GRENOBLE
29/09/2016

Microbiotes et pathologies humaines

«A pure culture is the foundation for all research on infectious diseases» R. Koch. 1881

Unité de Recherche sur les Maladies Infectieuses Tropicales Emergentes
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Viruses: Essential Agents of Life by Günther Witzany

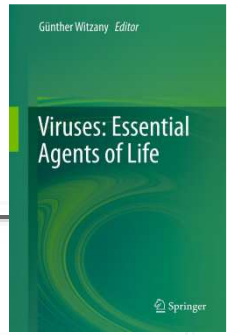


Table 1 Predicted diversity of cellular and viral species

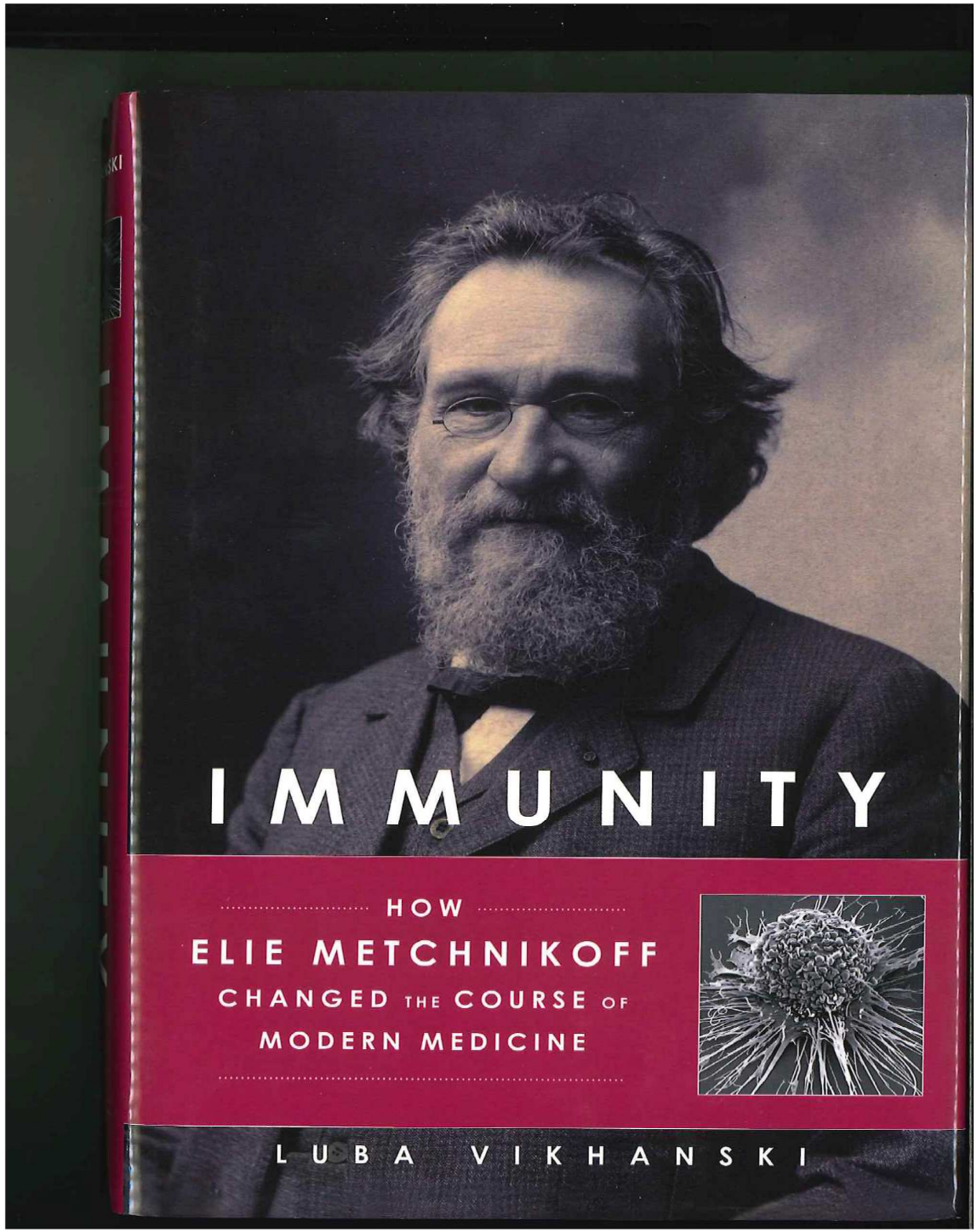
Taxonomic group	Known species	Predicted species[a]	Predicted viral species[b]	Source
Bacteria	10,000	$>10^7$	$>10^8$	Rohwer (2003) and Sogin et al. (2006)
Archaea	10,000	$>10^7$	$>10^8$	IUCN (2011)
Eukarya	1.74×10^6	1.5×10^7	10^8	IUCN (2011)
Animalia	1.37×10^6	1.2×10^7	10^8	IUCN (2011)
Vertebrates	65,000	100,000	10^6	IUCN (2011)
Invertebrates	1.3×10^6	1.2×10^7	10^8	Chapman (2009)
Arthropoda	1.1×10^6	1.1×10^7	10^8	IUCN (2011)
Insecta	950,000	9×10^6	10^8	May (1988)
Plantae	250,000	500,000	10^6	Chapman (2009)
Fungi	75,000	1.5×10^6	10^7	Hawksworth (2001)
Protista	50,000	100,000	10^6	IUCN (2011)

[a]A significant fraction of archaeal and bacterial species are yet to be discovered; the eukaryotic species count will remain dominated by members of class *Insecta*

[b]All cellular organisms were assumed to be subject to infection by an average of 10 unique viral genotypes

The field is open, run to find your own bug

p.64 By F.Rohwer


IMMUNITY
HOW
ELIE METCHNIKOFF
CHANGED THE COURSE OF
MODERN MEDICINE
LUBA VIKHANSKI

MICROBIOTE

- Protège des microbes extérieurs (*Clostridium difficile*)
- Rôle des probiotiques ?
- Suradapté : 4 phyla sur 70

Hugon P, Dufour JC, Colson P, Fournier PE, Sallah K, Raoult D. A comprehensive repertoire of prokaryotic species identified in human beings. Lancet Infect Dis. 2015 Oct;15(10):1211-9.

The compilation of the complete prokaryotic repertoire associated with human beings as commensals or pathogens is a major goal for the scientific and medical community. The use of bacterial culture techniques remains a crucial step to describe new prokaryotic species. The large number of officially acknowledged bacterial species described since 1980 and the recent increase in the number of recognised pathogenic species have highlighted the absence of an exhaustive compilation of species isolated in human beings. By means of a thorough investigation of several large culture databases and a search of the scientific literature, we built an online database containing all human-associated prokaryotic species described, whether or not they had been validated and have standing in nomenclature. We list 2172 species that have been isolated in human beings. They were classified in 12 different phyla, mostly in the Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes phyla. Our online database is useful for both clinicians and microbiologists and forms part of the Human Microbiome Project, which aims to characterise the whole human microbiota and help improve our understanding of the human predisposition and susceptibility to infectious agents.

STUDIES ON HUMAN MICROBIOTA

Molecular studies

- Metagenomic
- 16S rDNA broad spectum
- specific PCR
- problems and disequences
- extraction
- rare phylum

Culturomics

-Proof of concept and study

Microbiote

A : Gut

B : Respiratory tract

C : Urine

D : Vagina

E : Skin

F : Milk

G : Sinus

- Répertoire
- Obésité/malnutrition
- Infection
- Cancer
- Autre ?

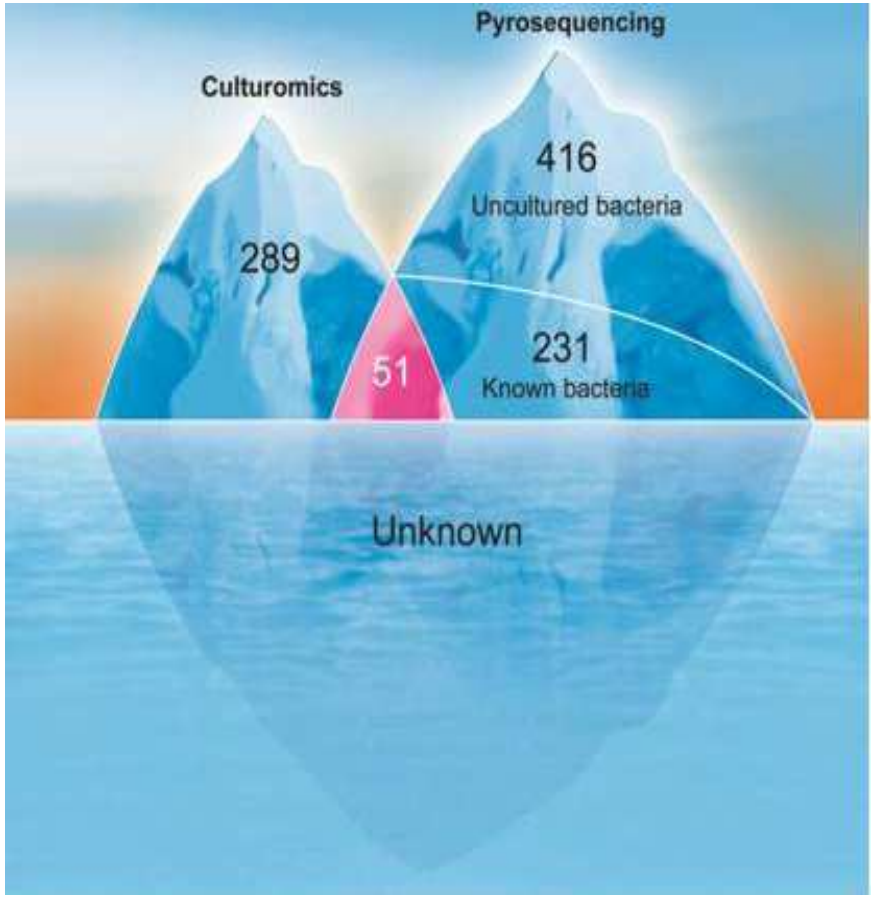
Microbial culturomics: paradigm shift in the human gut microbiome study.

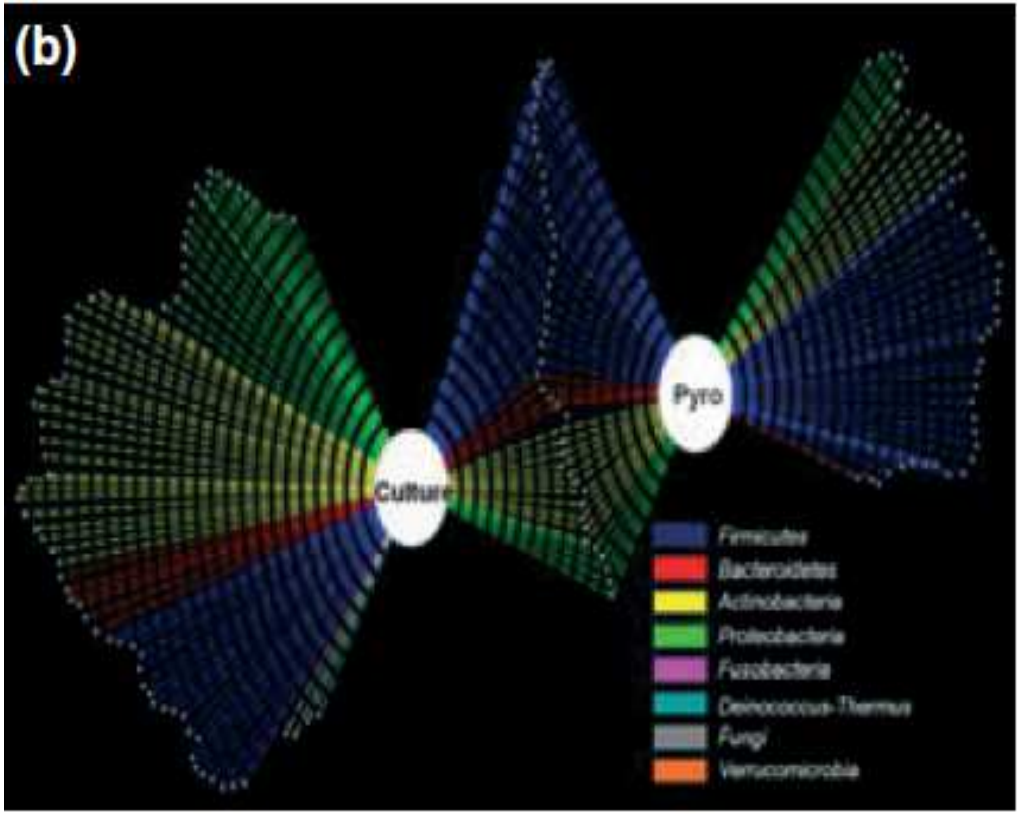
Lagier JC, Armougom F, Million M, Hugon P, Pagnier I, Robert C, Bittar F, Fournous G, Gimenez G, Maraninchi M, Trape JF, Koonin EV, La Scola B, Raoult D.

Clin Microbiol Infect. 2012 Sep 4. doi: 10.1111/1469-0691.12023

Comprehensive determination of the microbial composition of the gut microbiota and the relationships with health and disease are major challenges in the 21st century. Metagenomic analysis of the human gut microbiota detects mostly uncultured bacteria. We studied stools from two lean Africans and one obese European, using 212 different culture conditions (microbial culturomics), and tested the colonies by using mass spectrometry and 16S rRNA amplification and sequencing. In parallel, we analysed the same three samples by pyrosequencing 16S rRNA amplicons targeting the V6 region. The 32 500 colonies obtained by culturomics have yielded 340 species of bacteria from seven phyla and 117 genera, including two species from rare phyla (Deinococcus-Thermus and Synergistetes, five fungi, and a giant virus (Senegalvirus). The microbiome identified by culturomics included 174 species never described previously in the human gut, including 31 new species and genera for which the genomes were sequenced, generating c. 10 000 new unknown genes (ORFans), which will help in future molecular studies. Among these, the new species Microvirga massiliensis has the largest bacterial genome so far obtained from a human, and Senegalvirus is the largest virus reported in the human gut. Concurrent metagenomic analysis of the same samples produced 698 phylotypes, including 282 known species, 51 of which overlapped with the microbiome identified by culturomics. Thus, culturomics complements metagenomics by overcoming the depth bias inherent in metagenomic approaches.

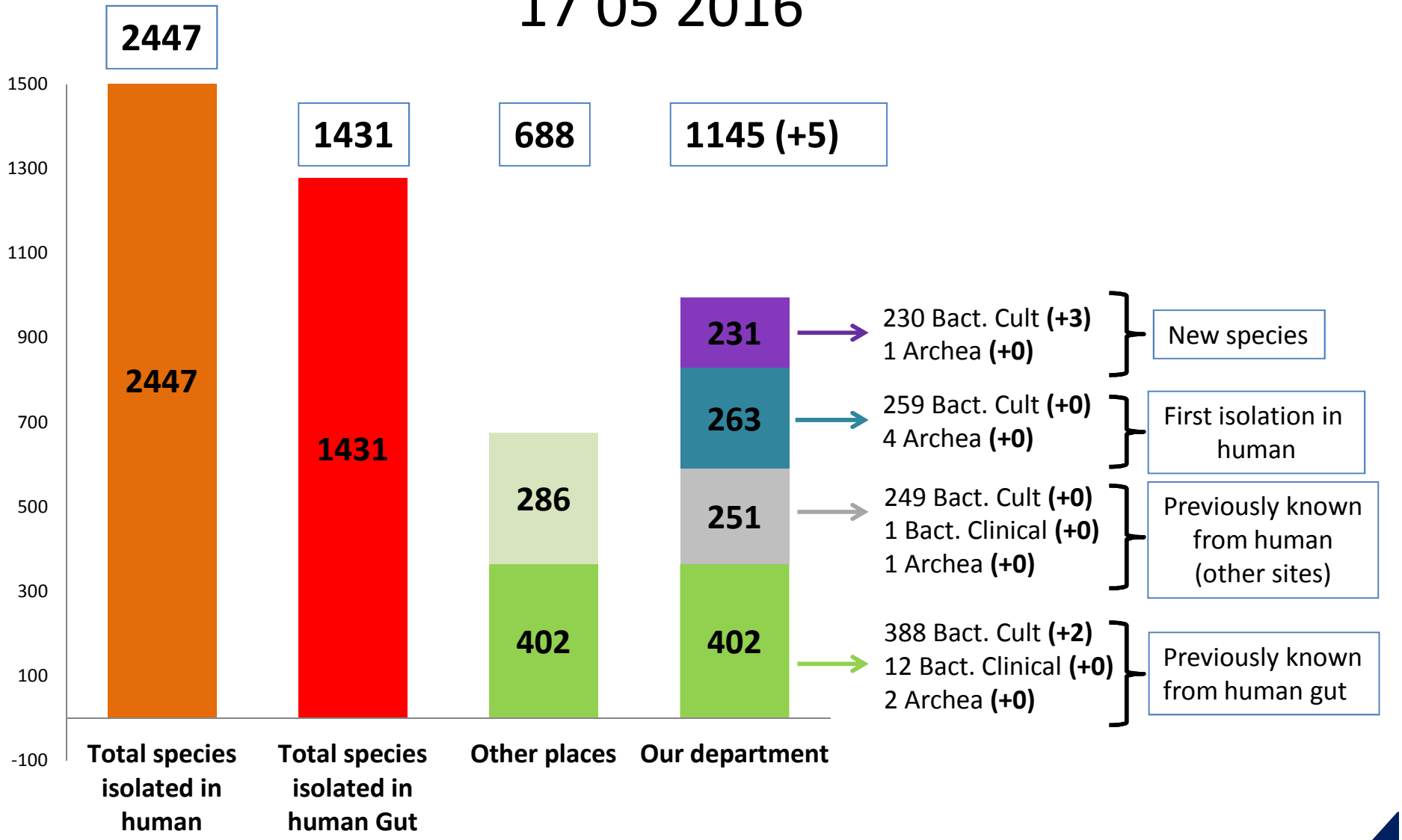
Identification of bacteria in the human gut by culturomics and metagenomics

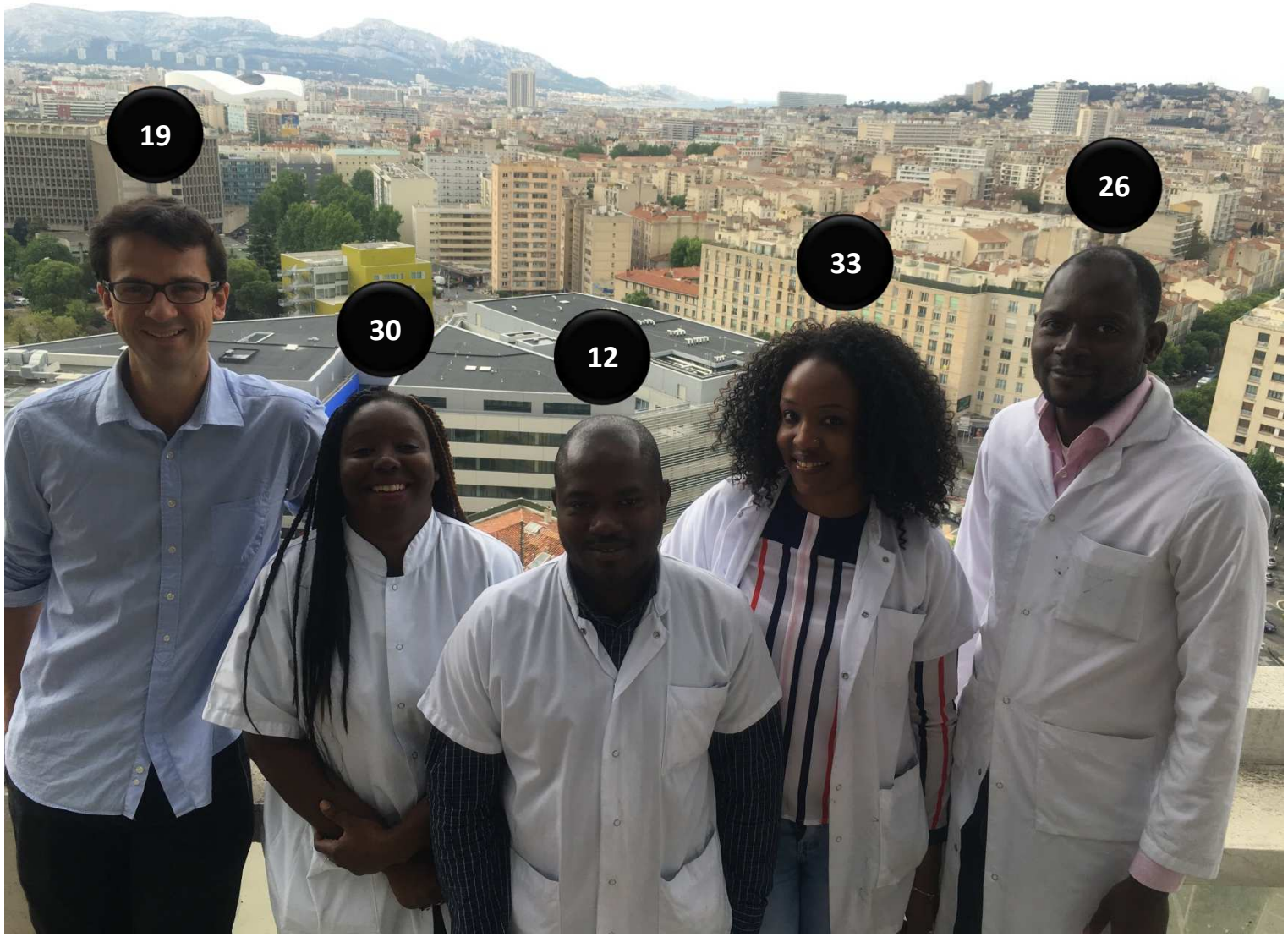




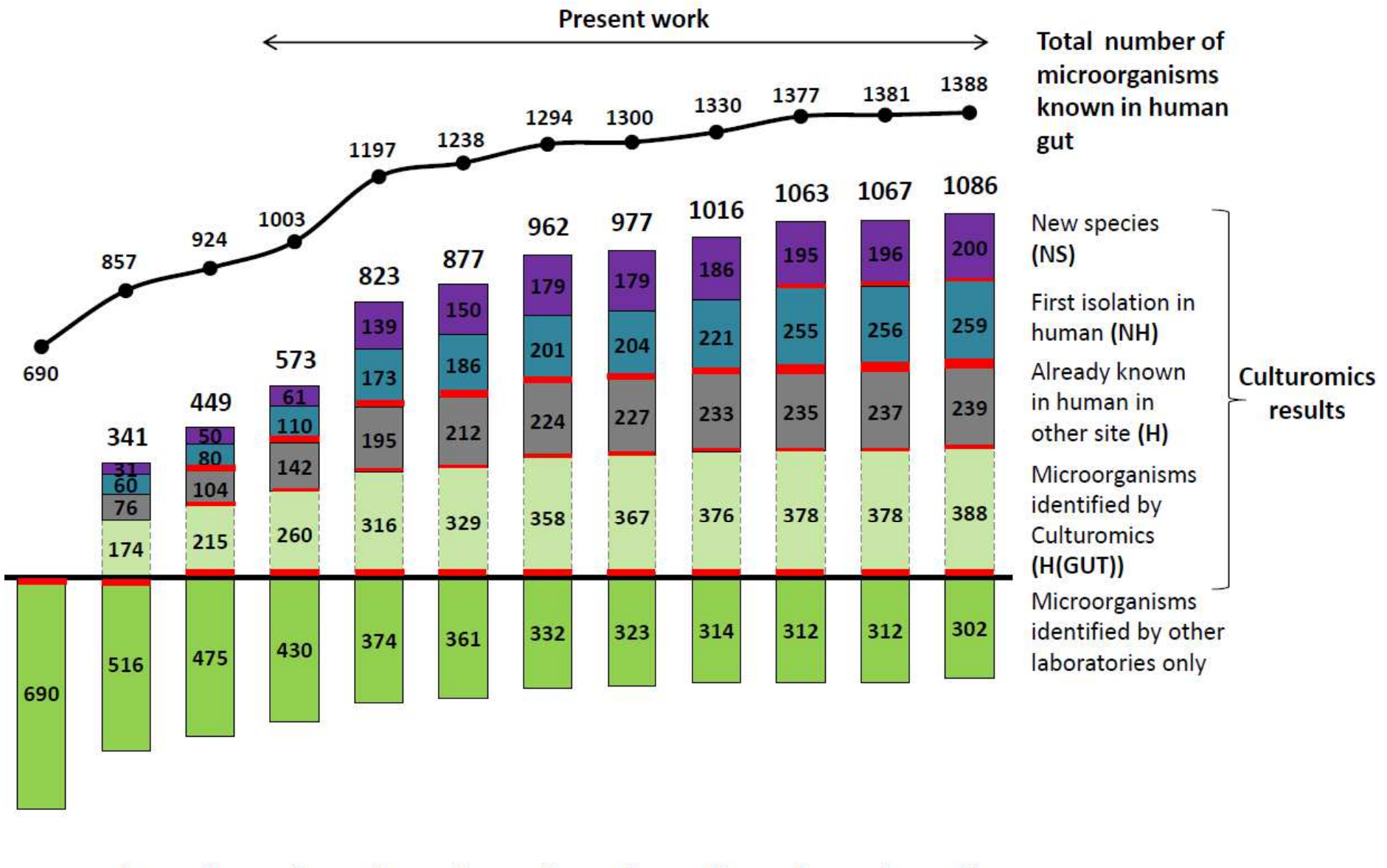
80% cultured species are undetected by molecular technique

Microbiote Gut
17 05 2016





JC. Lagier M. Tidjani Alou A. Hamidou Togo S. Ndongo S. Ibrahima Traoré


Present work
Total number of microorganisms known in human gut
690
857
924
1003
1197
1238
1294
1300
1330
1377
1381
1388
New species (NS)
First isolation in human (NH)
Already known in human in other site (H)
Microorganisms identified by Culturomics (H(GUT))
Culturomics results
Microorganisms identified by other laboratories only
341
449
573
823
877
962
977
1016
1063
1067
1086
31
60
76
174
50
80
104
215
61
110
142
260
139
173
195
316
150
186
212
329
179
201
224
358
179
204
227
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233
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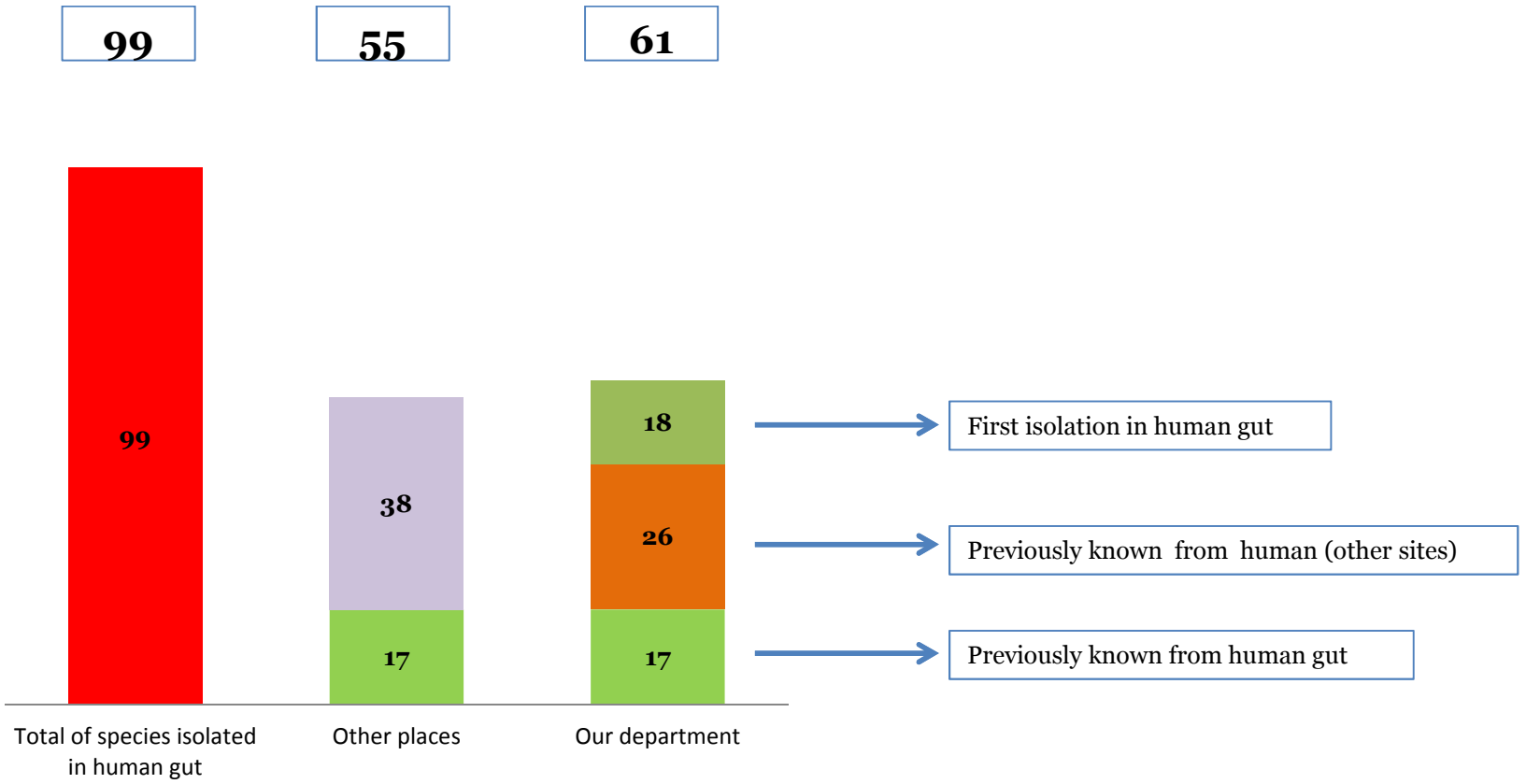
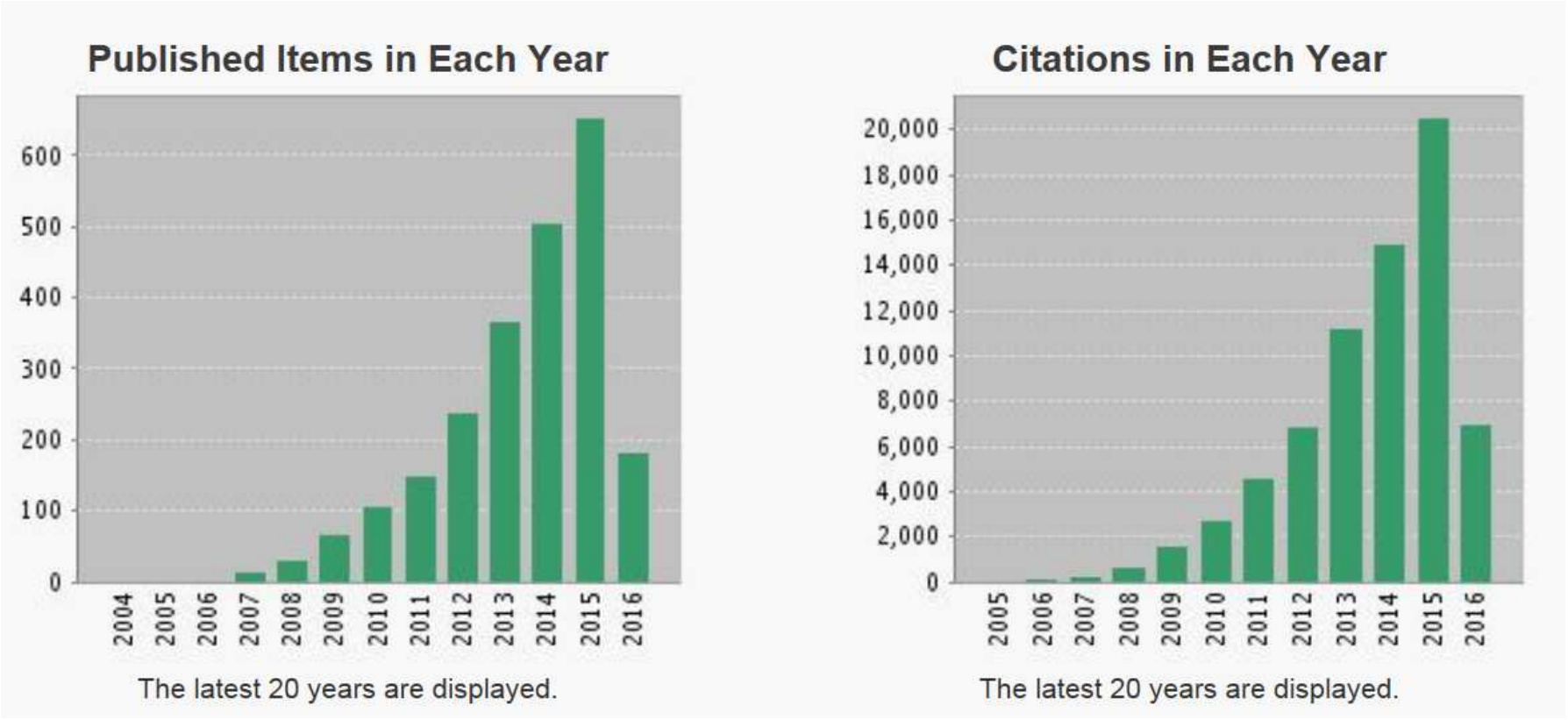
195
255
235
378
196
256
237
378
200
259
239
388
690
516
475
430
374
361
332
323
314
312
312
302
A B C D E F G H I J K
A: First culturomics study
B: Published culturomics studies
C: 70 culture conditions
D: 18 culture conditions
E: Cohorts
F: Fresh stools
G: Proteobacteria
H: Microaerophilic
I: Halophilic
J: Microcolonies
K: Duodenum
Archaea

REPERTOIRE FUNGI (URMITE)



- Répertoire
- Obésité/malnutrition
- Infection
- Cancer
- Autre ?

TOPIC: (microbiota) *AND* **TOPIC:** (obesity) ...
Timespan: All years.



Citation Report: 2 324

New light shed on obesityassociated gut microbiota

The findings of a recent study published in the *International Journal of Obesity* suggest that *Lactobacillus reuteri* is associated with obesity and that *Bifidobacterium animalis, Methanobrevibacter smithii* and other species of *Lactobacillus* are associated with normal weight.

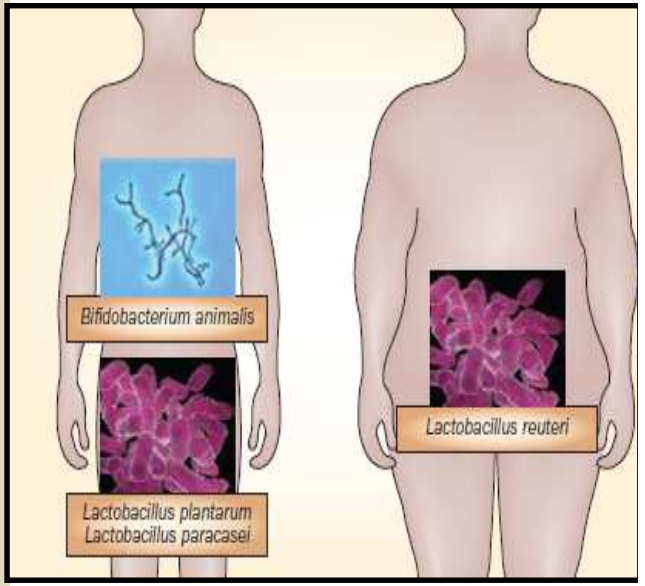
The prevalence of obesity is steadily increasing worldwide and it is a risk factor for a variety of diseases, including stroke and cancer. Many factors are thought to have a role in causing obesity. In particular, research has demonstrated that obesity is associated with a specific profile of gut microbiota. However, the associations between different bacterial species and their role in either protecting against or promoting obesity are complex, and data are limited.

Didier Raoult, corresponding author of the study, is investigating the possible (although controversial) idea that probiotics might have a role in promoting obesity by altering the gut microbiota. "Some bacteria … are used as probiotics in humans and as growth promoters in animals," he explains. Thus, the aim of this study was to investigate the association between certain bacterial strains that are marketed elsewhere as probiotics for human consumption and obesity.

To that end, the researchers analyzed the stools of 68 obese individuals and 47 controls. They used cultures and quantitative PCR to create a data bank to identify strains. "We found that *L. reuteri was significantly* linked with obesity; this strain has been used as a growth promoter in animals," reports Raoult. *B. animalis. L. plantarum and L. paracasei were* associated with normal weight, as was *M. smithii. The authors warn* that caution is required when considering these results as this is the first study to link a specific species of *Lactobacillus with obesity. Nonetheless,* Raoult concludes that "This work is a step forward in showing that some species of probiotics may be associated with weight gain and some with protection against obesity".

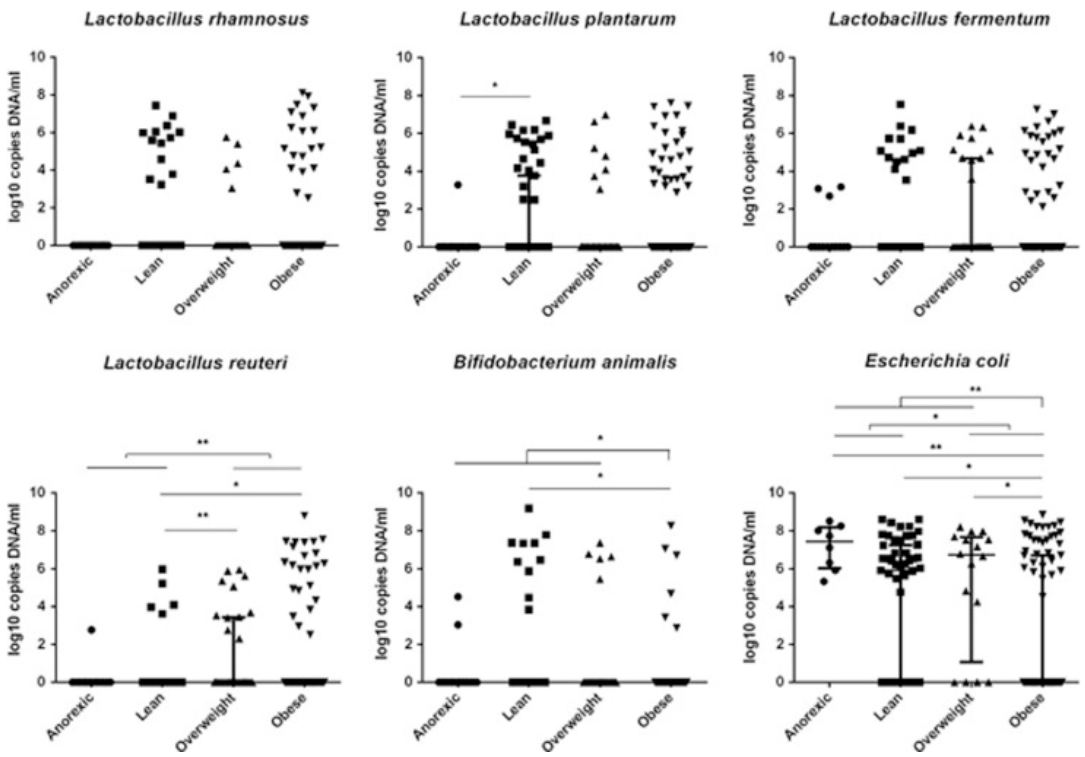
The authors now plan to perform a meta-analysis of the available data in the literature on probiotics in animals, to focus on species associated with either weight gain or protection from obesity.

Isobel Franks



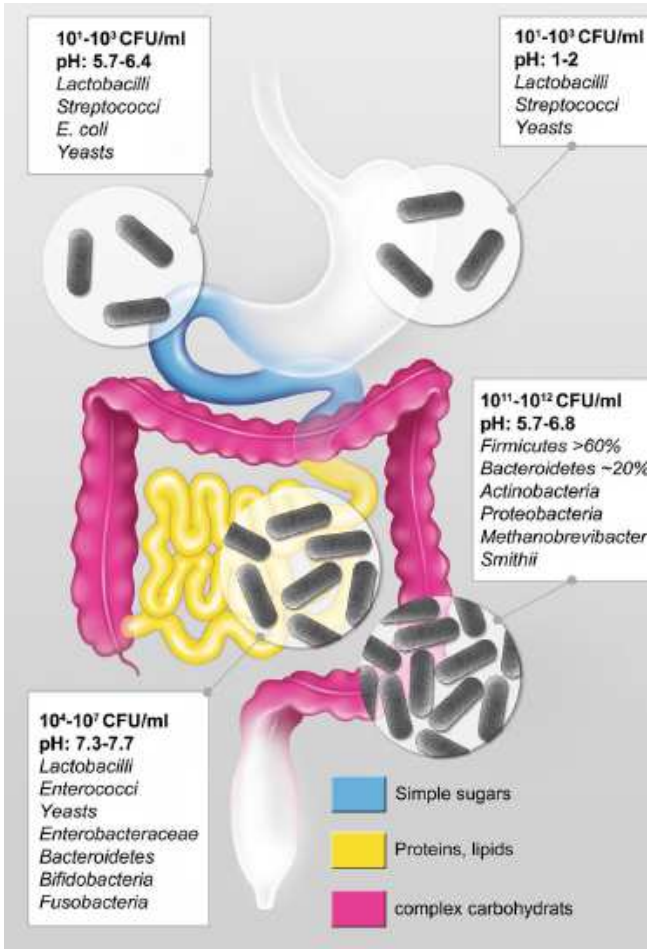
Original article Million, M. *et al. Obesity-associated gut microbiota is enriched in Lactobacillus reuteri* and depleted in *Bifidobacterium animalis and Methanobrevibacter smithii. Int. J. Obes. doi: 10.1038/* ijo.2011.153

WP4.1.7 Relationship microbiota obesity and malnutrities



International Journal of Obesity (2013) 37, 1460–1466

www.nature.com/ijo



ORIGINAL ARTICLE

Correlation between body mass index and gut concentrations of *Lactobacillus reuteri*, *Bifidobacterium animalis*, *Methanobrevibacter smithii* and *Escherichia coli*

M Million[1,2,7], E Angelakis[1,7], M Maraninchi[3], M Henry[1], R Giorgi[4,5], R Valero[3,6], B Vialettes[6] and D Raoult[1,2]

Eur J Epidemiol. 2014 May 17. [Epub ahead of print]

Are stool samples suitable for studying the link between gut microbiota and obesity?

Raoult D[1], Henrissat B.

Related actions of probiotics and antibiotics on gut microbiota and weight modification.
Angelakis E, Merhej V, Raoult D. Lancet Infect Dis. 2013 Oct;13(10):889-99

The Role of the Manipulation of the Gut Microbiota in Obesity.

Million M, Raoult D.

Curr Infect Dis Rep. 2012 Nov 6

The manipulation of the gut microbiota by diet, antibiotics, or probiotics could promote, prevent, or reverse the development of specific diseases, including obesity. A link has been proposed between obesity and the growth promoters (probiotics and antibiotics) that have been used in animals for more than 40 years to induce weight gain. Several species of the Lactobacillus genus that are frequently used as probiotics for human consumption merit particular attention because they are increased in the gut microbiota under high-fat diets, are more abundant in obese humans, and are selected by growth-promoter antibiotics; moreover, the administration of these bacteria in experimental models is linked to the development of obesity. However, other species or strains of the same genus are associated with an antiobesity effect. Newborns and infants are a particularly susceptible population in which the administration of antibiotics or probiotics could be related to the development of obesity in adulthood.

Vancomycin treatment of infective endocarditis is linked with recently acquired obesity.

Thuny F, Richet H, Casalta JP, Angelakis E, Habib G, Raoult D.

PLoS One. 2010 Feb 10;5(2):e9074

Abstract

BACKGROUND:

Gut microbiota play a major role in digestion and energy conversion of nutrients. Antibiotics, such as avoparcin (a vancomycin analogue), and probiotics, such as Lactobacillus species, have been used to increase weight in farm animals. We tested the effect of antibiotics given for infective endocarditis (IE) on weight gain (WG).

METHODOLOGY/PRINCIPAL FINDINGS:

Forty-eight adults with a definite diagnosis of bacterial IE (antibiotic group) were compared with forty-eight age-matched controls without IE. Their body mass index (BMI) was collected at one month before the first symptoms and one year after hospital discharge. The BMI increased significantly and strongly in vancomycin-plus-gentamycin-treated patients (mean [+/-SE] kg/m(2), +2.3 [0.9], p = 0.03), but not in controls or in patients treated with other antibiotics. Seventeen patients had a BMI increase of >or=10%, and five of the antibiotic group developed obesity. The treatment by vancomycin-plus-gentamycin was an independent predictor of BMI increase of >or=10% (adjusted OR, 6.7; 95% CI, 1.37-33.0; p = 0.02), but not treatment with other antibiotics. Weight gain was particularly high in male patients older than 65 who did not undergo cardiac surgery. Indeed, all three vancomycin-treated patients with these characteristics developed obesity.

CONCLUSIONS/SIGNIFICANCE:

A major and significant weight gain can occur after a six-week intravenous treatment by vancomycin plus gentamycin for IE with a risk of obesity, especially in males older than 65 who have not undergone surgery. We speculate on the role of the gut colonization by Lactobacillus sp, a microorganism intrinsically resistant to vancomycin, used as a growth promoter in animals, and found at a high concentration in the feces of obese patients. Thus, nutritional programs and weight follow-up should be utilized in patients under such treatment.

Improved lung function and body mass index associated with long-term use of Macrolide antibiotics.

Pirzada OM, McGaw J, Taylor CJ, Everard ML.

J Cyst Fibros. 2003 Jun;2(2):69-71.

BACKGROUND: A number of studies have suggested that the non-antimicrobial actions of macrolide antibiotics may be valuable in treating patients with cystic fibrosis. The use of long-term macrolide antibiotics for the management of CF patients colonised by Pseudomonas aeruginosa and progressive pulmonary disease was introduced into our clinic in 1997. A retrospective study was undertaken to assess of the impact of this therapy.

METHODS: Twenty patients with progressive pulmonary disease (>10% fall in FEV(1) over 12 months despite optimising conventional therapy) were commenced on Azithromycin, 250 mg daily during a 21-month period. At the time of assessment they had remained on therapy for a mean of 0.9 years. Changes in lung function, weight, body mass index (BMI) and frequency of pulmonary exacerbations were assessed. A group of 20 patients with stable lung function and matched as far as possible for age and sex was identified for comparison.

RESULTS: Pulmonary function increased significantly in the Azithromycin group with FEV1% predicted increasing from a mean of 50.2-59.1% (P=0.001) while FVC% predicted increase from 64.5 to 76.1% (P=0.002). There was small but non-significant fall in lung function in the comparison group. Body mass index increased by a mean of 1.1 in the Azithromycin group but remained unchanged in the comparison group. The number of pulmonary exacerbations requiring intravenous antibiotics declined by 48.3% in macrolide treated subjects compared to the pre-treatment period (P<0.025); frequency of exacerbations in the control group was unchanged.

CONCLUSION: Long-term Azithromycin treatment in patients with progressive deterioration in lung function appears to have led to an improvement in pulmonary function, increased body mass index and decreased the frequency of pulmonary exacerbations requiring intravenous antibiotics.

Infant antibiotic exposures and early-life body mass.

Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ.

Int J Obes (Lond). 2013 Jan;37(1):16-23.

Objectives:To examine the associations of antibiotic exposures during the first 2 years of life and the development of body mass over the first 7 years of life.Design:Longitudinal birth cohort study.Subjects:A total of 11 532 children born at □2500 g in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based study of children born in Avon, UK in 1991-1992.Measurements:Exposures to antibiotics during three different early-life time windows (<6 months, 6-14 months, 15-23 months), and indices of body mass at five time points (6 weeks, 10 months, 20 months, 38 months and 7 years).Results:Antibiotic exposure during the earliest time window (<6 months) was consistently associated with increased body mass (+0.105 and +0.083 s.d. unit, increase in weight-for-length Z-scores at 10 and 20 months, P<0.001 and P=0.001, respectively; body mass index (BMI) Z-score at 38 months +0.067 s.d. units, P=0.009; overweight OR 1.22 at 38 months, P=0.029) in multivariable, mixed-effect models controlling for known social and behavioral obesity risk factors. Exposure from 6 to 14 months showed no association with body mass, while exposure from 15 to 23 months was significantly associated with increased BMI Z-score at 7 years (+0.049 s.d. units, P=0.050). Exposures to non-antibiotic medications were not associated with body mass.Conclusions:Exposure to antibiotics during the first 6 months of life is associated with consistent increases in body mass from 10 to 38 months. Exposures later in infancy (6-14 months, 15-23 months) are not consistently associated with increased body mass. Although effects of early exposures are modest at the individual level, they could have substantial consequences for population health. Given the prevalence of antibiotic exposures in infants, and in light of the growing concerns about childhood obesity, further studies are needed to isolate effects and define life-course implications for body mass and cardiovascular risks.

PERSPECTIVE

Science, 2016, 352:544-45.

Antibiotic use and its consequences for the normal microbiome

Martin J. Blaser[1,2,3]

Anti-infectives, including antibiotics, are essentially different from all other drugs; they not only affect the individual to whom they are given but also the entire community, through selection for resistance to their own action. Thus, their use resides at the intersection of personal and public health. Antibiotics can be likened to a four-edged sword against bacteria. The first two edges of the antibiotic sword were identified immediately after their discovery and deployment in that they not only benefit an individual in treating their infection but also benefit the community in preventing the spread of that infectious agent. The third edge was already recognized by Alexander Fleming in 1945 in his Nobel acceptance speech, which warned about the cost to the community of antibiotic resistance that would inevitably evolve and be selected for during clinical practice. We have seen this cost mount up, as resistance curtails or precludes the activities of some of our most effective drugs for clinically important infections. But the fourth edge of the antibiotic sword remained unappreciated until recently, i.e., the cost that an antibiotic exerts on an individual's own health via the collateral damage of the drug on bacteria that normally live on or in healthy humans: our microbiota. These organisms, their genes, metabolites, and interactions with one another, as well as with their host collectively, represent our microbiome. Our relationship with these symbiotic bacteria is especially important during the early years of life, when the adult microbiome has not yet formed.

Related actions of probiotics and antibiotics on gut microbiota and weight modification

Emmanouil Angelakis, Vicky Merhej, Didier Raoult

Antibiotics and probiotics are widely used as growth promoters in agriculture. Most antibiotics prescribed in clinical practice are natural products that originate from *Streptomyces* spp, which were first used as agricultural probiotics. Antibiotics and probiotics both modify the gut microbiota. The effect of a probiotic species on the digestive flora depends on the strain and is largely determined by bacteriocin production. In human beings, as in animals, specific probiotics are associated with weight gain or loss. Improved understanding of the ability of specific probiotics to harvest energy from the host diet might lead to development of new treatments for obesity and malnutrition. In this Review, we present the effects of probiotics and antibiotics on the gut microbiota of human beings and animals and discuss their potential therapeutic use as interventions for weight gain and loss in human beings.

Lancet Infect Dis 2013; 13: 889–99

Unité des Rickettsies, Faculté de Médecine, Université de la Méditerranée, Marseille, France (E Angelakis MD, V Merhej PhD, Prof D Raoult MD)

Correspondence to:
Prof Didier Raoult, Unité des Rickettsies, Faculté de Médecine,

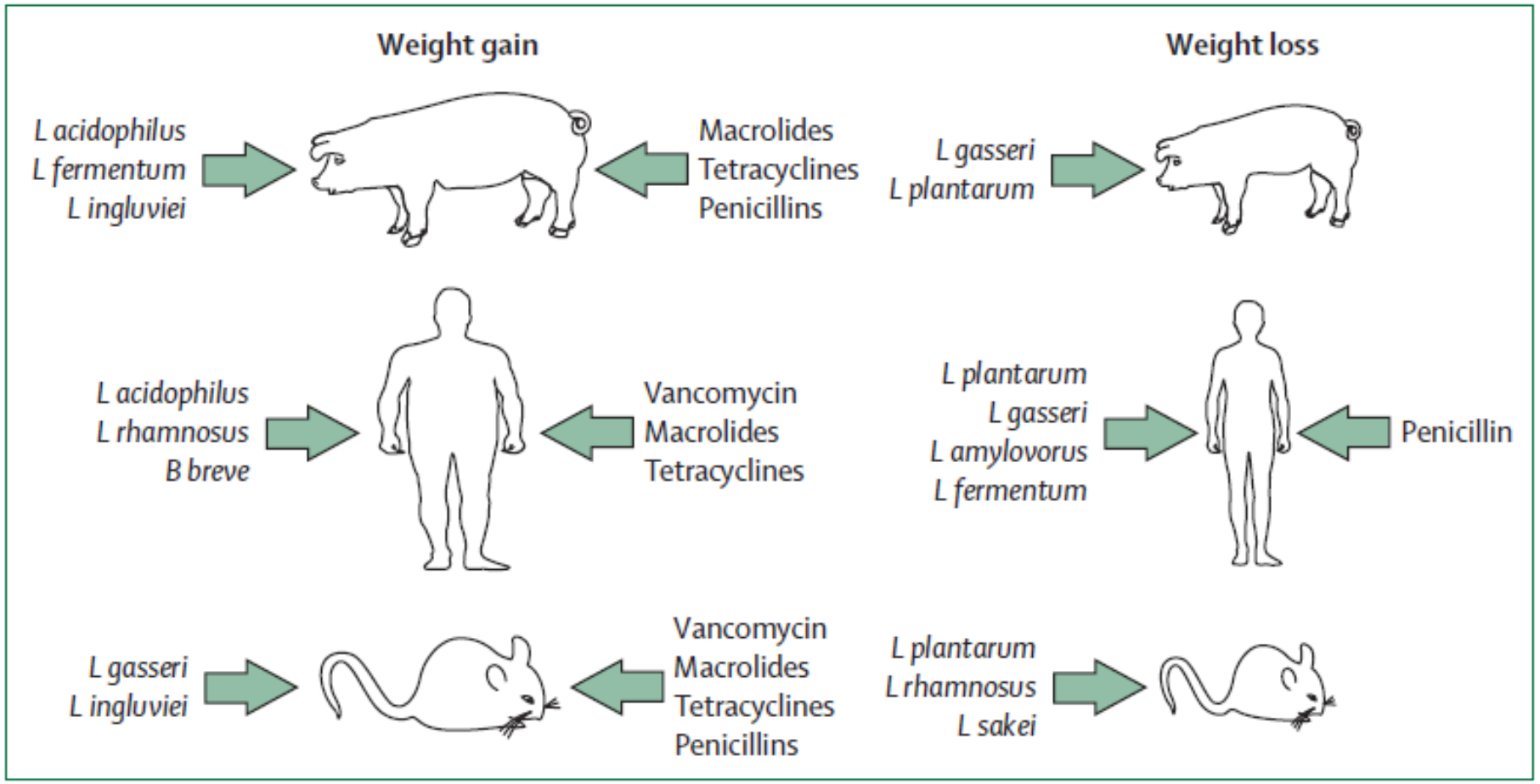


Figure 4: Weight changes after probiotic or antibiotic interventions

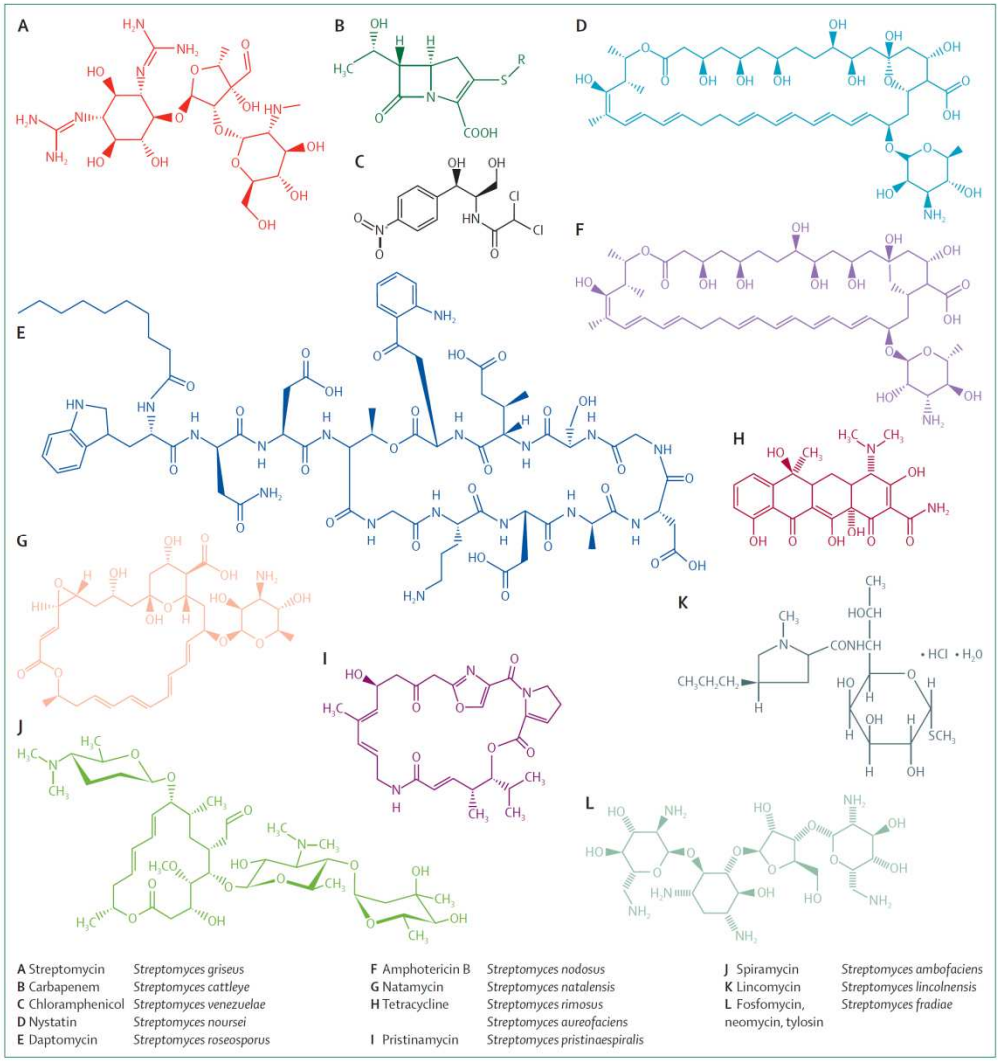


Figure 3: **Antibiotic compounds produced by *Streptomyces* spp**

Angelakis E, Merhej V, Raoult D. Related actions of probiotics and antibiotics on gut microbiota and weight modification. Lancet Infect Dis. 2013 Oct;13(10):889-99.

Million M, Diallo A, Raoult D. Gut microbiota and malnutrition. Microb Pathog. 2016 Feb 4. pii: S0882-4010(15)30212-6.

Malnutrition is the leading cause of death worldwide in children under the age of five, and is the focus of the first World Health Organization (WHO) Millennium Development Goal. Breastfeeding, food and water security are major protective factors against malnutrition and critical factors in the maturation of healthy gut microbiota, characterized by a transient bifidobacterial bloom before a global rise in anaerobes. Early depletion in gut Bifidobacterium longum, a typical maternal probiotic, known to inhibit pathogens, represents the first step in gut microbiota alteration associated with severe acute malnutrition (SAM). Later, the absence of the Healthy Mature Anaerobic Gut Microbiota (HMAGM) leads to deficient energy harvest, vitamin biosynthesis and immune protection, and is associated with diarrhea, malabsorption and systemic invasion by microbial pathogens. A therapeutic diet and infection treatment may be unable to restore bifidobacteria and HMAGM. Besides refeeding and antibiotics, future trials including non-toxic missing microbes and nutrients necessary to restore bifidobacteria and HMAGM, including prebiotics and antioxidants, are warranted in children with severe or refractory disease.

Million M, Diallo A, Raoult D. Gut microbiota and malnutrition. Microb Pathog. 2016 Feb 4. pii: S0882-4010(15)30212-6.

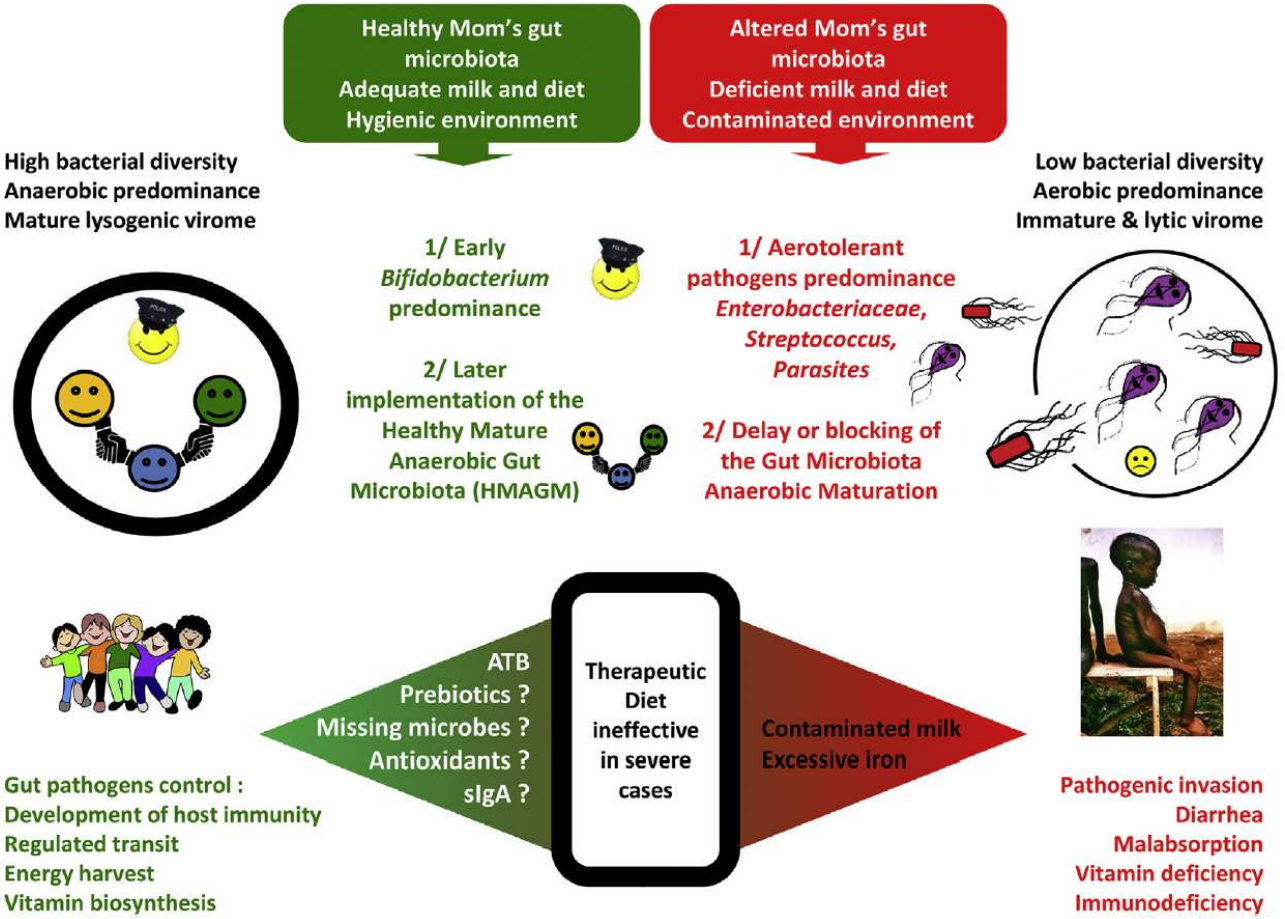


Fig. 2. Instrumental role of gut microbiota in malnutrition. HMAGM: healthy mature anaerobic gut microbiota, ATB: antibiotics. SIgA: secretory immunoglobulin A. The picture representing a child with kwashiorkor (right) is in the public domain (CDC/Dr. Lyle Conrad).

SCIENTIFIC REPORTS

OPEN

Increased Gut Redox and Depletion of Anaerobic and Methanogenic Prokaryotes in Severe Acute Malnutrition

Received: 22 October 2015
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Published: 17 May 2016

Matthieu Million[1,*], Maryam Tidjani Alou[1,*], Saber Khelaifia[1], Dipankar Bachar[1], Jean-Christophe Lagier[1], Niokhor Dione[1], Souleymane Brah[2], Perrine Hugon[1], Vincent Lombard[3,4], Fabrice Armougom[1], Julien Fromonot[5], Catherine Robert[1], Caroline Michelle[1], Aldiouma Diallo[6], Alexandre Fabre[7,8], Régis Guieu[5], Cheikh Sokhna[6], Bernard Henrissat[3,4,9], Philippe Parola[1] & Didier Raoult[1,9]

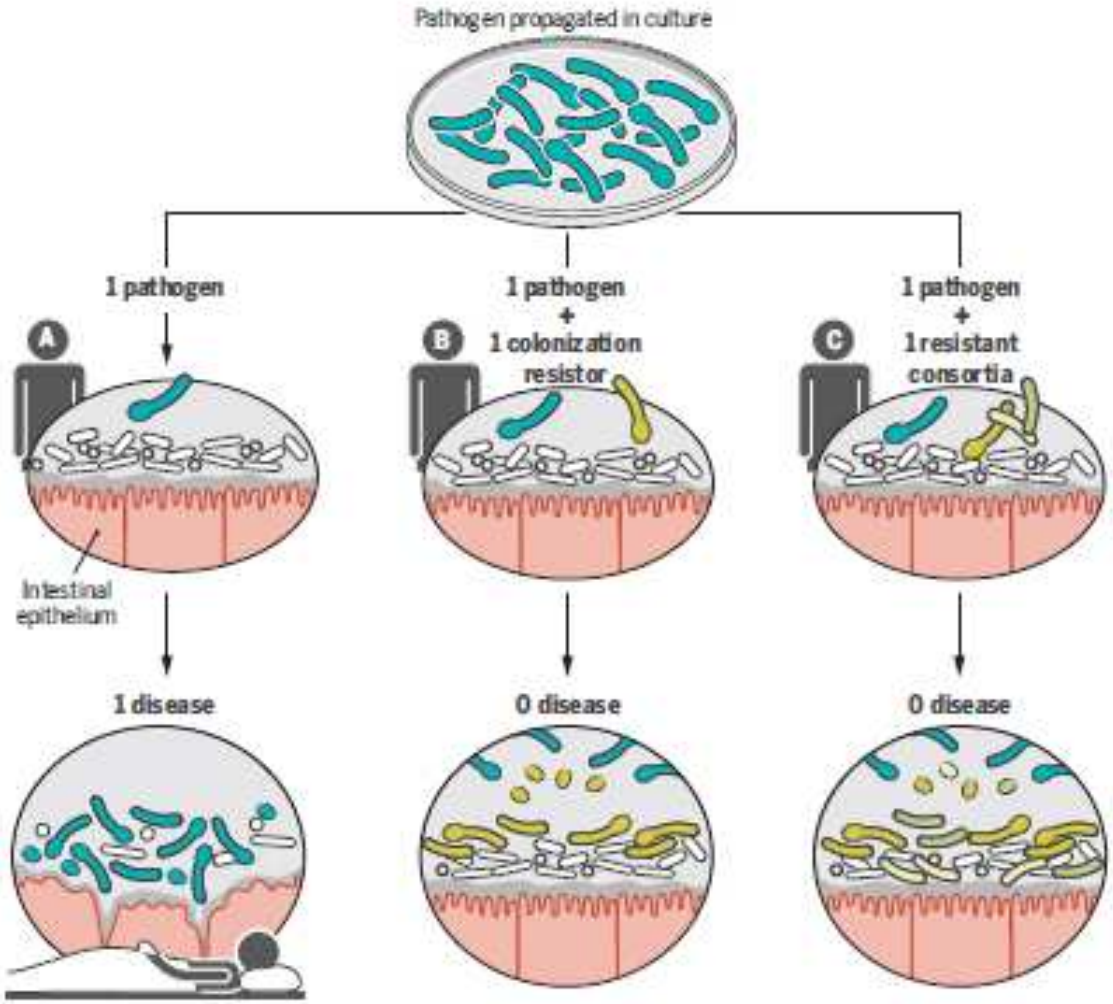
Severe acute malnutrition (SAM) is associated with inadequate diet, low levels of plasma antioxidants and gut microbiota alterations. The link between gut redox and microbial alterations, however, remains unexplored. By sequencing the gut microbiomes of 79 children of varying nutritional status from three centers in Senegal and Niger, we found a dramatic depletion of obligate anaerobes in malnutrition. This was confirmed in an individual patient data meta-analysis including 107 cases and 77 controls from 5 different African and Asian countries. Specifically, several species of the *Bacteroidaceae*, *Eubacteriaceae*, *Lachnospiraceae* and *Ruminococceae* families were consistently depleted while *Enterococcus faecalis*, *Escherichia coli* and *Staphylococcus aureus* were consistently enriched. Further analyses on our samples revealed increased fecal redox potential, decreased total bacterial number and dramatic *Methanobrevibacter smithii* depletion. Indeed, *M. smithii* was detected in more than half of the controls but in none of the cases. No causality was demonstrated but, based on our results, we propose a unifying theory linking microbiota specificity, lacking anaerobes and archaea, to low antioxidant nutrients, and lower food conversion.

- Répertoire
- Obésité/malnutrition
- Infection
- Cancer
- Autre ?

ADAPTING KOCH'S POSTULATES

Allyson L. Byrd, Julia A. Segre

Science 15 Jan 2016: Vol. 351, Issue 6270, pp. 224-226



Microbial protectors. (**A**) According to Koch's original postulates, a pathogenic organism in a host will induce disease. (**B**) This assumption is challenged when an organism is present that can protect against the pathogen. (**C**) In some cases, consortia of microbes can have an ever greater protective effect.

Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol. 2013 Nov;13(11):790-801. doi: 10.1038/nri3535. Epub 2013 Oct 7. Review.

Commensal bacteria inhabit mucosal and epidermal surfaces in mice and humans, and have effects on metabolic and immune pathways in their hosts. Recent studies indicate that the commensal microbiota can be manipulated to prevent and even to cure infections that are caused by pathogenic bacteria, particularly pathogens that are broadly resistant to antibiotics, such as vancomycin-resistant Enterococcus faecium, Gram-negative Enterobacteriaceae and Clostridium difficile. In this Review, we discuss how immune- mediated colonization resistance against antibiotic-resistant intestinal pathogens is influenced by the composition of the commensal microbiota. We also review recent advances characterizing the ability of different commensal bacterial families, genera and species to restore colonization resistance to intestinal pathogens in antibiotic-treated hosts.

Microbiome of HIV - infected people

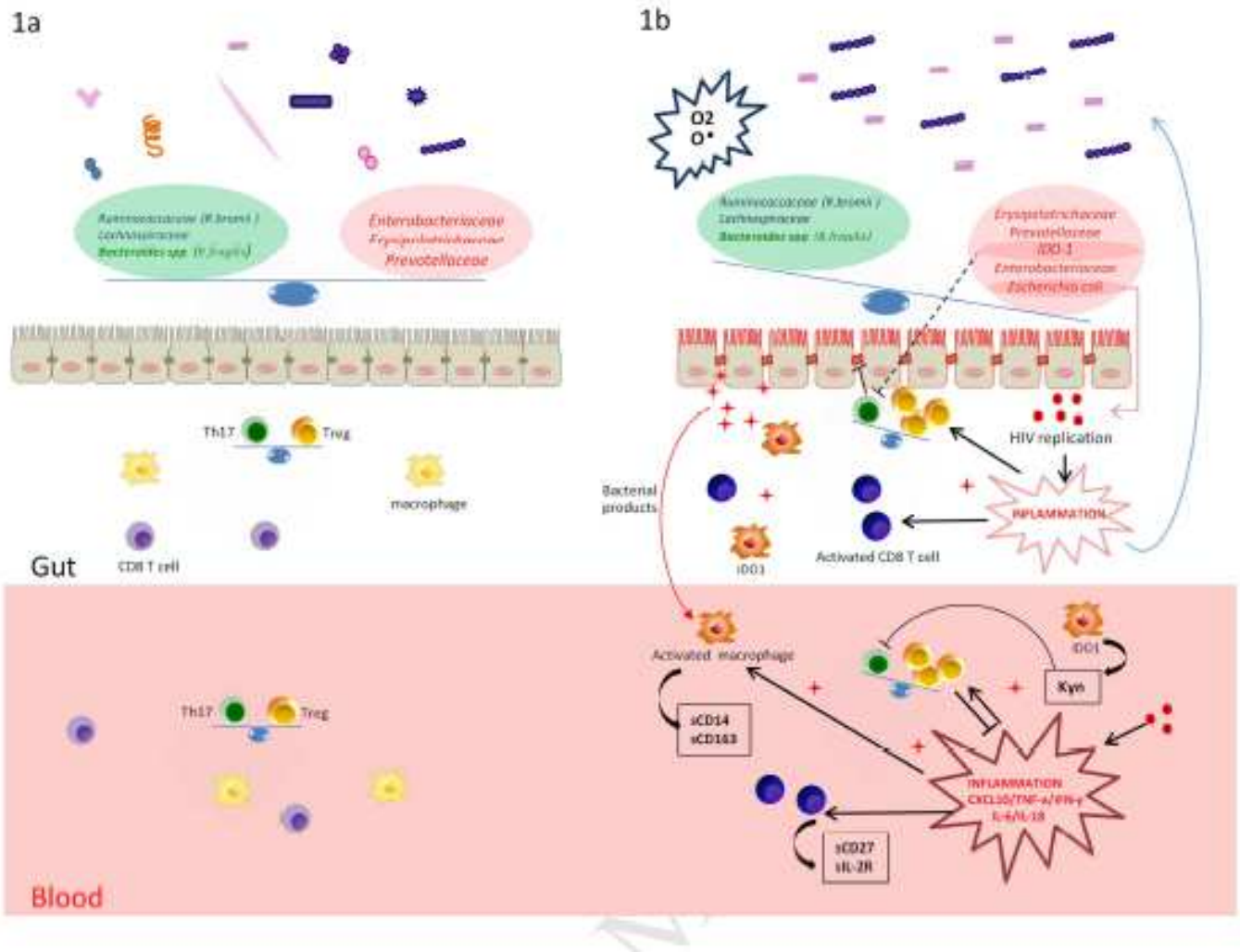
G.Dubourg, M.Surenaud, P.Y.Levy, S.Hüe, D.Raoult, Microbiome of HIV-infected people, référence YMPAT 2016 47.

ABSTRACT

Consistent interactions between the gut microbiome and adaptive immunity recently led several research groups to evaluate modifications of human gut microbiota composition during HIV infection. Herein we propose to review the shifts reported in infected individuals, as their correlation to disease progression. Though the gut microbiota is consistently altered in HIV individuals, the literature reveals several discrepancies, such as changes in microbial diversity associated with HIV status, taxa modified in infected subjects or influence of ART on gut flora restoration. Similarly, mechanisms involved in interactions between gut bacteria and immunity are to date poorly elucidated, emphasizing the importance of understanding how microbes can promote HIV replication. Further research is needed to propose adjuvant therapeutics dedicated to controlling disease progression through gut microbiome restoration.

Keywords: HIV/AIDS ; gut; microbiota; translocation; diversity; immunity

Running title: Gut microbiota and HIV infection


1a
1b
Enterobacteriaceae
Fusobacteriaceae
Prevotellaceae
Th17
Treg
macrophage
CD8 T cell
Gut
O2
O•
Erysipelotrichaceae
Prevotellaceae
IDO-1
Enterobacteriaceae
Escherichia coli
HIV replication
Bacterial products
INFLAMMATION
IDO1
Activated CD8 T cell
Activated macrophage
sCD14
sCD163
Kyn
INFLAMMATION
CXCL10/TNF-α/IFN-γ
IL-6/IL-1β
sCD27
sIL-2R
Blood

Science, 2016, 352:535-38.

REVIEW

Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens

Eric G. Pamer

The intestinal microbiota, which is composed of diverse populations of commensal bacterial species, provides resistance against colonization and invasion by pathogens. Antibiotic treatment can damage the intestinal microbiota and, paradoxically, increase susceptibility to infections. Reestablishing microbiota-mediated colonization resistance after antibiotic treatment could markedly reduce infections, particularly those caused by antibiotic-resistant bacteria. Ongoing studies are identifying commensal bacterial species that can be developed into next-generation probiotics to reestablish or enhance colonization resistance. These live medicines are at various stages of discovery, testing, and production and are being subjected to existing regulatory gauntlets for eventual introduction into clinical practice. The development of next-generation probiotics to reestablish colonization resistance and eliminate potential pathogens from the gut is warranted and will reduce health care–associated infections caused by highly antibiotic-resistant bacteria.

PUBLISHED: 27 JANUARY 2016 | ARTICLE NUMBER: 15029 | DOI: 10.1038/NMICROBIOL.2015.29

HOST RESPONSE

Microbiota prime antiviral response

By using the power of *Drosophila* genetics, a recent study has revealed how gut bacteria limit viral infection of insects.

Julie K. Pfeiffer

ANTIBIOTICS ANTIVIRAL

- Teicoplanin
- Ivermectin

Intestinal microbiota promote enteric virus replication and systemic pathogenesis

Kuss SK, Best GT, Etheredge CA, Pruijssers AJ, Frierson JM, Hooper LV, Dermody TS, Pfeiffer JK. Science. 2011 Oct 14;334(6053):249-52.

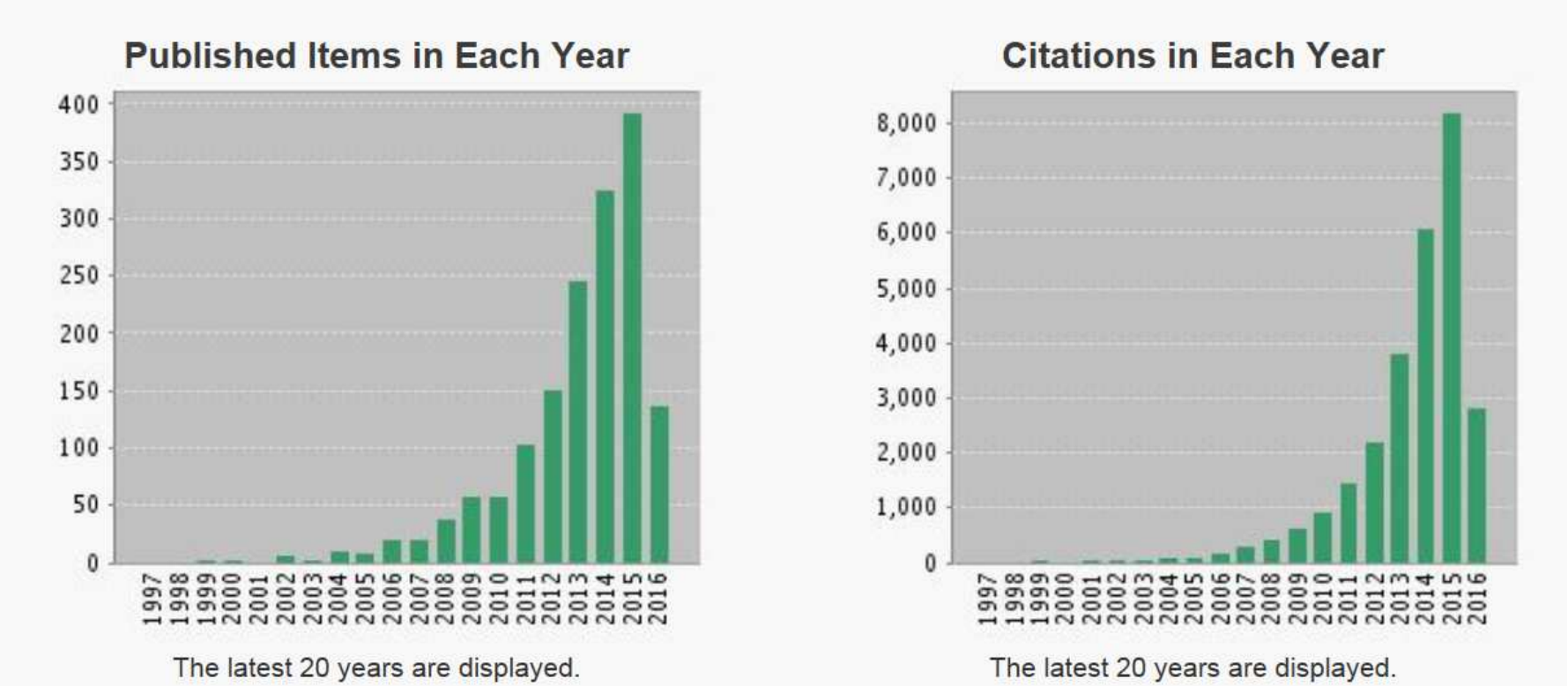
Intestinal bacteria aid host health and limit bacterial pathogen colonization. However, the influence of bacteria on enteric viruses is largely unknown. We depleted the intestinal microbiota of mice with antibiotics before inoculation with poliovirus, an enteric virus. Antibiotic-treated mice were less susceptible to poliovirus disease and supported minimal viral replication in the intestine. Exposure to bacteria or their N-acetylglucosamine-containing surface polysaccharides, including lipopolysaccharide and peptidoglycan, enhanced poliovirus infectivity. We found that poliovirus binds lipopolysaccharide, and exposure of poliovirus to bacteria enhanced host cell association and infection. The pathogenesis of reovirus, an unrelated enteric virus, also was more severe in the presence of intestinal microbes. These results suggest that antibiotic-mediated microbiota depletion diminishes enteric virus infection and that enteric viruses exploit intestinal microbes for replication and transmission.

Villarino NF, LeCleir GR, Denny JE, Dearth SP, Harding CL, Sloan SS, Gribble JL, Campagna SR, Wilhelm SW, Schmidt NW. Composition of the gut microbiota modulates the severity of malaria. Proc Natl Acad Sci U S A. 2016 Feb 23;113(8):2235-40.

Plasmodium infections result in clinical presentations that range from asymptomatic to severe malaria, resulting in ∼1 million deaths annually. Despite this toll on humanity, the factors that determine disease severity remain poorly understood. Here, we show that the gut microbiota of mice influences the pathogenesis of malaria. Genetically similar mice from different commercial vendors, which exhibited differences in their gut bacterial community, had significant differences in parasite burden and mortality after infection with multiple Plasmodium species. Germfree mice that received cecal content transplants from "resistant" or "susceptible" mice had low and high parasite burdens, respectively, demonstrating the gut microbiota shaped the severity of malaria. Among differences in the gut flora were increased abundances of Lactobacillus and Bifidobacterium in resistant mice. Susceptible mice treated with antibiotics followed by yogurt made from these bacterial genera displayed a decreased parasite burden. Consistent with differences in parasite burden, resistant mice exhibited an elevated humoral immune response compared with susceptible mice. Collectively, these results identify the composition of the gut microbiota as a previously unidentified risk factor for severe malaria and modulation of the gut microbiota (e.g., probiotics) as a potential treatment to decrease parasite burden.

- Répertoire
- Obésité/malnutrition
- Infection
- Cancer
- Autre ?

TOPIC: (microbiota) *AND* **TOPIC:** (cancer)
Timespan: All years.



Citation Report: 1 596

Li J, Sung CY, Lee N, Ni Y, Pihlajamäki J, Panagiotou G, El-Nezami H. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proc Natl Acad Sci U S A. 2016 Mar 1;113(9):E1306-15.

The beneficial roles of probiotics in lowering the gastrointestinal inflammation and preventing colorectal cancer have been frequently demonstrated, but their immunomodulatory effects and mechanism in suppressing the growth of extraintestinal tumors remain unexplored. Here, we adopted a mouse model and metagenome sequencing to investigate the efficacy of probiotic feeding in controlling s.c. hepatocellular carcinoma (HCC) and the underlying mechanism suppressing the tumor progression. Our result demonstrated that Prohep, a novel probiotic mixture, slows down the tumor growth significantly and reduces the tumor size and weight by 40% compared with the control. From a mechanistic point of view the down-regulated IL-17 cytokine and its major producer Th17 cells, whose levels decreased drastically, played critical roles in tumor reduction upon probiotics feeding. Cell staining illustrated that the reduced Th17 cells in the tumor of the probiotic-treated group is mainly caused by the reduced frequency of migratory Th17 cells from the intestine and peripheral blood. In addition, shotgun-metagenome sequencing revealed the crosstalk between gut microbial metabolites and the HCC development. Probiotics shifted the gut microbial community toward certain beneficial bacteria, including Prevotella and Oscillibacter, that are known producers of antiinflammatory metabolites, which subsequently reduced the Th17 polarization and promoted the differentiation of antiinflammatory Treg/Tr1 cells in the gut. Overall, our study offers novel insights into the mechanism by which probiotic treatment modulates the microbiota and influences the regulation of the T-cell differentiation in the gut, which in turn alters the level of the proinflammatory cytokines in the extraintestinal tumor microenvironment.

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

Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Rusakiewicz S, Routy B, Roberti MP, Duong CP, Poirier-Colame V, Roux A, Becharef S, Formenti S, Golden E, Cording S, Eberl G, Schlitzer A, Ginhoux F, Mani S, Yamazaki T, Jacquelot N, Enot DP, Bérard M, Nigou J, Opolon P, Eggermont A, Woerther PL, Chachaty E, Chaput N, Robert C, Mateus C, Kroemer G, **Raoult D**, Boneca IG, Carbonnel F, Chamaillard M, Zitvogel L.

Science. 2015 Nov 5.

Antibodies targeting CTLA-4 have been successfully used as cancer immunotherapy. We find that the antitumor effects of CTLA-4 blockade depend on distinct Bacteroides species. In mice and patients, T cell responses specific for B. thetaiotaomicron or B. fragilis were associated with the efficacy of CTLA-4 blockade. Tumors in antibiotic-treated or germ-free mice did not respond to CTLA blockade. This defect was overcome by gavage with B. fragilis, or by immunization with B. fragilis polysaccharides, or by adoptive transfer of B. fragilis-specific T cells. Fecal microbial transplantation from humans to mice confirmed that anti-CTLA-4 treatment of melanoma patients favored the outgrowth of B. fragilis with anticancer properties. This study reveals a key role for Bacteroidales in the immunostimulatory effects of CTLA-4 blockade.

Microbiote

A : Gut

B : Respiratory tract

C : Urine

D : Vagina

E : Skin

F : Milk

G : Sinus

Autres Microbiotes
17 05 2016

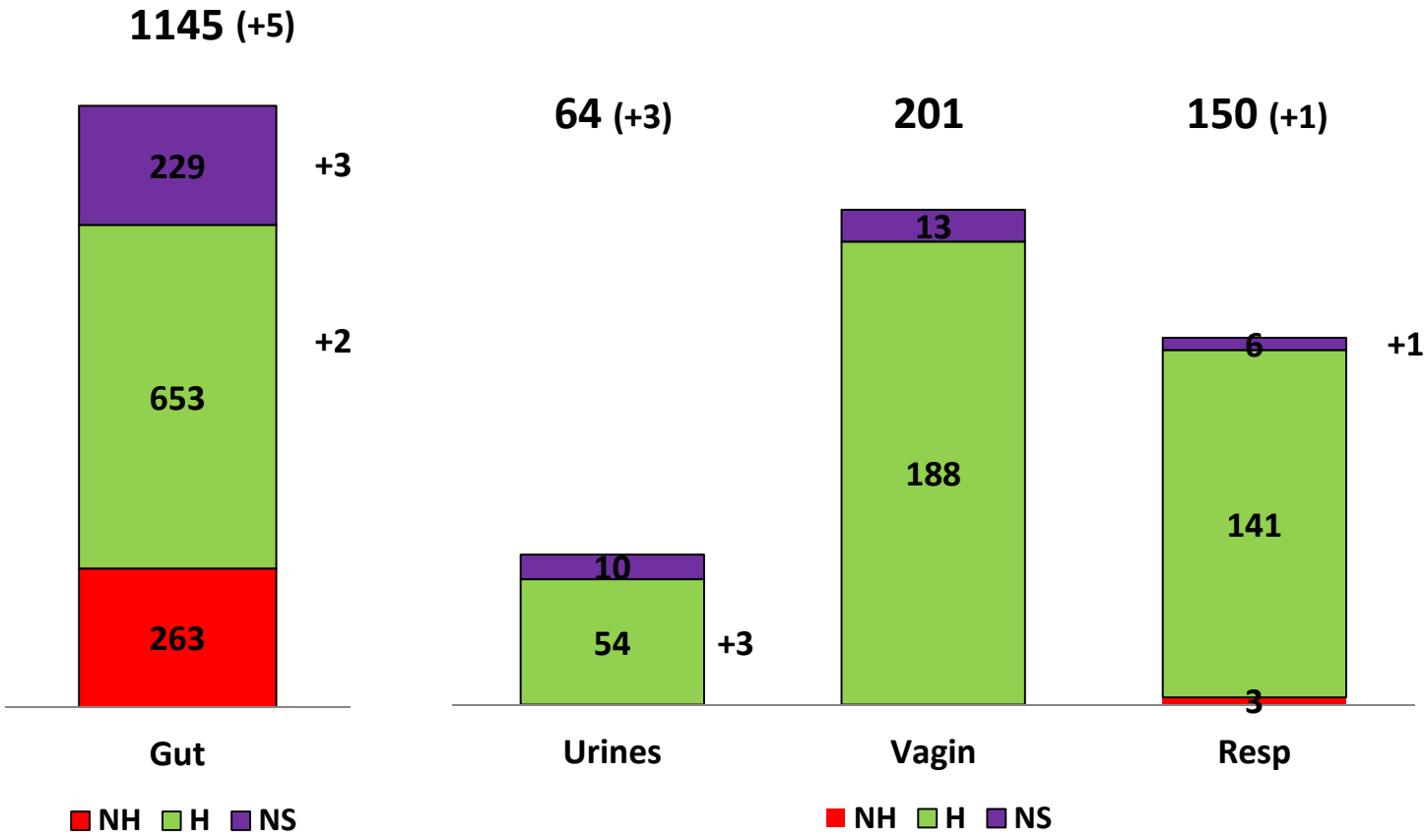


Figure 3.

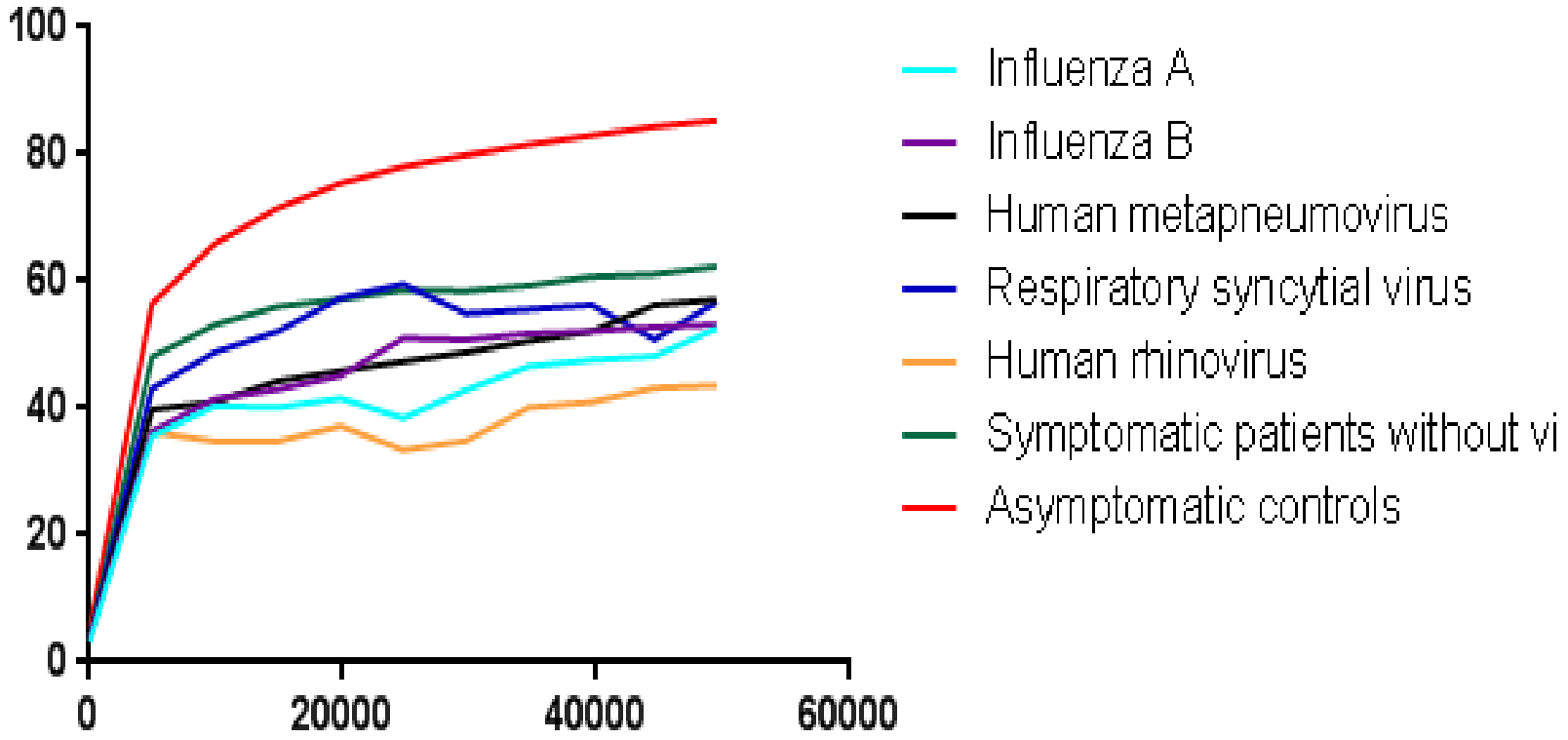

100
80
60
40
20
0
0
20000
40000
60000
Influenza A
Influenza B
Human metapneumovirus
Respiratory syncytial virus
Human rhinovirus
Symptomatic patients without vi
Asymptomatic controls

Figure 2

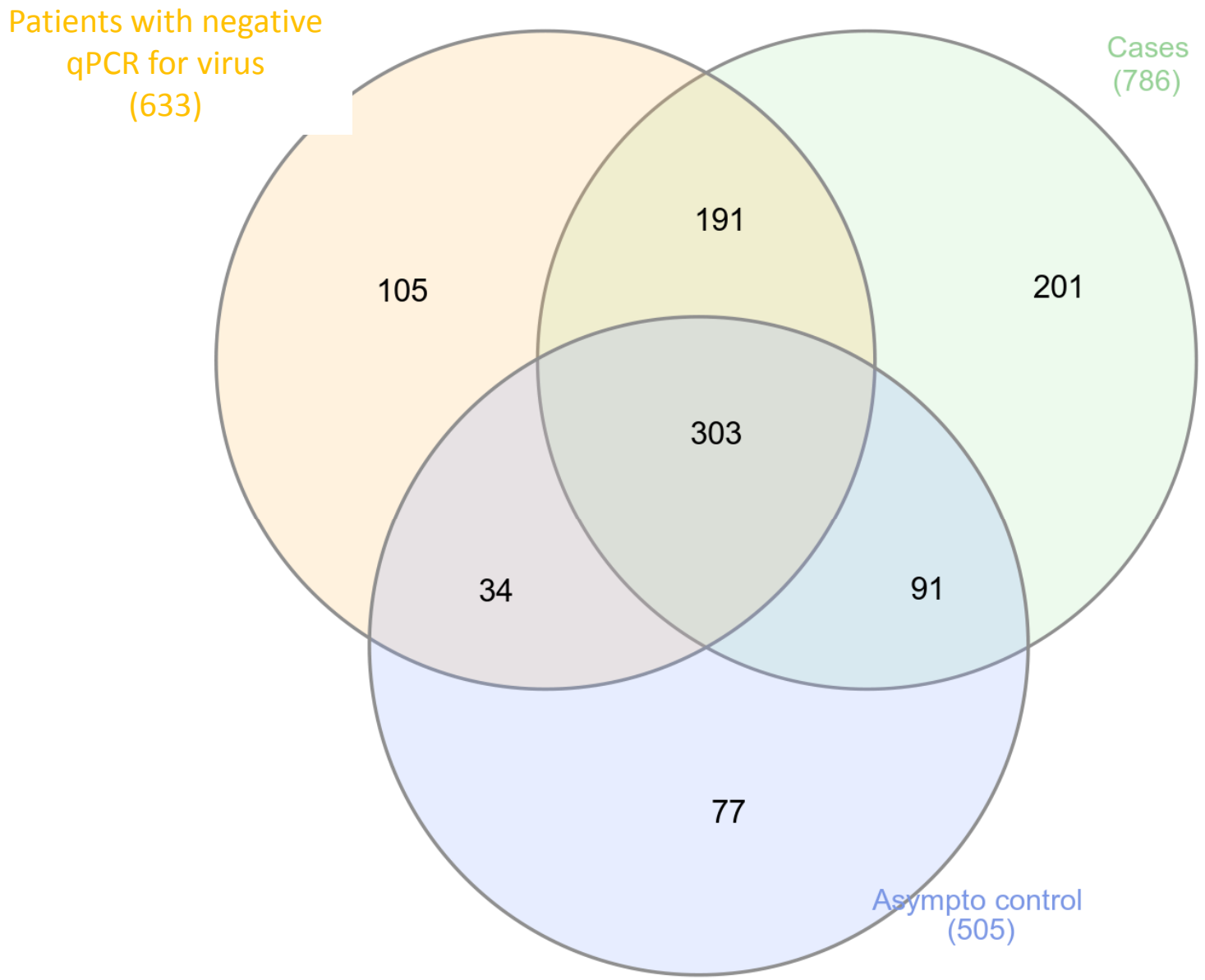
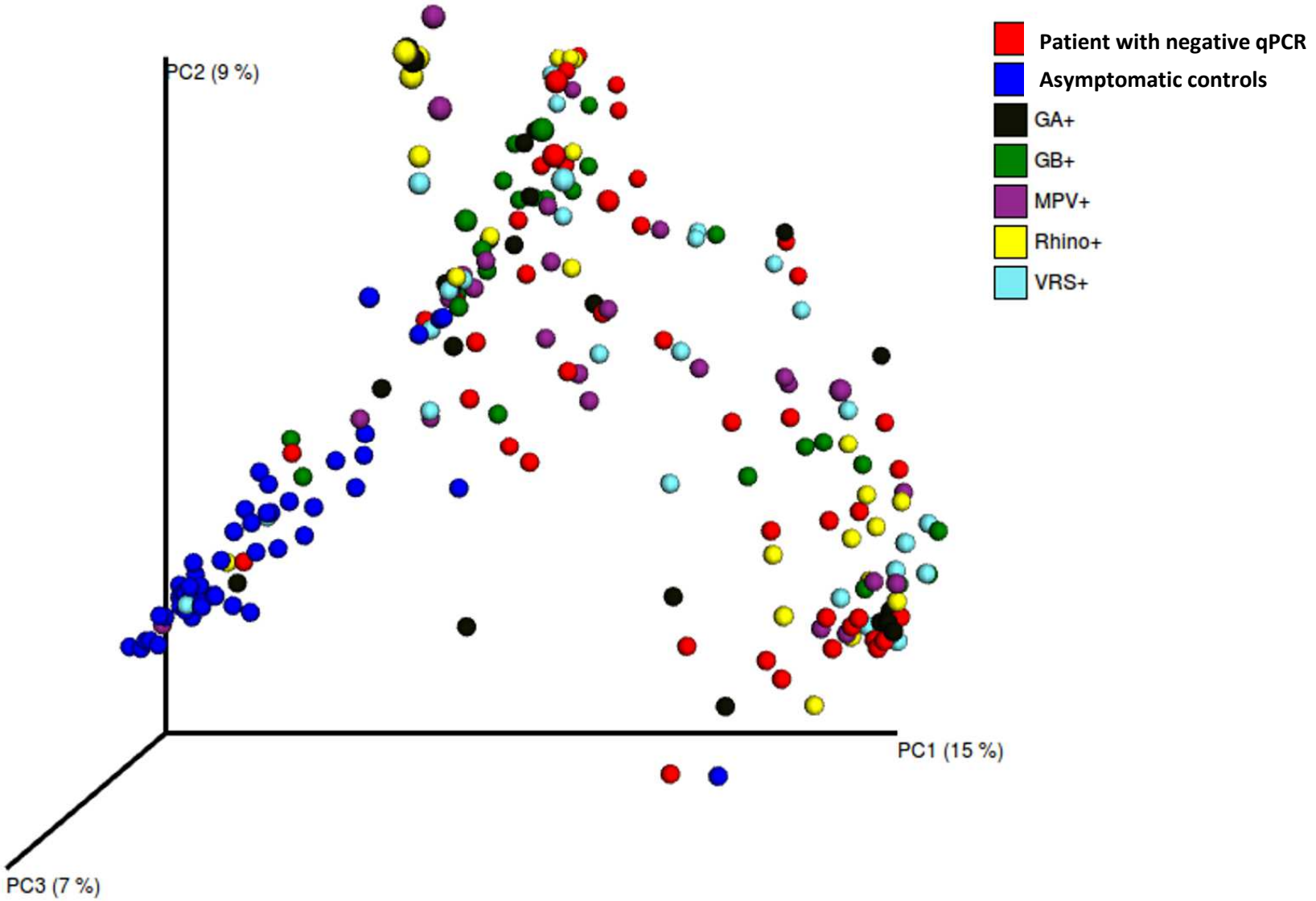

Patients with negative qPCR for virus (633)
Cases (786)
Asympto control (505)
105
191
201
303
34
91
77

Figure 5


Patient with negative qPCR
Asymptomatic controls
GA+
GB+
MPV+
Rhino+
VRS+
PC2 (9 %)
PC1 (15 %)
PC3 (7 %)

Microbiote

A : Gut

B : Respiratory tract

C : Urine

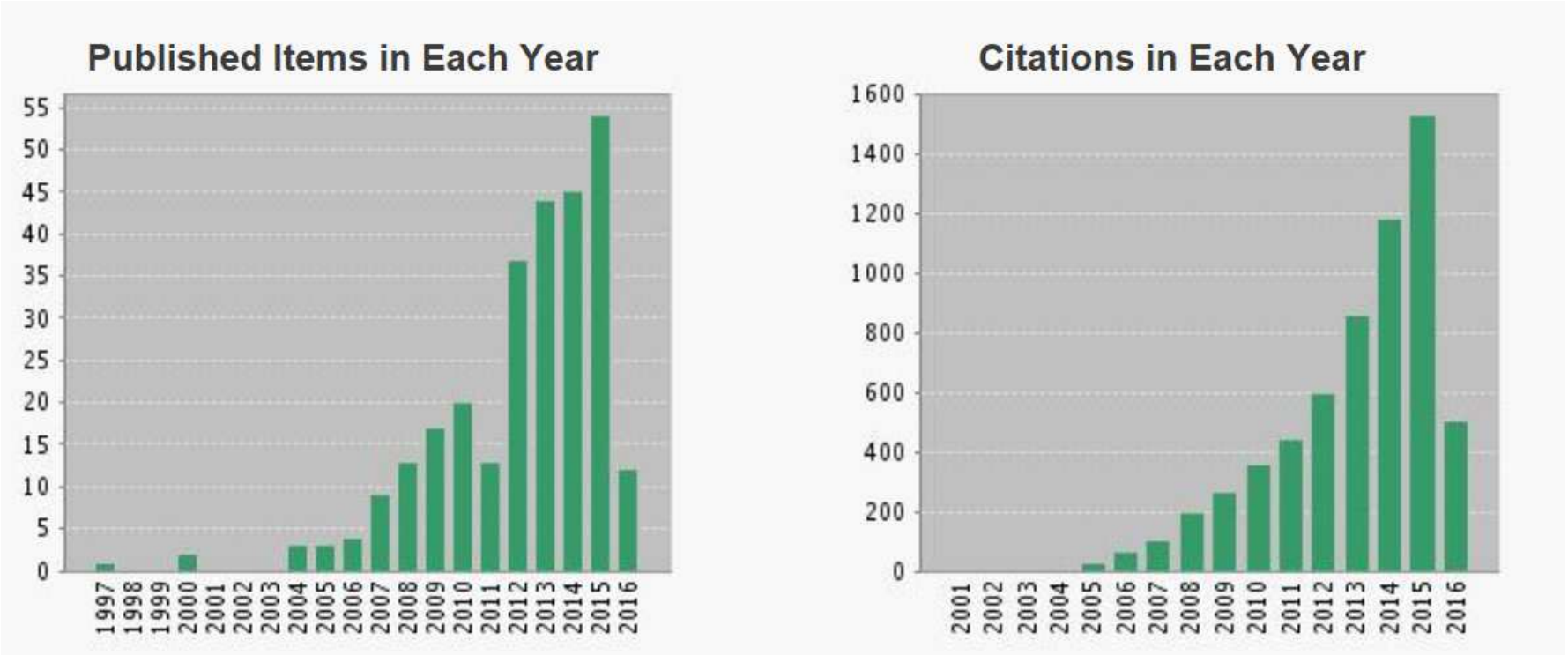
D : Vagina

E : Skin

F : Milk

G : Sinus

TOPIC: (human urine microbiota)
Timespan: All years.



Citation Report: 278

Microbiote

A : Gut

B : Respiratory tract

C : Urine

D : Vagina

E : Skin

F : Milk

G : Sinus

WEB OF SCIENCE™

Citation Report: **692**

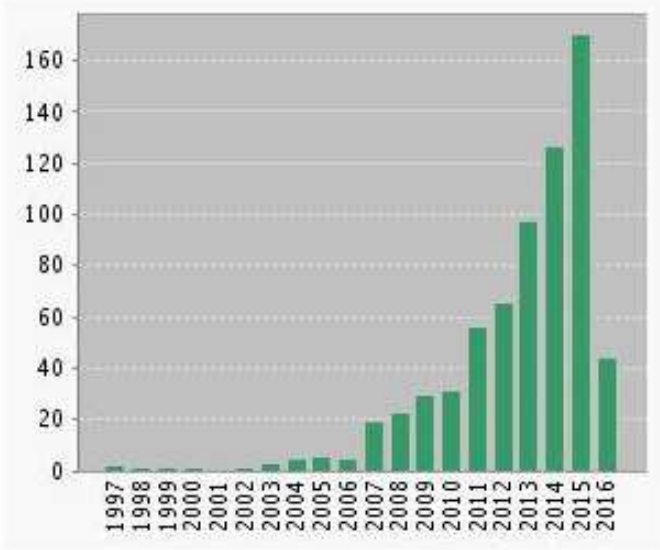
(from All Databases)

You searched for: **TOPIC:** (vaginal microbiota) ...More **TOPIC:** (vaginal microbiota)

Timespan: All years.
...Less

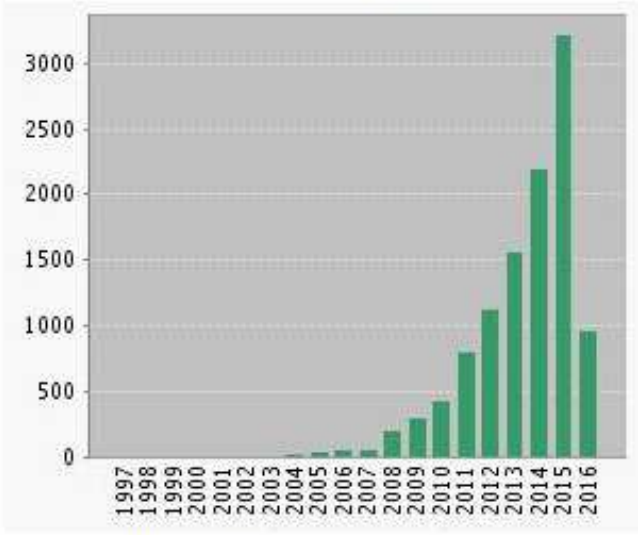
This report reflects citations to source items indexed within All Databases

Published Items in Each Year



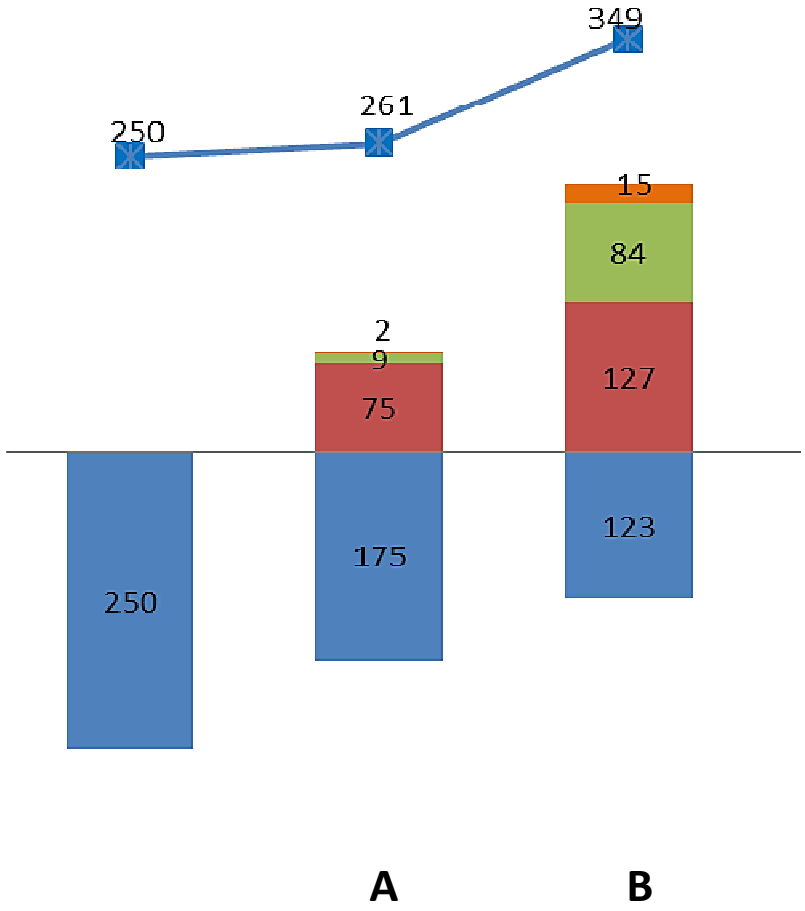
The latest 20 years are displayed.
View a graph with all years.

Citations in Each Year



The latest 20 years are displayed.
View a graph with all years.

Repertoire of vaginal microbiota



New species

First isolation in vagina

Microorganisms identified by Culturomics

Microorganisms identified by other laboratories only

A: First project of vaginome
B: Recent work

Microbiote

A : Gut

B : Respiratory tract

C : Urine

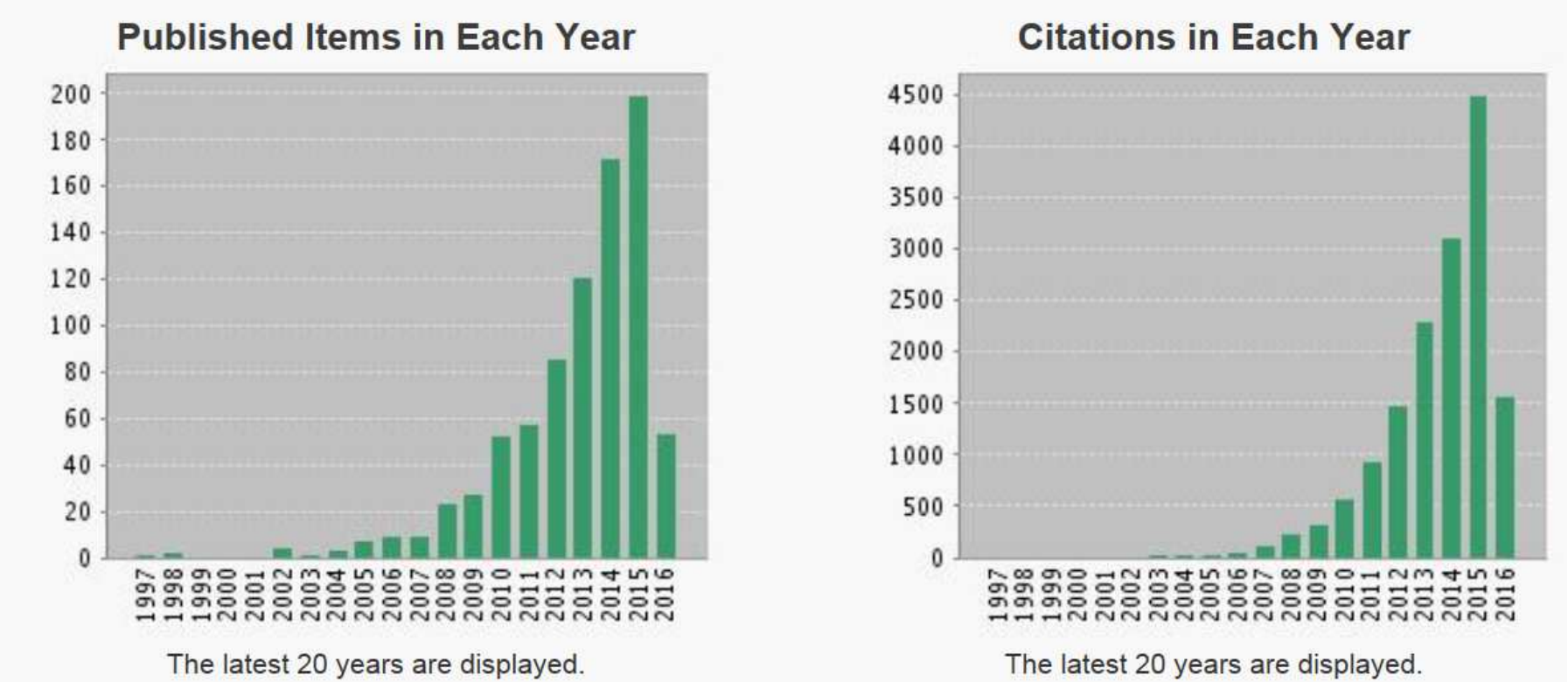
D : Vagina

E : Skin

F : Milk

G : Sinus

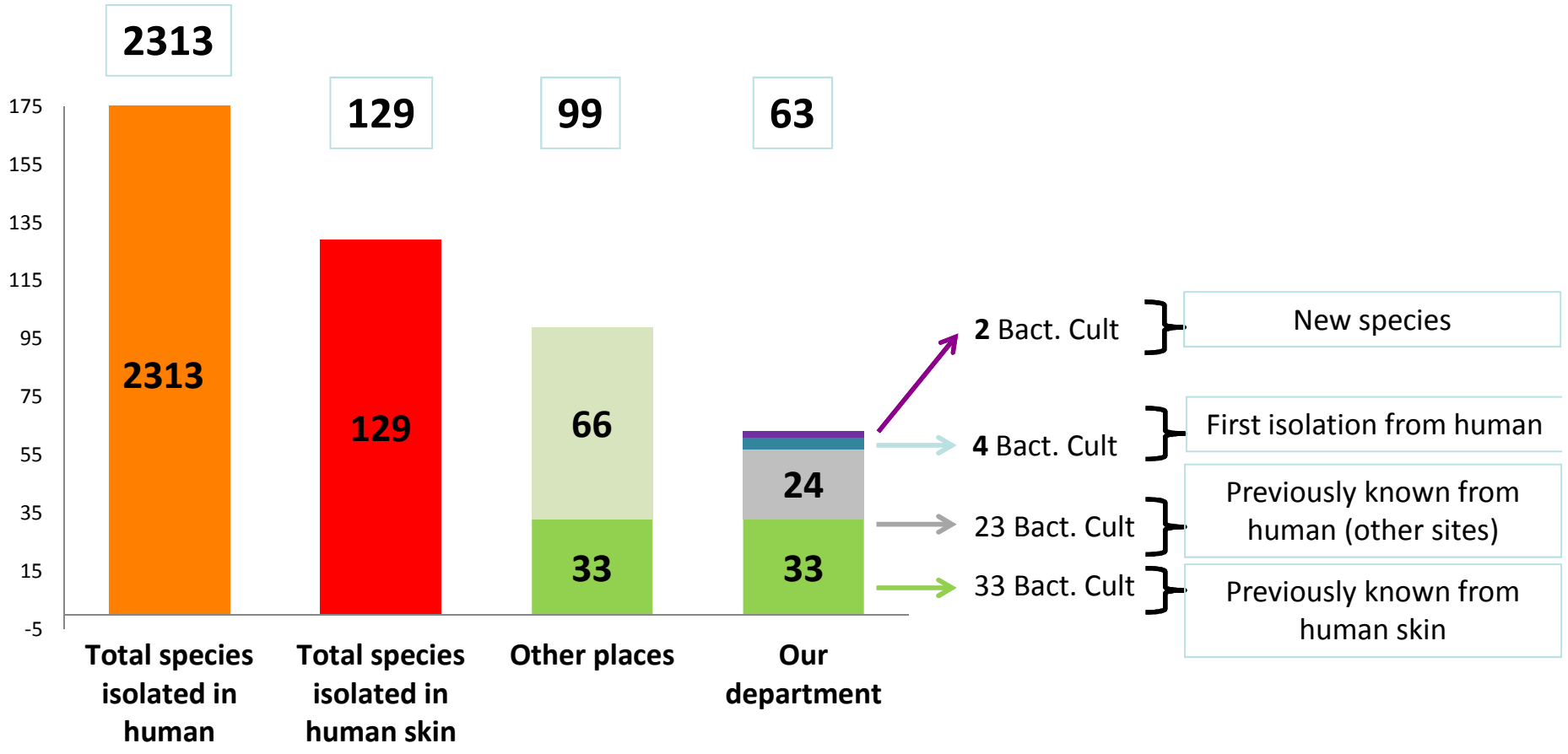
TOPIC: (microbiota) *AND* **TOPIC:** (skin)
Timespan: All years.



Citation Report: 844

Microbiote Skin

23 11 2015



Microbiote

A : Gut

B : Respiratory tract

C : Urine

D : Vagina

E : Skin

F : Milk

G : Sinus

Fernández L, Cárdenas N, Arroyo R, Manzano S, Jiménez E, Martín V, Rodríguez JM. Prevention of Infectious Mastitis by Oral Administration of Lactobacillus salivarius PS2 During Late Pregnancy. Clin Infect Dis. 2016 Mar 1;62(5):568-73.

BACKGROUND: Previous studies have shown that oral administration of lactobacilli can be an efficient approach to treat lactational infectious mastitis. In this trial, we have evaluated the potential of Lactobacillus salivarius PS2 to prevent this condition when orally administered during late pregnancy to women who had experienced infectious mastitis after previous pregnancies. METHODS: In this study, 108 pregnant women were randomly assigned to one of 2 groups. Those in the probiotic group (n = 55) ingested daily 9 log10 colony-forming units of L. salivarius PS2 from approximately week 30 of pregnancy until delivery, whereas those in the placebo group (n = 53) received a placebo. The occurrence of mastitis was evaluated during the first 3 months after delivery. RESULTS: Globally, 44 of 108 women (41%) developed mastitis; however, the percentage of women with mastitis in the probiotic group (25% [n = 14]) was significantly lower than in the control group (57% [n = 30]). When mastitis occurred, the milk bacterial counts in the probiotic group were significantly lower than those obtained in the placebo group. CONCLUSIONS: Oral administration of L. salivarius PS2 during late pregnancy appears to be an efficient method to prevent infectious mastitis in a susceptible population. CLINICAL TRIALS REGISTRATION: NCT01505361.

Microbiote

A : Gut

B : Respiratory tract

C : Urine

D : Vagina

E : Skin

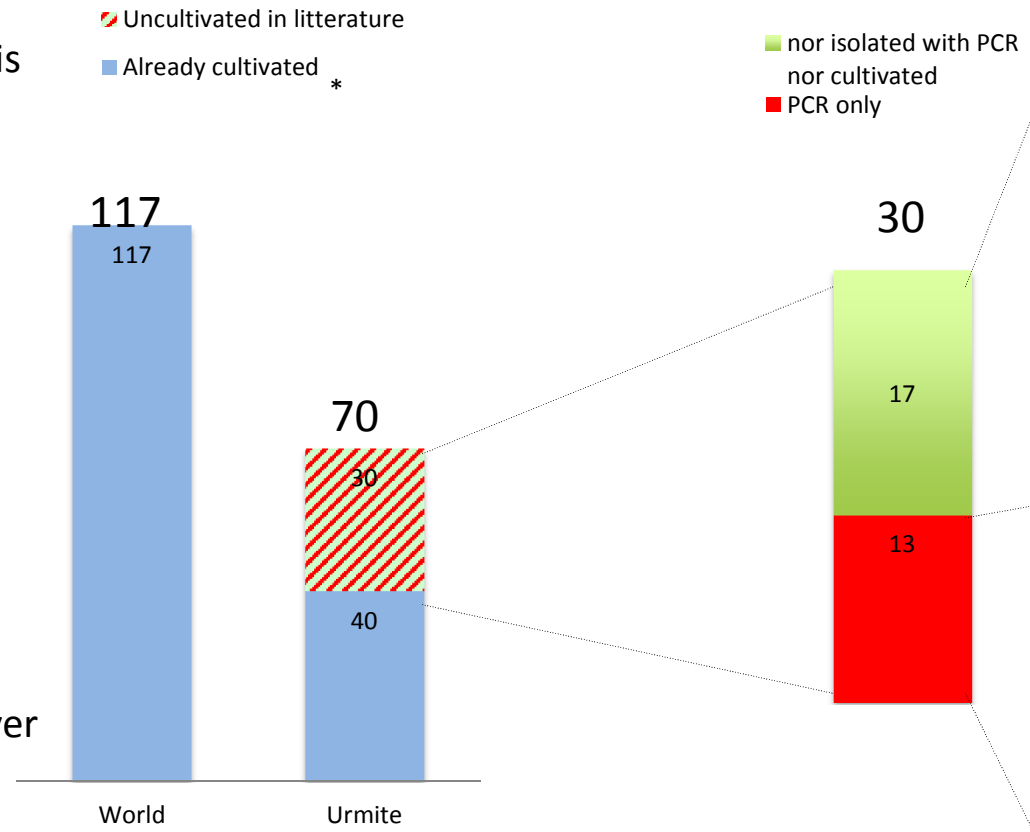
F : Milk

G : Sinus

Sinus microbiota - Culturomics

- 16 different patients, refractory chronic rhinosinusitis
- 2 different medium, in aerobic and anaerobic conditions
- 30 days of following
- 70 species
- 30 were never cultivated before

Not yet



Actinomyces naeslundii
Actinomyces oris
Atopobium rimae
Bacillus simplex
Campylobacter curvus
Citrobacter braakii
Clostridium sporogenes
Corynebacterium minutissimum
Enterobacter ludwigii
Facklamia languida

Anaerococcus octavius
Atopobium parvulum
Citrobacter farmeri
Citrobacter freundii
Gemella sanguinis
Streptococcus australis
Streptococcus cristatus
Streptococcus gordonii
Streptococcus mitis
Streptococcus oralis

* Analyse based on 26 main publications about sinus microbiota and 8 case reports for rare bacteria; systematic research had been performed each time a new bacteria is found in our samples (Pubmed® and Google Scholar®)

Pr. P-E.FOURNIER

I dont know

- Brain
- Inflamatory colitis
- Auto immunity
- Colic cancer

LETTER

doi:10.1038/nature17655

Normalizing the environment recapitulates adult human immune traits in laboratory mice

Lalit K. Beura[1], Sara E. Hamilton[2], Kevin Bi[3], Jason M. Schenkel[1], Oludare A. Odumade[2]†, Kerry A. Casey[1]†, Emily A. Thompson[1], Kathryn A. Fraser[1], Pamela C. Rosato[1], Ali Filali-Mouhim[4], Rafick P. Sekaly[4], Marc K. Jenkins[1], Vaiva Vezys[1], W. Nicholas Haining[3], Stephen C. Jameson[2] & David Masopust[1]

Our current understanding of immunology was largely defined in laboratory mice, partly because they are inbred and genetically homogeneous, can be genetically manipulated, allow kinetic tissue analyses to be carried out from the onset of disease, and permit the use of tractable disease models. Comparably reductionist experiments are neither technically nor ethically possible in humans. However, there is growing concern that laboratory mice do not reflect relevant aspects of the human immune system, which may account for failures to translate disease treatments from bench to bedside[1–8]. Laboratory mice live in abnormally hygienic specific pathogen free (SPF) barrier facilities. Here we show that standard laboratory mouse husbandry has profound effects on the immune system and that environmental changes produce mice with immune systems closer to those of adult humans. Laboratory mice—like newborn, but not adult, humans—lack effector-differentiated and mucosally distributed memory T cells. These cell populations were present in free-living barn populations of feral mice and pet store mice with diverse microbial experience, and were induced in laboratory mice after co-housing with pet store mice, suggesting that the environment is involved in the induction of these cells. Altering the living conditions of mice profoundly affected the cellular composition of the innate and adaptive immune systems, resulted in global changes in blood cell gene expression to patterns that more closely reflected the immune signatures of adult humans rather than neonates, altered resistance to infection, and influenced T-cell differentiation in response to a *de novo* viral infection. These data highlight the effects of environment on the basal immune state and response to infection and suggest that restoring physiological microbial exposure in laboratory mice could provide a relevant tool for modelling immunological events in free-living organisms, including humans.

Given reported species-specific differences in immune responses[1–8], CD8$^+$ T-cell lineages in the blood of adult humans and laboratory mice, focusing on species-specific markers that define functionally homologous populations of naive, central memory (T_{CM}), and terminally differentiated effector memory CD8$^+$ T (T_{EM} or T_{EMRA}) cells (Fig. 1c). Memory CD8$^+$ T cells were much scarcer in laboratory mice than in adult humans and were almost entirely comprised of T_{CM} rather than T_{EM} or T_{EMRA} cells. Also unlike humans, laboratory mice lacked CD27^{lo}/granzyme B$^+$ effector differentiated memory CD8$^+$ T cells, which are thought to respond most immediately to infection[13,14] (Fig. 1c). Thus, memory CD8$^+$ T cells in laboratory mice were scarcer and strikingly different from those in adult humans and,

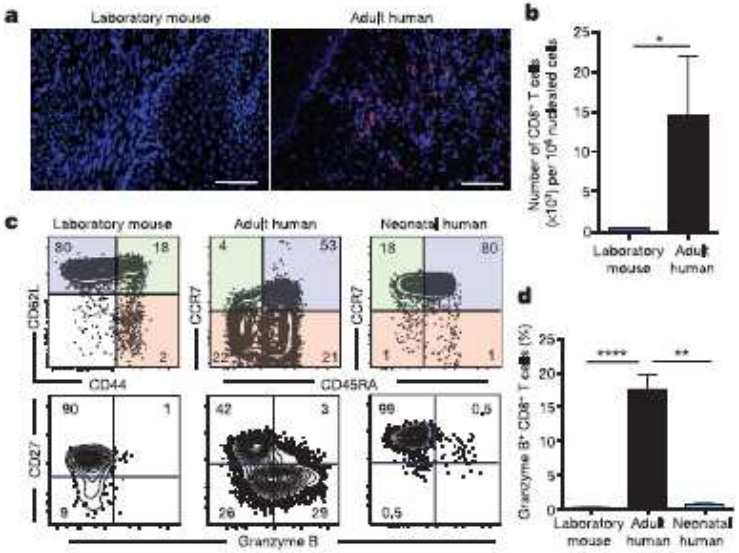
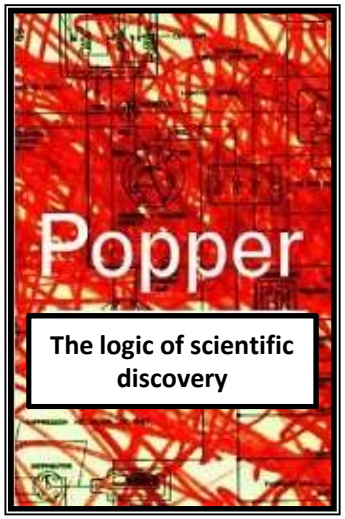


Figure 1 | Laboratory mice, like neonatal but not adult humans, lack



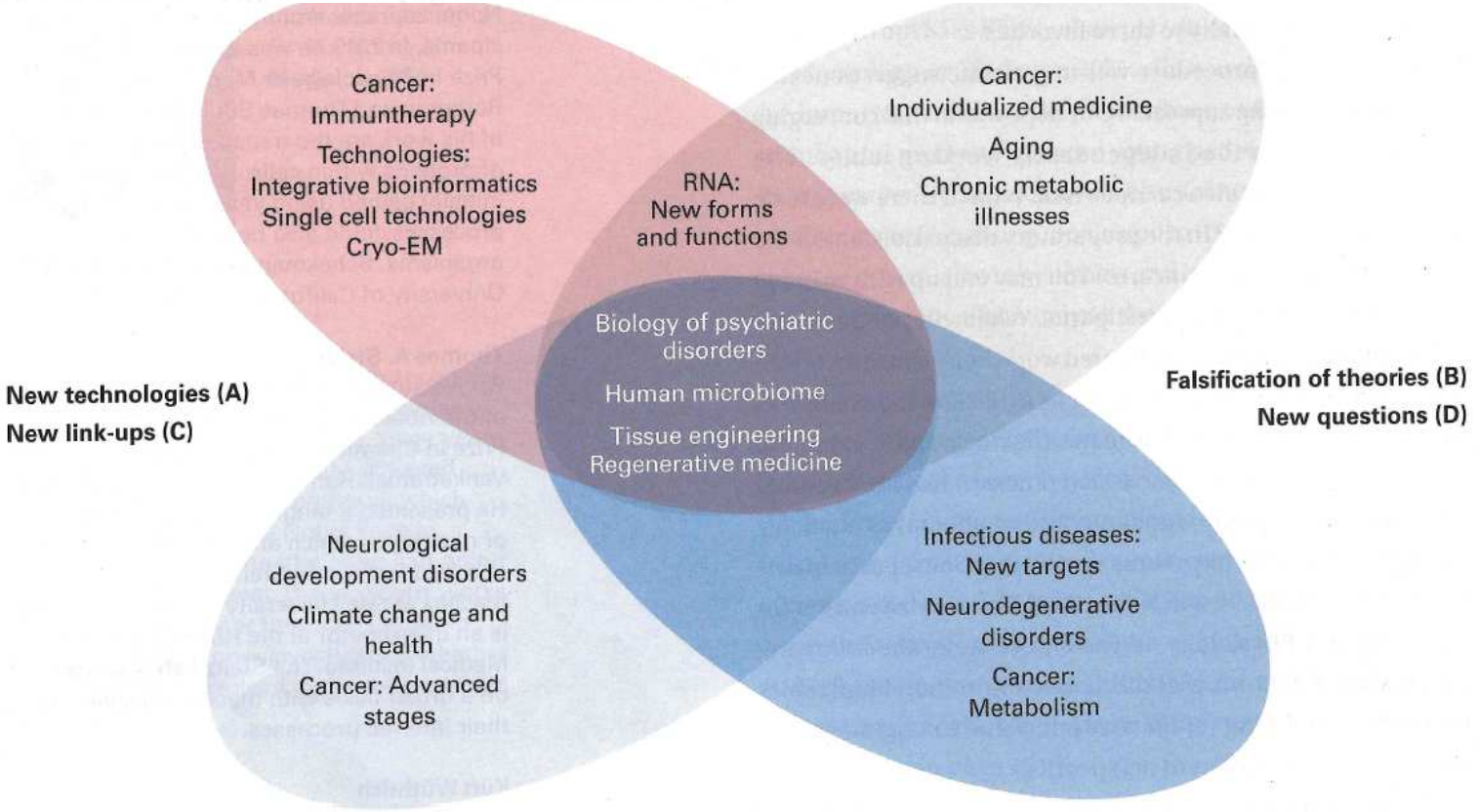
According to K.Popper :
« Never fight for a world » and « **new tools** create new theories ».

According to T.Kuhn :
« when theories are unstable we need a **change in paradigm** ».

A Workshop with Intelligent Minds

Inspiration for the Future

Nobel Prize winners, young researchers and senior editors of well-known specialist journals: some 40 scientists came together on June 29, 2014 to discuss seminal fields of medical research. The Else Kröner-Fresenius-Stiftung (EKFS) availed itself of the inspiring environment of the Nobel Laureates conference in Lindau for the workshop.



Nature Volume 527(7577) pp. 2-268 November 12, 2015