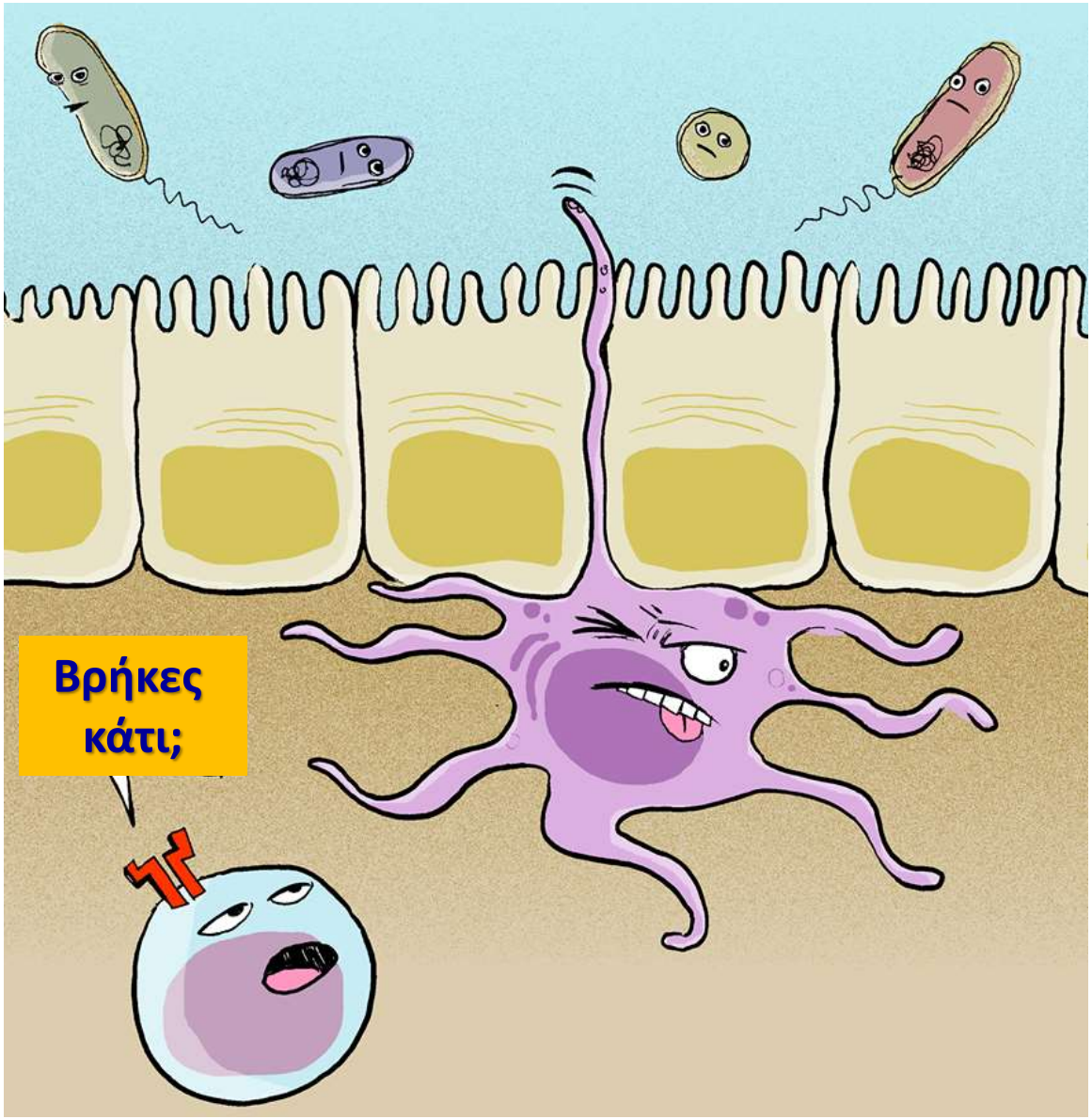

(Rescigno & Sabatino. J Clin Invest 2009)

# Ανοχή (tolerance)



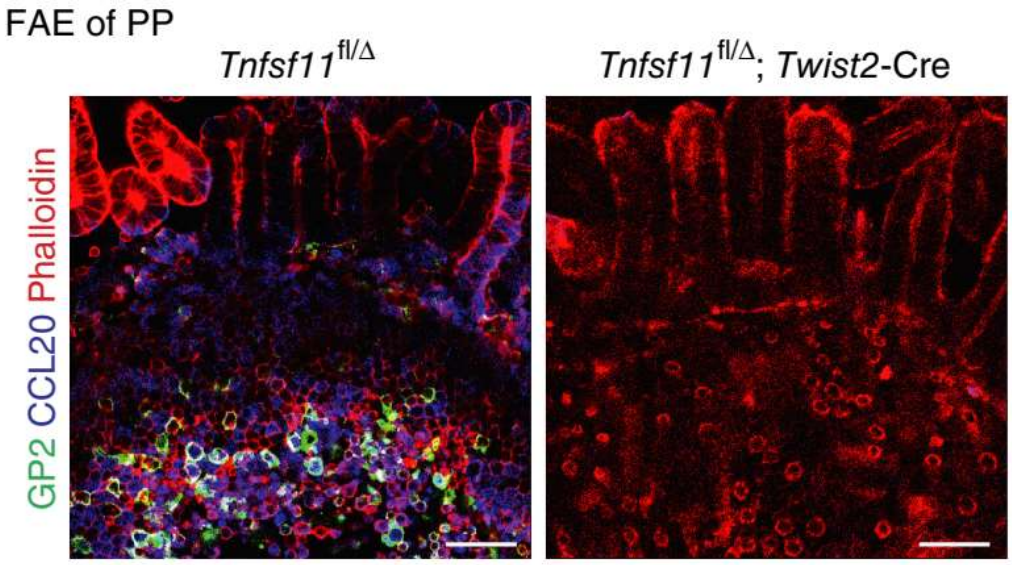



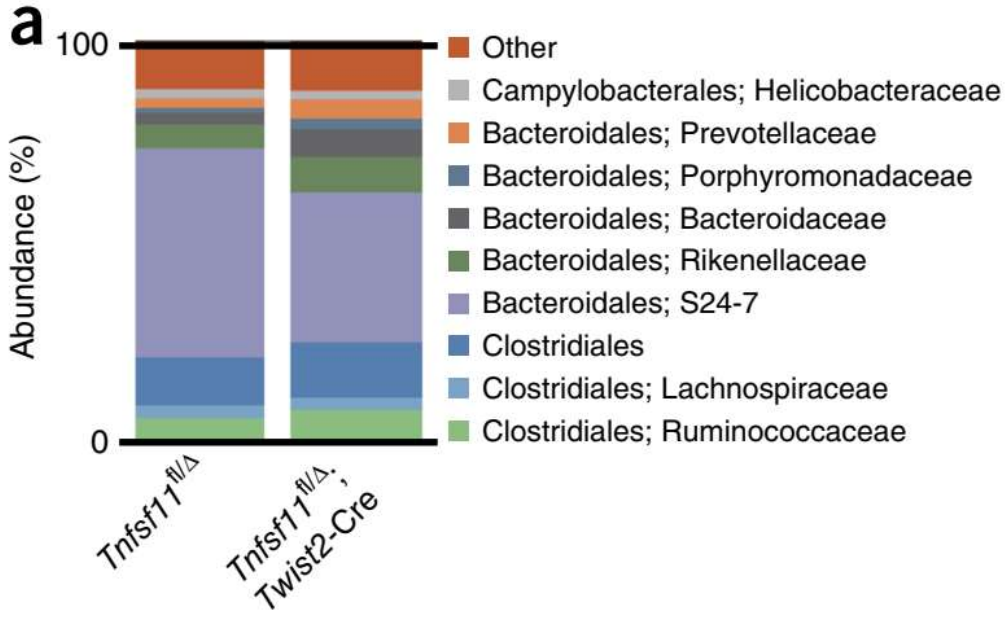

(Niess et al. Science 2005)



# Identification of subepithelial mesenchymal cells that induce IgA and diversify gut microbiota

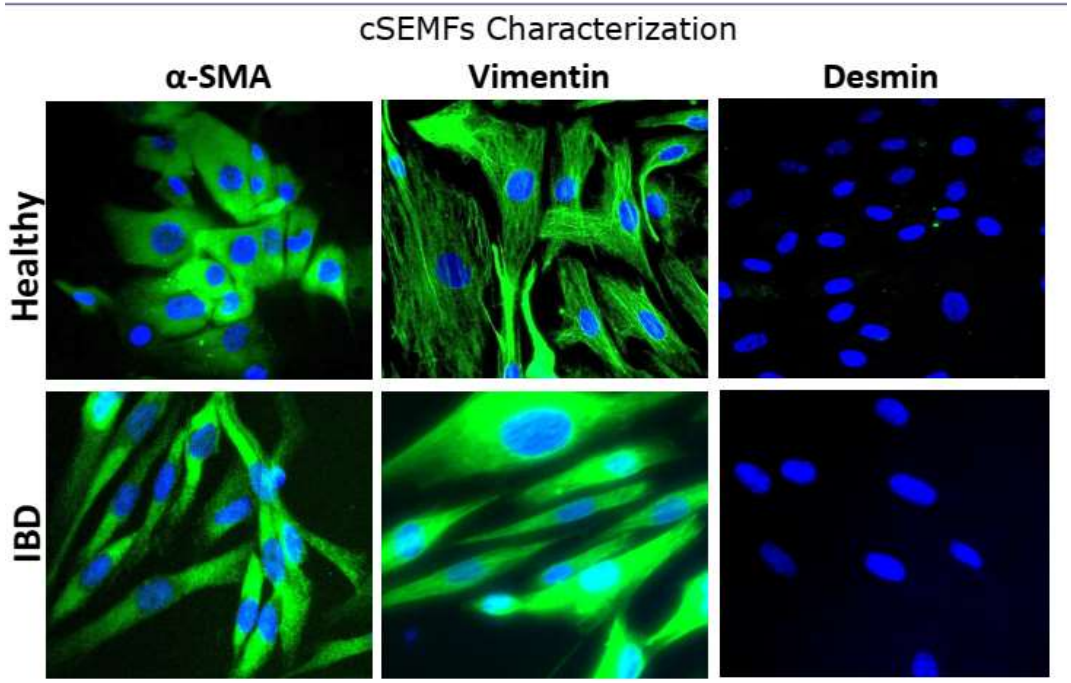
Kazuki Nagashima[1], Shinichiro Sawa[1,2], Takeshi Nitta[1], Masanori Tsutsumi[1], Tadashi Okamura[3,4], Josef M Penninger[5], Tomoki Nakashima[6–8] & Hiroshi Takayanagi[1]




(Nature Immunology 2017)

- **Methods** Primary SEMFs were isolated from endoscopically-obtained colonic biopsies from healthy individuals and were found a-SMA and vimentin positive and desmin negative by immunofluorescence.
- Healthy SEMFs were stimulated with **$10^2$, $10^4$, $10^8$ BU/ml** of a mix of ***Lactobacillus Plantarum***, ***Saccharomyces Boulardii***, ***Bifidobacterium Lactis***, ***Lactobacillus Acidophillus*** for 6 or 48 hours. Total RNA was collected at 6h and mRNA transcripts for profibrotic factors were measured by reverse transcription quantitative PCR. At 48h, supernatants were collected, and total collagen protein secreted was measured by Sircol Assay.



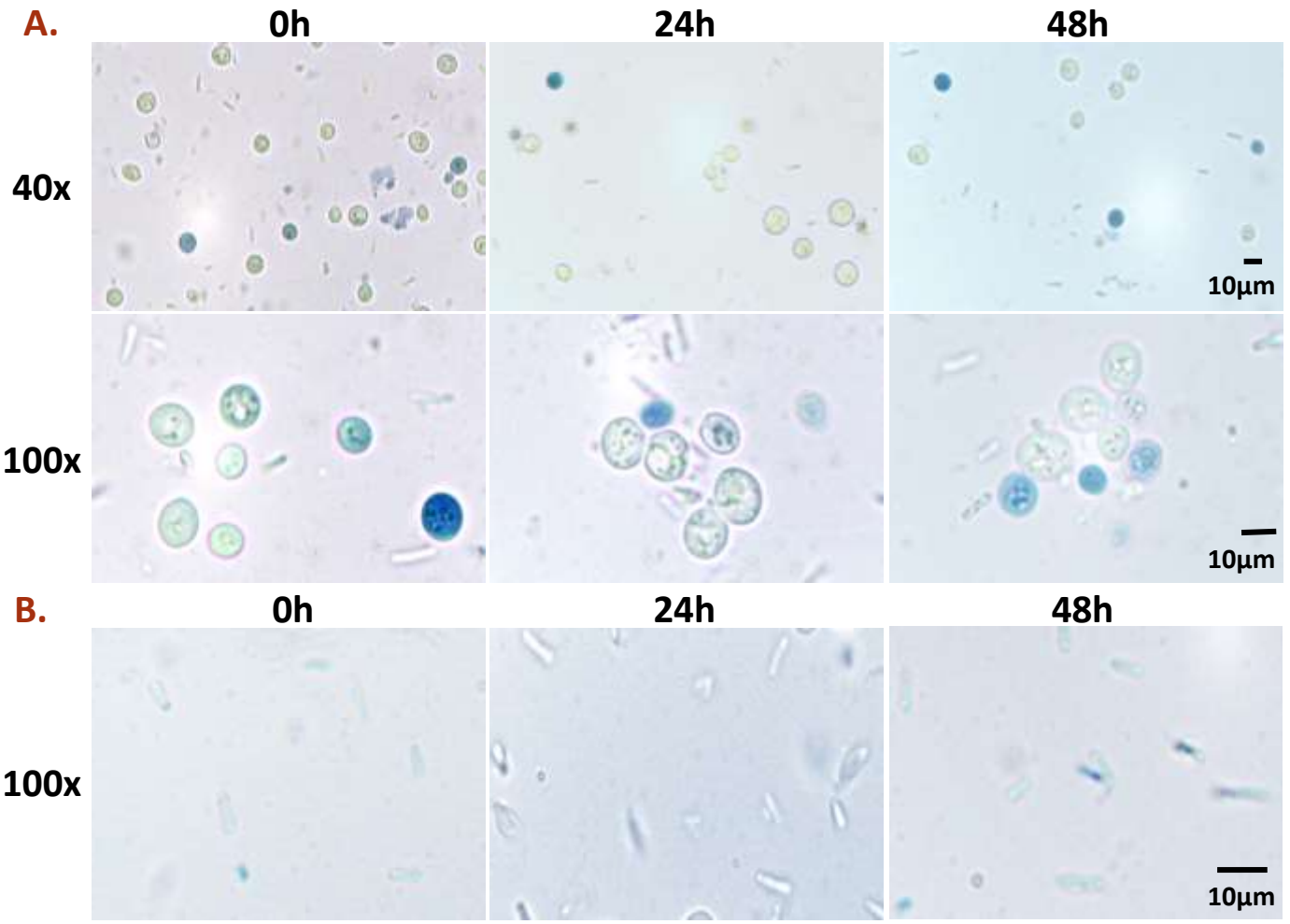

**(Unpublished data)**

# Έλεγχος βιωσιμότητας με Trypan Blue

Σχεδόν όλα τα κύτταρα παρέμειναν ζωντανά, καθώς δεν βάφτηκαν με τη χρώση με Trypan Blue:

**A.** μείγμα των στελεχών ***Lactobacillus acidophillus, Lactobacillus plantarum, Bifidobacterium lactis, Saccharomyces boulardii***

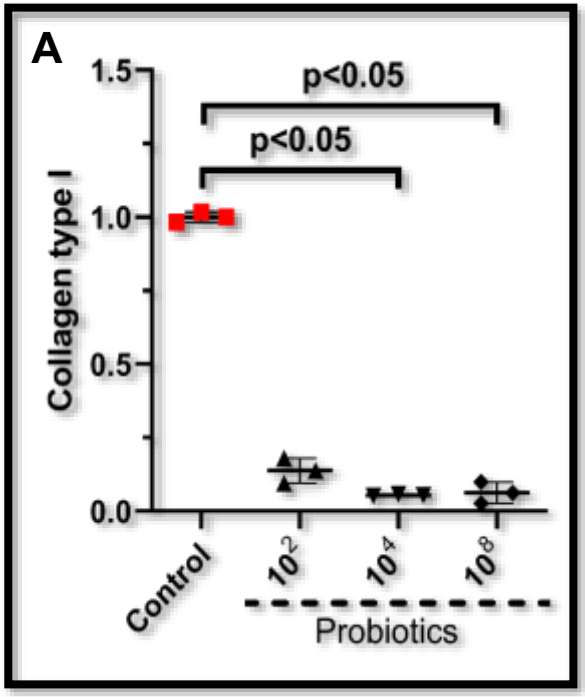
**B.** ***Lactobacillus plantarum***.

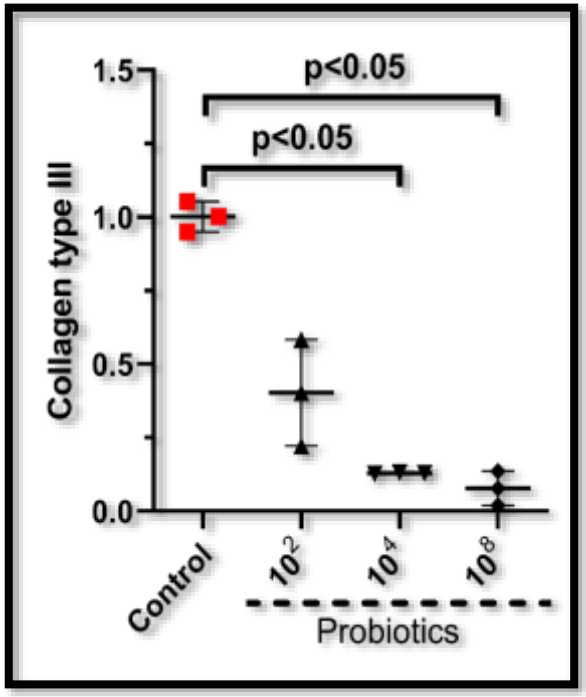


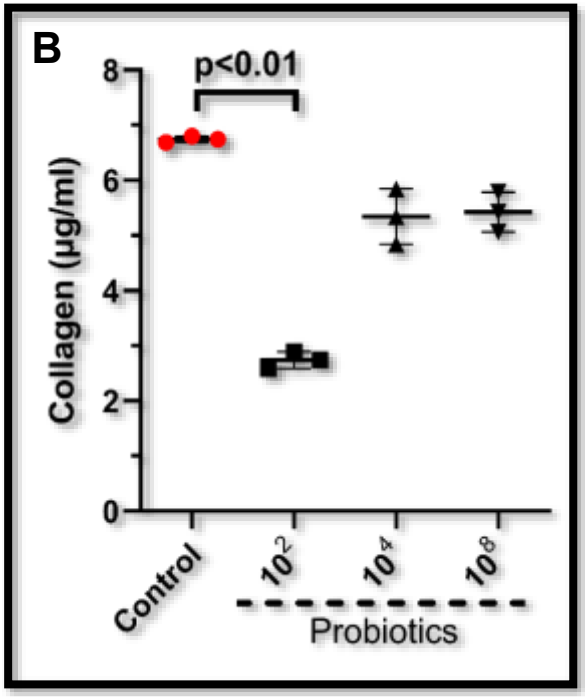
# Collagen type I, III, and total protein

The mix of ***Lactobacillus Plantarum***, ***Saccharomyces Boulardii***, ***Bifidobacterium Lactis*** and ***Lactobacillus Acidophillus*** resulted in **decreased**:

- **collagen protein expression** ($10^2$ BU/ml: 3.057-fold, 2.586-2.894, $p<0.01$)
- **mRNA collagen type I expression** ($10^4$ BU/ml: 2.717-fold, 0.05231-0.05731, $p<0.05$; $10^8$ BU/ml: 2.265-fold, 0.02628-0.09979, $p<0.05$) and
- **mRNA collagen type III expression** ($10^4$ BU/ml: 2.378-fold, 0.1272-0.1317, $p<0.05$; $10^8$ BU/ml: 2.717-fold, 0.01924-0.1363, $p<0,05$)




**(Unpublished data)**

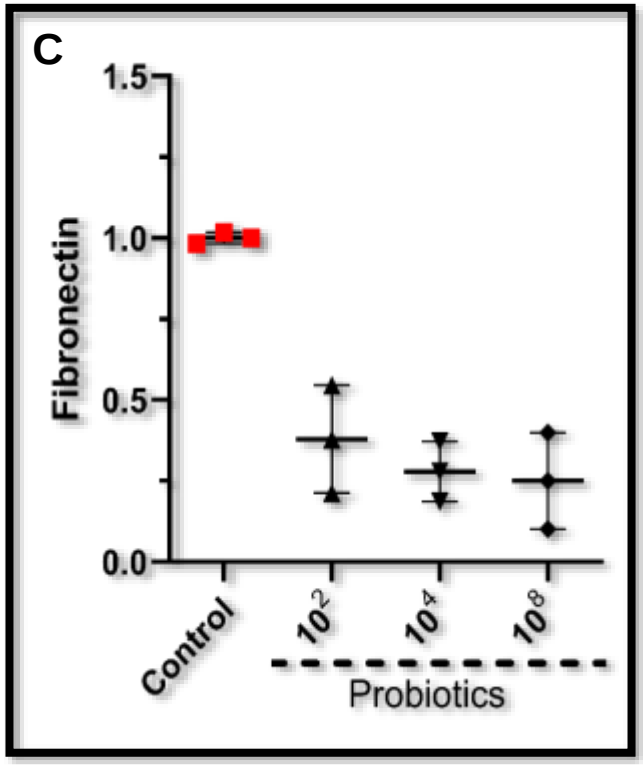
# Fibronectin, tissue factor, α-Smooth Muscle Actin

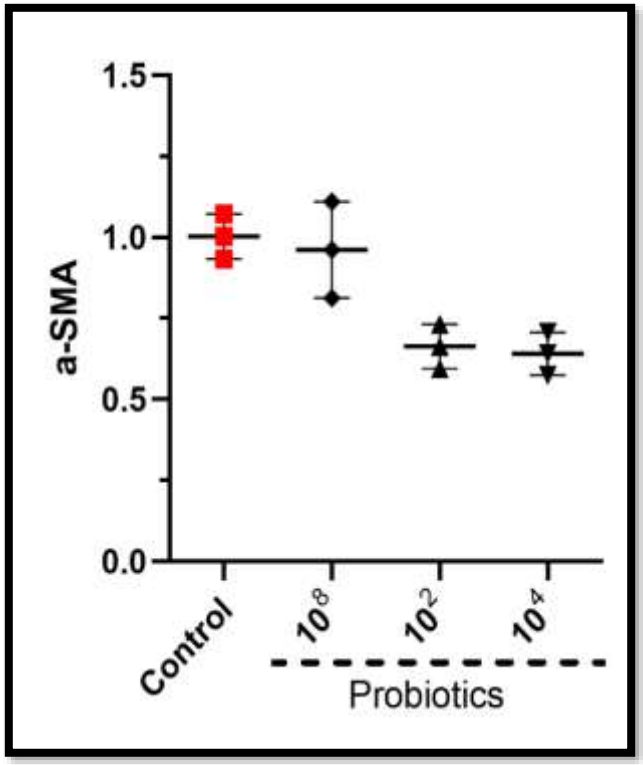
The mix of ***Lactobacillus Plantarum***, ***Saccharomyces Boulardii***, ***Bifidobacterium Lactis*** and ***Lactobacillus Acidophillus*** resulted in **decreased**:

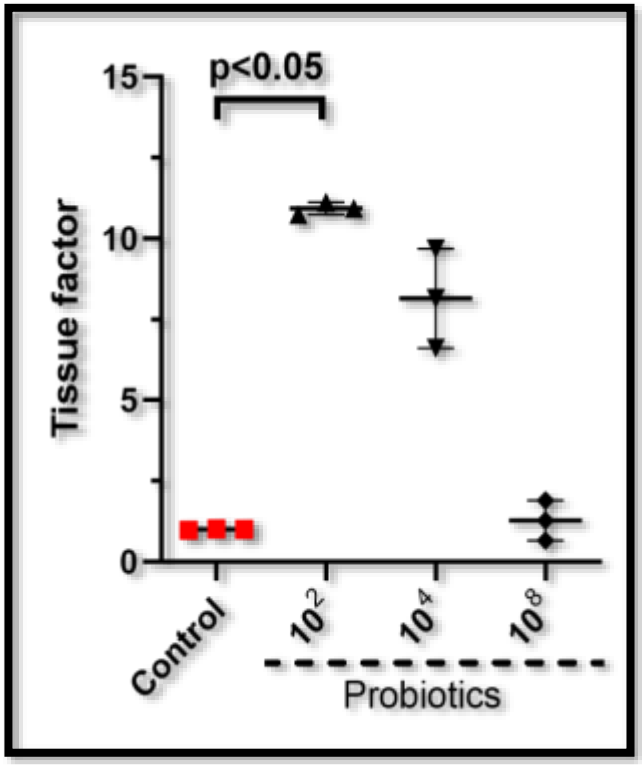
- **mRNA Fibronectin and α-SMA expression** (although not statistically significant)

And in **increased**:

- **mRNA Tissue Factor expression** ($10^2$ BU/ml: 2.717-fold, 10.74-11.12, $p<0.05$)



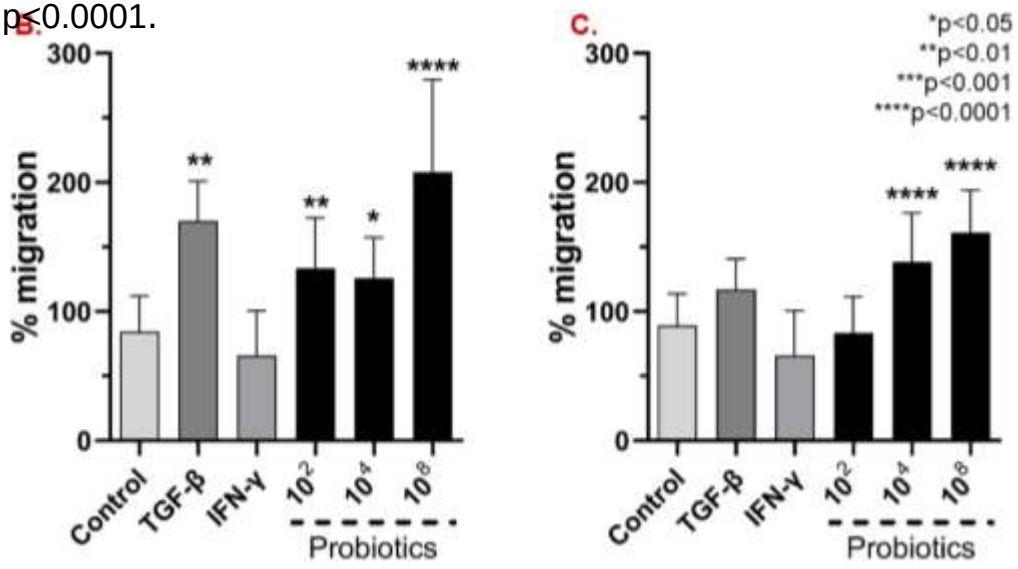



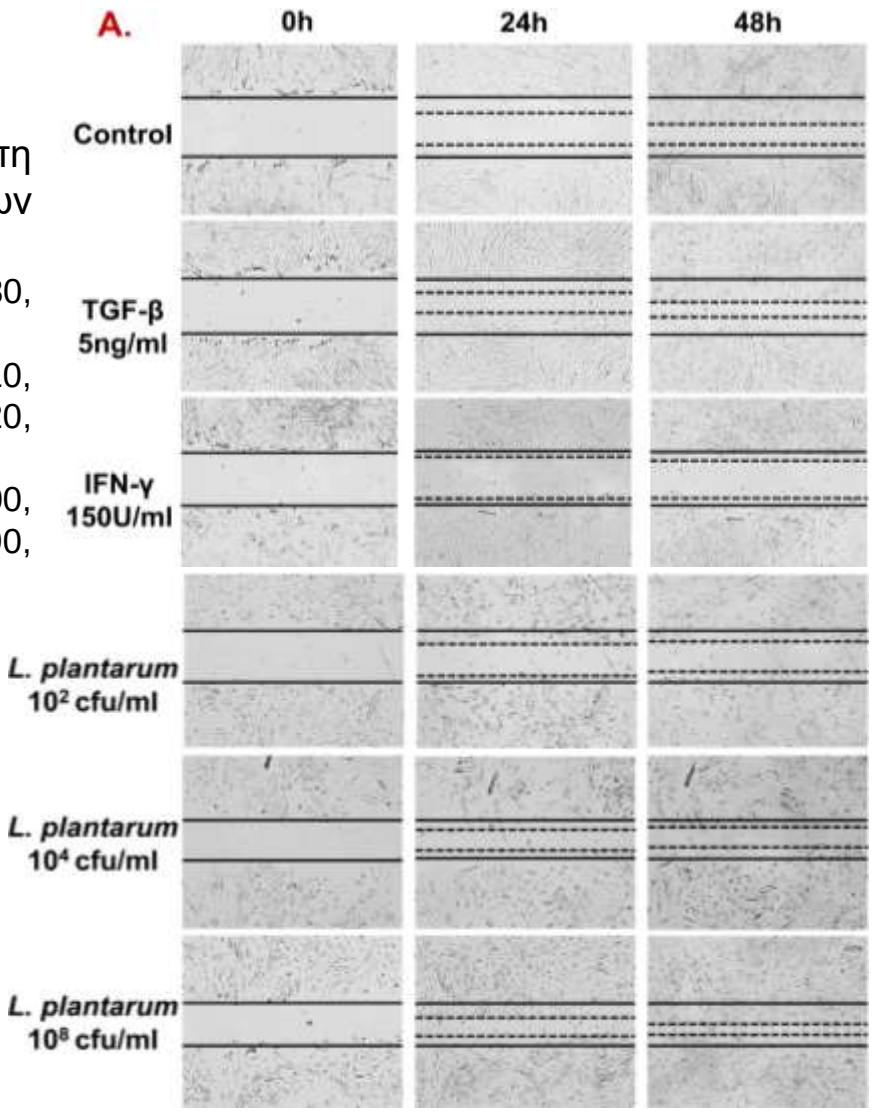

**(Unpublished data)**

# Επίδραση του *L. plantarum* στο μεταναστευτικό ρυθμό των ΕΥΜ

Το μεμονωμένο στέλεχος ***Lactobacillus plantarum*** οδήγησε στη **δοσοεξαρτώμενη αύξηση** του ρυθμού μετανάστευσης των ΕΥΜ:

- **$10^2$ cfu/ml:** μετά από 24 ώρες κατά **128.30%**, IQR: 100.60 – 161.80, p<0.05,
- **$10^4$ cfu/ml:** μετά από 24 ώρες κατά **124.10%**, IQR: 96.09 – 156.10, p<0.05 και μετά από 48 ώρες κατά **146.90%**, IQR: 101.80 – 175.20, p<0.0001,
- **$10^8$ cfu/ml:** μετά από 24 ώρες κατά **222.20%**, IQR: 153.10 – 271.00, p<0.0001 και μετά από 48 ώρες κατά **162.70%**, IQR: 146.30 – 179.90, p<0.0001.

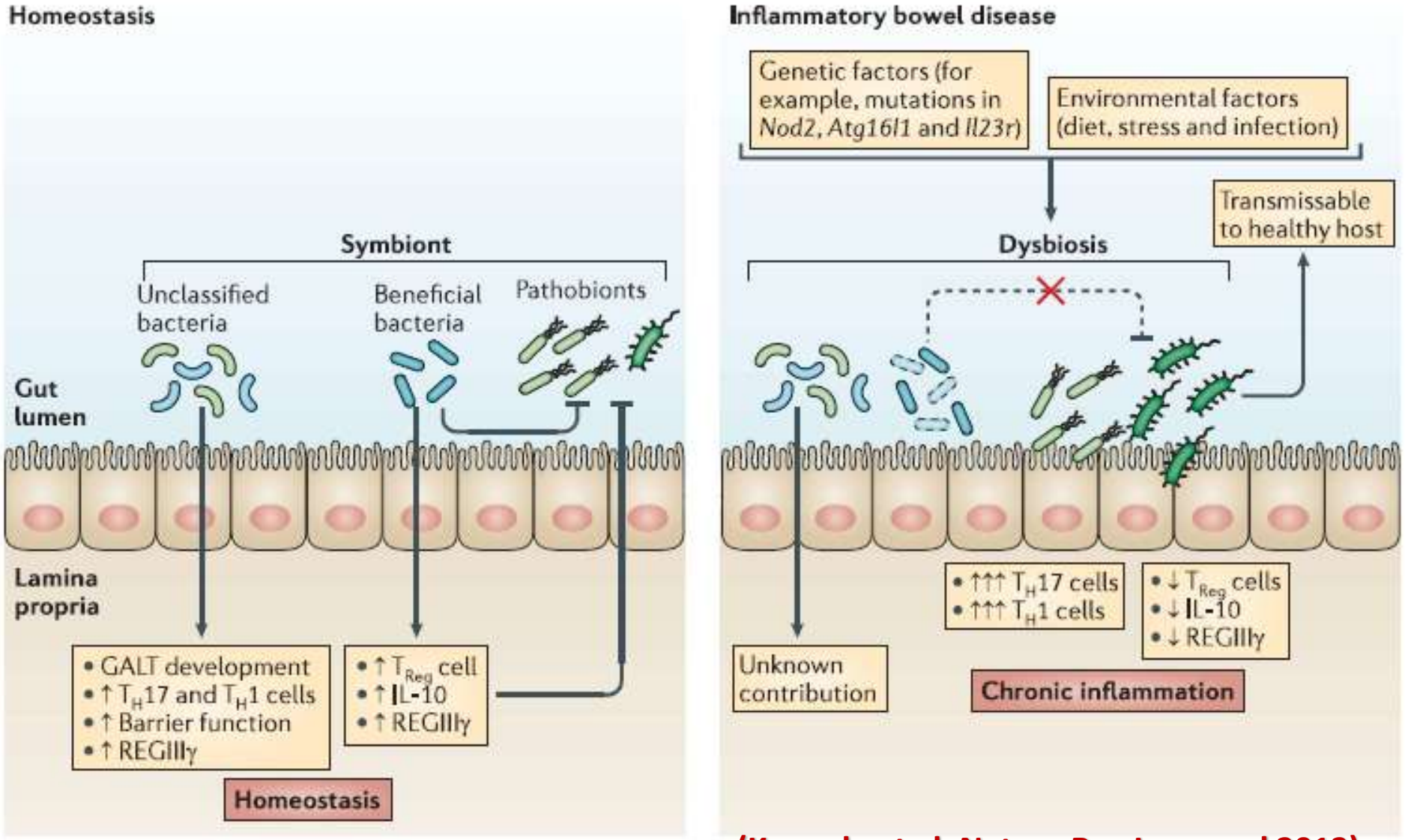





**(Unpublished data)**

# Ευβίωση και δυσβίωση

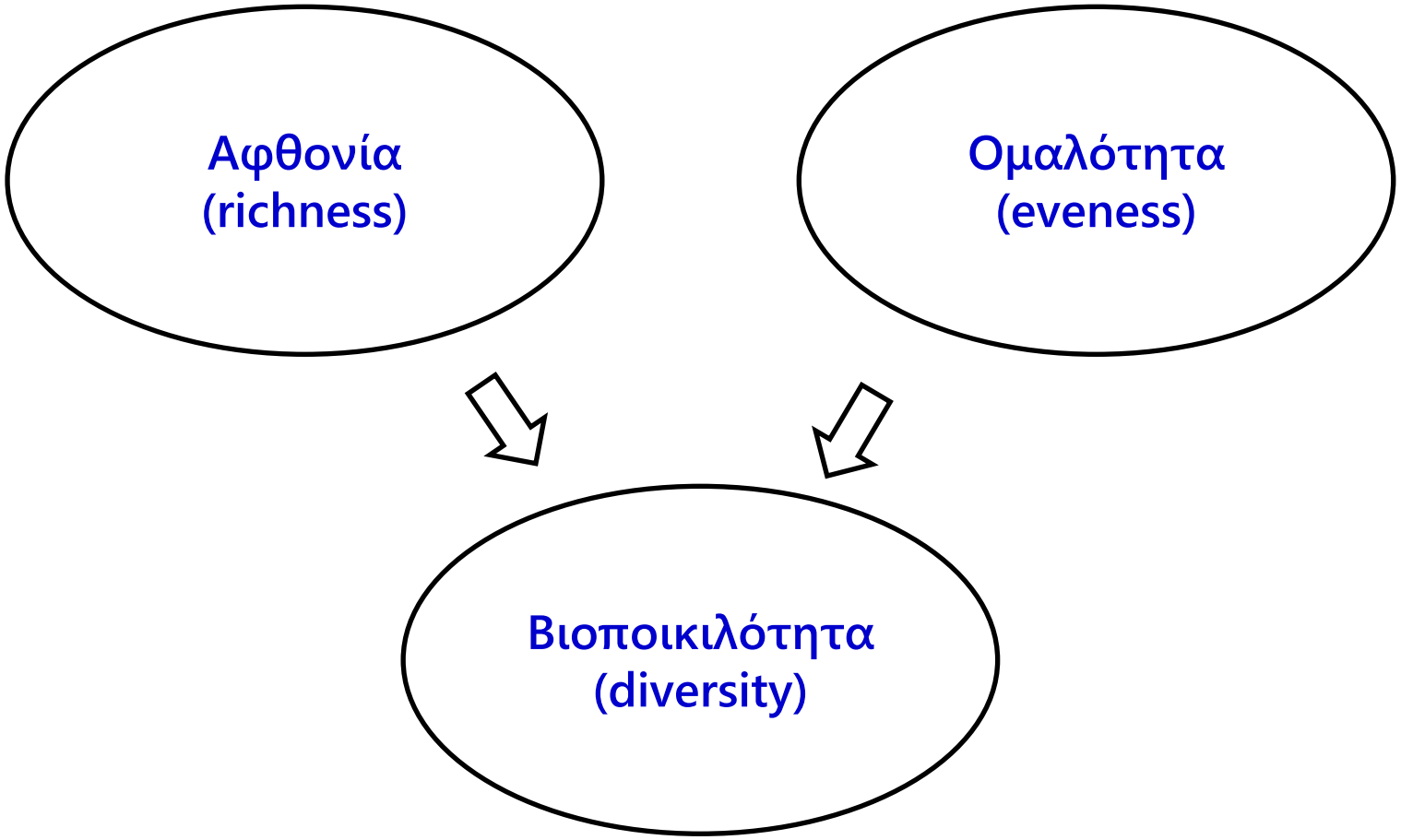



(Kamada et al. Nature Rev Immunol 2013)

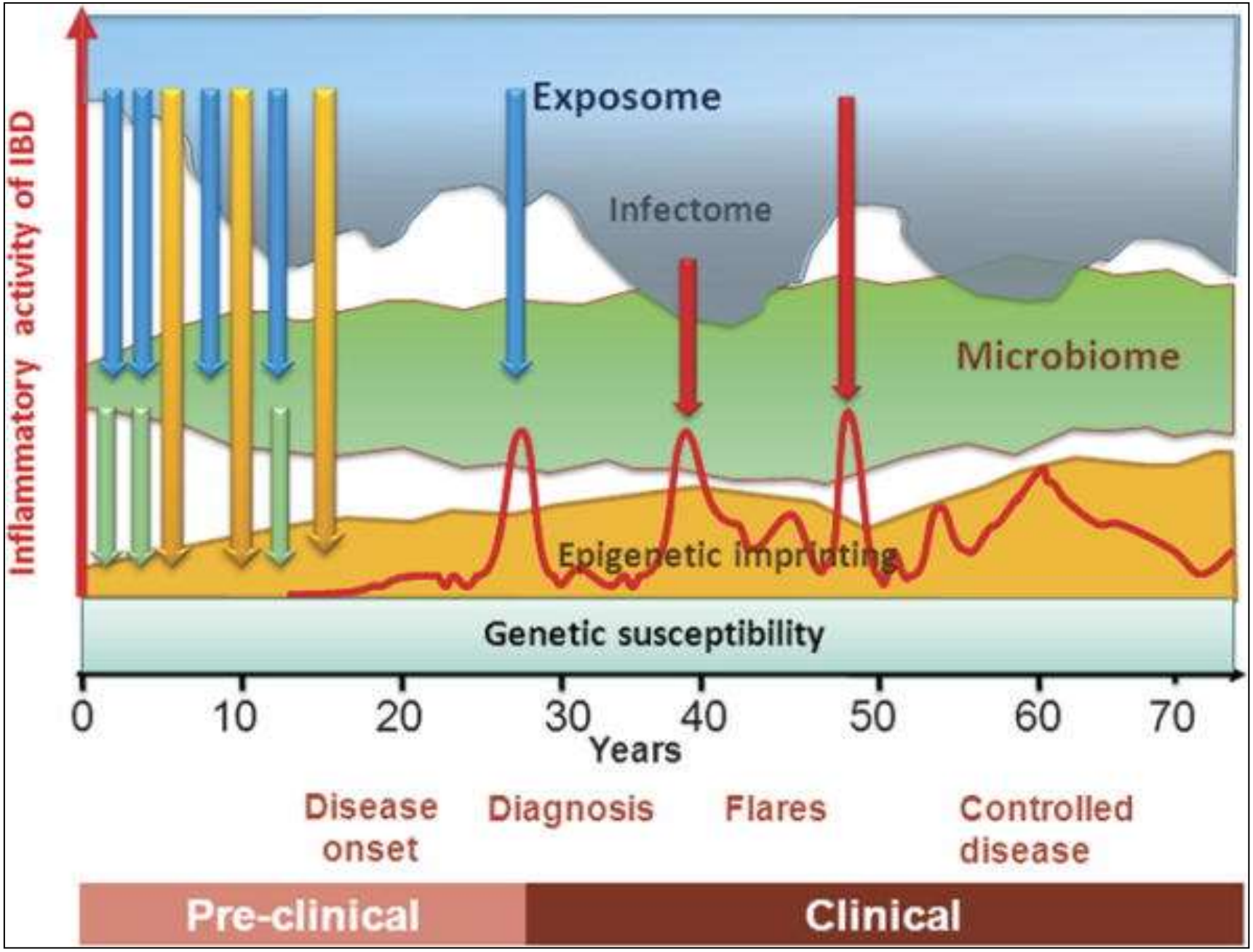
# Τύποι δυσβίωσης

- Ελάττωση βιο-ποικιλότητας εντερικής χλωρίδας
- Μεταβολή της σχετικής σύστασης της χλωρίδας (αναλογική συμμετοχή φύλων)
- Υπερανάπτυξη δυνητικών παθογόνων/εξαφάνιση προστατευτικών μικροοργανισμών
- Μεταβολές στη λειτουργική σύνθεση της χλωρίδας
- Διαταραγμένη αναγνώριση της χλωρίδας από το βλεννογονικό ανοσολογικό σύστημα

# Βασικά χαρακτηριστικά του μικροβιώματος



# Εντερική χλωρίδα του ανθρώπου και περιβαλλοντικές επιδράσεις




(Rogler & Vavricka Inflamm Bowel Dis. 2015;21:400-408)

# Εξωγενείς επιδράσεις στην εντερική χλωρίδα

- Δίαιτα
- Ηλικία
- Φάρμακα
- Κανόνες Υγιεινής
- Επάγγελμα
- Περιβάλλον
  - *E. Coli* serogroups
- Κινητικότητα του εντέρου
- Κύηση
- Φλεγμονές
- Ανοσολογικό σύστημα
- Χρόνια νοσήματα
  - Αλκοολισμός
  - Διαβήτης

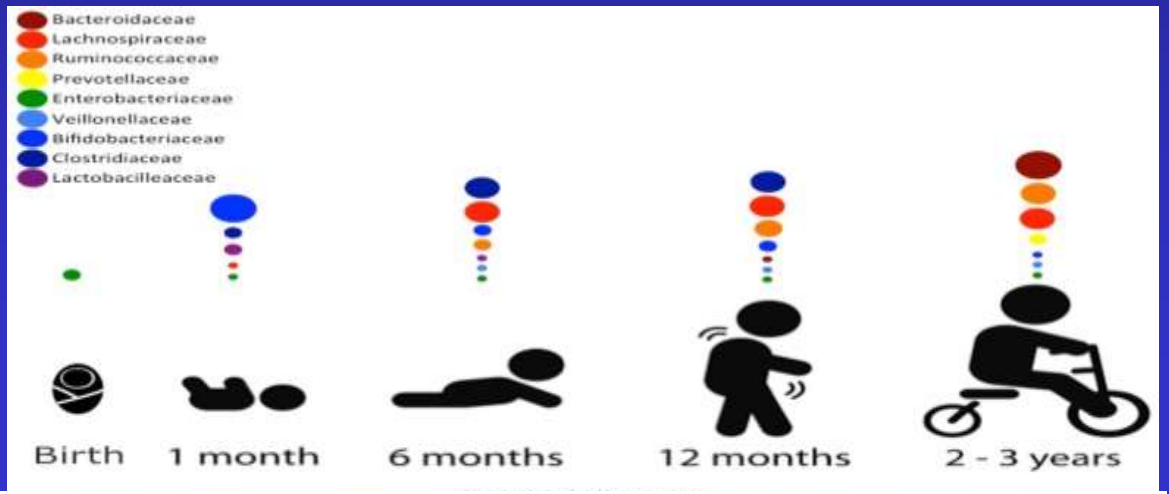
(Ogra PL. Adv Exp Med Biol. 2009)

## Γέννηση: το έντερο είναι “στείρο”

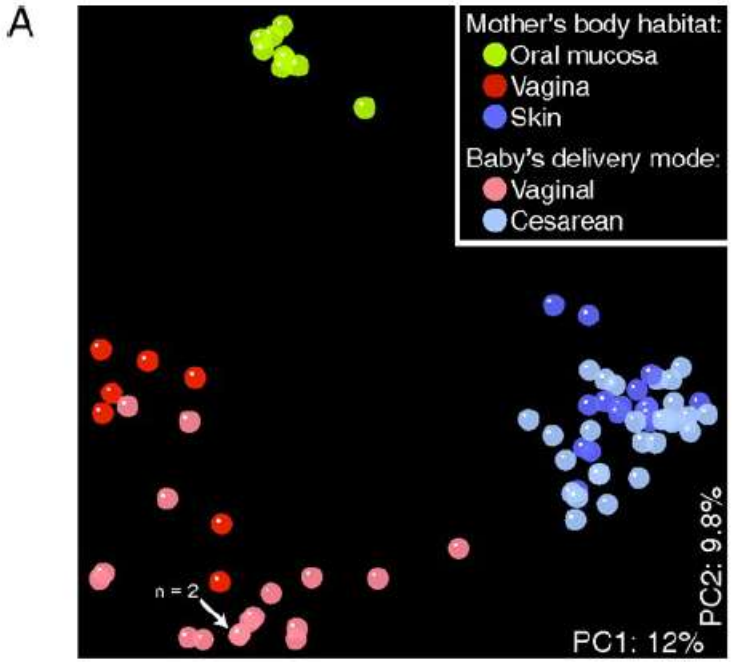
Εποικισμός από βακτήρια

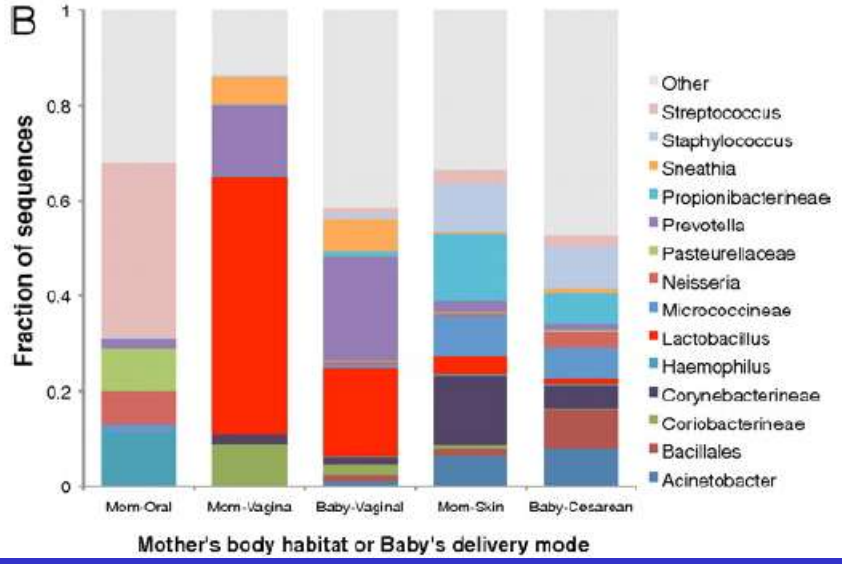
Περιβάλλον και παράγοντες ξενιστή

## Απόκτηση χλωρίδας του ενηλίκου (2 έτη)




(Marie-Claire Arrieta Front Immunol. 2014; 5: 427)




- Vaginal delivery:
  - ✓intestinal colonization reflective of maternal vaginal flora
  - ✓Lactobacillus
  - ✓Prevotella
- Cesarean delivery:
  - ✓Epidermal colonization
  - ✓Clostridium
  - ✓Staphylococcus
  - ✓Propionobacterium
  - ✓Corynebacterium
  - ✓↓ anaerobes: lower numbers of Bacteroides and Bifidobacterium

(Gritz & Bhandari. Front Pediatr. 2015 )

Published in final edited form as:
*Nat Med*. 2016 March ; 22(3): 250–253. doi:10.1038/nm.4039.

# Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

**Maria G. Dominguez-Bello**[1,2,*], **Kassandra M. De Jesus-Laboy**[2], **Nan Shen**[8], **Laura M. Cox**[1], **Amnon Amir**[3,7], **Antonio Gonzalez**[3,7], **Nicholas A. Bokulich**[1], **Se Jin Song**[3,4], **Marina Hoashi**[5], **Juana I. Rivera-Vina**[6], **Keimari Mendez**[6], **Rob Knight**[3,7], and **Jose C. Clemente**[8,9,*]

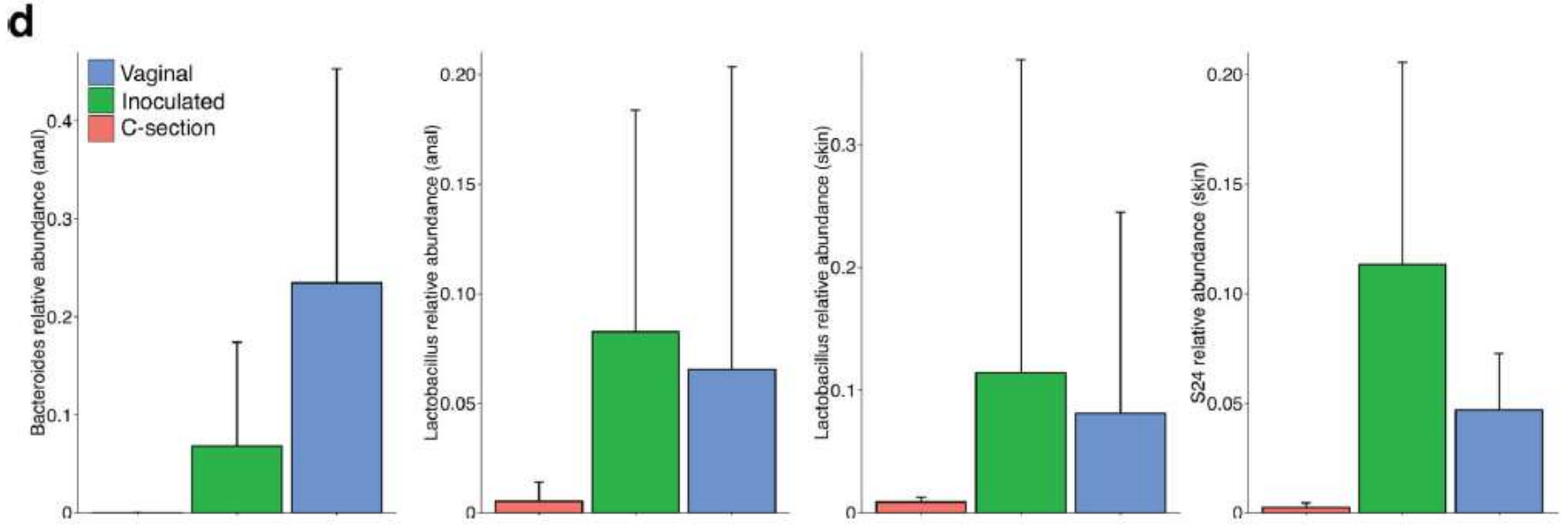



**Figure 1. Restoring the maternal microbiota in infants born by C-section**

# Μητρικό γάλα

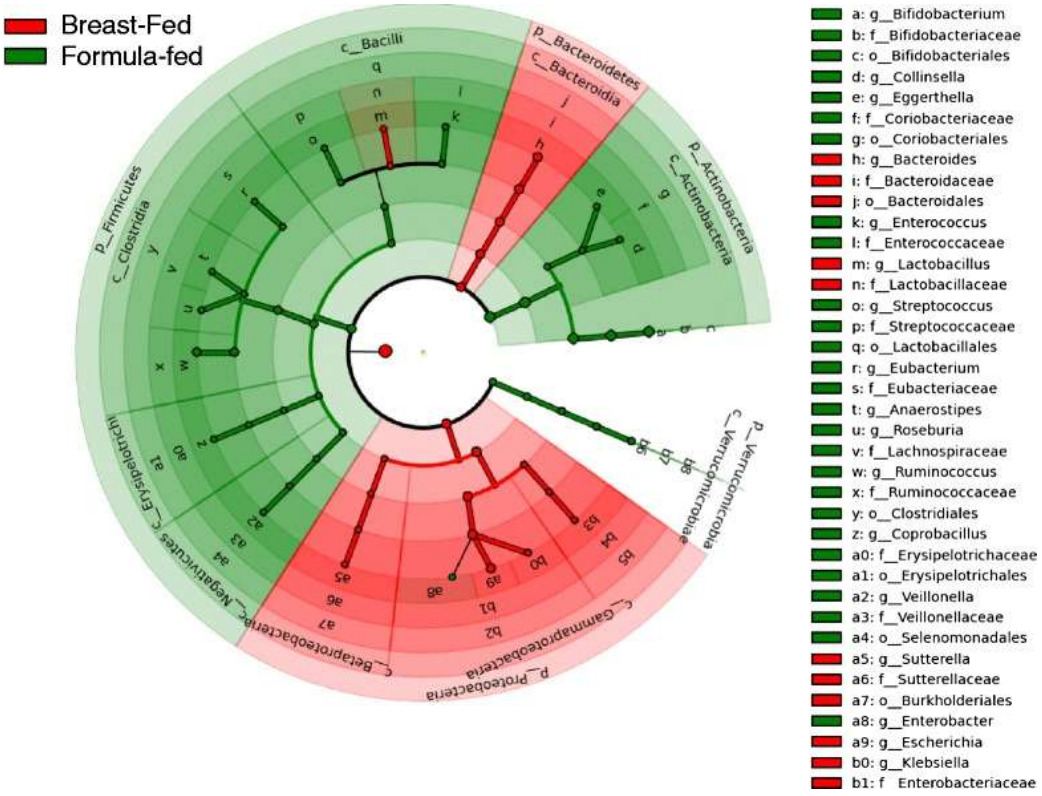
Praveen et al. Microbiome (2015) 3:41
DOI 10.1186/s40168-015-0104-7

Microbiome

RESEARCH Open Access

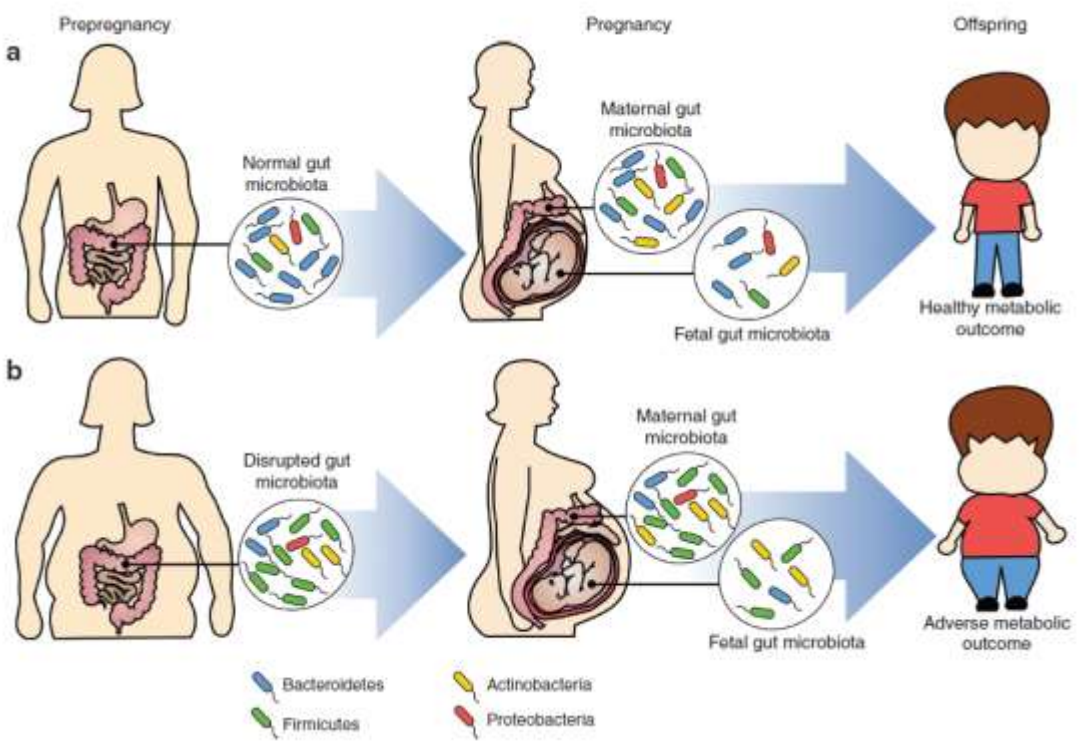
## The role of breast-feeding in infant immune system: a systems perspective on the intestinal microbiome

Paurush Praveen[1*], Ferenc Jordan[1], Corrado Priami[1,2] and Melissa J. Morine[1,2]

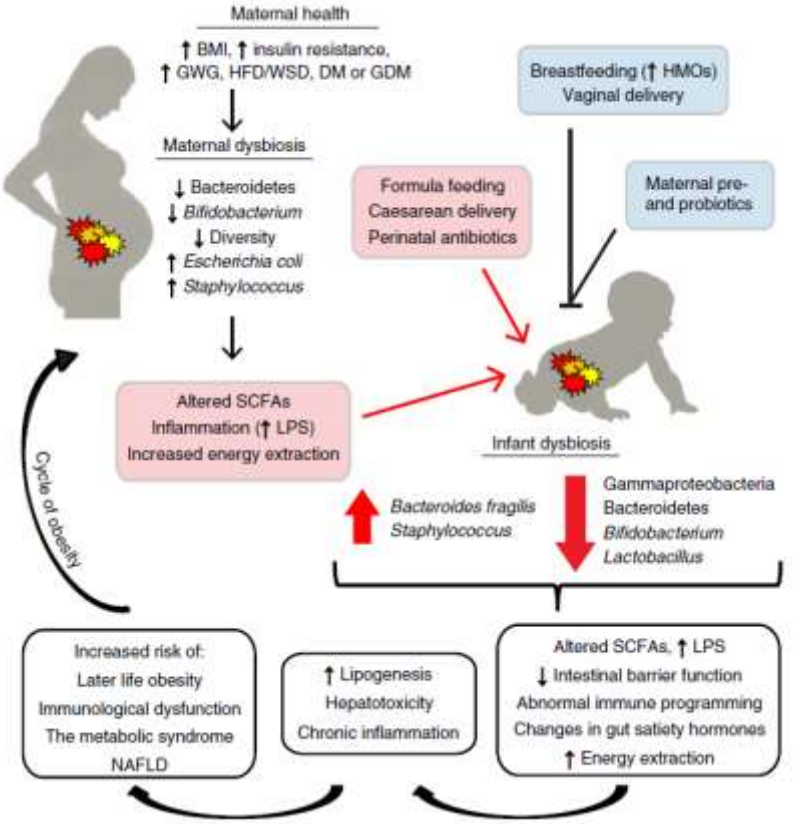



Conclusions: Our findings revealed that there is co-expression of more genes in breast-fed samples but lower microbial diversity compared to formula-fed.

# Παχυσαρκία μητέρας και μικροβίωμα εμβρύου




(Gohir et al. Pediatr Res. 2015)




(Soderborg et al. Diabetologia 2016)

# The influence of antibiotics and dietary components on gut microbiota

**Ruth K. Dudek-Wicher, Adam Junka, Marzenna Bartoszewicz**

Department of Pharmaceutical Microbiology and Parasitology, Medical University of Wroclaw, Wroclaw, Poland

Gastroenterology Rev 2018; 13 (2): 85–92

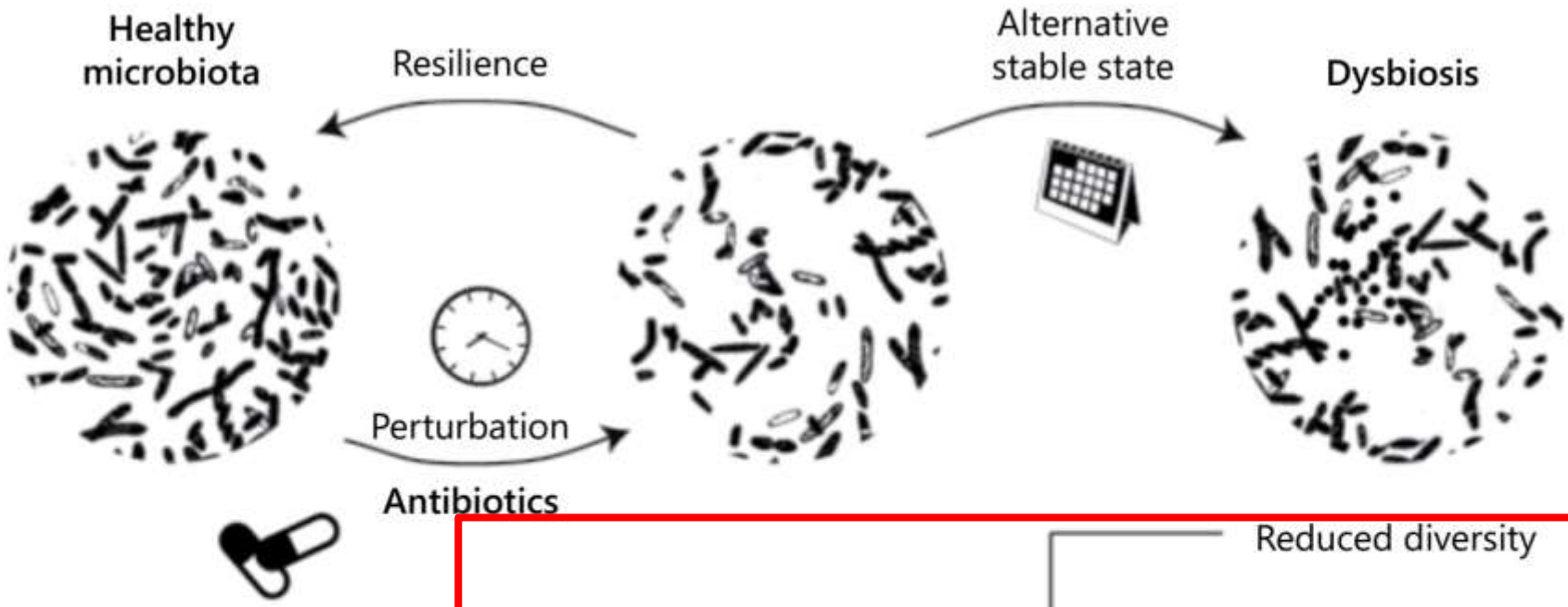
| Factor | Alteration | Clinical relevance |
|---|---|---|
| Fluoroquinolones and β-lactams [24] | Decreased microbial diversity, reduced number of taxa, changed *Bacteroidetes/Firmicutes* ratio, increased average microbial load [24] | Systematic use of antibiotics can reshape the microbiota in favor of resistant bacterial strains in the long term [24] |
| Clindamycin [25] | Reduced resistance to colonization by pathogens [25] | High risk of pseudomembranous colitis due to *Clostridium difficile* overgrowth, gastritis and diarrhea, bloating and intestinal pain [25] |
| Moxifloxacin, cefazolin, ampicillin/sulbactam, amoxicillin, penicillin G/ clindamycin [27] | Qualitative and quantitative changes in genera [27] | Increased risk of opportunistic infections caused by *Escherichia* spp. or *Klebsiella* spp. [27] |
| Antibiotic treatment [17, 28, 29] | Fucose, sialic acid liberated from mucins [28, 29]. Alteration of intestinal commensal bacteria causes immune defense modification [17] | Expansion of the opportunistic pathogens *Salmonella typhimurium*, *C. difficile* and *E. coli* [28, 29]. Allergy and viral infection promotion [17] |

# Effects of Antibiotics on Gut Microbiota

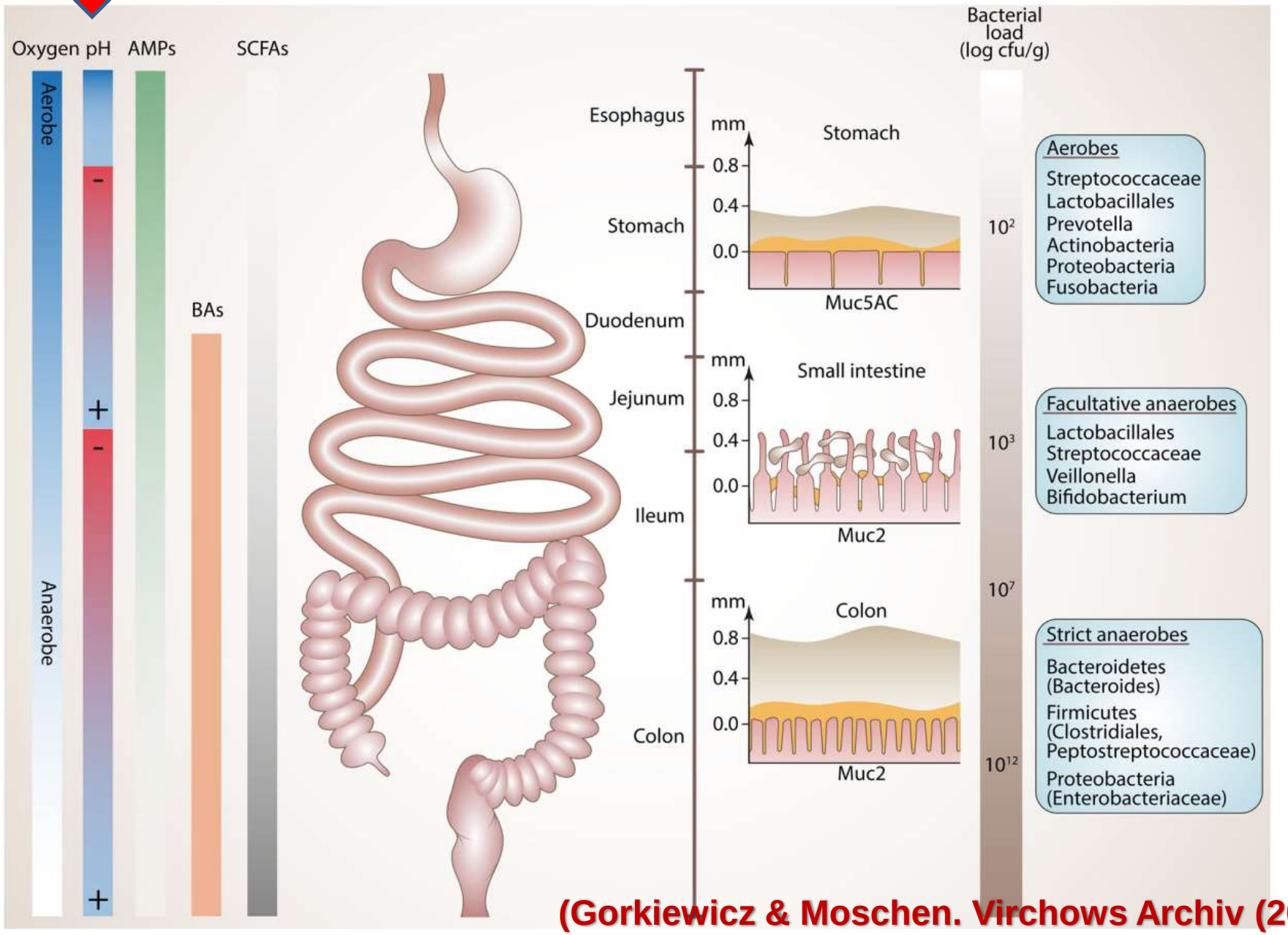
Kathleen Lange[a] Martin Buerger[a] Andreas Stallmach[a, b] Tony Bruns[a]

Dig Dis 2016;34:260–268

[a]Department of Internal Medicine IV (Gastroenterology, Hepatology, and Infectious Diseases), and [b]The Integrated Research and Treatment Center for Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany



# Stomach microflora



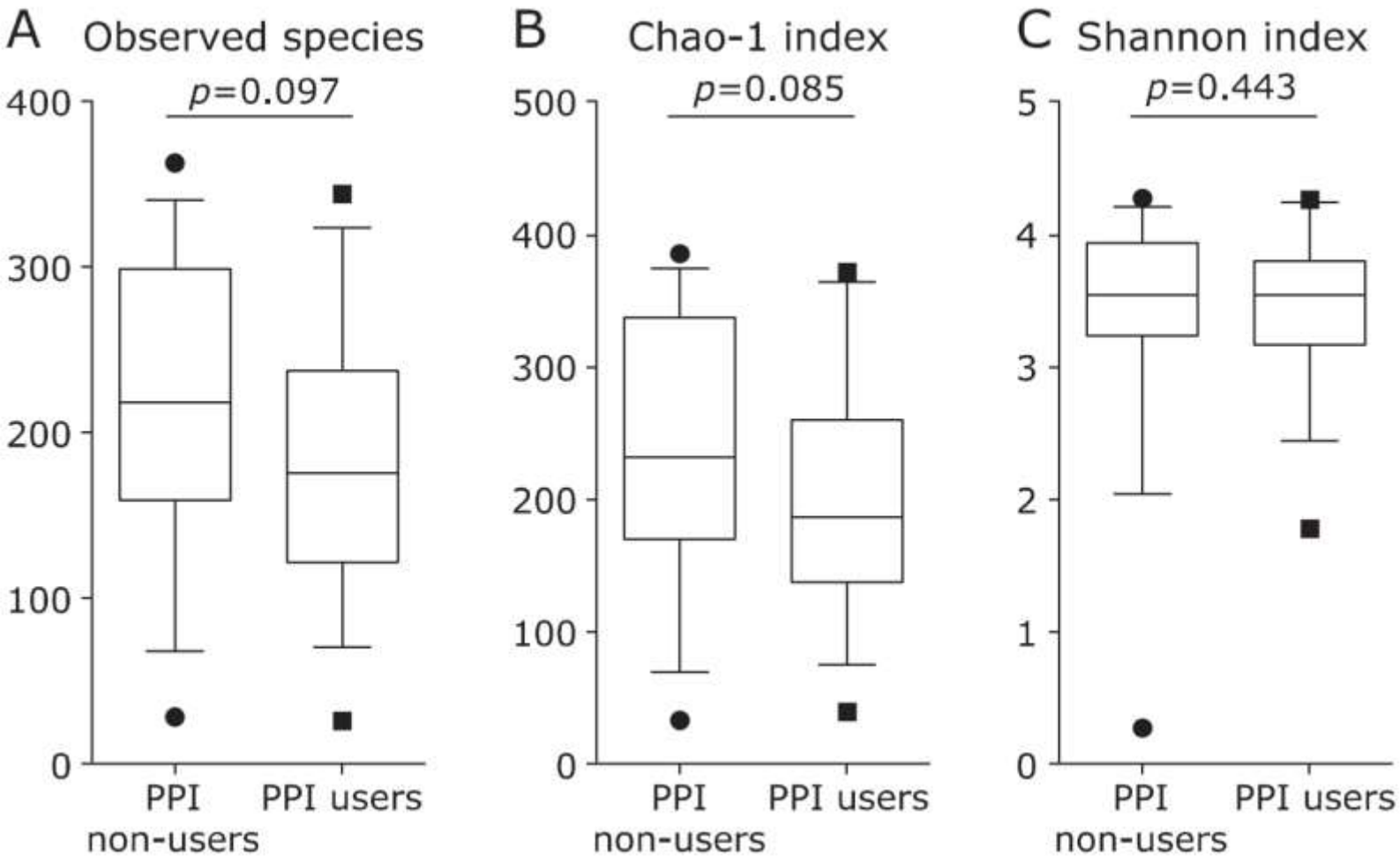

(Gorkiewicz & Moschen. Virchows Archiv (2018)

# Proton pump inhibitors

## Adverse drug reactions

- Τα τελευταία χρόνια, μελέτες έχουν δείξει ότι η εντερική χλωρίδα ασθενών που κάνουν χρήση PPIs εμφανίζει σημαντική μείωση της βιοποικιλότητας της, με σαφή τροποποίηση ορισμένων τάξεων μικροοργανισμών.
- Η αλλαγή αυτή φαίνεται να σχετίζεται με αυξημένο κίνδυνο διαταραχών του πεπτικού, όπως λοιμώξεις με κλωστηρίδιο Difficile. **(Freedberg et al. Clin Lab Med 2014; Seto et al. Microbiome 2014; Clooney et al. Aliment Pharmacol Ther 2016; Jackson et al. Gut 2016)**

# α-Diversity Indices




(J. Clin. Biochem. Nutr. 2018)

frontiers in Microbiology

REVIEW

published: 11 September 2018
doi: 10.3389/fmicb.2018.02013

# Effects of Psychological, Environmental and Physical Stressors on the Gut Microbiota

*J. Philip Karl[1]*, Adrienne M. Hatch[1], Steven M. Arcidiacono[2], Sarah C. Pearce[3], Ida G. Pantoja-Feliciano[2], Laurel A. Doherty[2] and Jason W. Soares[2]*

[1] *Military Nutrition Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA, United States,*

**Military training**
Karl et al., 2017a

**Psychological stress**
Knowles et al., 2008

Kato-Kataoka et al., 2016

**Circadian disruption/**
Benedict et al., 2016

**Travelers' diarrhea**
Kampmann et al., 2016

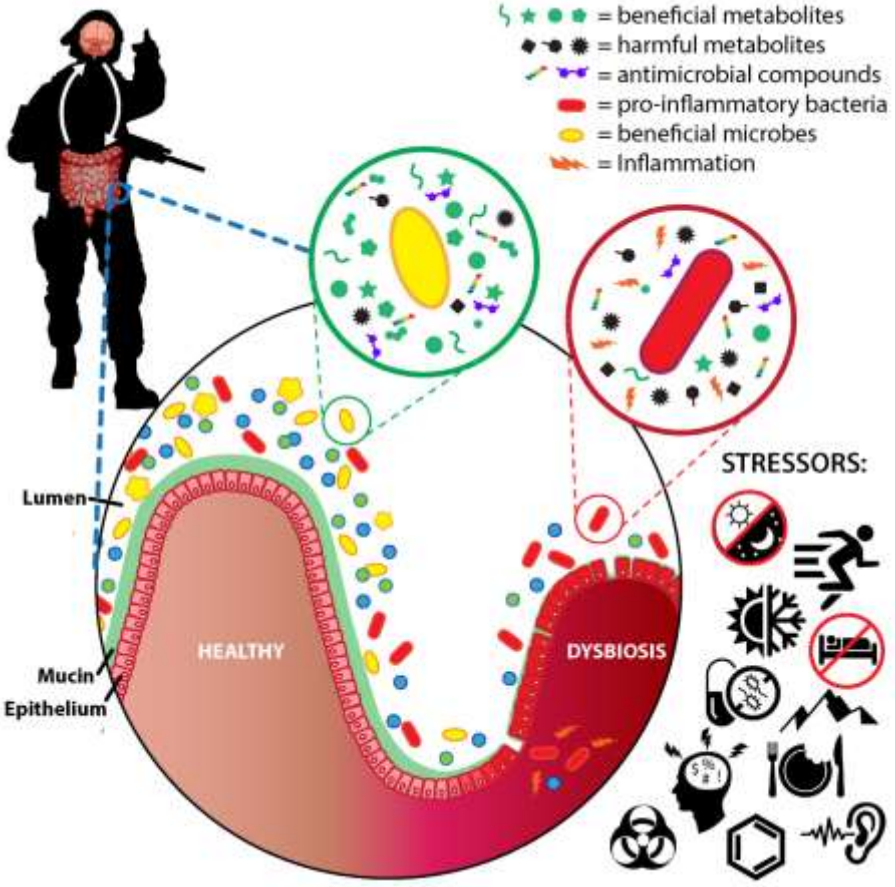
**High Altitude**
Kleessen et al., 2005

**Noise**

**Diet**

**Food Restriction**

**Diet Composition**



# Δίαιτα

## Η τροφή είναι ο σύνδεσμος της εντερικής χλωρίδας με το περιβάλλον

- Η διατροφή είναι κυρίαρχος παράγοντας, που επηρεάζει τη σύνθεση και τη δραστηριότητα της εντερικής χλωρίδας.
- Τόσο η βιοποικιλότητα όσο και οι μεταβολικές αποδόσεις της εντερικής χλωρίδας μεταβάλλονται μέσα σε λίγες ημέρες μετά από αλλαγές της δίαιτας,
- ένα αποτέλεσμα που πιστεύεται ότι συμβαίνει μέσω πολλαπλών αλληλένδετων οδών.

**(David et al Nature 2014; Read and Holmes, Front Immunol. 2017)**

*Nature*. 2014 January 23; 505(7484): 559–563. doi:10.1038/nature12820.

# Diet rapidly and reproducibly alters the human gut microbiome

**Lawrence A. David**[1,2,#], **Corinne F. Maurice**[1], **Rachel N. Carmody**[1], **David B. Gootenberg**[1], **Julie E. Button**[1], **Benjamin E. Wolfe**[1], **Alisha V. Ling**[3], **A. Sloan Devlin**[4], **Yug Varma**[4], **Michael A. Fischbach**[4], **Sudha B. Biddinger**[3], **Rachel J. Dutton**[1], and **Peter J. Turnbaugh**[1,*]

[1]FAS Center for Systems Biology, Harvard University, Cambridge, MA, 02138, USA.

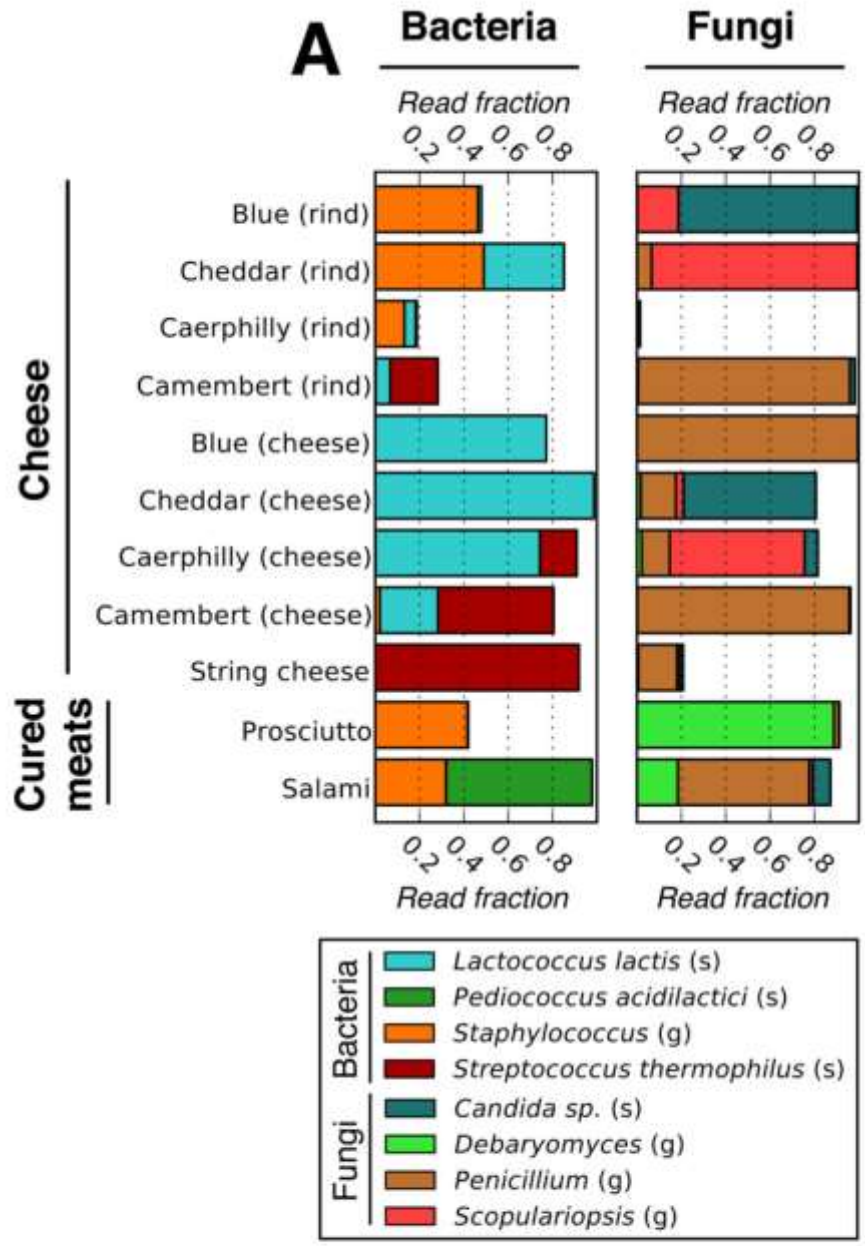
[2]Society of Fellows, Harvard University, Cambridge, MA, 02138, USA.

[3]Division of Endocrinology, Children's Hospital Boston, Harvard Medical School, Boston, MA, 02115, USA.

[4]Department of Bioengineering & Therapeutic Sciences and the California Institute for Quantitative Biosciences, University of California, San Francisco, San Francisco, CA, 94158, USA.

## Abstract

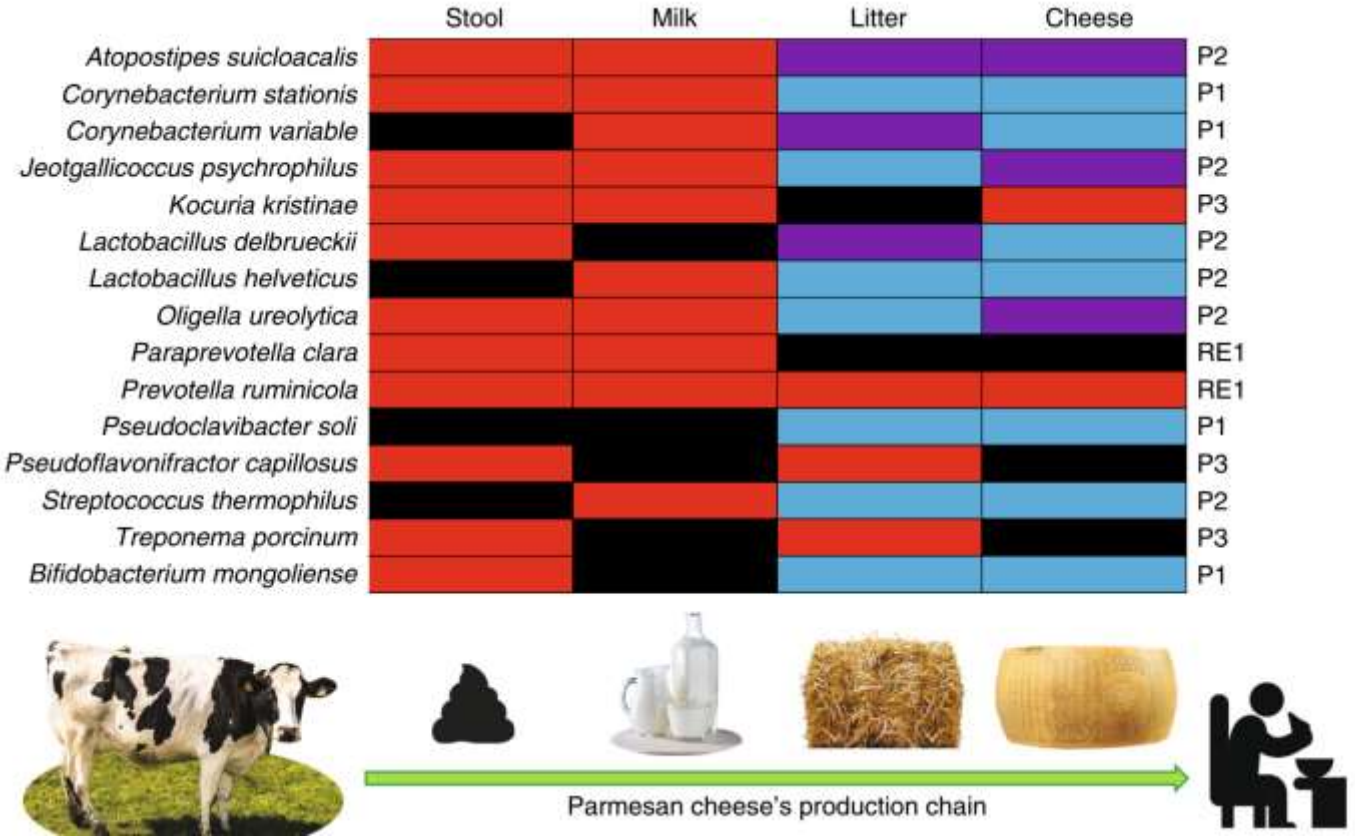
Long-term diet influences the structure and activity of the trillions of microorganisms residing in the human gut[1–5], but it remains unclear how rapidly and reproducibly the human gut microbiome responds to short-term macronutrient change. Here, we show that the short-term consumption of diets composed entirely of animal or plant products alters microbial community structure and overwhelms inter-individual differences in microbial gene expression. The animal-based diet increased the abundance of bile-tolerant microorganisms (*Alistipes, Bilophila*, and *Bacteroides*) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (*Roseburia, Eubacterium rectale*, and *Ruminococcus bromii*). Microbial activity mirrored differences between



# Colonization of the human gut by bovine bacteria present in Parmesan cheese

Christian Milani [1], Sabrina Duranti[1], Stefania Napoli[2], Giulia Alessandri[3], Leonardo Mancabelli[2],

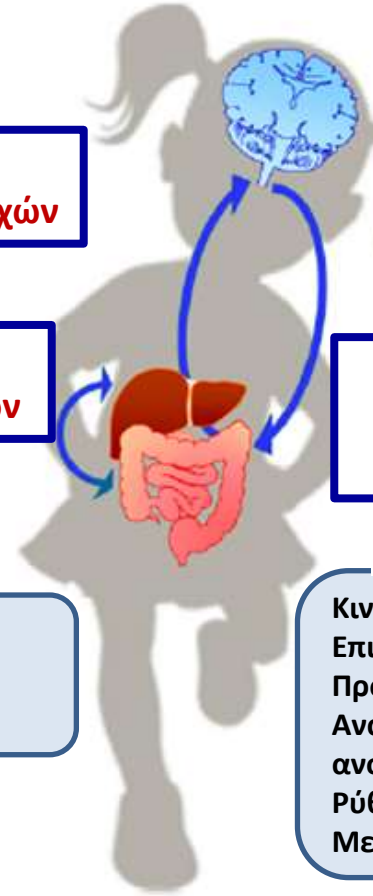
study showing that Bifidobacterium mongoliense strains from cheese can transiently colonize the human gut, a process that can be enhanced by cow milk consumption.




(NATURE COMMUNICATIONS | (2019) 10:1286 )

# Εντερική χλωρίδα και νοσολογία

# Μικροβίωμα – Ο ρόλος του στην υγεια?



**Άξονας Μικροβιώματος –Ανοσολογικών διαταραχών**

**Άξονας Μικροβιώματος –Μεταβολικών νόσων**

**Άξονας Μικροβιώματος – Εγκεφάλου**

**Λειτουργία ΚΝΣ**

- Γνωστική λειτουργία
- Διάθεση
- Άγχος
- Stress

**Μεταβολισμός**

- Πρόσληψη/αποθήκευση ενέργειας
- Παραγωγή SCFA
- Σύνθεση βιταμινών

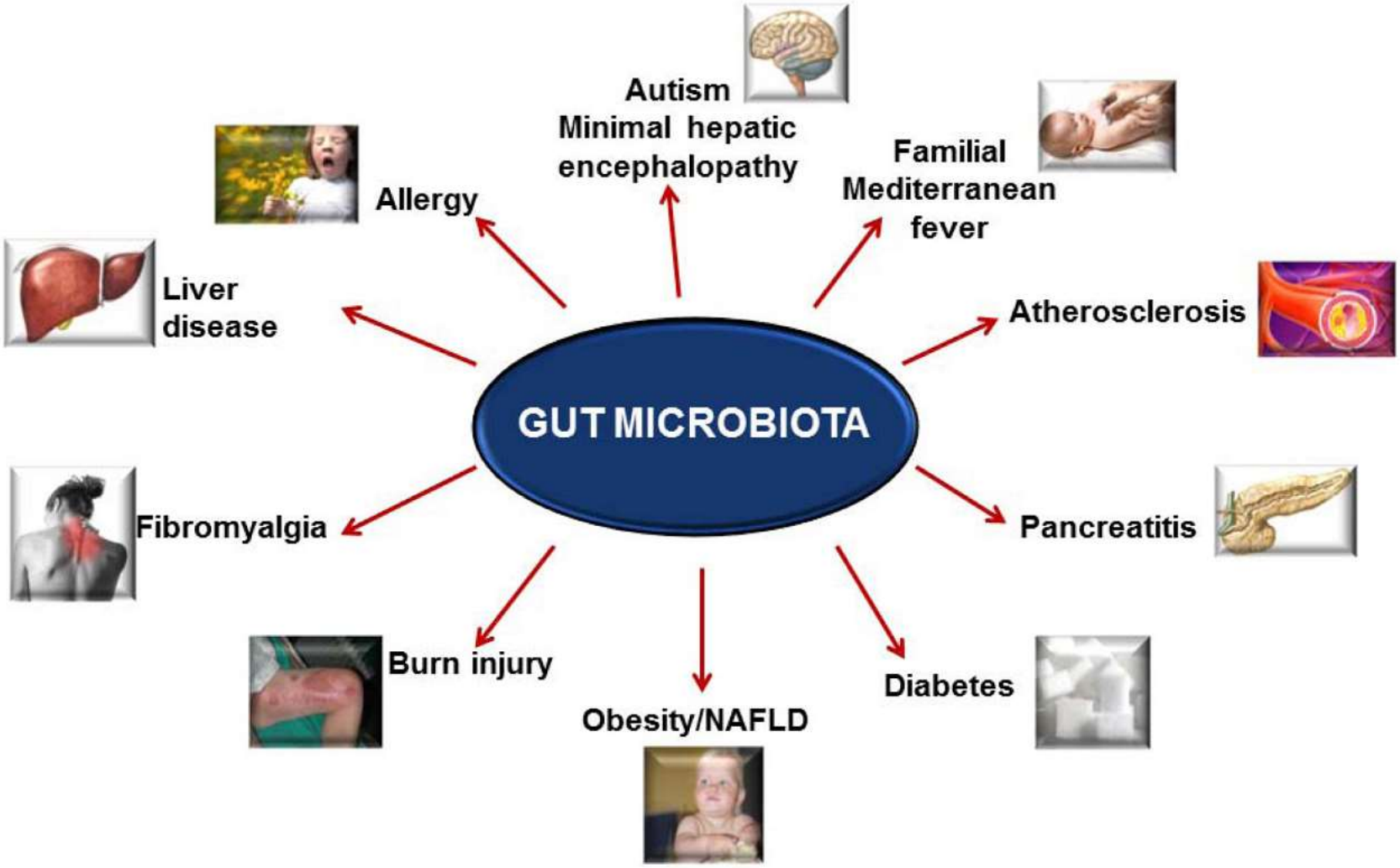
**Εντερική λειτουργία**

- Κινητικότητα εντέρου
- Επιθηλιακός φραγμός/λειτουργία
- Προστασία από παθογόνα
- Ανάπτυξη και ομοιόσταση ανοσοποιητικού συστήματος
- Ρύθμιση φλεγμονής
- Μεταβολισμός ξενοβιωτικών

**(American Society for Nutrition Adv. Nutr. 2016;7:323-330)**

# Δυσβίωση ως νοσογόνος μηχανισμός

## Το φάσμα των παθήσεων με πιθανή συμμετοχή του μικροβιώματος

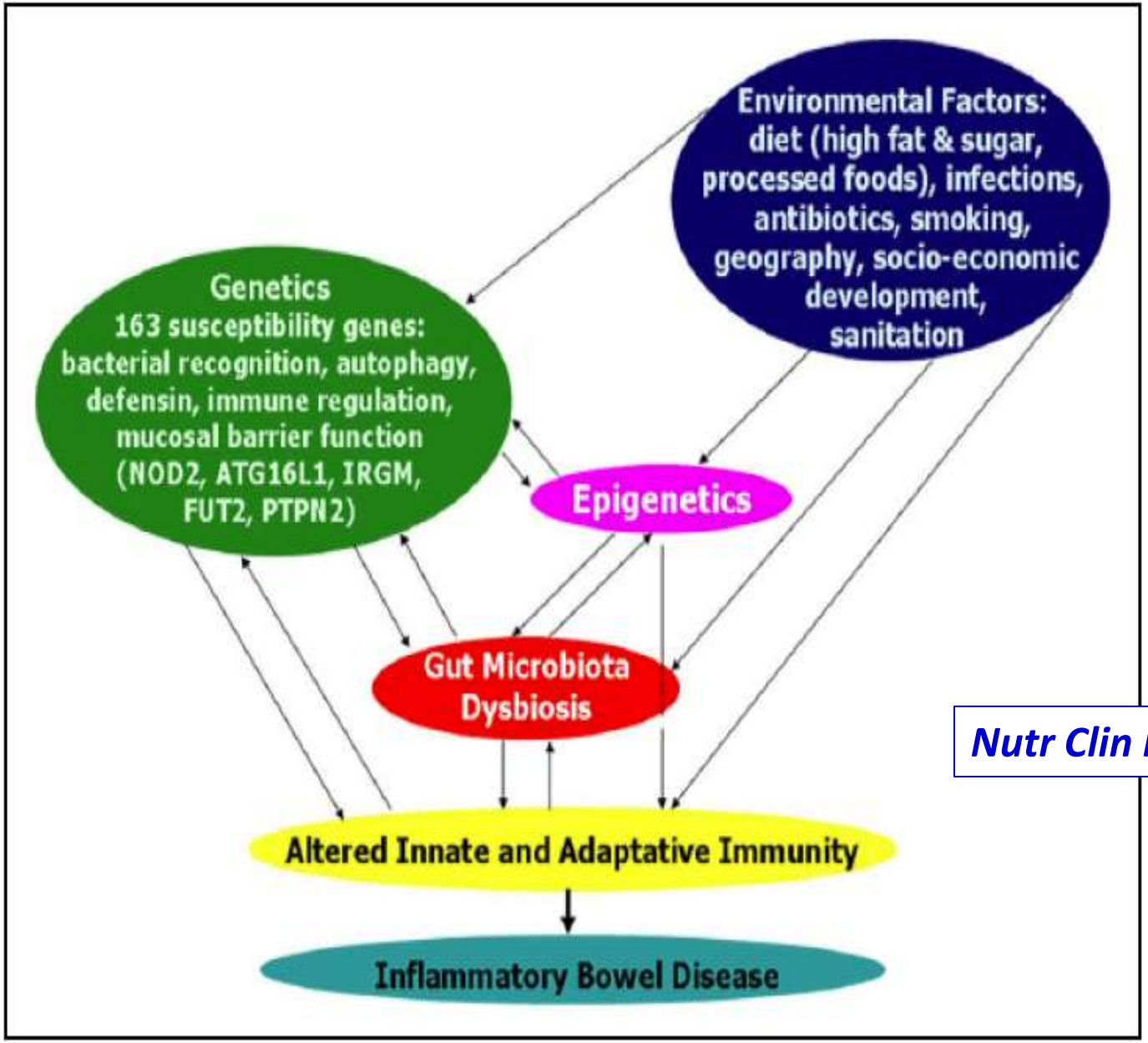


Disease associations with the intestinal microbial community (examples).

| | References |
|---|---|
| Allergies/Allergy protection | [23,59,64–66] |
| Atherosclerosis/Thrombosis/Cardiovascular Diseases | [46–48,67–70] |
| Cancer | [40,71,72] |
| Diabetes mellitus | [42,73] |
| Immune-Mediated Inflammatory Diseases | |
| –Inflammatory bowel diseases | [26,27,30,31,74,75] |
| –Multiple sclerosis | [76,77] |
| –Rheumatoid arthritis | [78] |
| –Psoriasis | [79] |
| Kwashiorkor | [43,44] |
| Liver Diseases | [80,81] |
| Metabolic Syndrome/Obesity | [41,82–85] |
| Neurodevelopmental, Psychiatric and Neuro-degenerative diseases | |
| –Autism | [49,86] |
| –Depression | [49,87] |
| –Alzheimer's Disease, Parkinson's Disease | [49,53,54,88,89] |

(Hubert E. Blum. Advances in Medical Sciences 2017)

# Inflammatory Bowel Diseases




*Nutr Clin Pract 2015*

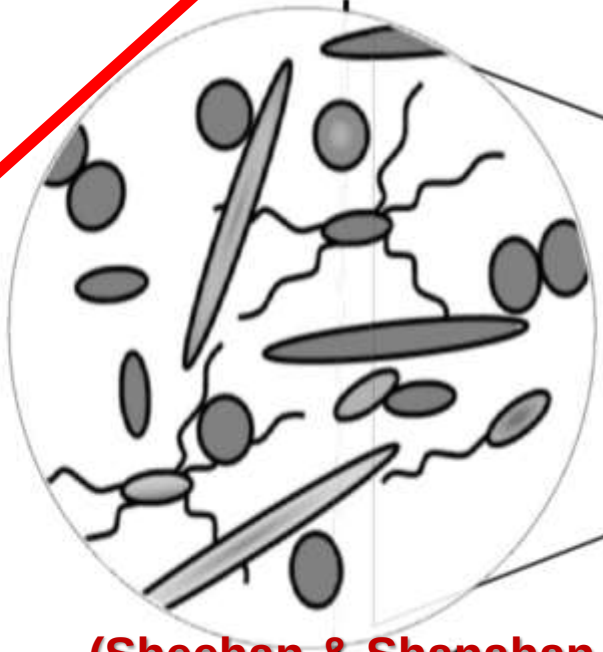
| Increased in IBD | Decreased in IBD |
|---|---|
| • Mucosal bacterial numbers | • Diversity |
| • Adherent–invasive *Escherichia coli* | • Bacteriodes |
| • *Enterobacteriaceae* | • Clostridia |
| • *Fusobacteriaceae* | • *Bifidobacteriaceae* |
| • *Mycobacterium avium paratuberculosis* | • *Faecalibacterum prausnitizi* |
| • *Clostridium difficile* | |

**Archaea???**

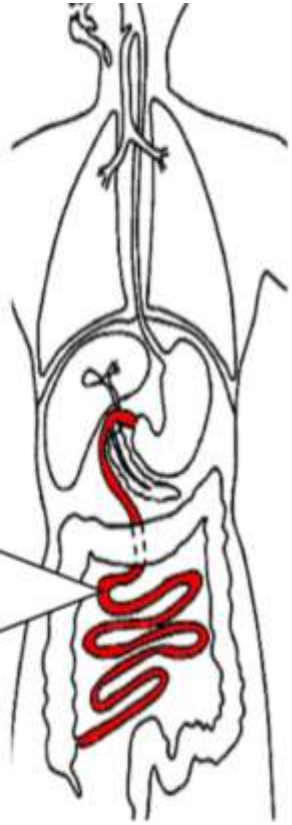
Lifestyle & Environment

- Antibiotics
- Sanitation & hygiene
- Urbanisation
- Reduced parasitism
- Decline in *H. pylori*
- Family size
- Refrigeration
- Diet
- Sedentary life

Loss of ancestral organisms
('old friends')



Intestinal & Immune Development



(Sheehan & Shanahan. Gastroenterol Clin N Am 2016)

# Gut microbiota in the pathogenesis of inflammatory bowel disease

Atsushi Nishida[1] · Ryo Inoue[2] · Osamu Inatomi[1] · Shigeki Bamba[1] · Yuji Naito[3] · Akira Andoh[1]

## Dysbiosis in IBD

- Reduced diversity of the microbiota (Decrease of Firmicutes)
- Decrease of SCFA-producing bacteria (Decrease of *Clostridium* cluster IV, XIVa, XVII and *Faecalibacterium prausnitzzi*)
- Increase of mucolytic bacteria (*Ruminococcus gnavas*, *Ruminococcus torques*)
- Increase of sulfate-reducing bacteria (*Desulfovibrio*)
- Increase of pathogenic bacteria (Adhesion/invasive *E. coli*)

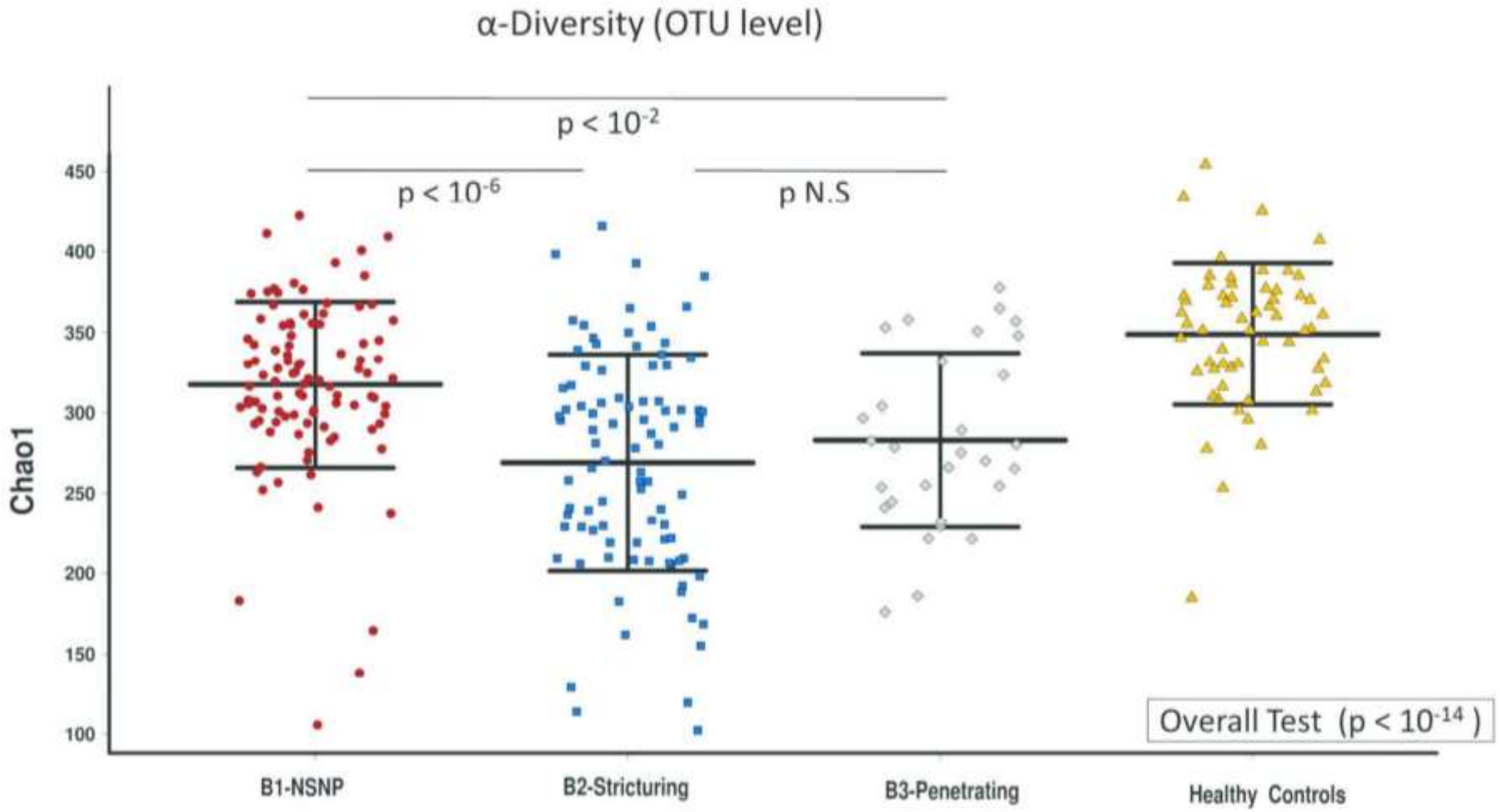
## Outcome in host immune systems and mucosal integrity

- Decrease of energy source in epithelial cell growth and differentiation
- The alteration of regulatory T cell differentiation
- Degradation of mucus
- Increase of bacterial invasion
- Enhancement of epithelial cells damage
- Induction of mucosal inflammation
- Alteration of mucosal permeability

(Clinical Journal of Gastroenterology 2018)

# Gut Microbial Signatures Underline Complicated Crohn's Disease but Vary Between Cohorts: An In Silico Approach

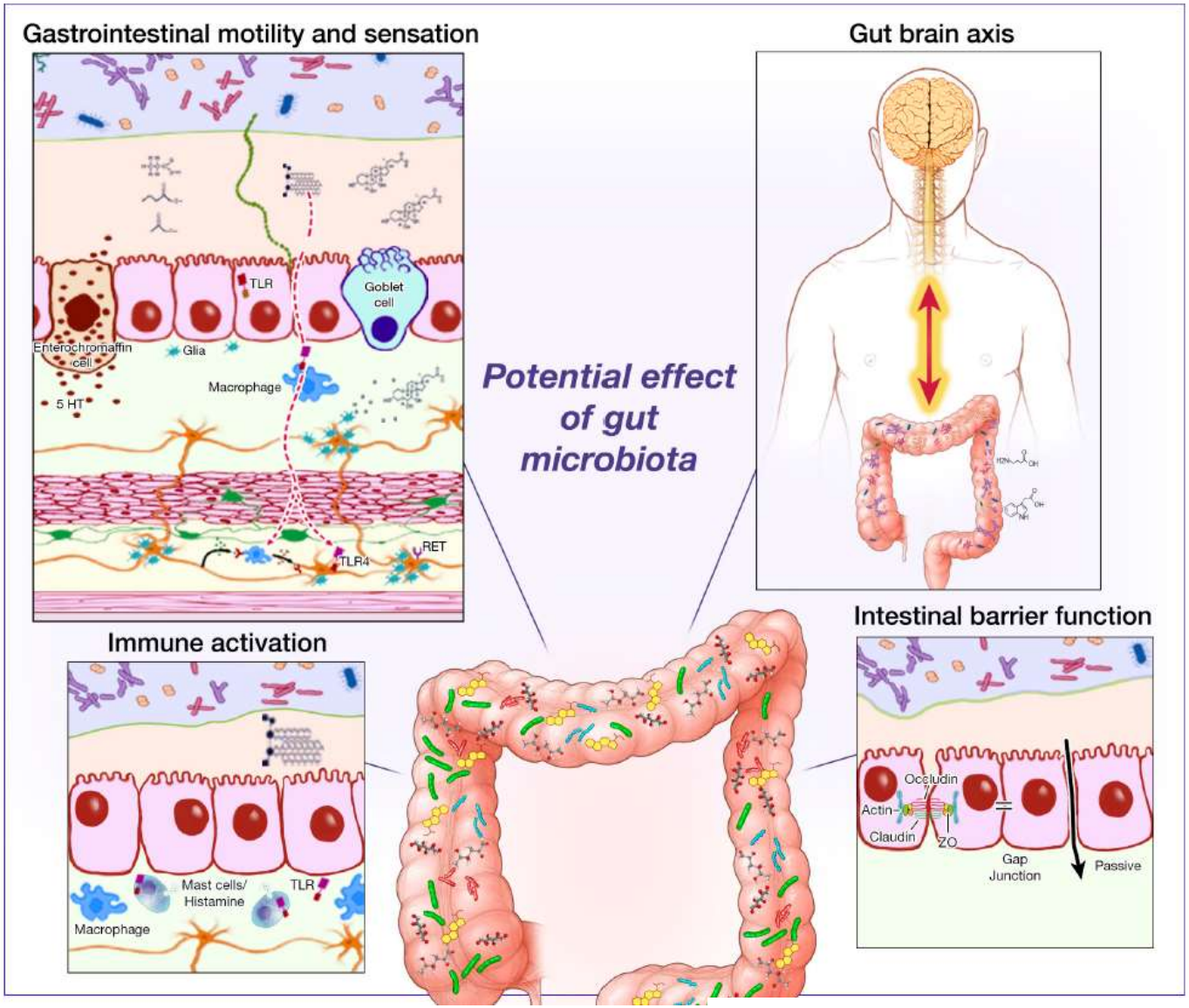
*Nikolas Dovrolis, MSc,[*,§] Ioannis Drygiannakis, MD, PhD,[†] Eirini Filidou, PhD,[*] Leonidas Kandilogiannakis, MSc,[*] Konstantinos Arvanitidis, PhD,[*] Ioannis Tentes, PhD,[‡] George Kolios, MD, PhD,[*] and Vassilis Valatas, MD, PhD[†]*




**(Dovrolis et al. Inflamm Bowel Dis. 2019)**

# Irritable bowel syndrome: a gut microbiota-related disorder?

Yogesh Bhattarai,[1,2] David A. Muniz Pedrogo,[1,2] and Purna C. Kashyap[1,2]




(Am J Physiol Gastrointest Liver Physiol , 2016)

# Similar Fecal Microbiota Signatures in Patients With Diarrhea-Predominant Irritable Bowel Syndrome and Patients With Depression

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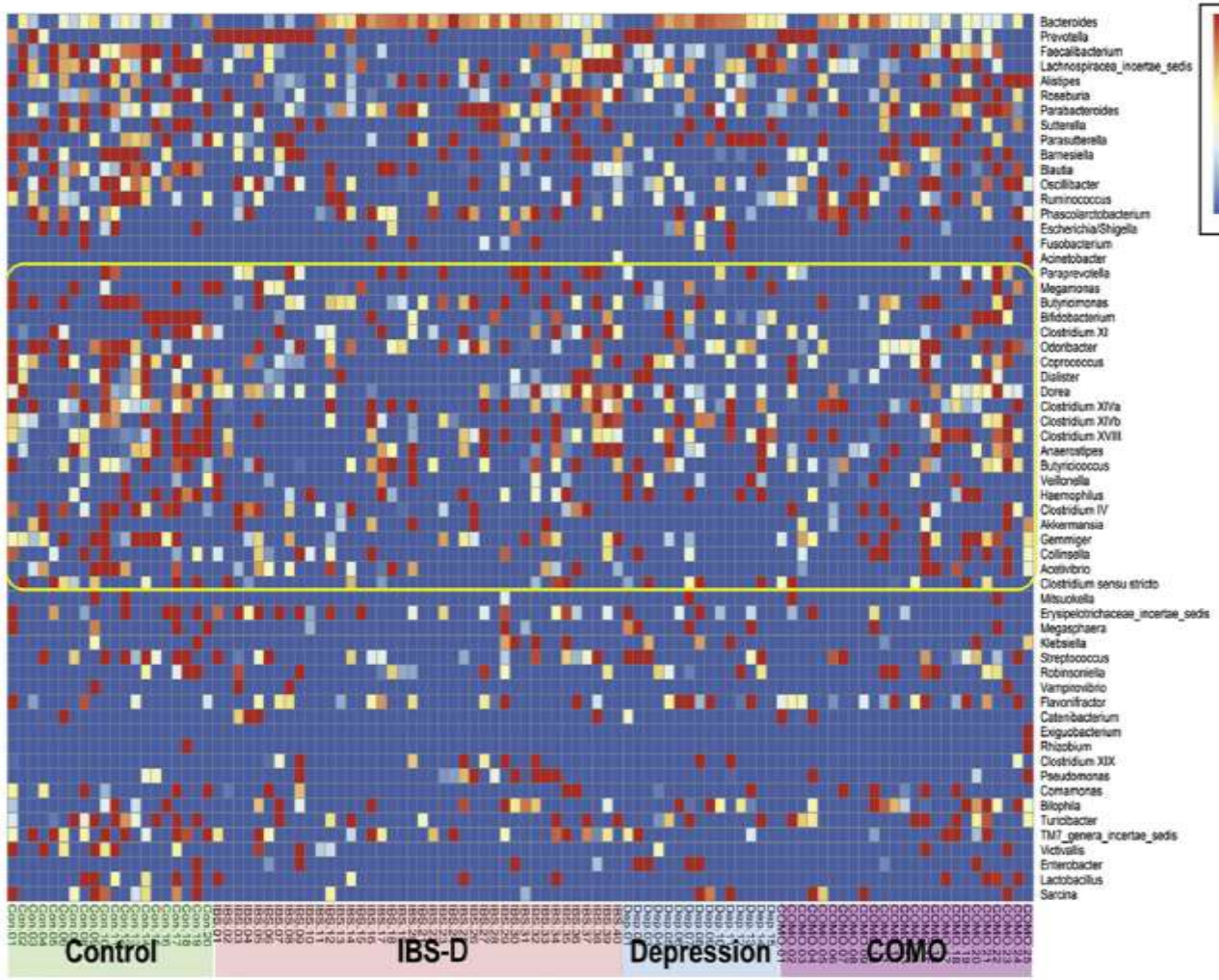
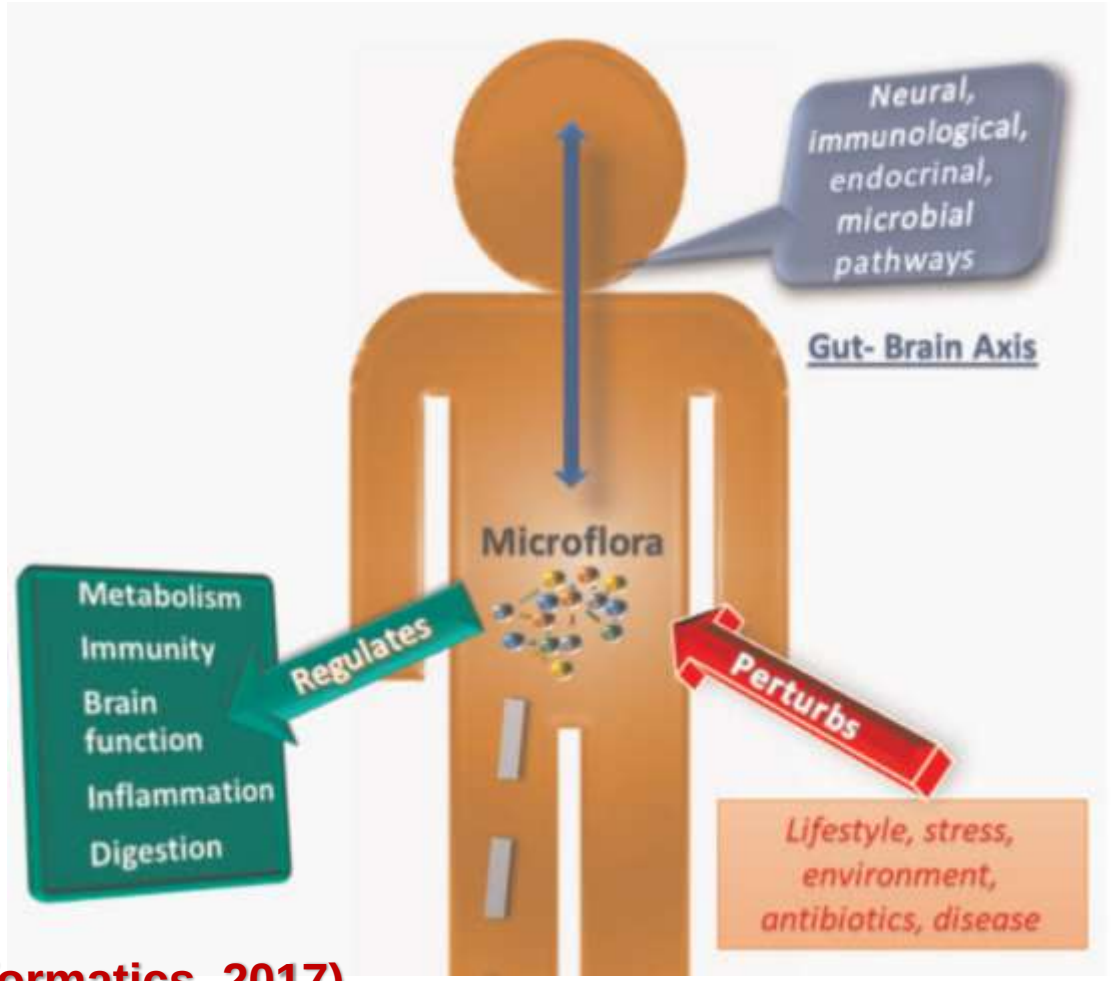



Clinical Gastroenterology and Hepatology 2016;14:1602–1611

# Computational profiling of the gut–brain axis: microflora dysbiosis insights to neurological disorders

Nikolas Dovrolis, George Kolios, George M. Spyrou and Ioanna Maroulakou

Corresponding author: Ioanna Maroulakou, Laboratory of Genetics, Department of Molecular Biology & Genetics, Democritus University of Thrace, Alexandroupolis, 68100, Greece. Tel.: +30-25510-30666; E-mail: imaroula@mbg.duth.gr




**(Briefings in Bioinformatics, 2017)**

# New perspectives of *Lactobacillus plantarum* as a probiotic: The gut-heart-brain axis

**(Liu et al. Journal of Microbiology 2018)**

Table 1. *Lactobacillus plantarum* strains with efficacy against inflammatory bowel diseases (IBD), dyslipidemia, hypercholesterolemia and diabetes in *in vivo* models

| Strains of *Lactobacillus plantarum* | Experimental model | Dose used in the study | Mechanisms/Efficacy | Reference |
|---|---|---|---|---|
| **Alleviation of inflammatory bowel diseases (IBD)** | | | | |
| *Lactobacillus plantarum* 21 (LAB21) | Colonic injection of TNBS (31 mg/kg) induces UC in female Wistar rats | Oral administration of $1 \times 10^{10}$ CFU/rat/day for 2 weeks | 1. Immunomodulation: upregulated IL-10 and downregulated IL-1β.<br>2. Antioxidation: increased the glutathione concentration and decreased lipid | Satish Kumar *et al.* (2015) |
| *Lactobacillus pl* | | | | |
| *Lactobacillus pl* | | | | |
| *Lactobacillus pl* | | | | *l.* |
| *Lactobacillus pl* CCM7766 | inflammation in female Sprague Dawley (SD) rats. | | concentrations of IL-2, IL-6, IL-17, and TNF-α. | *al.* |
| *Lactobacillus plantarum* CLP-0611 | Male ICR mice intrarectally injected with TNBS (2.5 mg/mouse) to induce colitis. | Oral administration of $1 \times 10^{8}$ or $1 \times 10^{9}$ CFU/mouse/day for 3 days | 1. Anti-inflammation: reduced colonic MPO activity, iNOS, COX-2, TNF-α, IL-6, and IL-1β.<br>2. Inhibition of the NF-κB and MAPK signaling pathways. | Jang *et al.* (2014) |

the classification and taxonomy, and the relation of these with safety aspects are introduced. Characteristics of *L. plantarum* to fulfill the criteria as a probiotic are discussed. Emphasis are also given to the beneficial functions of *L. plantarum* in gut disorders such as inflammatory bowel diseases, metabolic syndromes, dyslipidemia, hypercholesteromia, obesity, and diabetes, and brain health aspects involving psychological disorders.

OPEN ACCESS

ORIGINAL RESEARCH

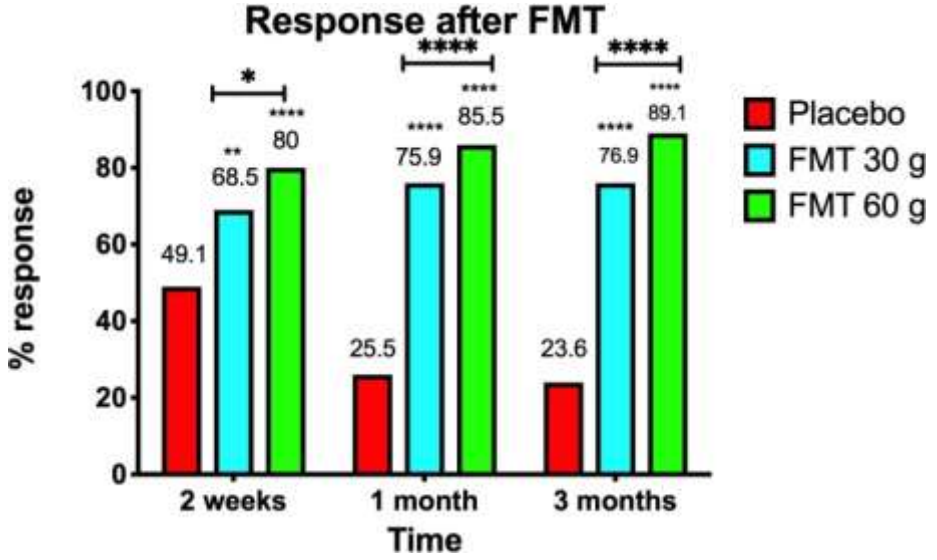
# Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study

(Gut 2020)

Magdy El-Salhy ,[1,2] Jan Gunnar Hatlebakk,[2] Odd Helge Gilja,[2] Anja Bråthen Kristoffersen [3] Trygve Hausken[2]

Gut: first published as 10

**Design** This randomised, double-blind, placebo-controlled study randomised 165 patients with IBS to placebo (own faeces), 30 g FMT or 60 g FMT at a ratio of 1:1:1. The material for FMT was obtained from one healthy, well-characterised donor, frozen and administered via gastroscope. The primary outcome was a reduction in the IBS symptoms at 3 months after FMT (response). A response was defined as a decrease of 50 or more points in the total IBS symptom score. The secondary outcome was a reduction in the dysbiosis index (DI) and a change in the intestinal bacterial profile, analysed by 16S rRNA gene sequencing, at 1 month following FMT.




**Conclusions** FMT is an effective treatment for patients with IBS. Utilising a well-defined donor with a normal DI and favourable specific microbial signature is essential for successful FMT. The response to FMT increases with the dose.

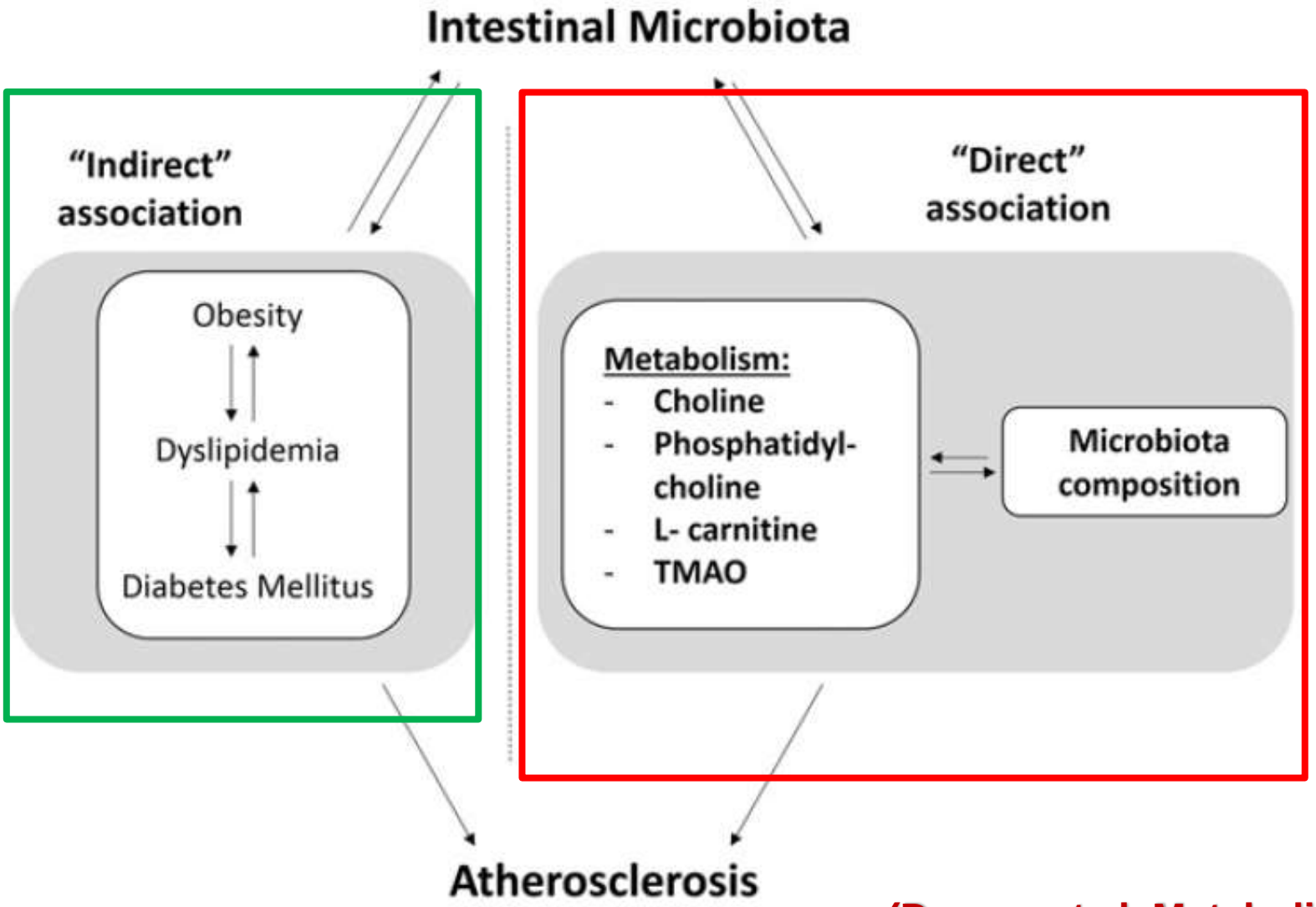
# Broken Biome or Broken Host?

- Is this an abnormal immune response to a normal microbiota or is this an appropriate response to an abnormal microbiota?
- It is now clear from various animal models that both situations may arise and may overlap.
- Genetically determined anomalies of the innate immune system can lead to a modification of the microbiota, which becomes colitogenic upon transfer to an otherwise normal recipient.
- In addition, because the microbiota shapes the maturation of the immune system in early life, any disruption of the microbiota such as that caused by antibiotic exposure may lead to suboptimal immunity and/or risk of IBD in later life

**(Sheehan & Shanahan. Gastroenterol Clin N Am - (2016)**

# New Aspects on the Metabolic role of Intestinal Microbiota in the Development of Atherosclerosis

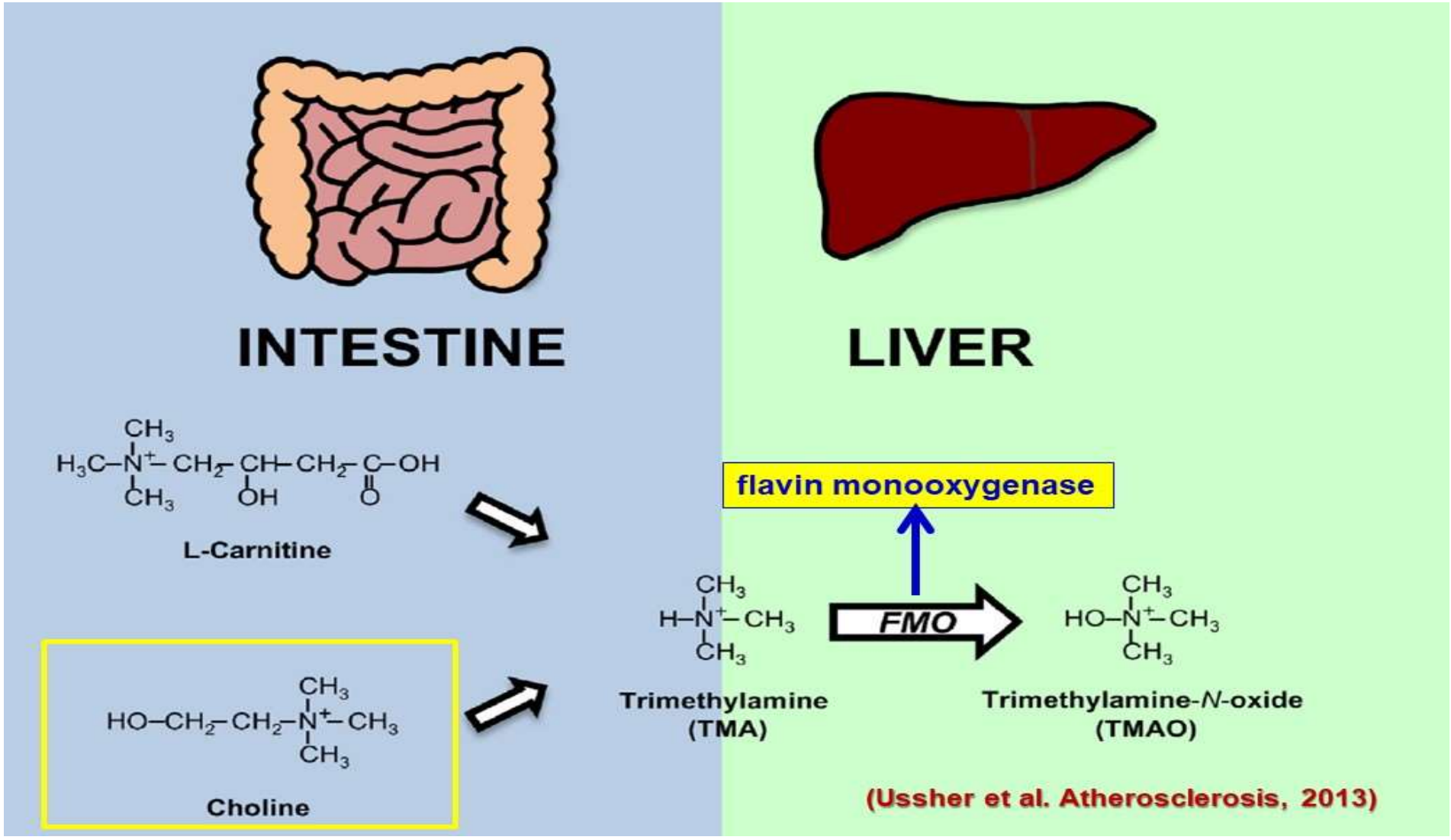
*Ioannis Drosos, Anna Tavridou*, George Kolios*



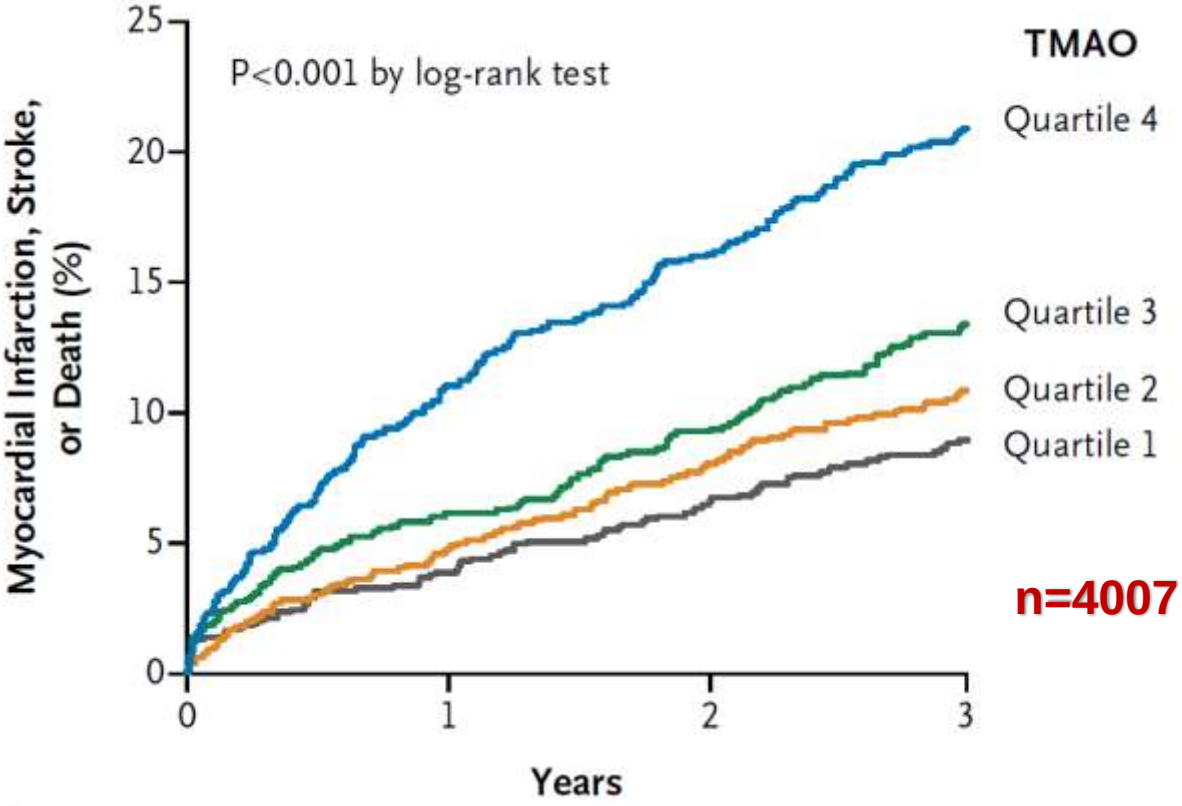

(Drosos et al. Metabolism 2015)

*Nature*. 2011 April 7; 472(7341): 57–63. doi:10.1038/nature09922.

# Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease



# Kaplan–Meier Estimates of Major Adverse Cardiovascular Events, According to the Quartile of TMAO Level




**The quartiles of TMAO levels are as follows:**

- ✓**quartile 1, less than 2.43 μM;**
- ✓**quartile 2 2.43 to 3.66 μM;**
- ✓**quartile 3, 3.67 to 6.18 μM; and**
- ✓**quartile 4, more than 6.18 μM.**

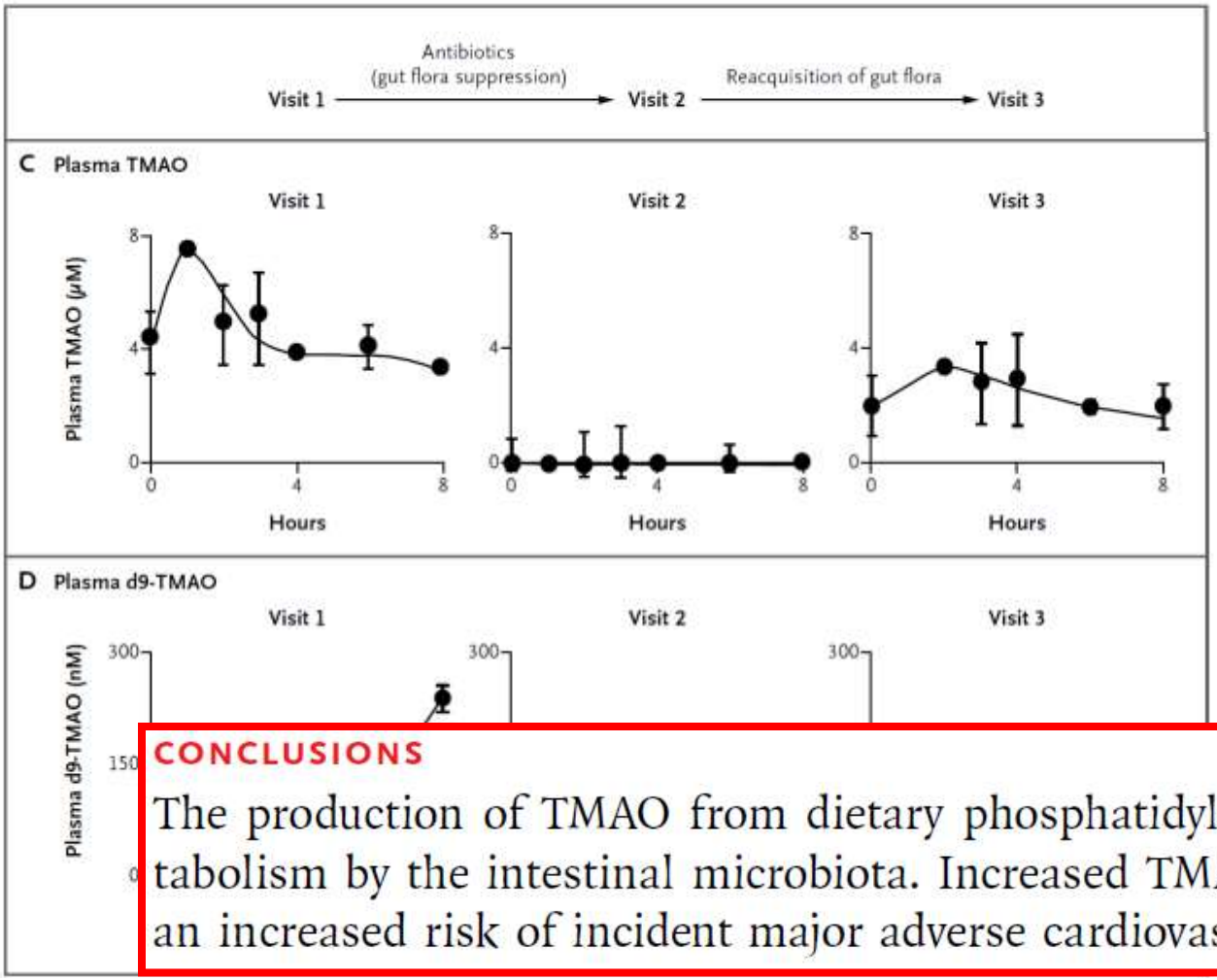
**n=4007**

**(Wilson Tang et al. NEJM 2013)**

**Table 2. Risk of a Major Adverse Cardiovascular Event at 3 Years, According to Quartile of TMAO Level.***

| Risk of Event | TMAO Level | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | | Quartile 3 | | Quartile 4 | |
| | reference | hazard ratio (95% CI) | P value | hazard ratio (95% CI) | P value | hazard ratio (95% CI) | P value |
| Unadjusted hazard ratio | 1.00 | 1.24 (0.93–1.66) | 0.15 | 1.53 (1.16–2.02) | 0.003 | 2.54 (1.96–3.28) | <0.001 |

# Effects of a Phosphatidylcholine Challenge and Administration of Antibiotics on Mean Levels of Trimethylamine-*N*-Oxide (TMAO) and Its d9 Isotopologue (d9-TMAO).




**Dietary phosphatidylcholine challenge:**
- ✓**deuterium-labeled phosphatidylcholine (250 mg d9-phosphatidylcholine) and**
- ✓**two hard-boiled eggs (appr. 250 mg of total choline each).**

**Broad-spectrum antibiotics for 1 week:**
- ✓**metronidazole (500 mg twice daily)**
- ✓**ciprofloxacin (500 mg once daily)**

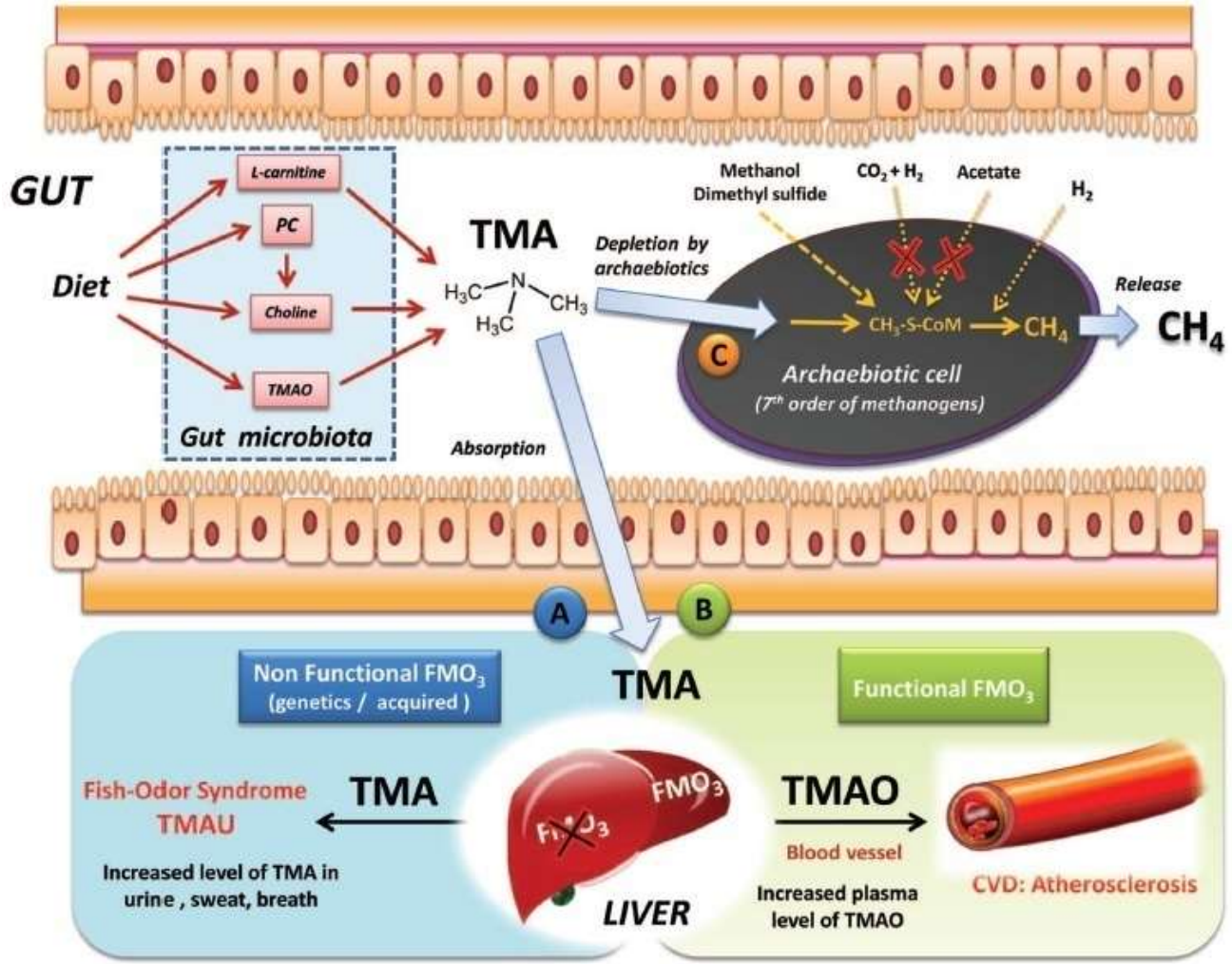
**CONCLUSIONS**

The production of TMAO from dietary phosphatidylcholine is dependent on metabolism by the intestinal microbiota. Increased TMAO levels are associated with an increased risk of incident major adverse cardiovascular events.

**(Wilson Tang et al. NEJM 2013)**

# Archaebiotics

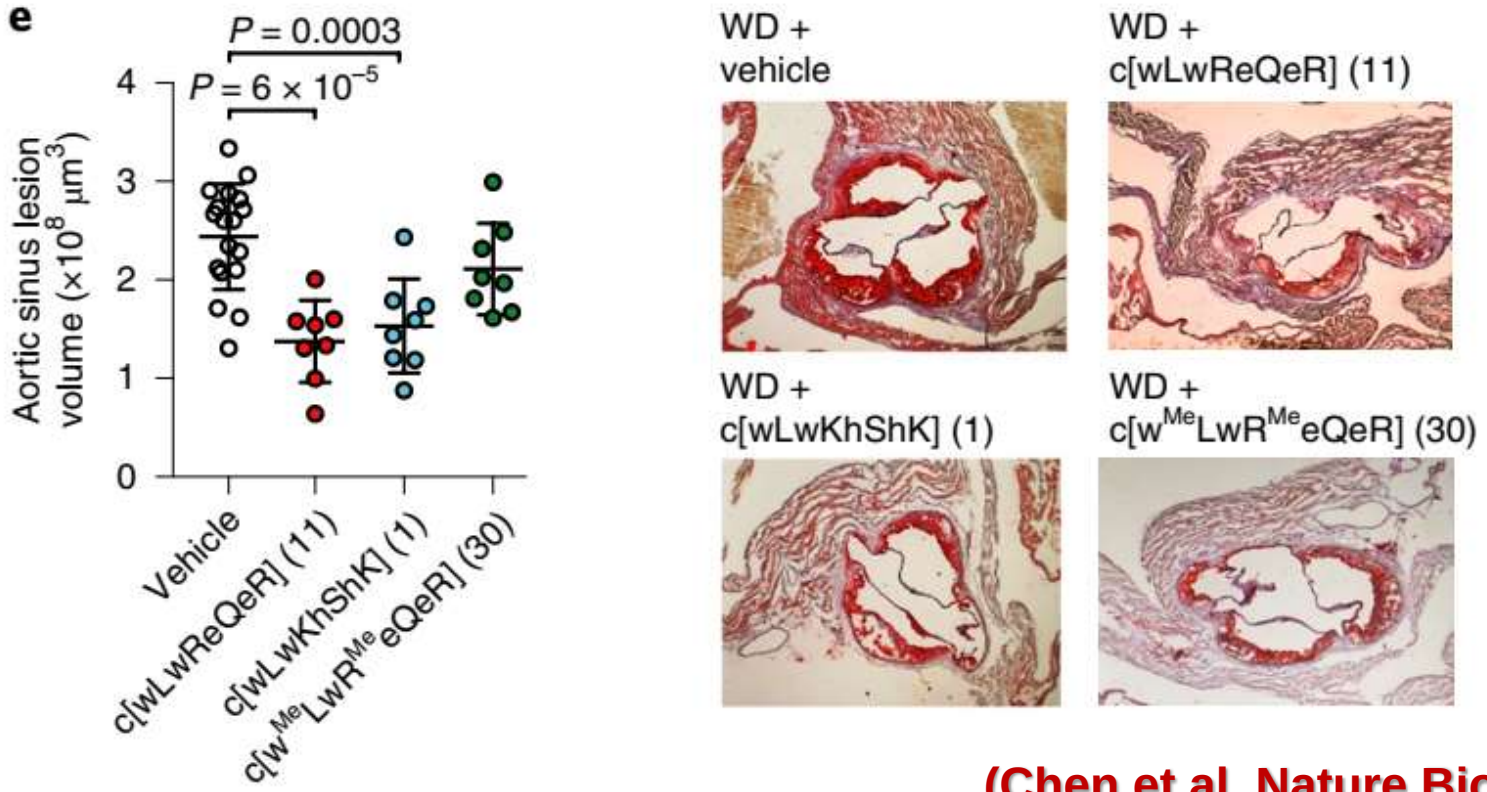
## Proposed therapeutic use of archaea to prevent trimethylaminuria and cardiovascular disease




(Brugere et al. Gut Microbes 2014)

# Directed remodeling of the mouse gut microbiome inhibits the development of atherosclerosis

**of the mouse gut microbiome to discover molecules that can selectively modify bacterial growth. This approach was used to identify cyclic D,L-α-peptides that remodeled the Western diet (WD) gut microbiome toward the low-fat-diet microbiome state. Daily oral administration of the peptides in WD-fed *LDLr*$^{-/-}$ mice reduced plasma total cholesterol levels and atherosclerotic plaques. Depletion of the microbiome with antibiotics abrogated these effects. Peptide treatment reprogrammed the microbiome transcriptome, suppressed the production of pro-inflammatory cytokines (including interleukin-6, tumor necrosis factor-α and interleukin-1β), rebalanced levels of short-chain fatty acids and bile acids, improved gut barrier integrity and increased intestinal T regulatory cells. Directed chemical manipulation provides an additional tool for deciphering the chemical biology of**

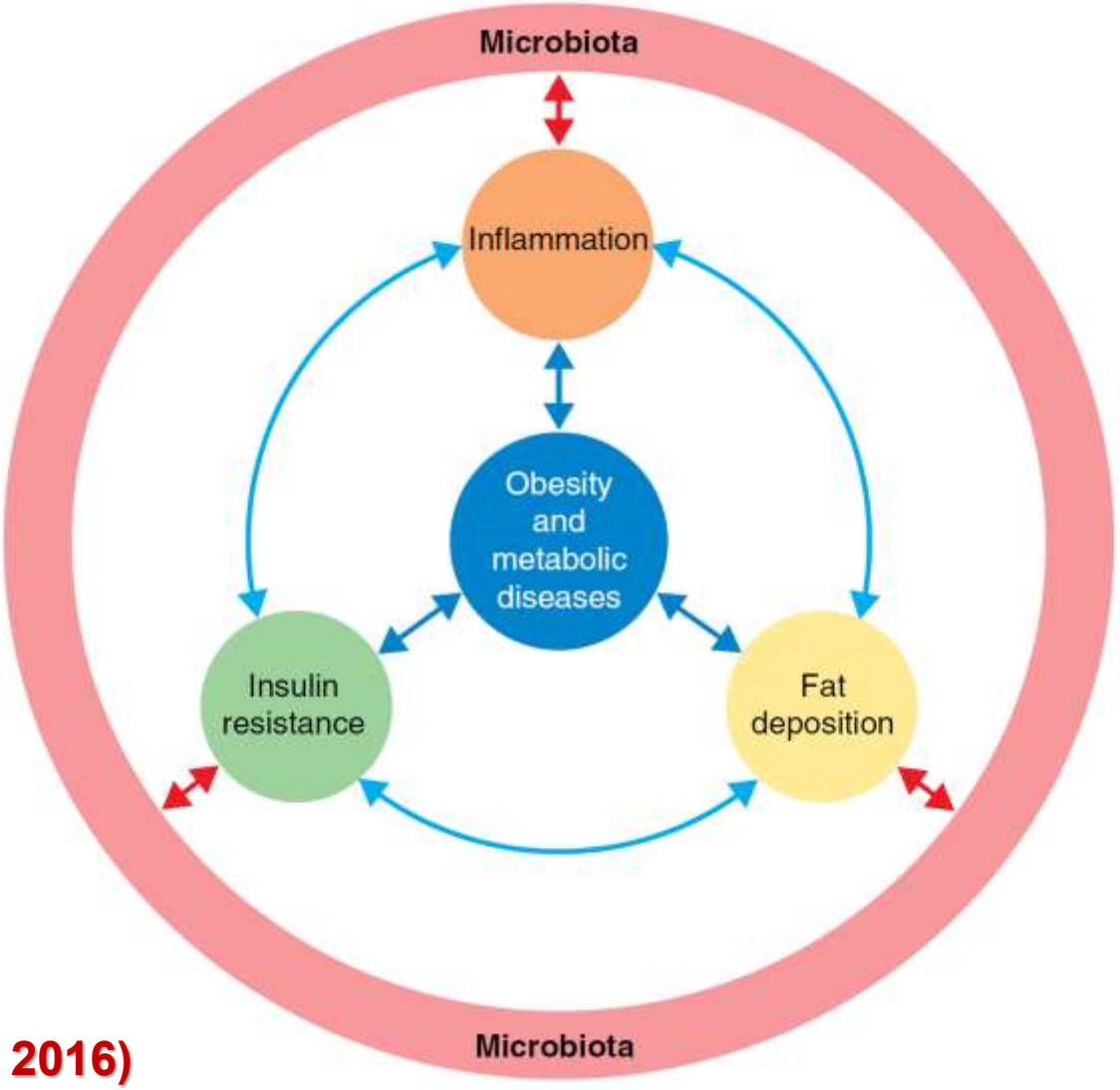



(Chen et al. Nature Biotech. 2020)

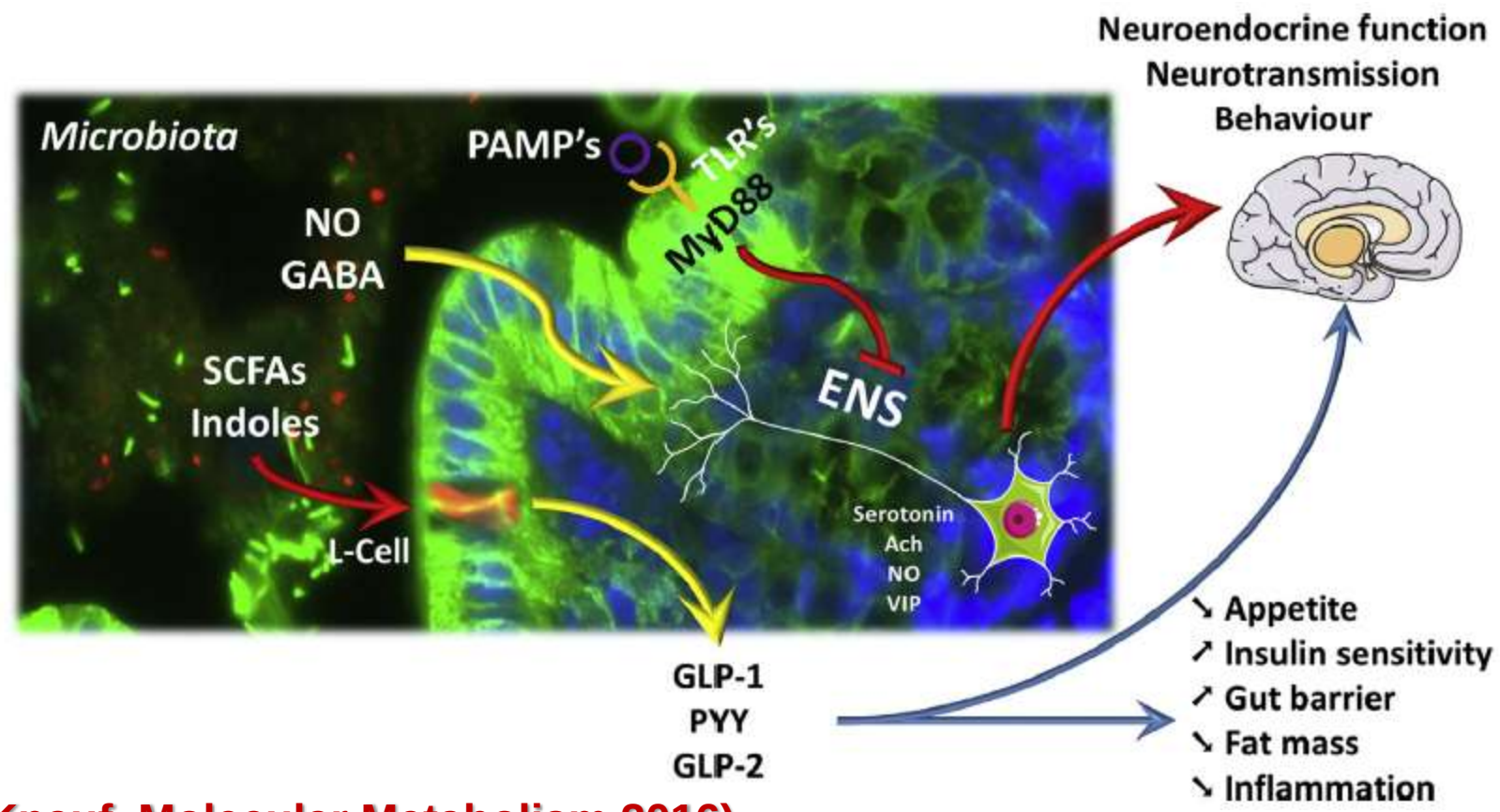
# Gut Microbiota and metabolic disease

- The gut microbiota can contribute to:
- ✓ host insulin resistance,
- ✓ low grade inflammation, and
- ✓ fat deposition

- through a range of molecular interactions with the host and therefore can indirectly participate in the onset of obesity and metabolic diseases




**(Boulangé et al. Genome Medicine 2016)**




**(Cani & Knauf. Molecular Metabolism 2016)**

- SCFAs and Indoles are recognized by specific Gprotein coupled receptors expressed at the surface of enteroendocrine cells such as L-cells, producing GLP-1, GLP-2, and PYY.
- Secondary messengers, including NO, serotonin, acetylcholine (Ach) or vasoactive intestinal polypeptide (VIP) release, are involved in the brain axis.
- Pathogen-associated molecular patterns (PAMPs) are recognized by Toll-Like receptors (TLR's) regulate numerous metabolic functions such as for instance leptin sensitivity, gut hormones signaling to the brain, hence controlling whole-body energy homeostasis.

# Acetate mediates a microbiome–brain–β-cell axis to promote metabolic syndrome

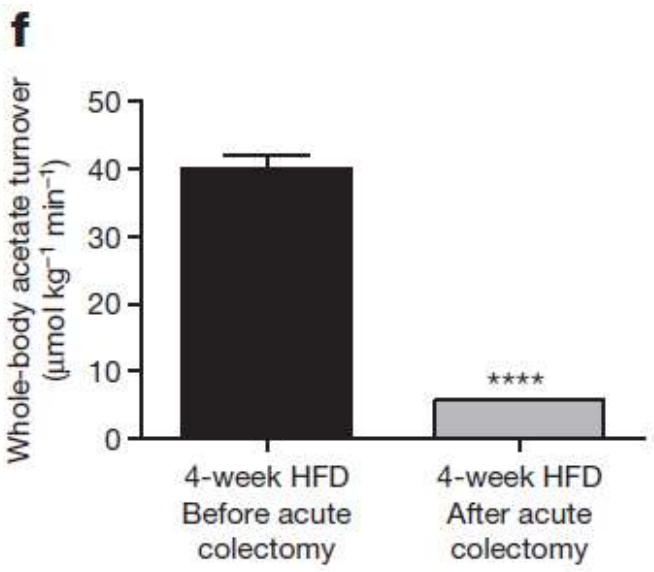
Rachel J. Perry[1], Liang Peng[1], Natasha A. Barry[2,3], Gary W. Cline[1], Dongyan Zhang[4], Rebecca L. Cardone[1], Kitt Falk Petersen[1,5], Richard G. Kibbey[1,6], Andrew L. Goodman[2,3] & Gerald I. Shulman[1,4,5,6]

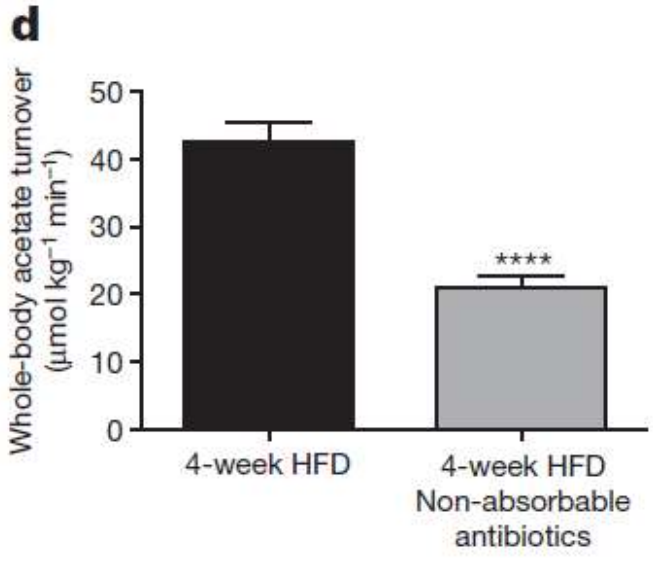
**Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06520, USA**

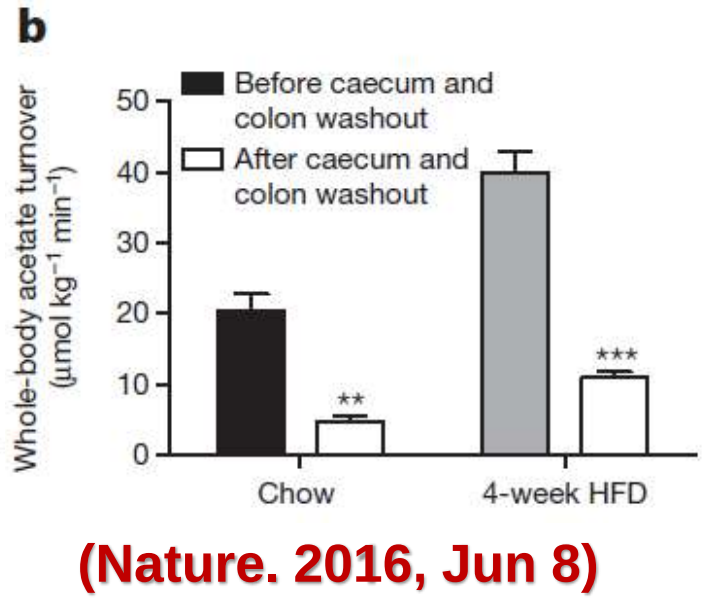
centrations may not fully represent the SCFA load presented to the body, we developed a method to measure whole-body turnover rates of acetate, propionate, and butyrate by gas chromatography–mass spectrometry (GC–MS; as described in the Supplementary Methods) and found that, in contrast to propionate and butyrate, whole-body acetate turnover as well as plasma and faecal acetate concentrations were markedly increased in insulin-resistant rats after 3 days or 4 weeks on a high-fat diet (HFD) (Fig. 1a, b and Extended Data Fig. 2a–j).

Next we sought to determine the source of the increased acetate turnover in HFD-fed rats. We measured tissue acetate concentrations and

ectopic lipid deposition in liver and skeletal muscle, and liver and muscle insulin resistance (Extended Data Fig. 1). The increased acetate production that occurs when the gut microbiota are exposed to calorically dense nutrients may mediate an important positive feedback loop between the gut microbiota and the CNS that promotes hyperphagia (due to increased ghrelin secretion) and increased energy storage as fat (due to increased GSIS) in foraging animals when they stumble across calorically dense foodstuffs in the wilderness. However, in the setting of chronic exposure to calorically




**(Nature. 2016, Jun 8)**

# Microbial signals to the brain control weight

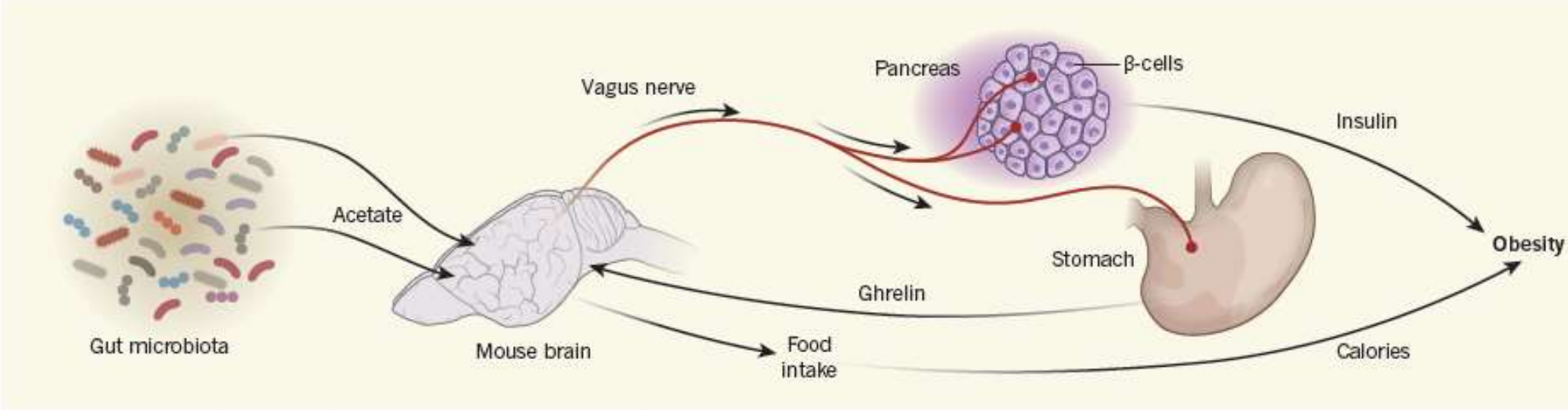
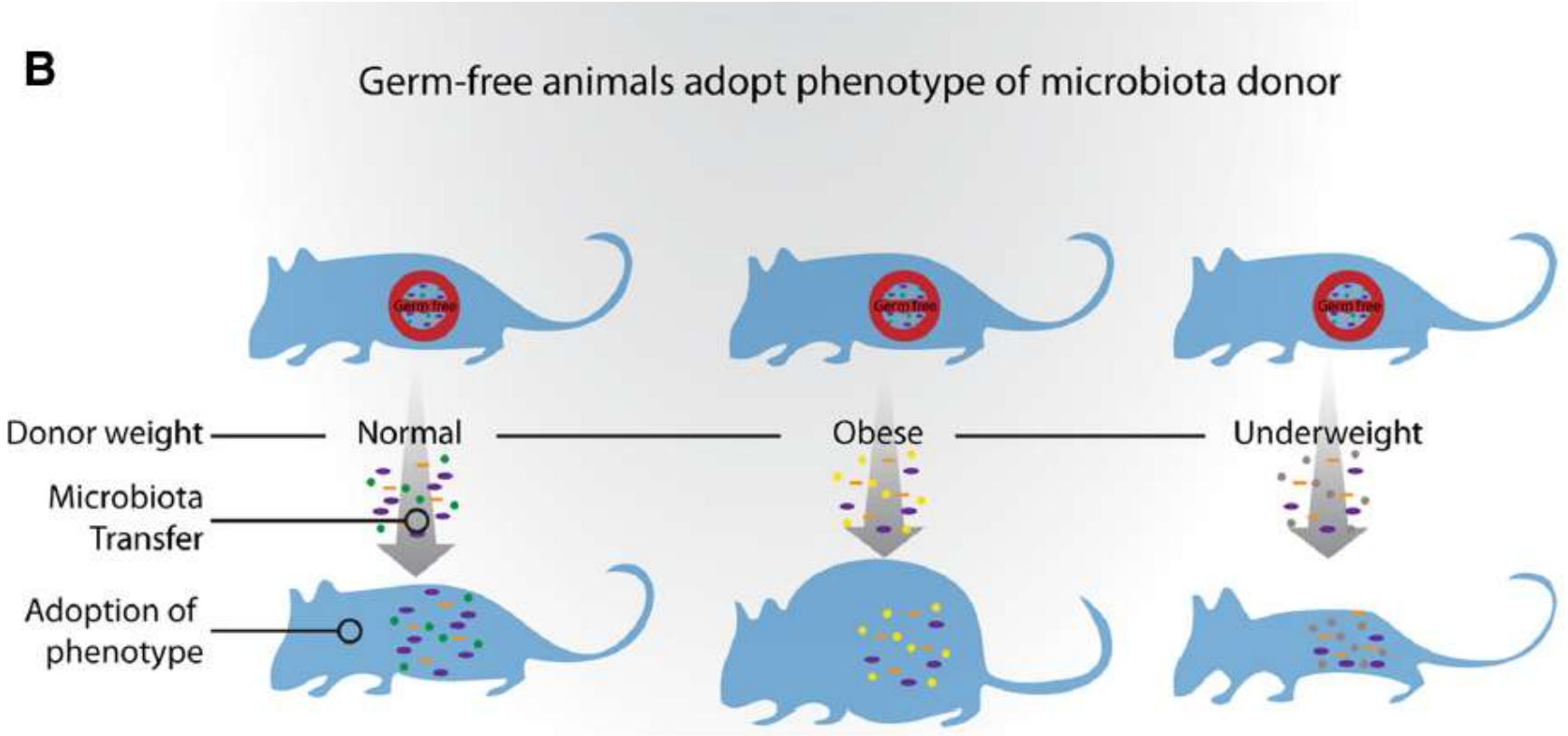



**Figure 1 | A mechanism for microbiota-mediated weight gain.** Perry *et al.*[2] report that, in rodents, production of acetate molecules from dietary nutrients by the bacteria that colonize the gut (the microbiota) increases the brain's stimulation of the parasympathetic nervous system, which includes the vagus nerve. Signals from the vagus nerve trigger secretion of the 'hunger hormone' ghrelin from the stomach, leading to increased food intake. The vagus nerve also potentiates glucose-stimulated insulin secretion from β-cells in the pancreas, promoting calorie storage and fat gain. In this way, the gut microbiota influences obesity.

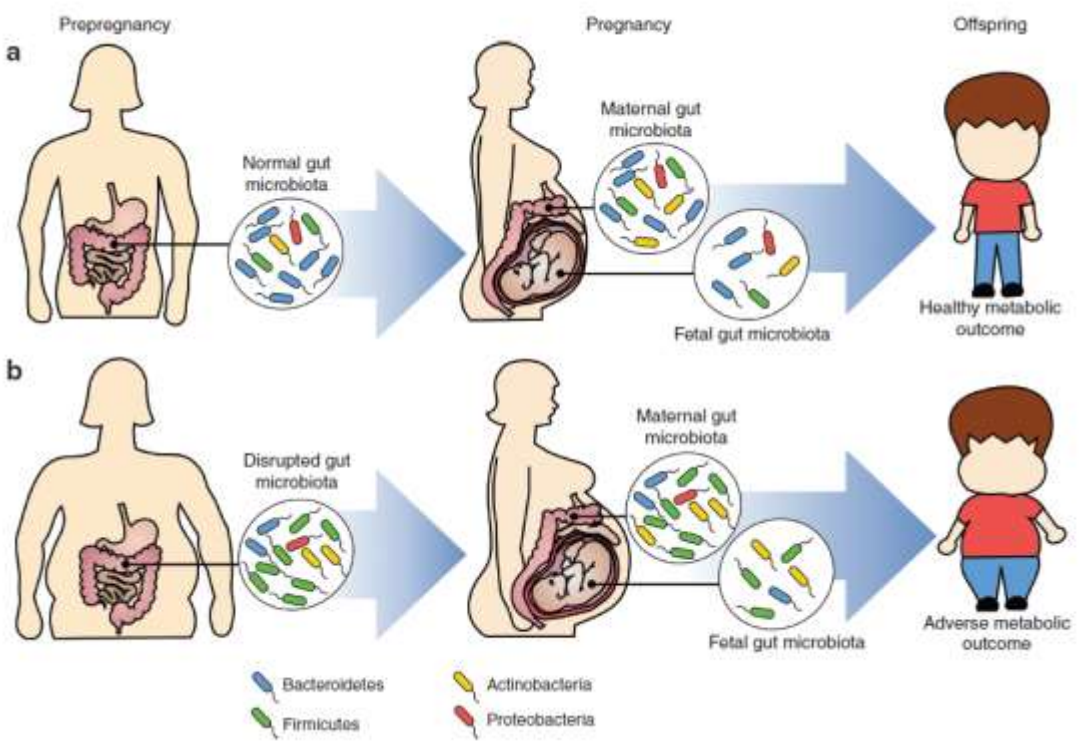
**(Trajkovs K I & Wollheim. Nature 2016)**

# Μικροβιακή χλωρίδα και παχυσαρκία

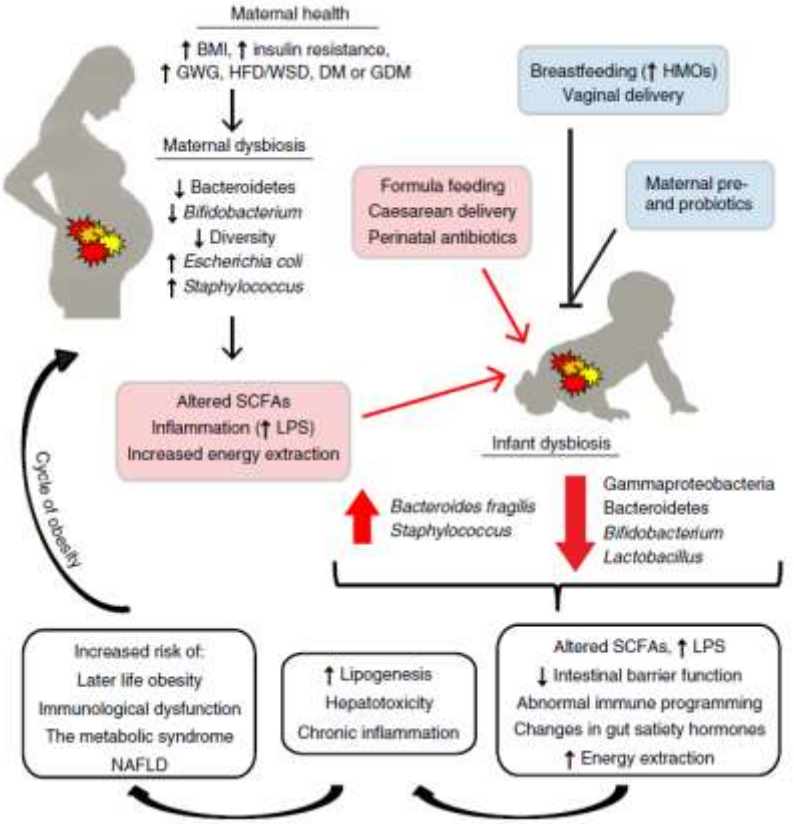



(Clarke et al. Molecular Endocrinology 2014)

# Παχυσαρκία μητέρας και μικροβίωμα εμβρύου




(Gohir et al. Pediatr Res. 2015)




(Soderborg et al. Diabetologia 2016)

# Germs and joints: the contribution of the human microbiome to rheumatoid arthritis

Geraint B Rogers

**Rheumatoid arthritis (RA) is a debilitating autoimmune disorder, the etiology of which is poorly understood. A new study reveals dysbiosis in gut and oral microbiomes of affected individuals, potentially providing a basis for patient stratification and clues to pathophysiological mechanisms of RA onset and progression.**

# The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment

Xuan Zhang[1,13], Dongya Zhang[2,3,13], Huijue Jia[2,3,13], Qiang Feng[2,4,5,13], Donghui Wang[2,5,13], Di Liang[1,13],

015 Nature America, Inc. All rights res

We carried out metagenomic shotgun sequencing and a metagenome-wide association study (MGWAS) of fecal, dental and salivary samples from a cohort of individuals with rheumatoid arthritis (RA) and healthy controls. Concordance was observed between the gut and oral microbiomes, suggesting overlap in the abundance and function of species at different body sites. Dysbiosis was detected in the gut and oral microbiomes of RA patients, but it was partially resolved after RA treatment. Alterations in the gut, dental or saliva microbiome distinguished individuals with RA from healthy controls, were correlated with clinical measures and could be used to stratify individuals on the basis of their response to therapy. In particular, *Haemophilus* spp. were depleted in individuals with RA at all three sites and negatively correlated with levels of serum autoantibodies, whereas *Lactobacillus salivarius* was over-represented in individuals with RA at all three sites and was present in increased amounts in cases of very active RA. Functionally, the redox environment, transport and metabolism of iron, sulfur, zinc and arginine were altered in the microbiota of individuals with RA. Molecular mimicry of human antigens related to RA was also detectable. Our results establish specific alterations in the gut and oral microbiomes in individuals with RA and suggest potential ways of using microbiome composition for prognosis and diagnosis.

**(Geraint B Rogers Nat. Med. 21, 839–841 2015; Zhang et al. Nat. Med. 21, 895–905 2015)**

OPEN ACCESS

# Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population

Toshihiro Kishikawa,[1,2] Yuichi Maeda,[3,4] Takuro Nii,[3,4] Daisuke Motooka,[5]

**What is already known about this subject?**

- Rheumatoid arthritis (RA) is one of the diseases for which the microbiome may have an important role in pathology. Gut microbiome has been implied to lead immune abnormality in RA patients such as the activation of immune responses via Th17 cells by *Prevotella copri*.

**Methods** We conducted MWAS of the RA gut microbiome in the Japanese population ($n_{case}$=82, $n_{control}$=42) by using whole-genome shotgun sequencing of high depth (average 13 Gb per sample). Our MWAS consisted of three major bioinformatic analytic pipelines (phylogenetic analysis, functional gene analysis and pathway analysis).

**(Kishikawa et al. Ann Rheum Dis 2020)**

**What does this study add?**

- Multiple *Prevotella spp.* other than *P. copri* were related to RA etiology in the gut microbiome of the Japanese population.
- A redox reaction–related gene (R6FCZ7) was abundant in the gut metagenome of the Japanese patients with RA.
- A population-specific biological pathway link between the metagenome and the host genome was identified by comparing the RA metagenome-wide association study (MWAS) and the RA genome-wide association study (GWAS).
- Our study indicated a value of metagenome-wide shotgun sequencing rather than classical amplicon sequencing of 16S ribosomal RNA (rRNA) genes of microbiomes.

**How might this impact on clinical practice or future developments?**

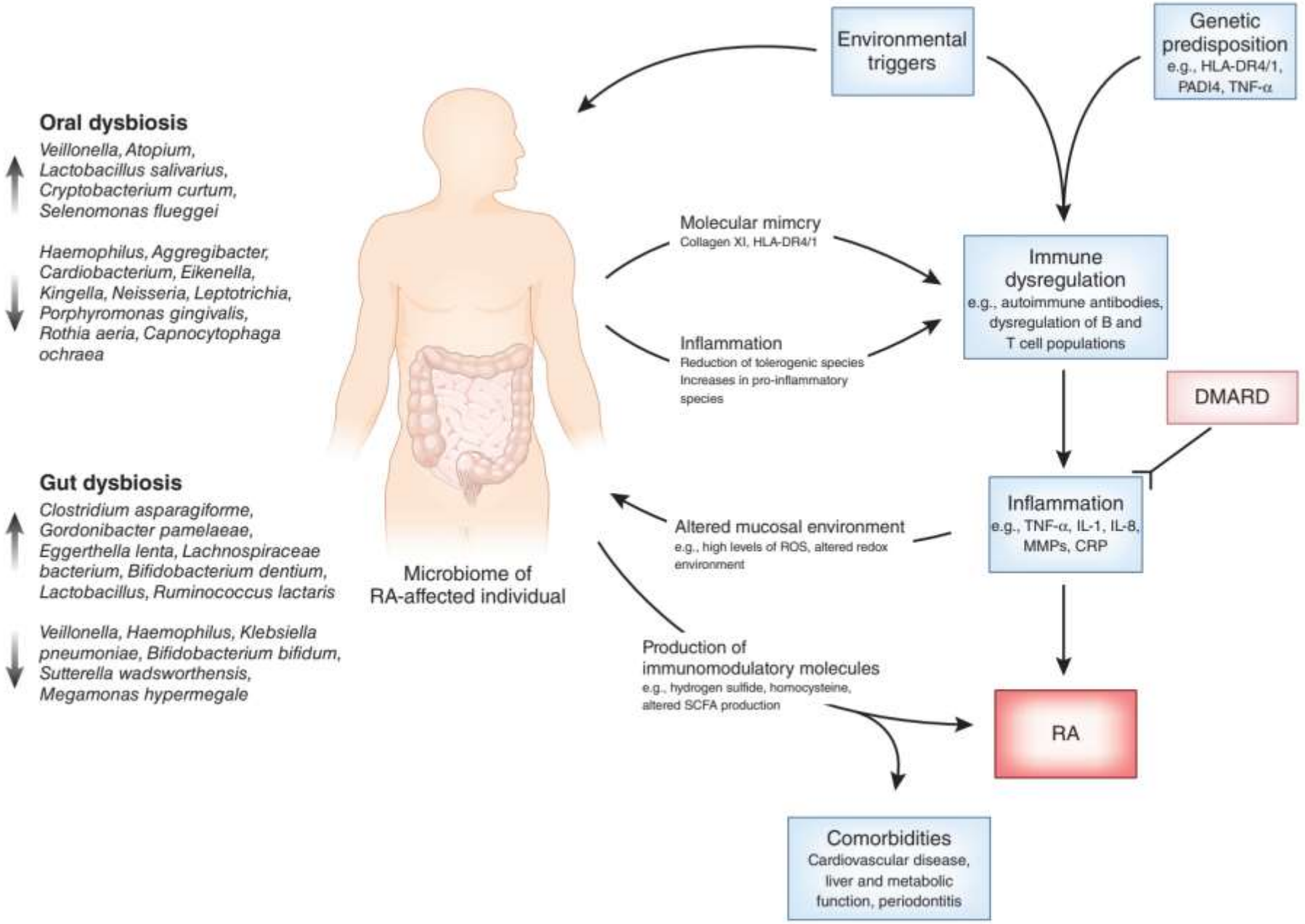
- We revealed a novel link between the gut microbiome, host genome and pathology of RA. Our study will be a platform model of the microbiome studies to elucidate etiology of rheumatic diseases.

# Interactions between Gut Microbiota and Immunomodulatory Cells in Rheumatoid Arthritis

Table 1: The alteration of the gut microbiota in RA patients and animal models.

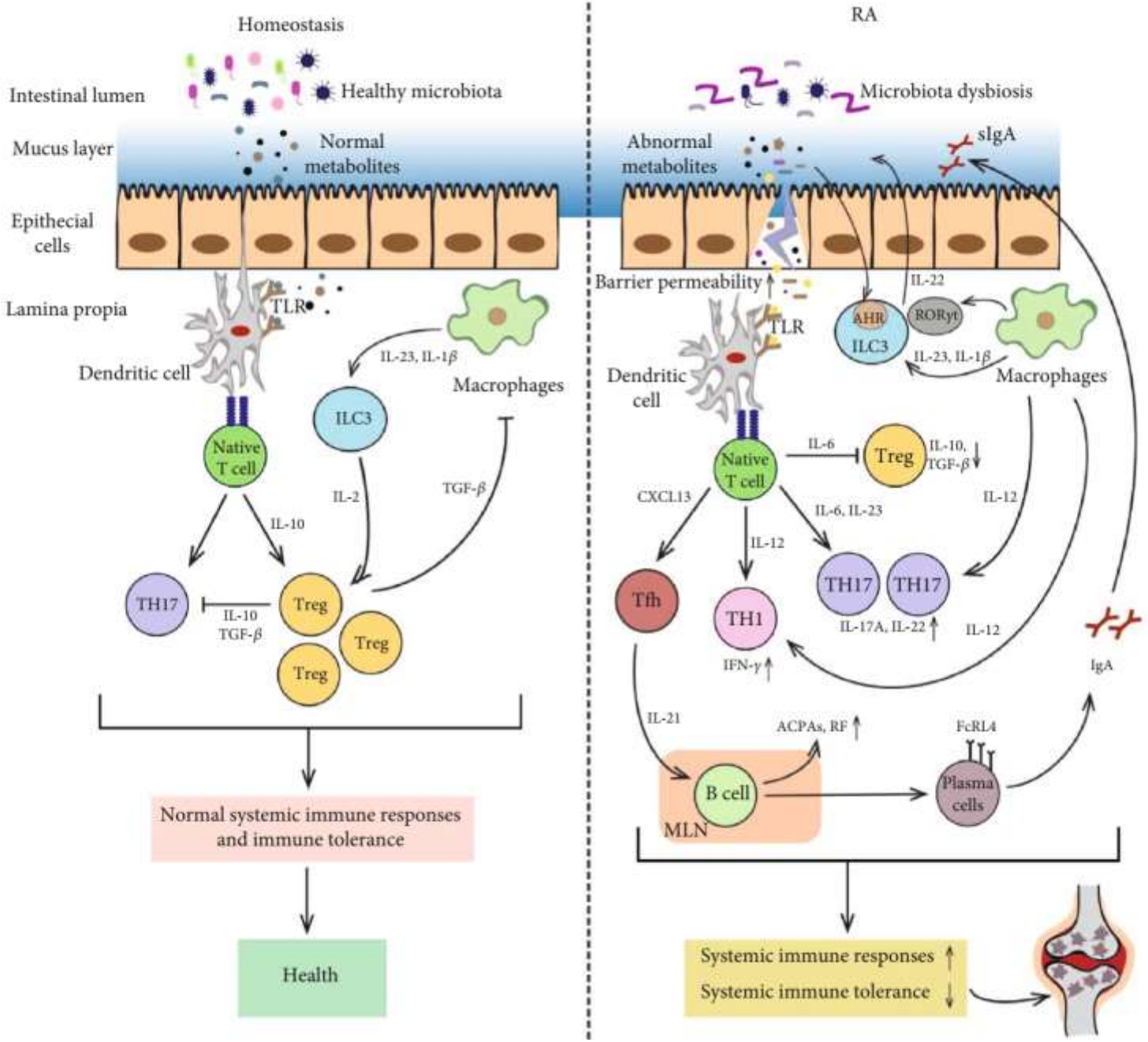
| Study objects | Sample type | Technology | Increased | Decreased | References |
|---|---|---|---|---|---|
| Human, compared RA patients with nonarthritic controls | Stool | Metagenomic shotgun sequencing | Clostridiaceae | | [80] |
| Human, compared RA patients with osteoarthritis patients | Stool | 16S ribosome (r)RNA sequencing | *Lactobacilli*, *Prevotella* | *Bacteroides*, *Bifidobacterium*, Bacteroidetes/Firmicutes | [81] |
| Human, compared RA patients with healthy controls | Stool | 16S rRNA sequencing | *Bacteroides*, *Escherichia-Shigella* | *Lactobacillus*, *Alloprevotella*, *Enterobacter*, *Odoribacter* | [78] |
| Human, compared RA patients with healthy controls | Stool | Whole-genome shotgun sequencing | *Prevotella* | | [73] |
| Human, compared RA patients with healthy controls | Stool | 16S rRNA sequencing | Verrucomicrobiae, *Akkermansia* | | [75] |
| Human, compared preclinical RA patients with first-degree relatives (FDR) of RA patients | Stool | 16S rRNA sequencing | Prevotellaceae, *Prevotella* spp. | | [70] |
| Human, compared FDR of RA patients with healthy controls | Stool | 16S rRNA sequencing | *Collinsella* | Actinobacteria | [69] |
| Human, compared RA patients with healthy controls | Stool | Metagenomic shotgun sequencing | *Lactobacillus salivarius* | *Haemophilus* spp. | [77] |
| Human, compared RA patients with healthy controls | Stool | qPCR | *Bacteroides*, *Prevotella* | *Clostridium leptum* | [97] |
| Mouse, compared mice with CIA at the initial peak and relapse of arthritis with healthy controls | Stool | 16S rRNA gene sequencing | *Bacteroides*, Bacteroidales | Firmicutes | [86] |
| Mouse, compared mice with CIA with healthy controls | Stool | 16S rRNA gene sequencing | Clostridiales, Deferribacterales, *Mucispirillum* | Enterobacteriales | [94] |

(Xu et al. Med.Inflamm.2020)



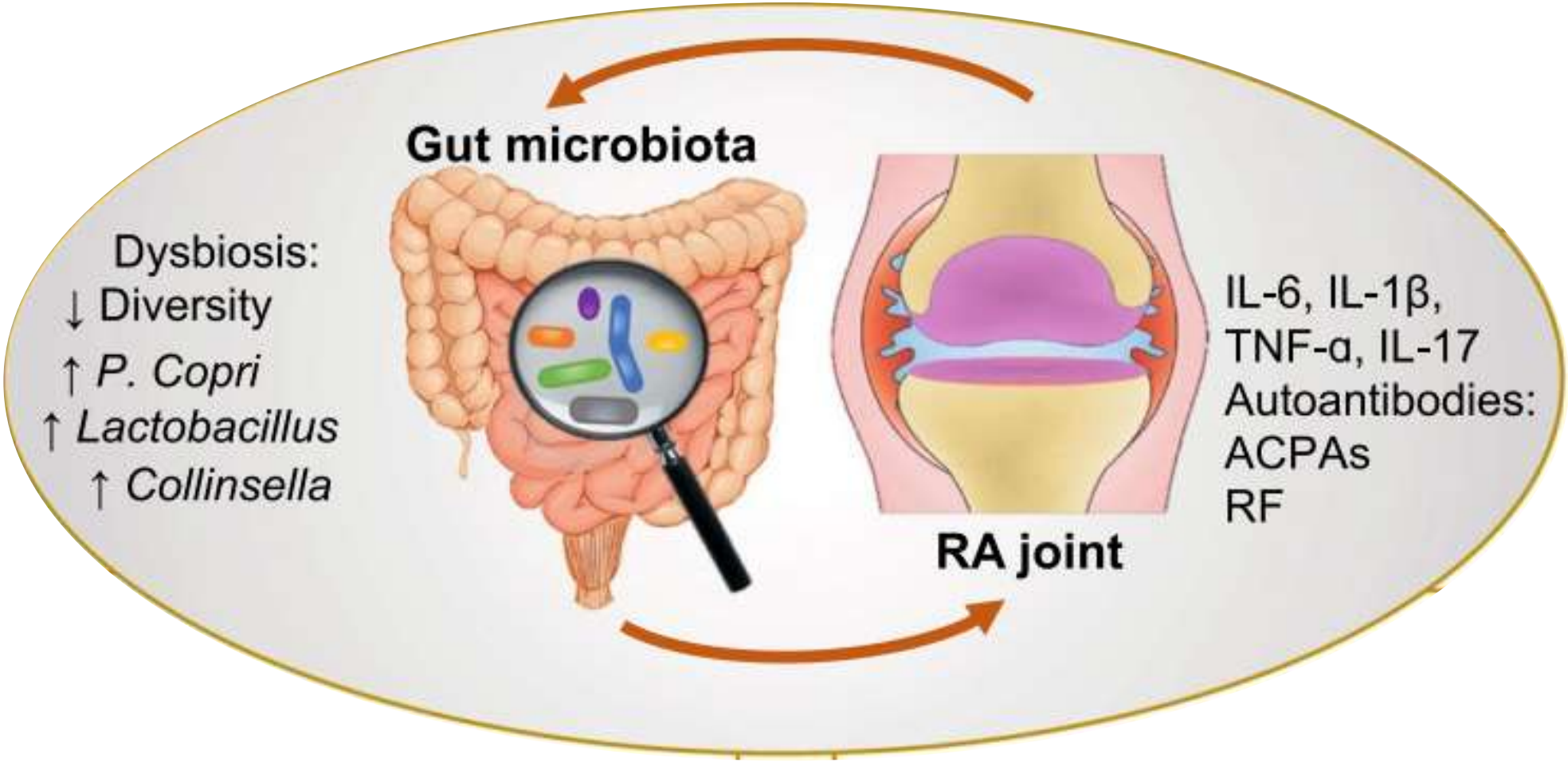

ture America, Inc. All rights reserved.

(Geraint B Rogers Nat. Med. 21, 839–841 2015)

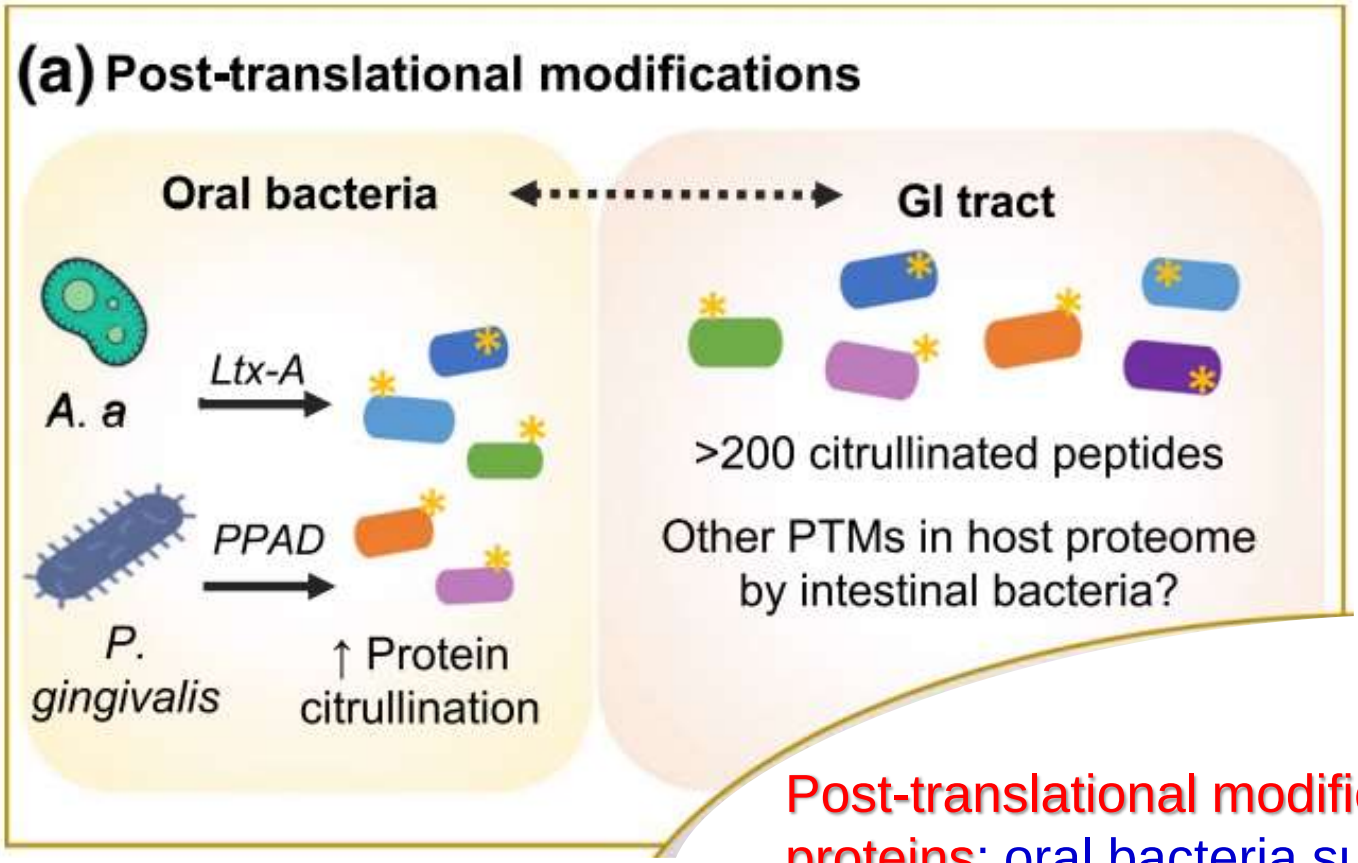



(Xu et al. Med.Inflamm.2020)

# Troublesome friends within us: the role of gut microbiota on rheumatoid arthritis etiopathogenesis and its clinical and therapeutic relevance

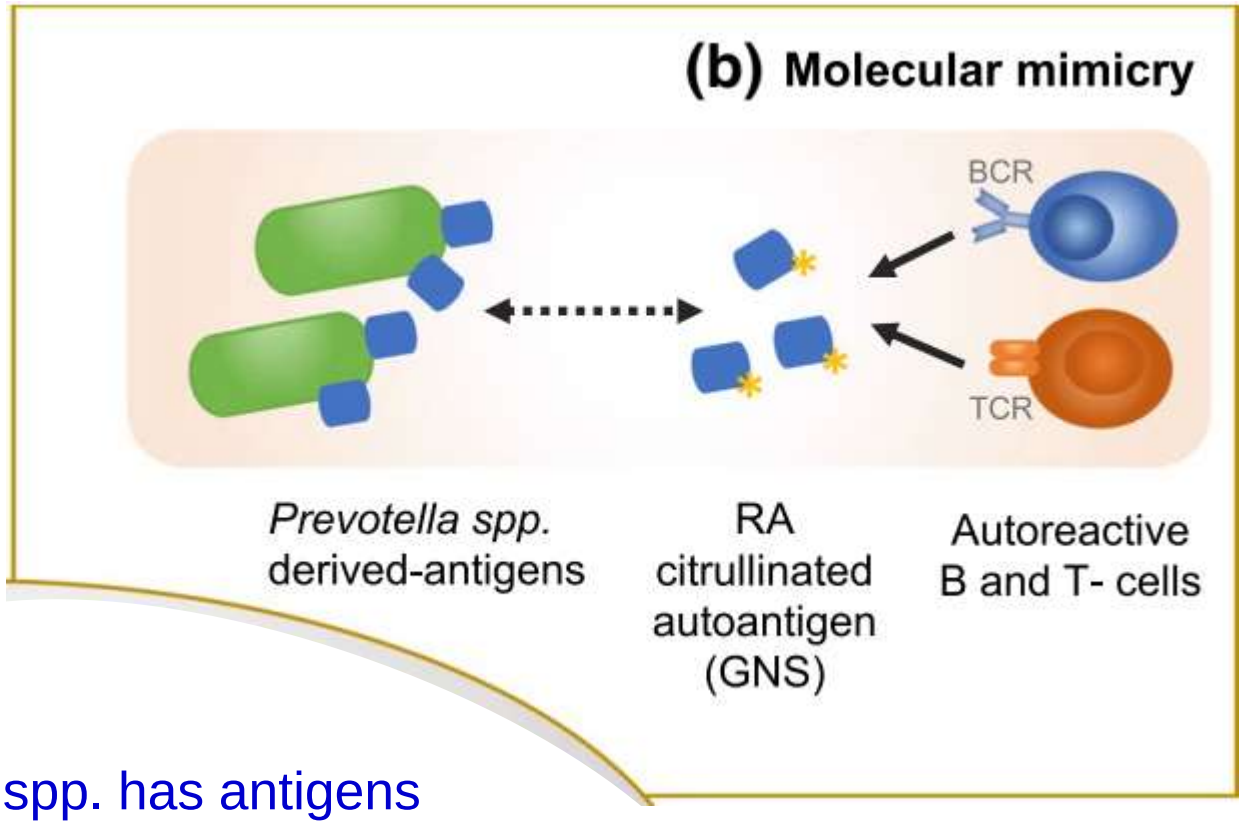



(Reyes-Castillo et al. Clin. Exp. Med. 2020)




Post-translational modification (PTM) of host proteins; oral bacteria such as *Aggregatibacter a. (A.a)* and *Porphyromonas g.* augment protein citrullination by leucotoxin-A (Ltx-A) production and Porphyromonas-PAD (PPAD) enzyme activity, respectively. More than 200 citrullinated peptides are detected in colon and it is possible that some of these in host proteome are mediated by intestinal bacteria.

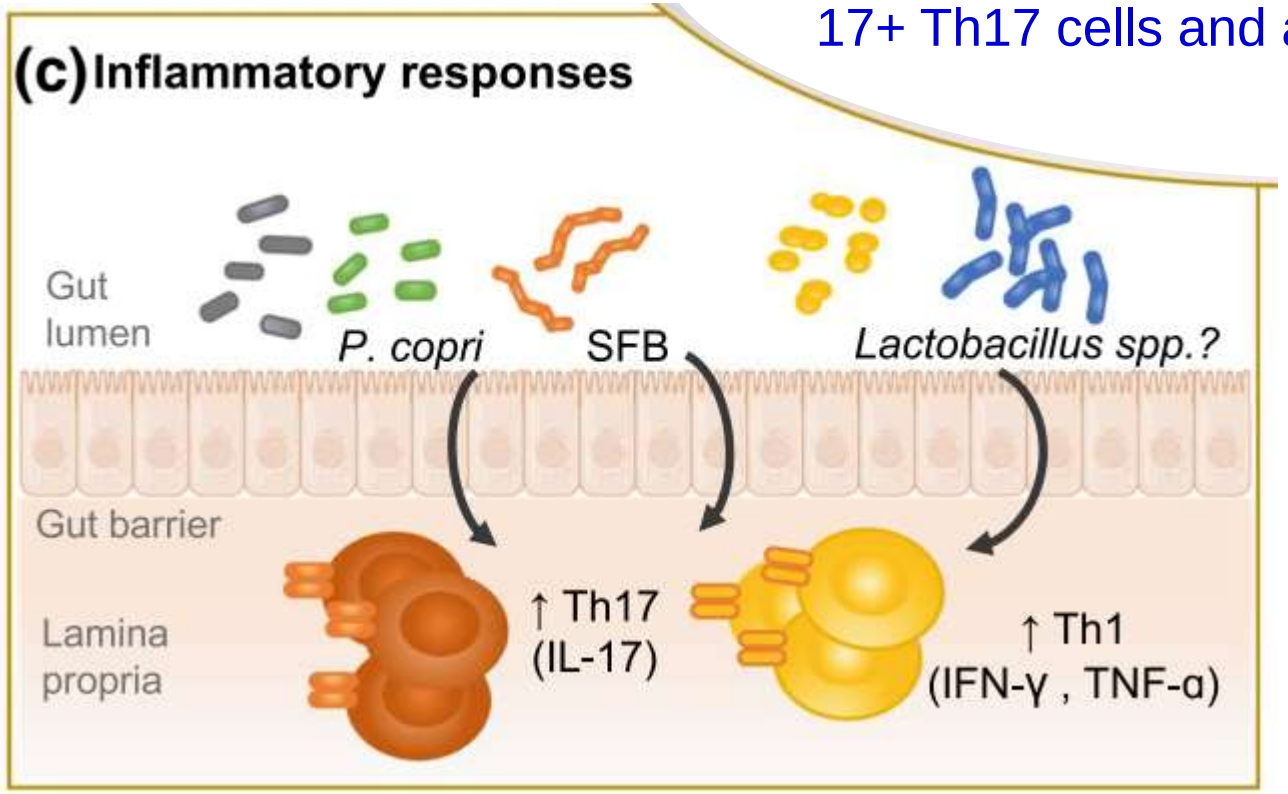
**(Reyes-Castillo et al. Clin. Exp. Med. 2020)**




Molecular mimicry;
the intestinal genus Prevotella spp. has antigens that are structurally similar to an RA-citrullinated autoantigen, N-acetylglucosamine-6-sulfatase (GNS), which activates T and B cell responses in about 50% of RA patients.

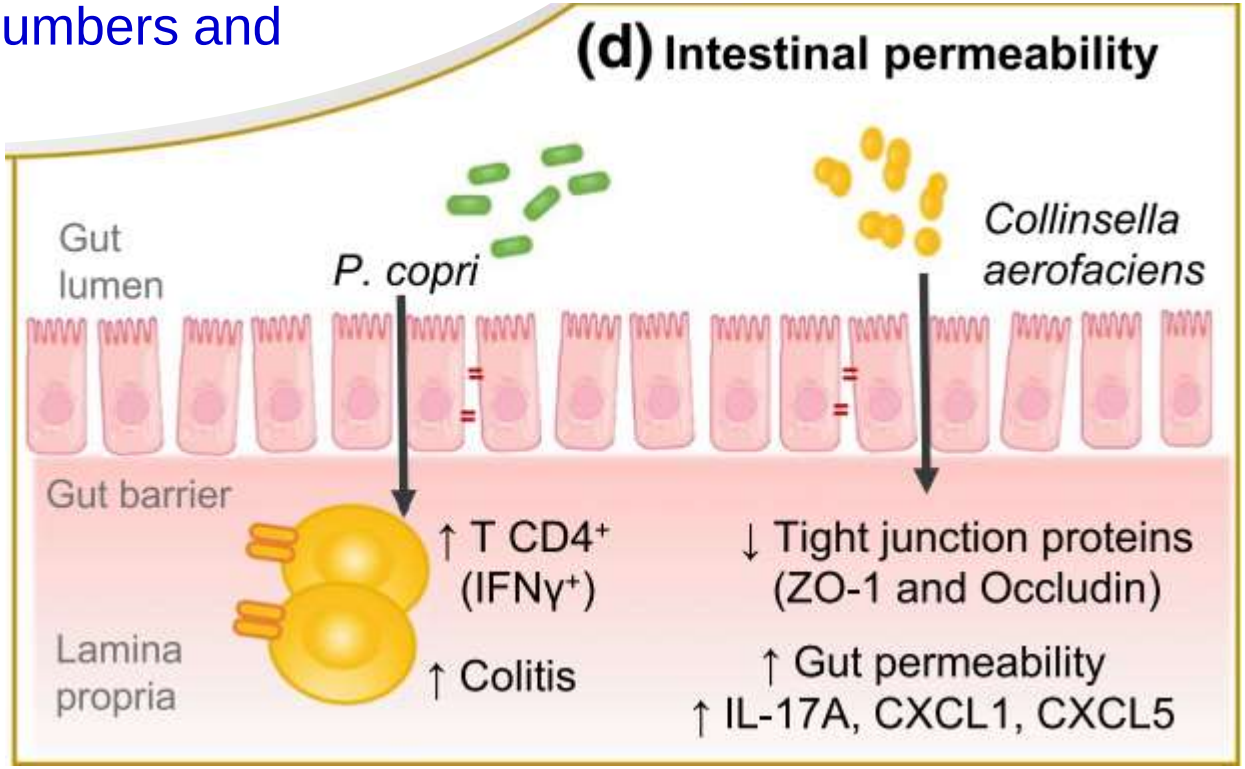
**(Reyes-Castillo et al. Clin. Exp. Med. 2020)**

Inflammatory responses;
in experimental arthritis, P. copri, segmented filamentous bacteria (SFB) and Lactobacillus species have demonstrated effects on CD4+ T cells, specifically by increasing the numbers of IL-17+ Th17 cells and activating Th1 cell responses.




**(Reyes-Castillo et al. Clin. Exp. Med. 2020)**

Intestinal permeability;
in RA murine models, C. aerofaciens treatment was shown to promote intestinal permeability by increasing inflammatory mediators and chemokines (IL-17A, CXCL1, CXCL5) and reducing the expression of tight junction proteins (ZO-1 and occludin), whereas P. copri colonization increased CD4+ (IFNγ+) T cell numbers and induced colitis in mice.




**(Reyes-Castillo et al. Clin. Exp. Med. 2020)**

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
https://doi.org/10.1080/1744666X.2018.1519395

Taylor & Francis
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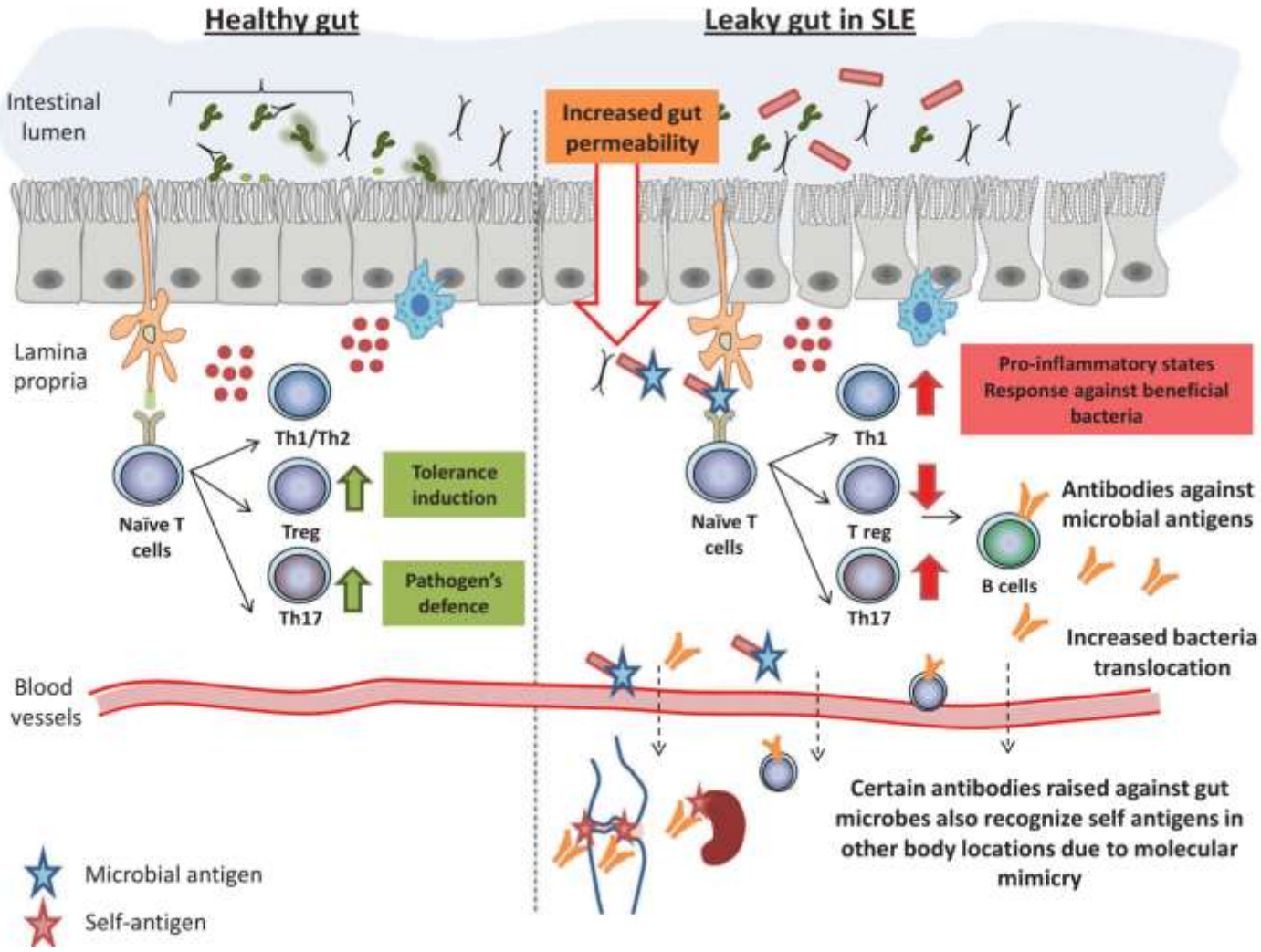
SPECIAL REPORT

Check for updates

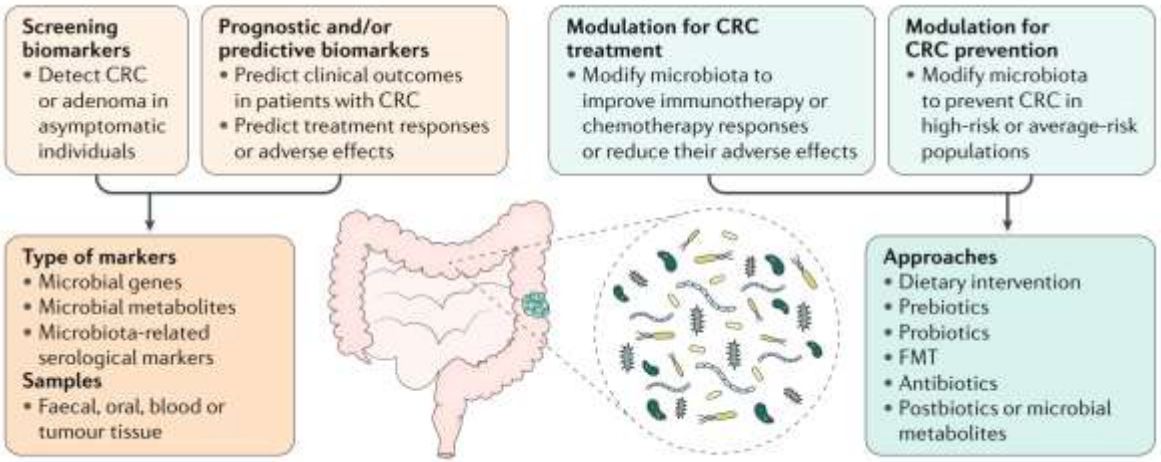
# The role of gut microbiota in lupus: what we know in 2018?

Lorena Ruiz[a], Patricia López[b,c], Ana Suárez[b,c], Borja Sánchez[a] and Abelardo Margolles[a]



# Gut microbiota in colorectal cancer: mechanisms of action and clinical applications (Nature reviews | GastroenteroloGy & HepatoloGy 2019)

Sunny H. Wong[1,2] and Jun Yu[1,2]*



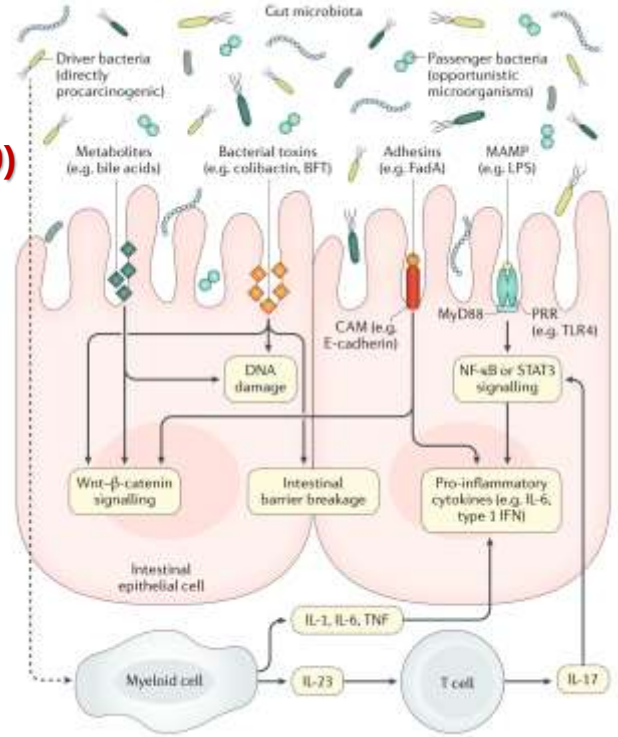
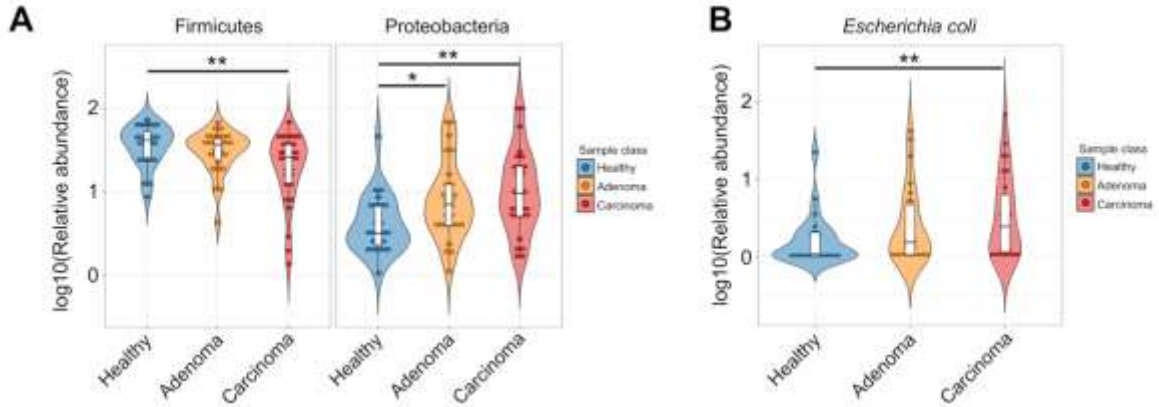




Fig. 2 | **Potential clinical applications related to gut microbiota in colorectal cancer.** Several potential clinical

# Altered Fecal Small RNA Profiles in Colorectal Cancer Reflect Gut Microbiome Composition in Stool Samples

Sonia Tarallo,[a] Giulio Ferrero,[b] Gaetano Gallo,[c,d] Antonio Francavilla,[a] Giuseppe Clerico,[d] Alberto Realis Luc,[d]

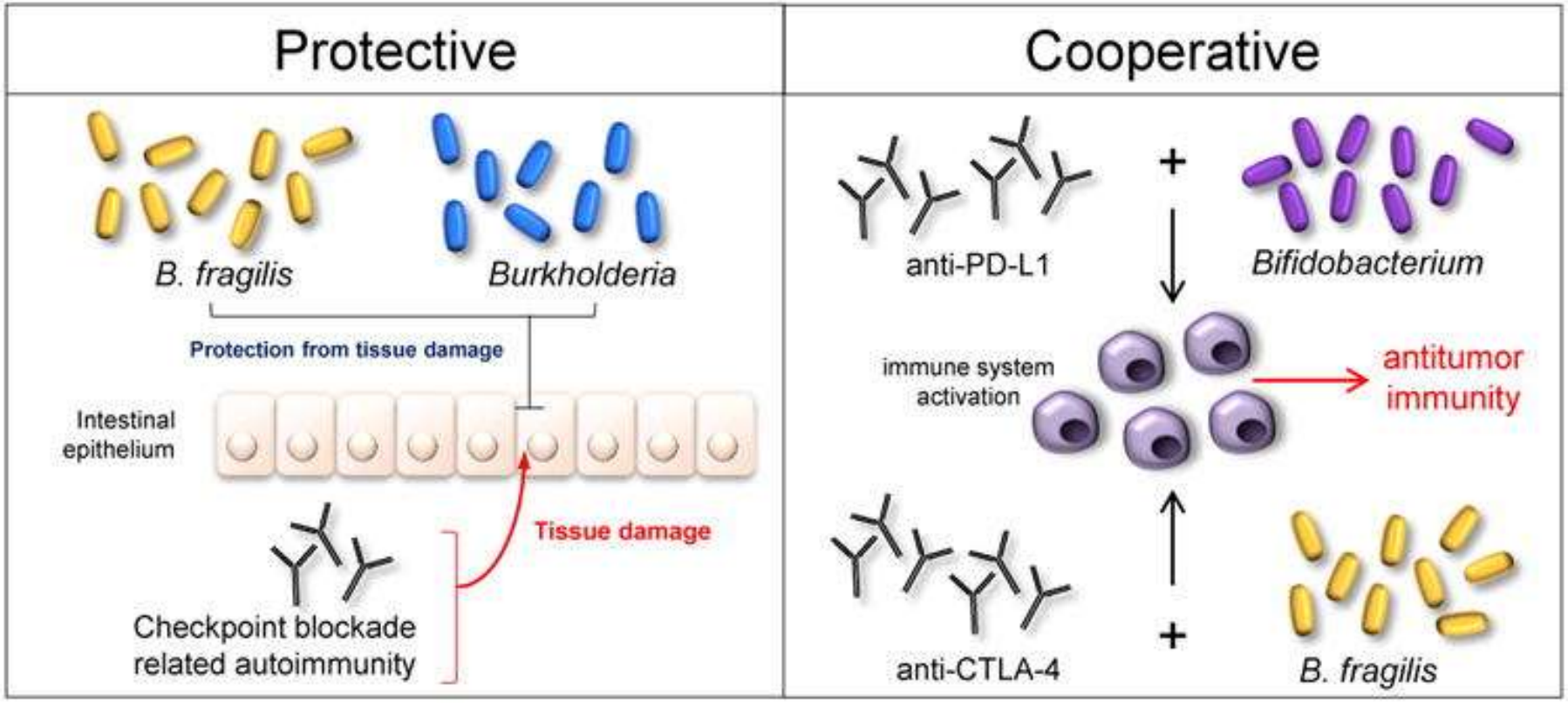



(Tarallo et al. mSystems. 2019)

CANCER IMMUNOTHERAPY

# Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou,[1,2,3] Jonathan M. Pitt,[1,2,3] Romain Daillère,[1,2,3] Patricia Lepage,[4]



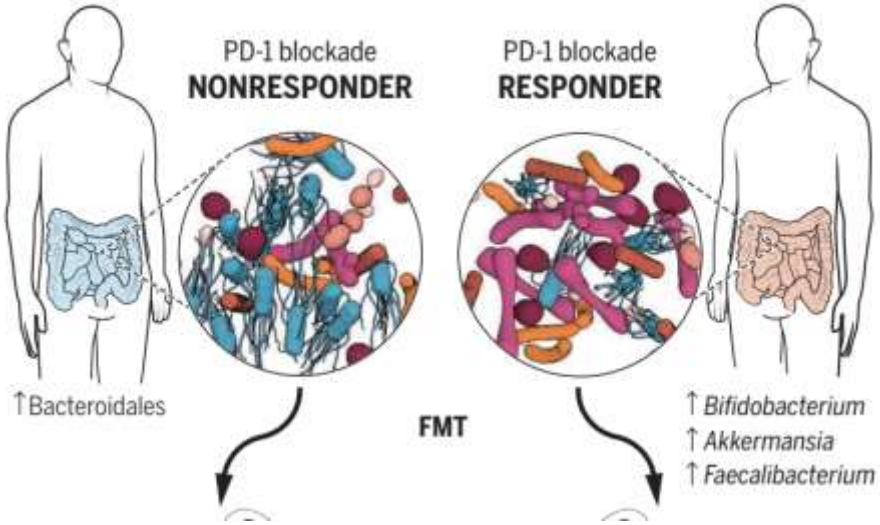

Trends Immunol. 2016 Jun; 37(6): 354–363 Science, Nov 2015

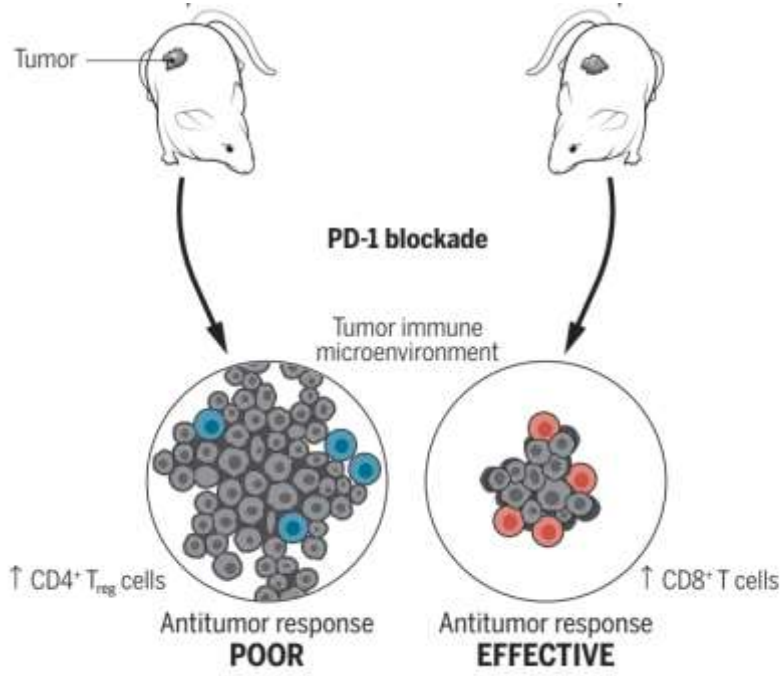
CANCER THERAPY

# *Precision medicine using microbiota*

Intestinal microbiota influence cancer patient responses to immunotherapy

therapeutic drugs. For example, bacteria modulate the antitumor efficacy in preclinical models of various chemotherapies (*2*–*4*) and immunotherapeutic agents (*5*, *6*). Conceptually, these findings suggest that immune system are essential for optimal drug efficacy. However, there is limited information regarding the functional impact of the composition of the human microbiome and therapeutic outcomes in cancer patients. On pages 91, 97, and 104 of this




(Christian Jobin Science 2018)

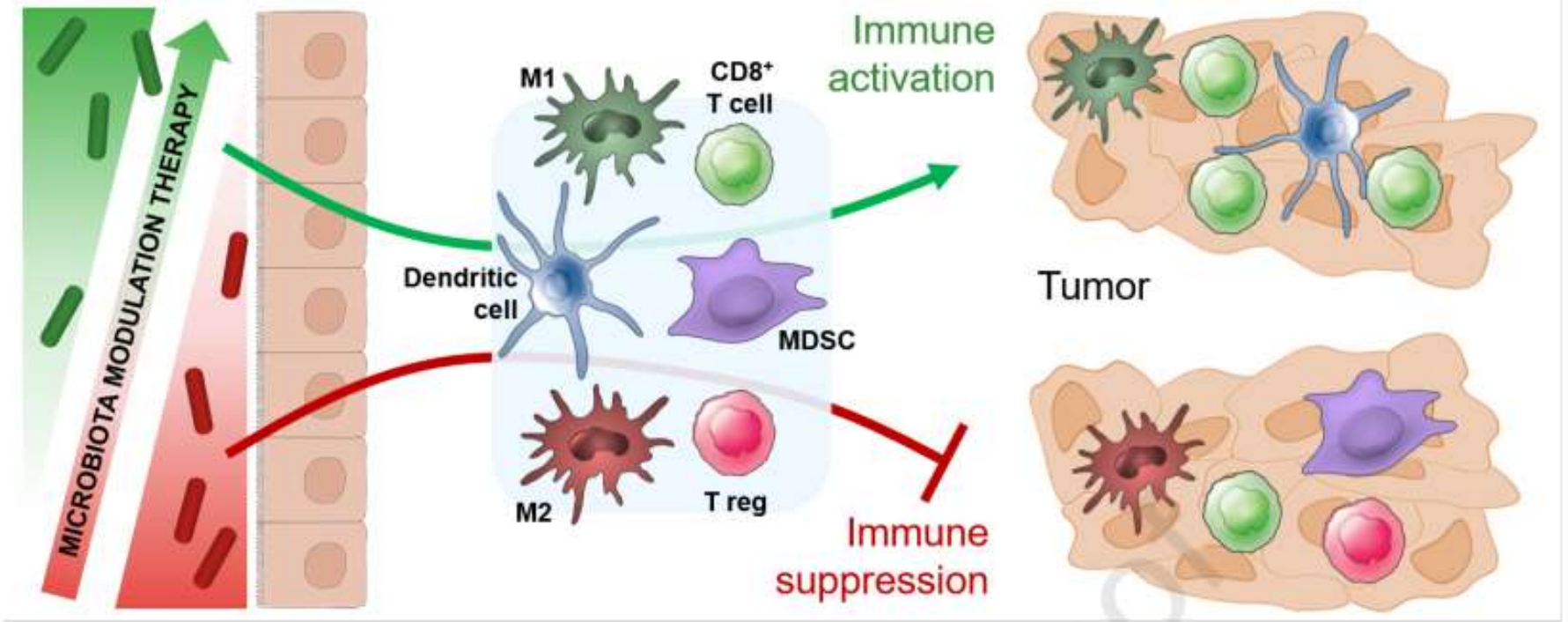
Gastroenterology 2021;160:600–613

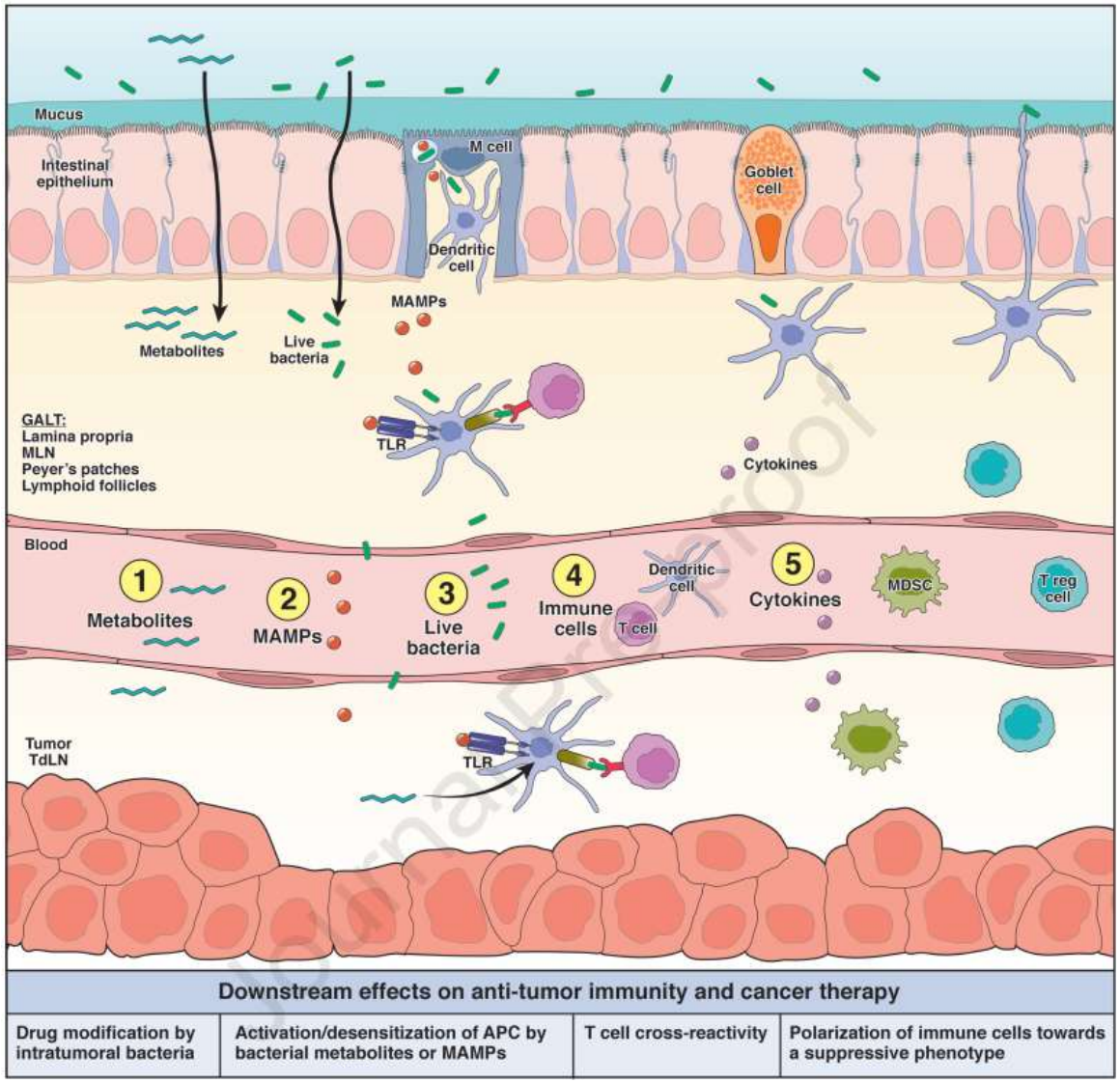
# Cancer and the Microbiome—Influence of the Commensal Microbiota on Cancer, Immune Responses, and Immunotherapy



*Vyara Matson* *Carolina Soto Chervin* *Thomas F. Gajewski*

*The University of Chicago, Chicago, Illinois*






The gut microbiota could Modulate immunotherapy outcomes by stimulating or inhibiting anti-tumor immunity. The messengers could be:

1) bacterial metabolites;
2) microbe-associated molecular patterns (MAMPs);
3) whole viable bacteria;
4) immune cells conditioned by sensing microbiota signals;
5) cytokines released in the GALT in response to microbial stimuli.

**(Gastroenterology 2021)**

# Targeting gut microbiota for precision medicine: Focusing on the efficacy and toxicity of drugs

Wuwen Feng[1,2], Juan Liu[2], Hui Ao[2], Shijun Yue[3], Cheng Peng[1,2]✉



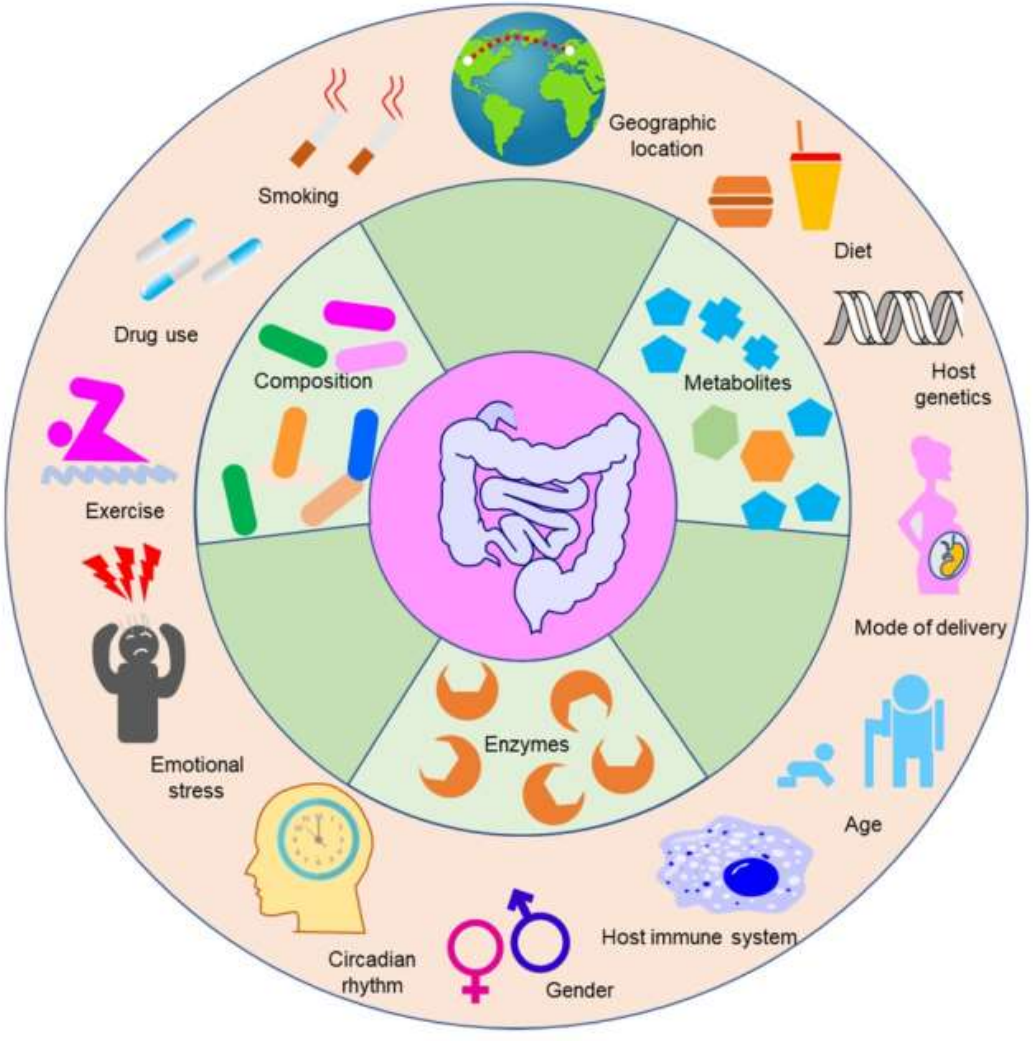
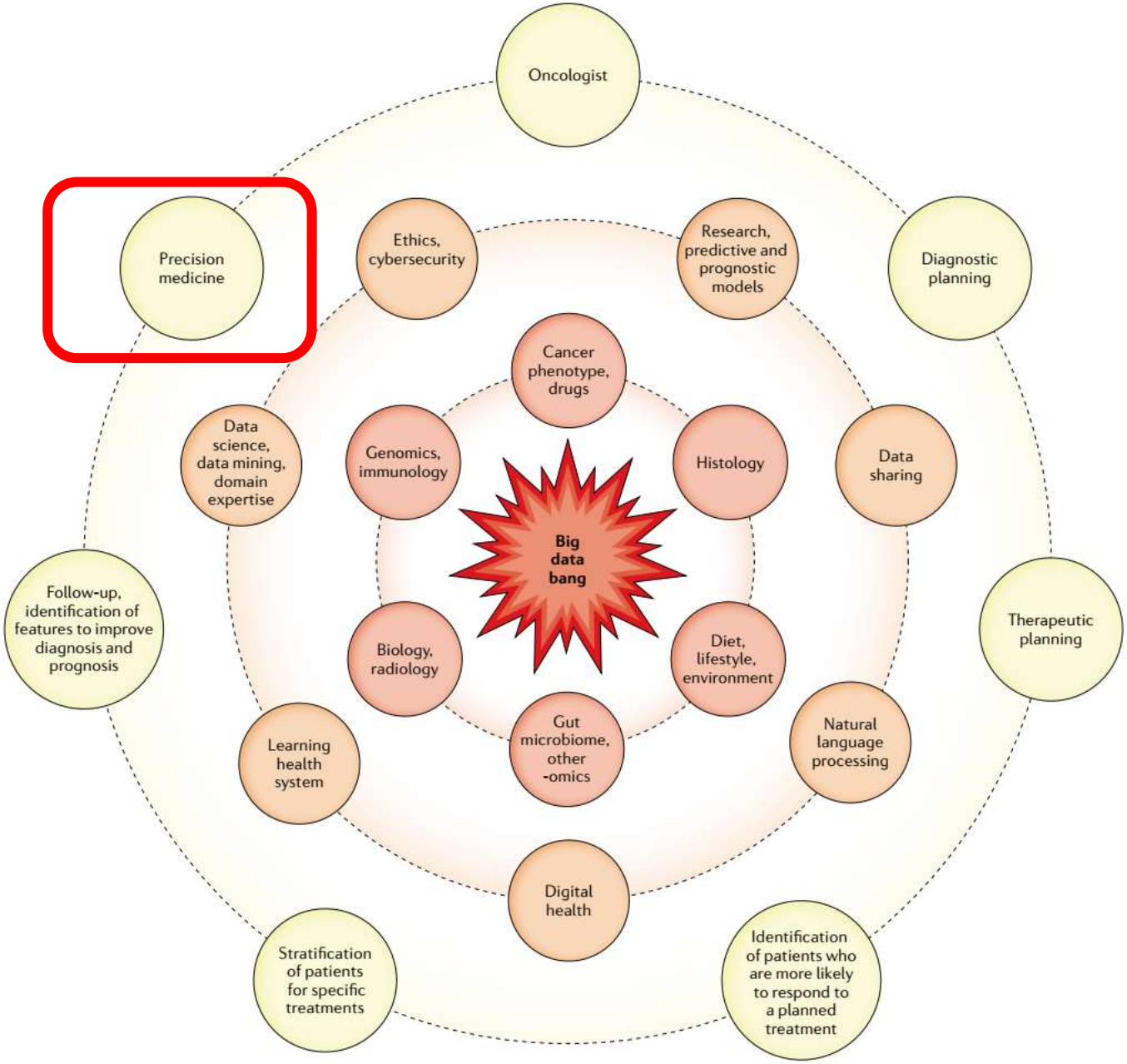



**Figure 4. The factors influencing the composition and function of gut microbiota.** Gut microbiota can modulate the efficacy and toxicity of drugs. However, the



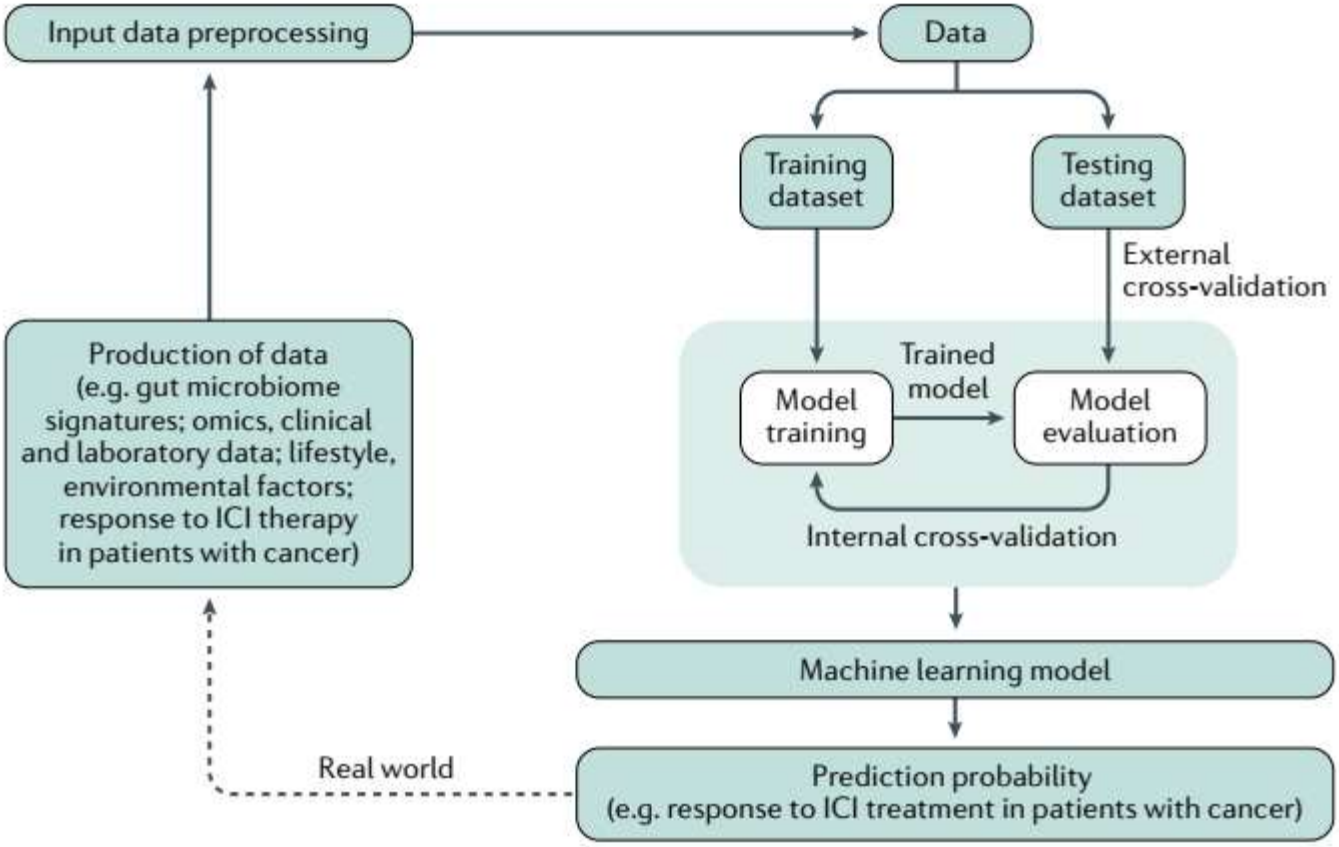

**(Nat Rev Gastroenterol Hepatol. 2020 Oct;17(10):635-648)**

# Gut microbiome, big data and machine learning to promote precision medicine for cancer

*Giovanni Cammarota, Gianluca Ianiro, Anna Ahern, Carmine Carbone, Andriy Temko, Marcus J. Claesson, Antonio Gasbarrini and Giampaolo Tortora*

large scale naturally requires new analytical tools, in addition to the formulation of specific experimental questions, the annotation and cleaning of open data and the performance of appropriate retrospective analysis by powerful software (such as artificial intelligence (AI)-based models and advanced machine learning (ML), which are particularly useful in translational medicine).

ML-driven analysis of gut microbiota could be particularly useful in oncology owing to the plethora of evidence relating




**(Nat Rev Gastroenterol Hepatol. 2020 Oct;17(10):635-648)**

# Diet, Microbiome, and Epigenetics in the Era of Precision Medicine

**Gabriela Riscuta, Dan Xi, Dudith Pierre-Victor, Pamela Starke-Reed, Jag Khalsa, and Linda Duffy**

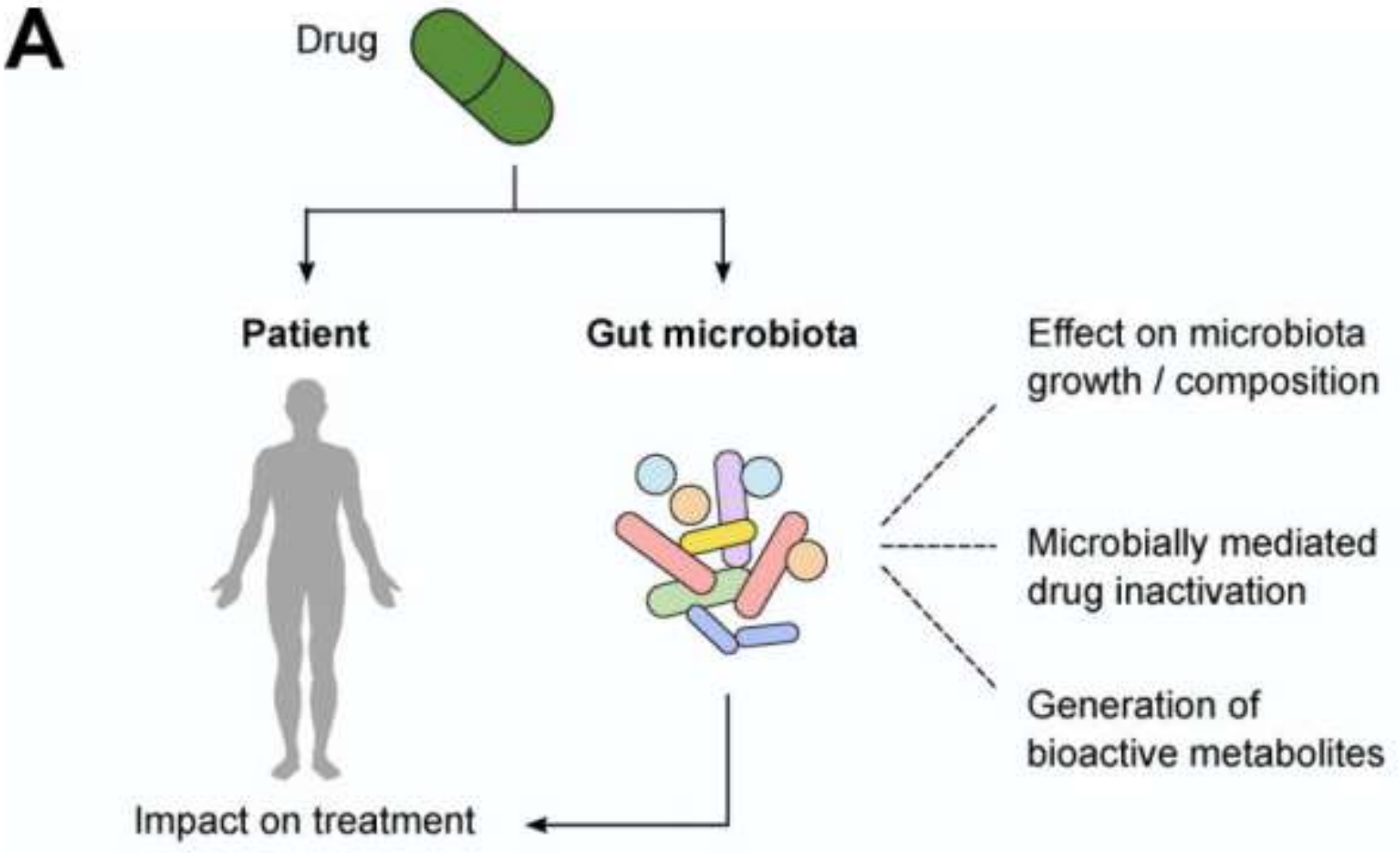
treatment of multiple diseases including cancer. Many factors contribute to the response to an intervention. The microbiome and microbially produced metabolites are capable of epigenetic modulation of gene activity, and can influence the response through these mechanisms. The fact that diet has an impact on microbiome implies that it will also affect the epigenetic mechanisms involving microbiota. In this chapter,

The concepts of precision medicine have evolved because of advances in molecular or omics technologies such as genomics, transcriptomics, proteomics, metabolomics, and metabonomics which can potentially lead to unique patient phenotypes and inter-individual differences in treatment responses [67]. The microbiome plays a crucial role in health and disease, as it influences endocrinology, physiology, and even neurology, thereby altering the outcome of many different disease states and augments drug responses and tolerance [68]. There is a bidirectional interaction:

**(Methods in Molecular Biology 2018)**

# Precision medicine goes microscopic: engineering the microbiome to improve drug outcomes

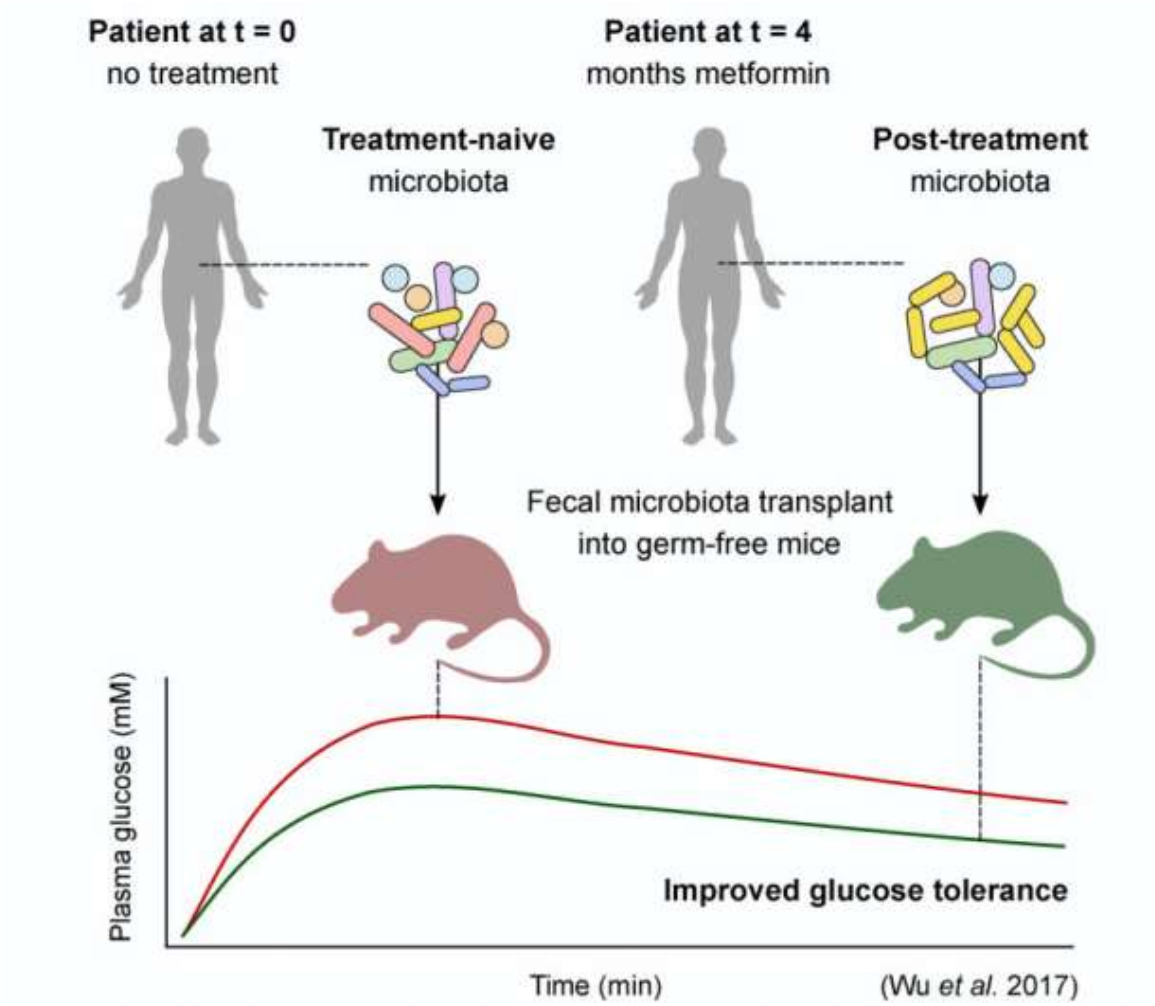
Kathy N. Lam[1,+], Margaret Alexander[1,+], Peter J. Turnbaugh[1,2,3,*]




(Cell Host Microbe 2019)

# Precision medicine goes microscopic: engineering the microbiome to improve drug outcomes

Kathy N. Lam[1,+], Margaret Alexander[1,+], Peter J. Turnbaugh[1,2,3,*]




**(Cell Host Microbe 2019)**

# Microflora-Microbiome

## New players?

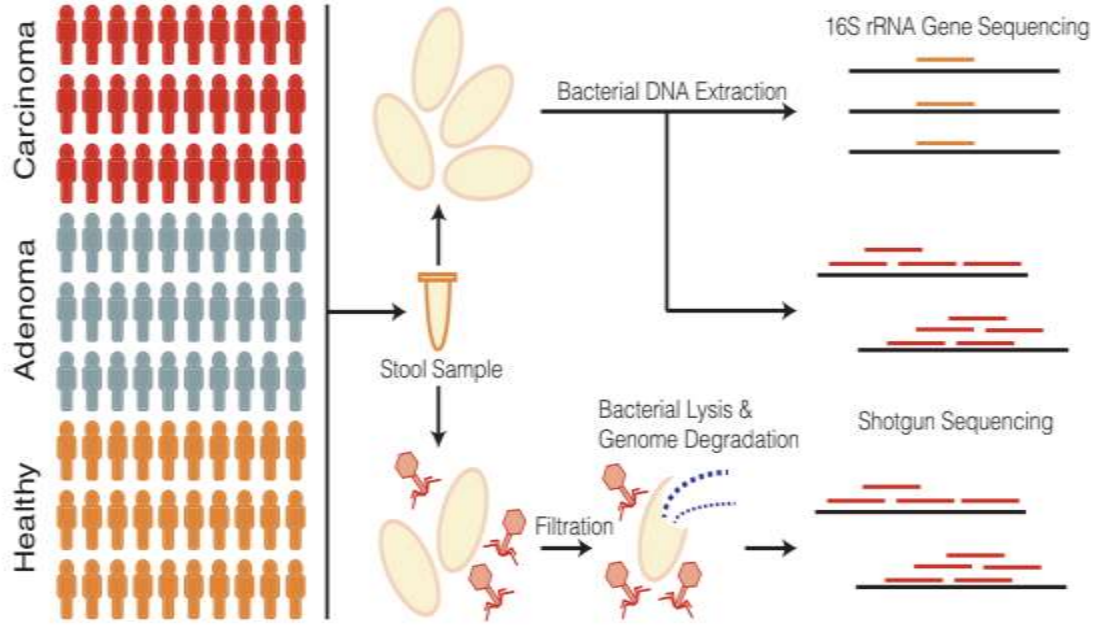
# Diagnostic Potential and Interactive Dynamics of the Colorectal Cancer Virome

**(MBio. 2018)**

Geoffrey D. Hannigan,[a] Melissa B. Duhaime,[b] Mack T. Ruffin IV,[c] Charlie C. Koumpouras,[a] Patrick D. Schloss[a]

[a]Department of Microbiology and Immunology, University of Michigan, Ann Arbor, Michigan, USA

**Our study cohort consisted of stool samples collected from 90 human subjects, 30 of whom had healthy colons, 30 of whom had adenomas, and 30 of whom had carcinomas. Half of each stool sample was used to sequence the bacterial communities using both 16S rRNA gene and shotgun sequencing techniques. The other half of each stool sample was purified for virus-like particles (VLPs) before genomic DNA extraction and shotgun metagenomic sequencing were performed.**

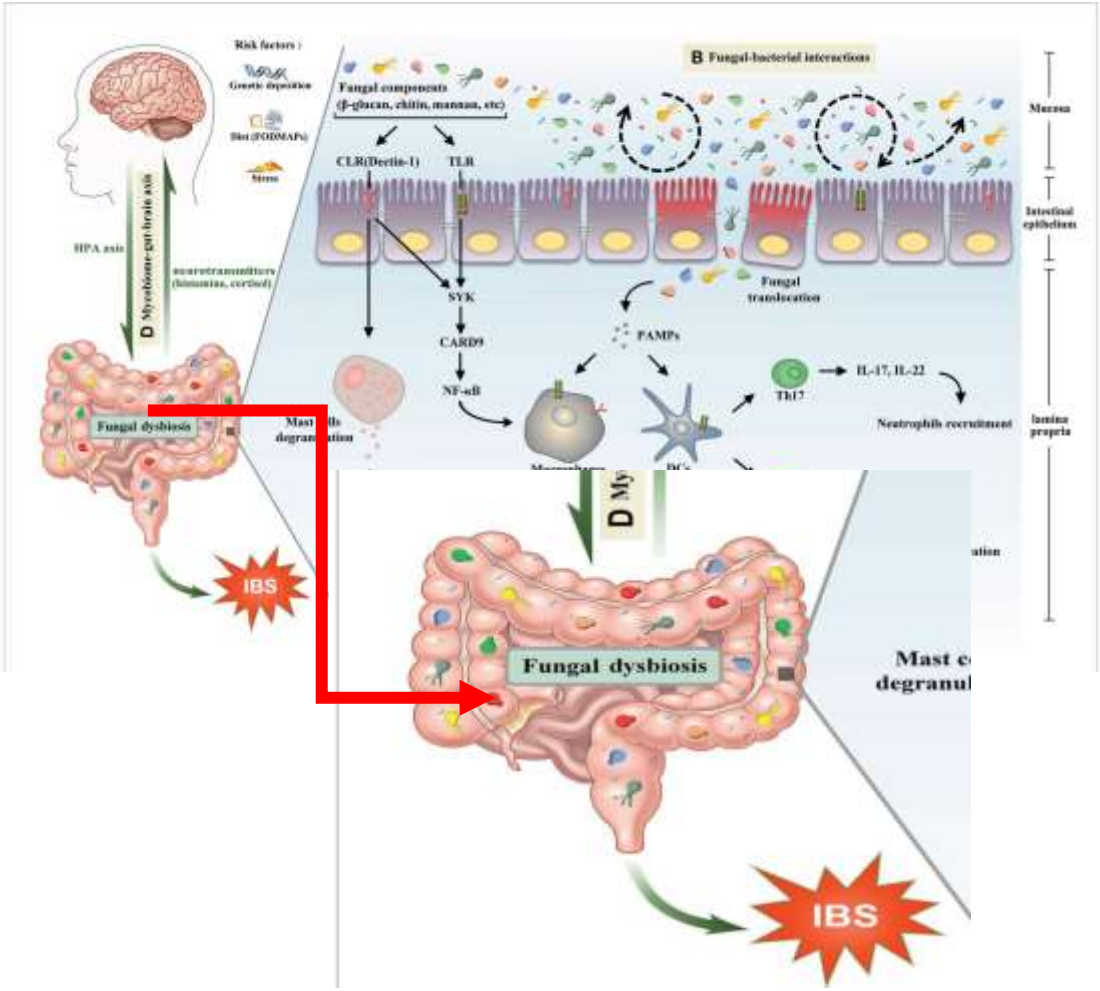



network hubs. These results provide foundational evidence that bacteriophage communities are associated with colorectal cancer and potentially impact cancer progression by altering the bacterial host communities.

# The Potential Role of Gut Mycobiome in Irritable Bowel Syndrome

*Yu Gu†, Guoqiong Zhou†, Xiali Qin, Shumin Huang, Bangmao Wang and Hailong Cao**

*Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin, China*




(Front in Microbiol 2019)

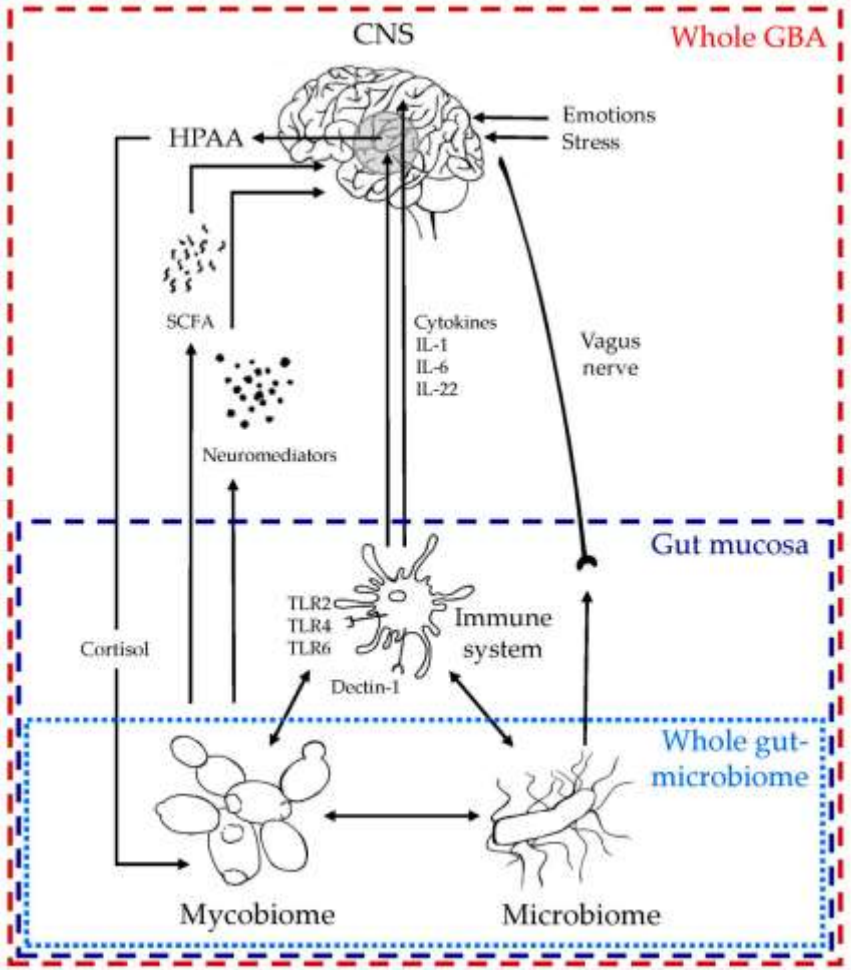
*microorganisms*

MDPI

*Review*

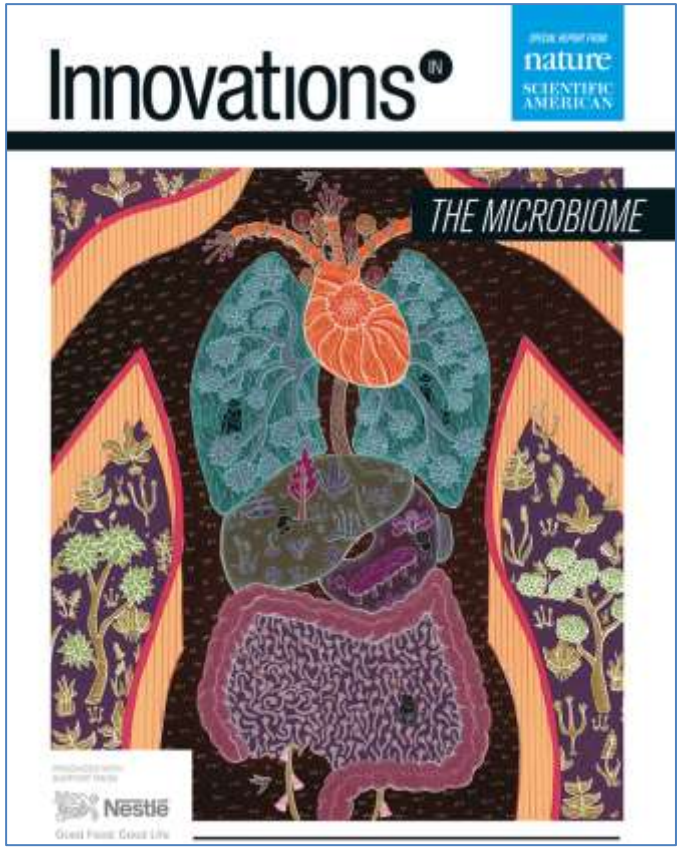
# The Mycobiome: A Neglected Component in the Microbiota-Gut-Brain Axis

**Raphaël Enaud [1,2,3,*], Louise-Eva Vandenborght [1,3,4], Noémie Coron [1,2,3], Thomas Bazin [1,2],**




(Microorganisms 2018)

# Το εντερικό μικροβίωμα στο κέντρο της σύγχρονης έρευνας





# Το εντερικό μικροβίωμα στο επίκεντρο της σύγχρονης χρηματοδότησης

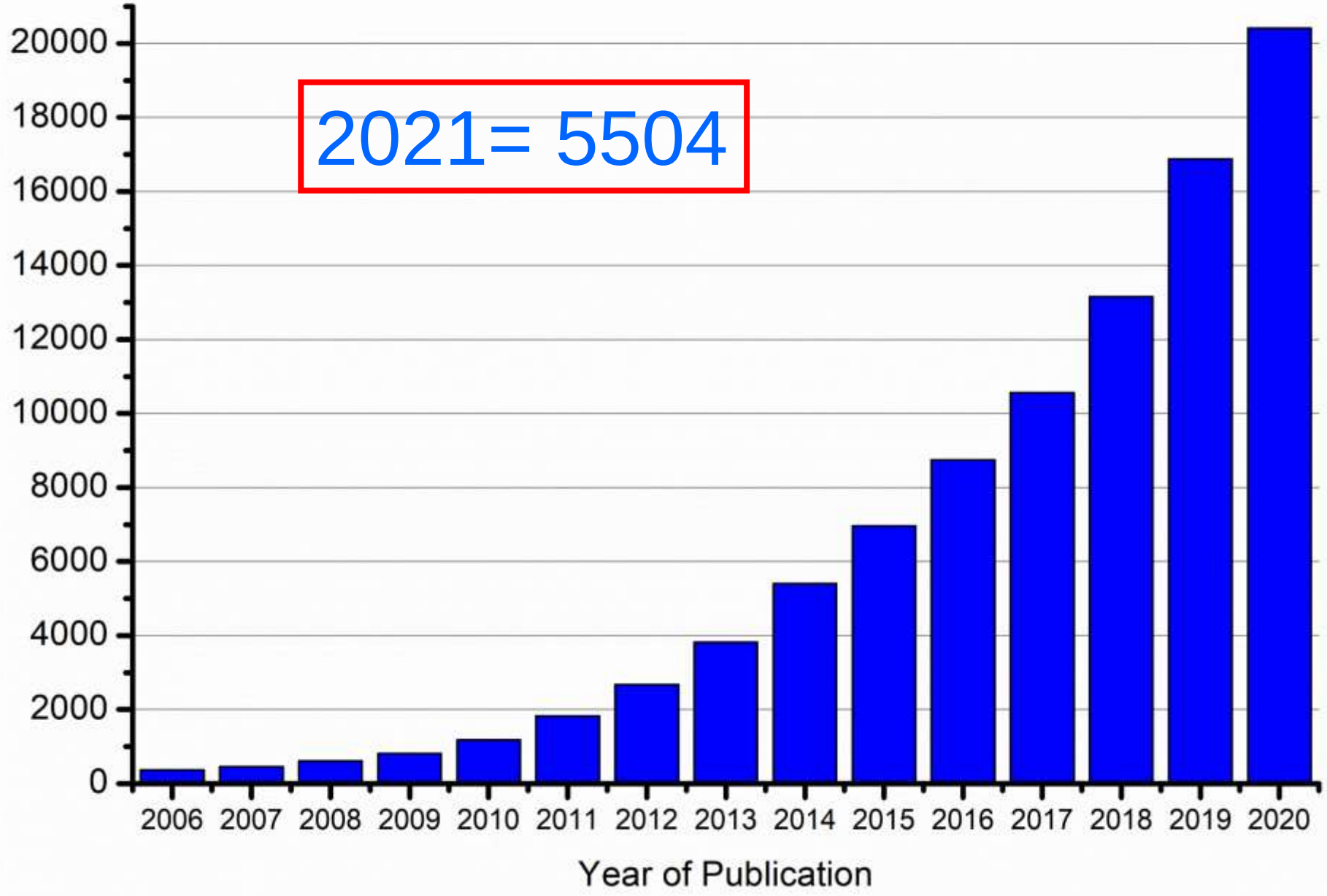
NIH HUMAN MICROBIOME PROJECT


MetaHIT

# Το εντερικό μικροβίωμα στο στόχαστρο της σύγχρονης φαρμακοβιομηχανίας


- Global sales of Probiotics – 31.1 billion in 2015
- Fastest growing segment of the global dietary supplement & functional food industries

# Papers in PubMed with Keyword Microbiome vs Year



PLOS | BIOLOGY

PERSPECTIVE

# Big Data: Astronomical or Genomical?

**Zachary D. Stephens[1], Skylar Y. Lee[1], Faraz Faghri[2], Roy H. Campbell[2], Chengxiang Zhai[3], Miles J. Efron[4], Ravishankar Iyer[1], Michael C. Schatz[5]*, Saurabh Sinha[3]*, Gene E. Robinson[6]***

**Table 1. Four domains of Big Data in 2025.** In each of the four domains, the projected annual storage and computing needs are presented across the data lifecycle.

| Data Phase | Astronomy | Twitter | YouTube | Genomics |
|---|---|---|---|---|
| **Acquisition** | 25 zetta-bytes/year | 0.5–15 billion tweets/year | 500–900 million hours/year | 1 zetta-bases/year |
| **Storage** | 1 EB/year | 1–17 PB/year | 1–2 EB/year | 2–40 EB/year |
| **Analysis** | In situ data reduction | Topic and sentiment mining | Limited requirements | Heterogeneous data and analysis |
| | Real-time processing | Metadata analysis | | Variant calling, ~2 trillion central processing unit (CPU) hours |
| | Massive volumes | | | All-pairs genome alignments, ~10,000 trillion CPU hours |
| **Distribution** | Dedicated lines from antennae to server (600 TB/s) | Small units of distribution | Major component of modern user's bandwidth (10 MB/s) | Many small (10 MB/s) and fewer massive (10 TB/s) data movement |

**(Stephens et al PLoS Biol. 2015)**

# Σαν συμπέρασμα…

- Ο άνθρωπος και η μικροβιακή του χλωρίδα είναι δύο συμβιωτικοί οργανισμοί,
- Που έχουν απόλυτη ανάγκη ο ένας τον άλλον
- Παίζει σημαντικό ρόλο στην παθοφυσιολογία και ανοσολογία του γαστρεντερικού σωλήνα.
- Διαταραχές της εντερικής χλωρίδας φαίνεται να εμπλέκονται στην παθογένεια πολλών διαταραχών, πέραν του πεπτικού.
- Η δυσβίωση της εντερικής χλωρίδας φαίνεται να συνδέεται άμεσα με τους παθογενετικούς μηχανισμούς ανοσολογικών διαταραχών
- Η περαιτέρω μελέτης της χλωρίδας και του μικροβιώματος πιθανόν να μας αποκαλύψει παθογενετικούς μηχανισμούς ή/και να αποτελέσει στόχο νέων θεραπευτικών στρατηγικών.


Ευχαριστώ πολύ!!!!!!