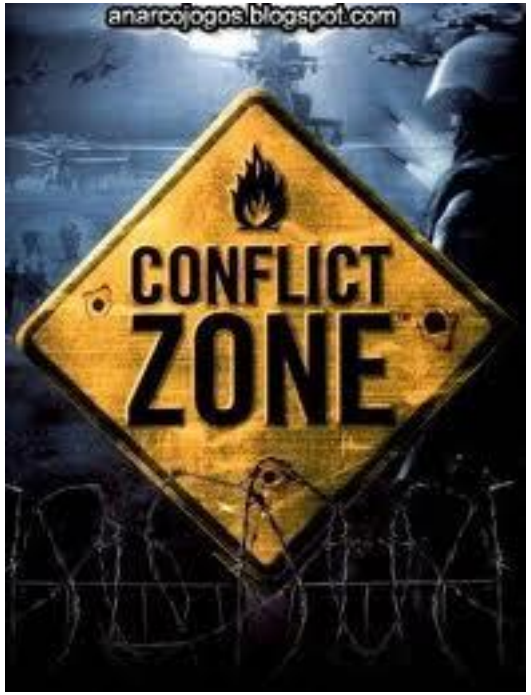
Le microbiote intestinal : et si c'était une nouvelle approche thérapeutique ?

Prof. Jacques Schrenzel

Responsable du Laboratoire Central de Bactériologie (LCB)
et du Laboratoire de Recherche Génomique (GRL)

Service des Maladies Infectieuses, HUG

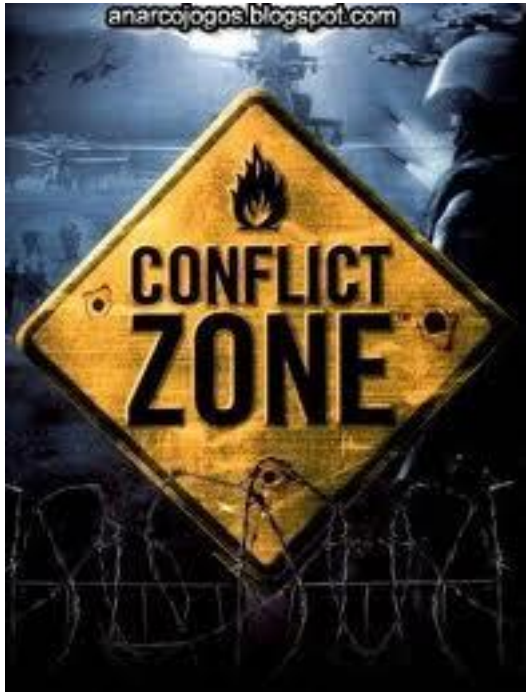
Un changement de perspective



Infectiologue:
Elargir le spectre?
Désescalader les AB?

Echecs de ttt
Résistance AB

Un changement de perspective



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Microbiologiste:
Résultat rapide
Cliniquement utile

Diagnostic moléculaire (MDx)
Séquençage à haut débit

Un changement de perspective

Analyse du microbiote => métagénomique
Transplantation de microbiote fécal => écologie

Infectiologue:
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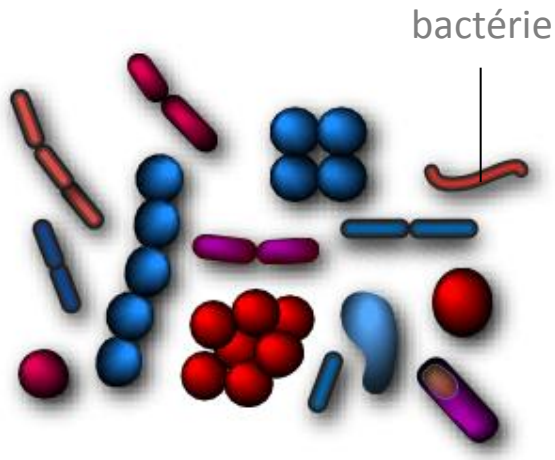
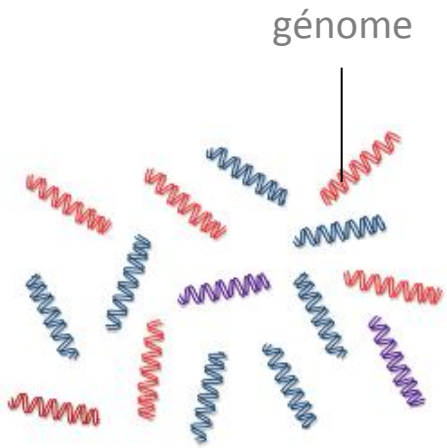
Qu’est-ce que le microbiote?





Microbiote
(= flore microbienne)

Culture

Microbiome
(= métagénome microbien)

Métagénomique

Qu’est-ce que le microbiote?

Microbiote
(= flore microbienne)

Culture

Microbiome
(= métagénome microbien)

Métagénomique

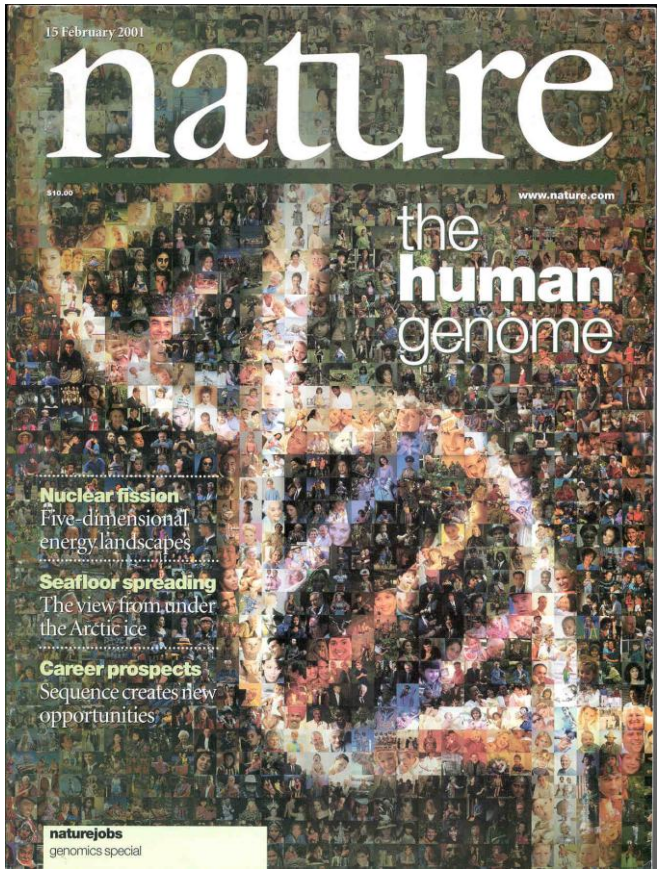
Qu’est-ce que le microbiote?

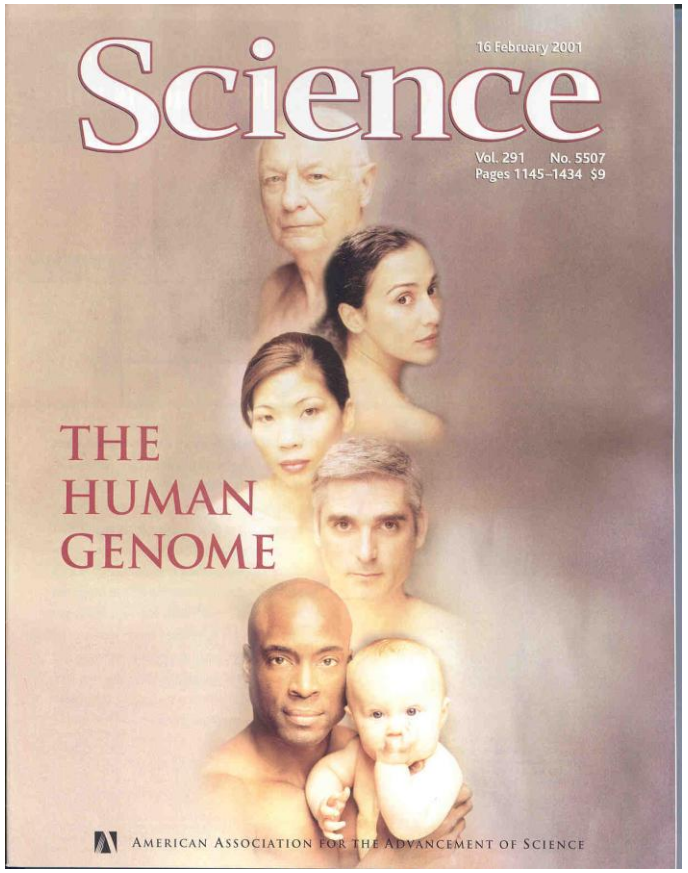
Les espèces bactériennes classiquement analysées et cultivées représentent <1% des bactéries

(Staley & Konopka, Annu Rev Microbiol 39:321, 1985)

Pourquoi cette mode de la métagénomique?

Un vieux rêve: connaître notre génome





Le séquençage de nouvelle génération (NGS)

Des séquenceurs de plus en plus performants
et de moins en moins coûteux

Human microbiota

- **10^{14} bacterial cells**

  (Whitman et al, PNAS 95:6578, 1998)

- **Bacteria outnumber human host cells by a fact**

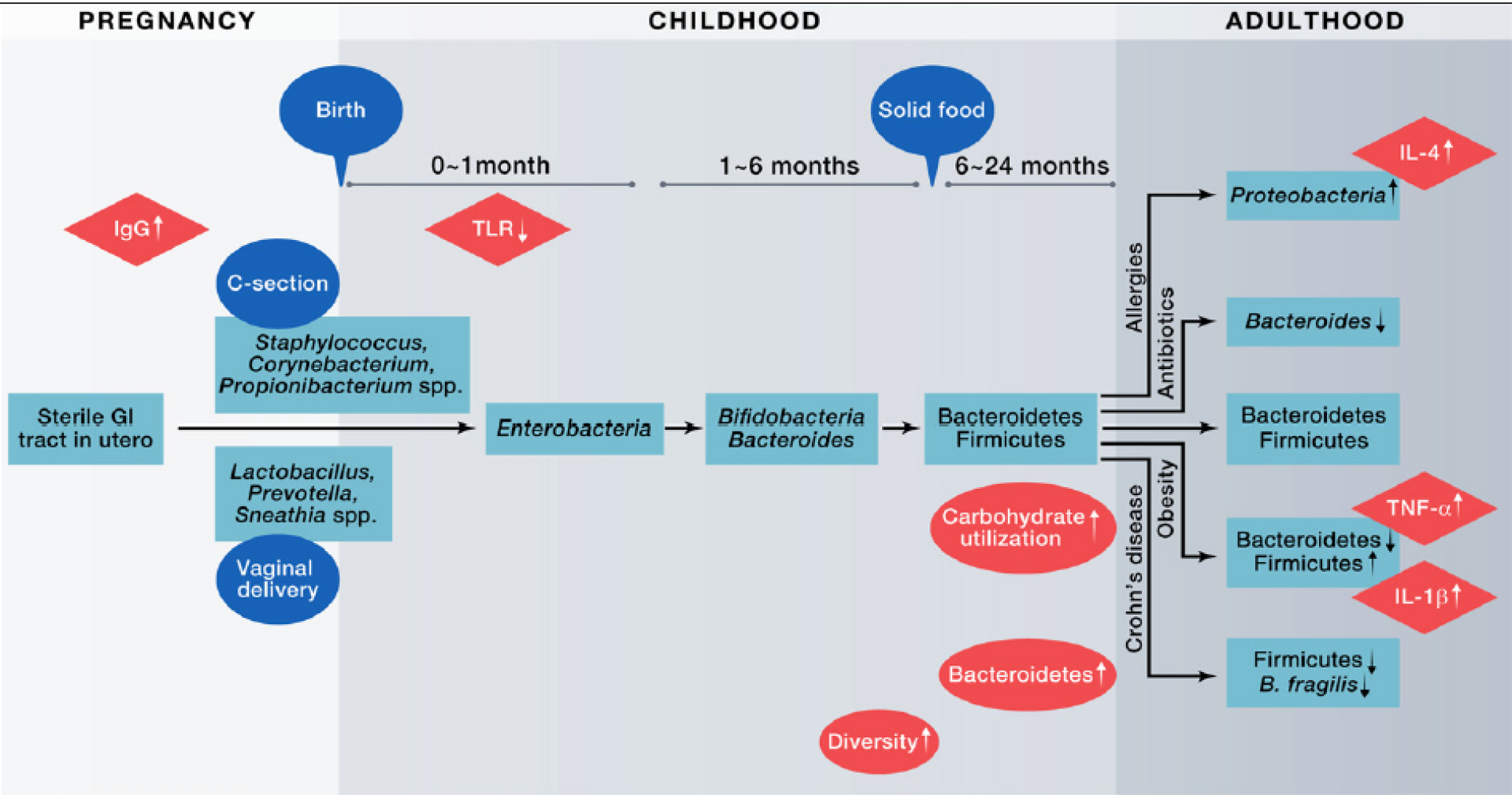
- **Bacteria outnumber human gene diversity by a**

  (Qin J et al, Nature 464:59, 2010)

- **We constitute a super-organism!**

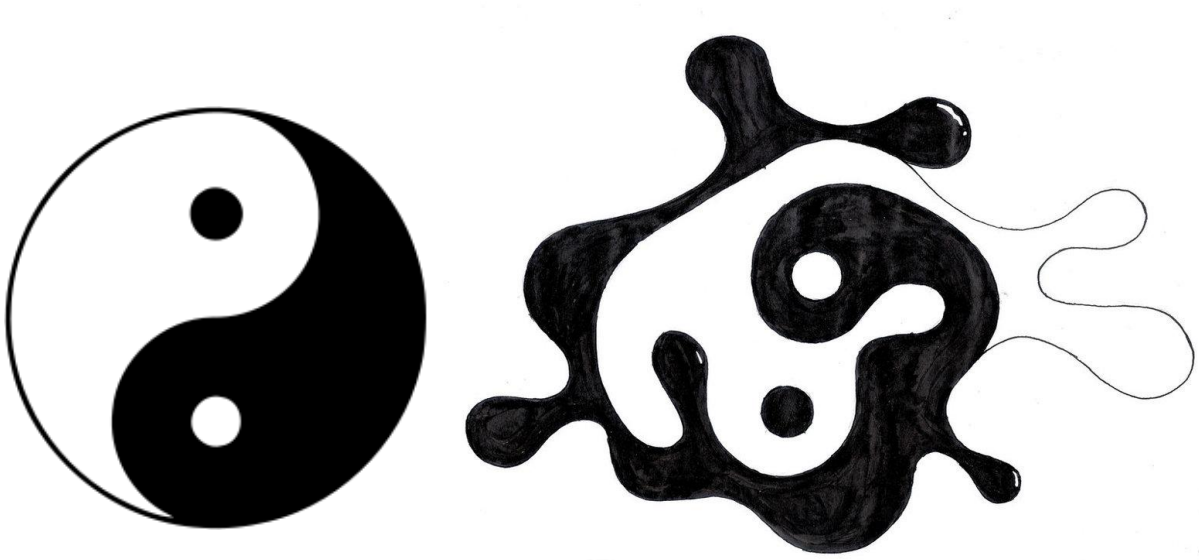
Lifetime changes of microbiota

- **Gut microbiota changes during lifetime**
  (Clemente, Cell 148:1258, 2012)



Microbiota changes and health

- **Disease might arise from a disturbed microbial community**
  (Friedrich et al, JAMA 300:777, 2008)



Comparison of energy extraction

Capacity of harvesting energy	**increased efficiency**	**(tout lui profite…)**
Microbiota and obesity	**transmissible**	**(épidémie d'obésité…)**
Composition of microbiota	**more Firmicutes**	**(e.g. *Clostridium*)**

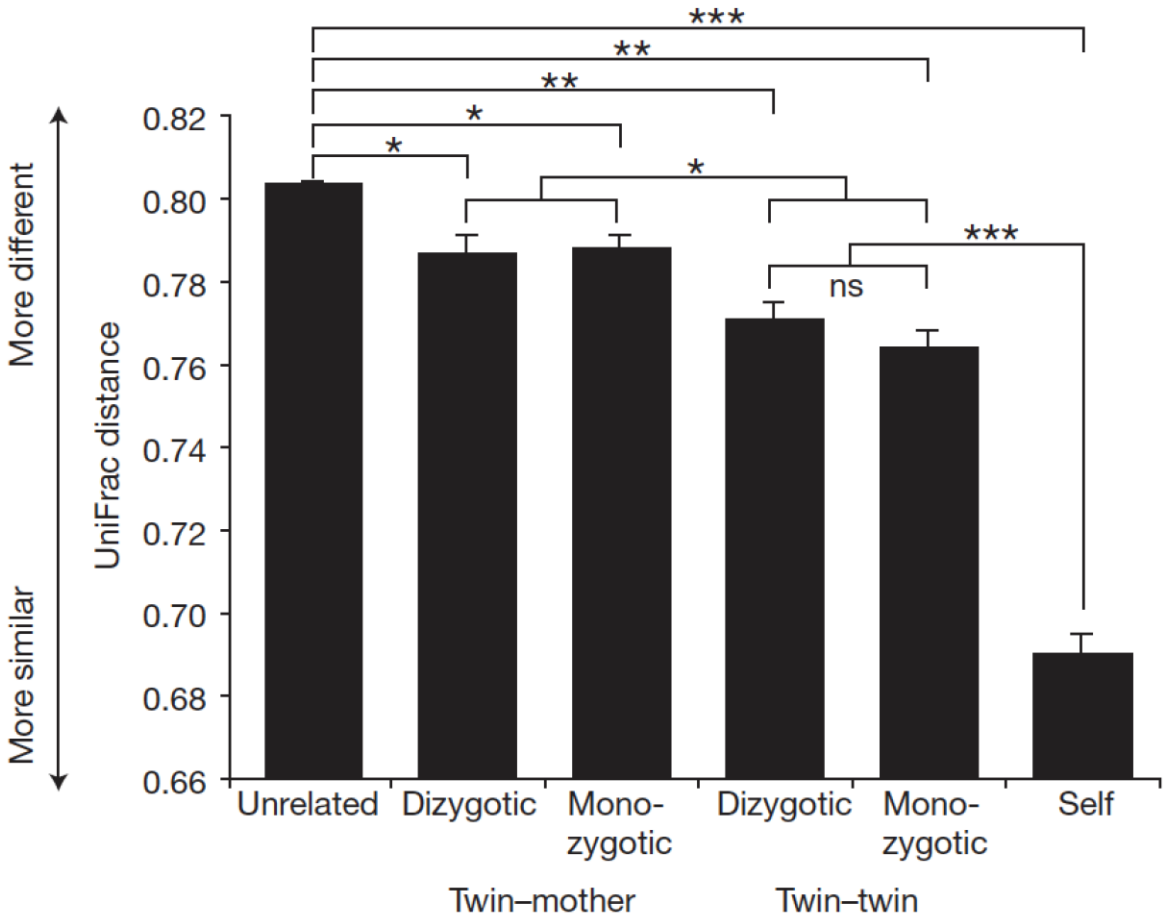
Vol 444|21/28 December 2006|doi:10.1038/nature05414 nature

An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh[1], Ruth E. Ley[1], Michael A. Mahowald[1], Vincent Magrini[2], Elaine R. Mardis[1,2] & Jeffrey I. Gordon[1]

(Turnbaugh et al, Nature 444:1027, 2006)

Diversity of gut microbiota in humans



Adult female monozygotic and dizygotic twin pairs concordant for leanness or obesity, and their mothers => **compare twins or perform sequential studies**

(Turnbaugh et al, Nature 457:480, 2009)

Affecting gut microbiota

- 1) using antimicrobials
- 2) using probiotics
- 3) using TMF, or simplified Tx

Vancomycin exposure and obesity

PLoS One. 2010 Feb 10;5(2):e9074. doi: 10.1371/journal.pone.0009074.

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

Thuny F[1], Richet H, Casalta JP, Angelakis E, Habib G, Raoult D.

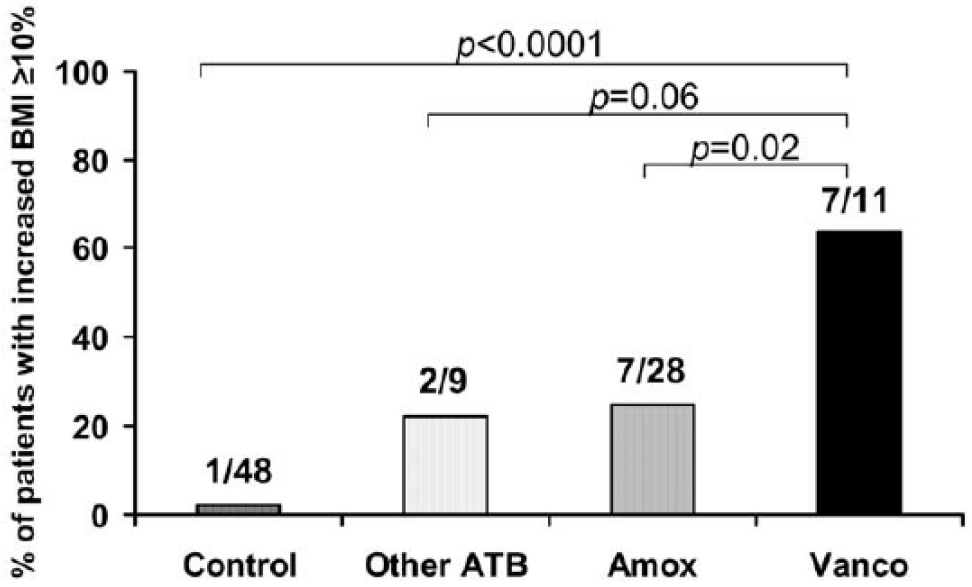


Figure 2. Percentage of patients with a major increase (≥10%) of body mass index (BMI), defined as an increase.

Vancomycin therapy is associated with weight gain !

(Thuny et al, PLoS One 5:e9074, 2010)

Vancomycin exposure and obesity

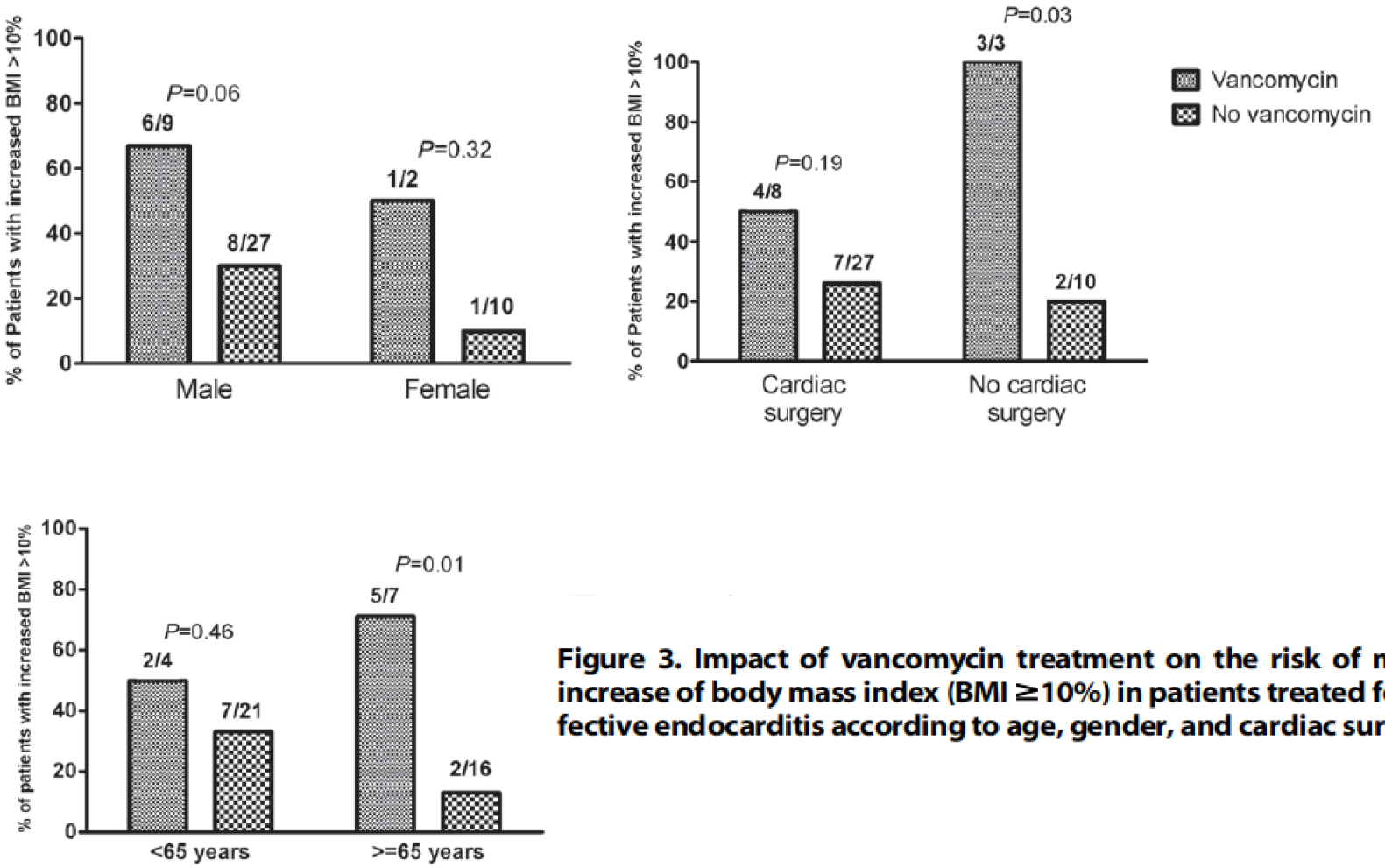


Figure 3. Impact of vancomycin treatment on the risk of major increase of body mass index (BMI ≥10%) in patients treated for infective endocarditis according to age, gender, and cardiac surgery.

(Thuny et al, PLoS One 5:e9074, 2010)

Vancomycin exposure and obesity

Nutr Diabetes. 2013 Sep 9;3:e87. doi: 10.1038/nutd.2013.28.

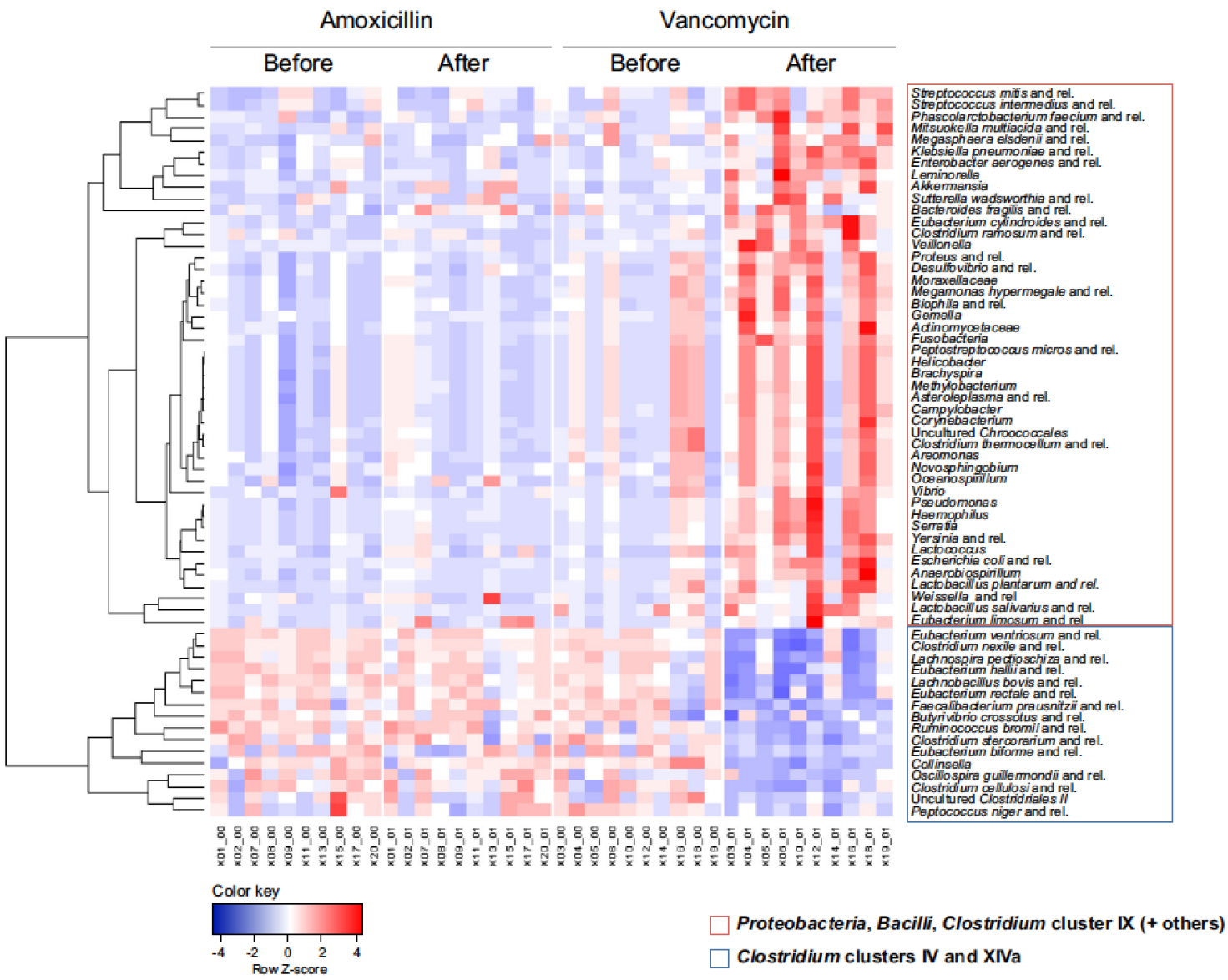
Lactobacillus reuteri and Escherichia coli in the human gut microbiota may predict weight gain associated with vancomycin treatment.

Million M[1], Thuny F, Angelakis E, Casalta JP, Giorgi R, Habib G, Raoult D.

Lactobacillus reuteri, which is resistant to vancomycin and produces broad bacteriocins, may have an instrumental role in this effect (favoring weight gain).

Remember the crusade of Prof. Didier Raoult against Danone…

Vancomycin exposure in humans



(Vrieze et al, 2014)

Affecting gut microbiota

- 1) using antimicrobials
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- 3) using TMF, or simplified Tx

Loose weight by changing microbiota?

ARTICLE

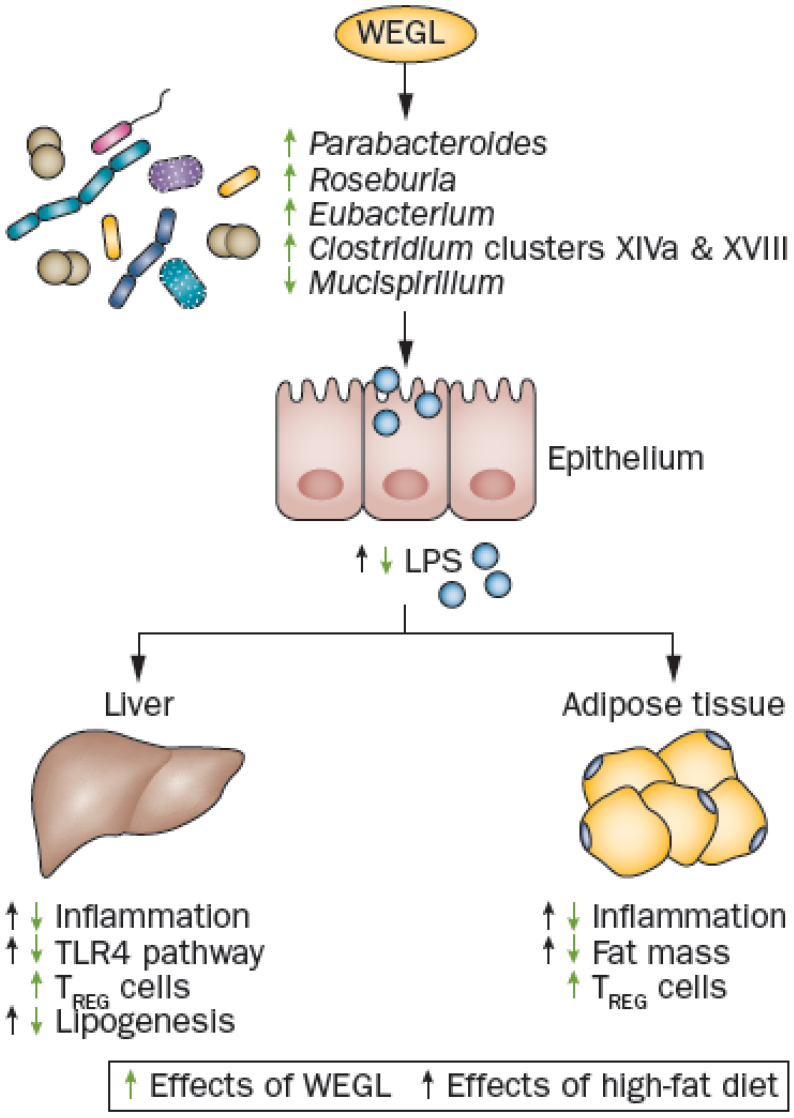
Received 16 Dec 2014 | Accepted 14 May 2015 | Published 23 Jun 2015

DOI: 10.1038/ncomms8489 OPEN

Ganoderma lucidum reduces obesity in mice by modulating the composition of the gut microbiota

Chih-Jung Chang[1,2,3,4,5,*], Chuan-Sheng Lin[1,2,3,5,*], Chia-Chen Lu[6], Jan Martel[1], Yun-Fei Ko[7,8], David M. Ojcius[1,9], Shun-Fu Tseng[5], Tsung-Ru Wu[2,3], Yi-Yuan Margaret Chen[4], John D. Young[1,7,8,10] & Hsin-Chih Lai[1,2,3,5]

Loose weight by changing microbiota?



(Delzenne N, Nat Rev GEH 2015)

Affecting gut microbiota

- 1) using antimicrobials
- 2) using probiotics
- 3) using TMF, or simplified Tx

Specificity of « drugs » from the microbiome

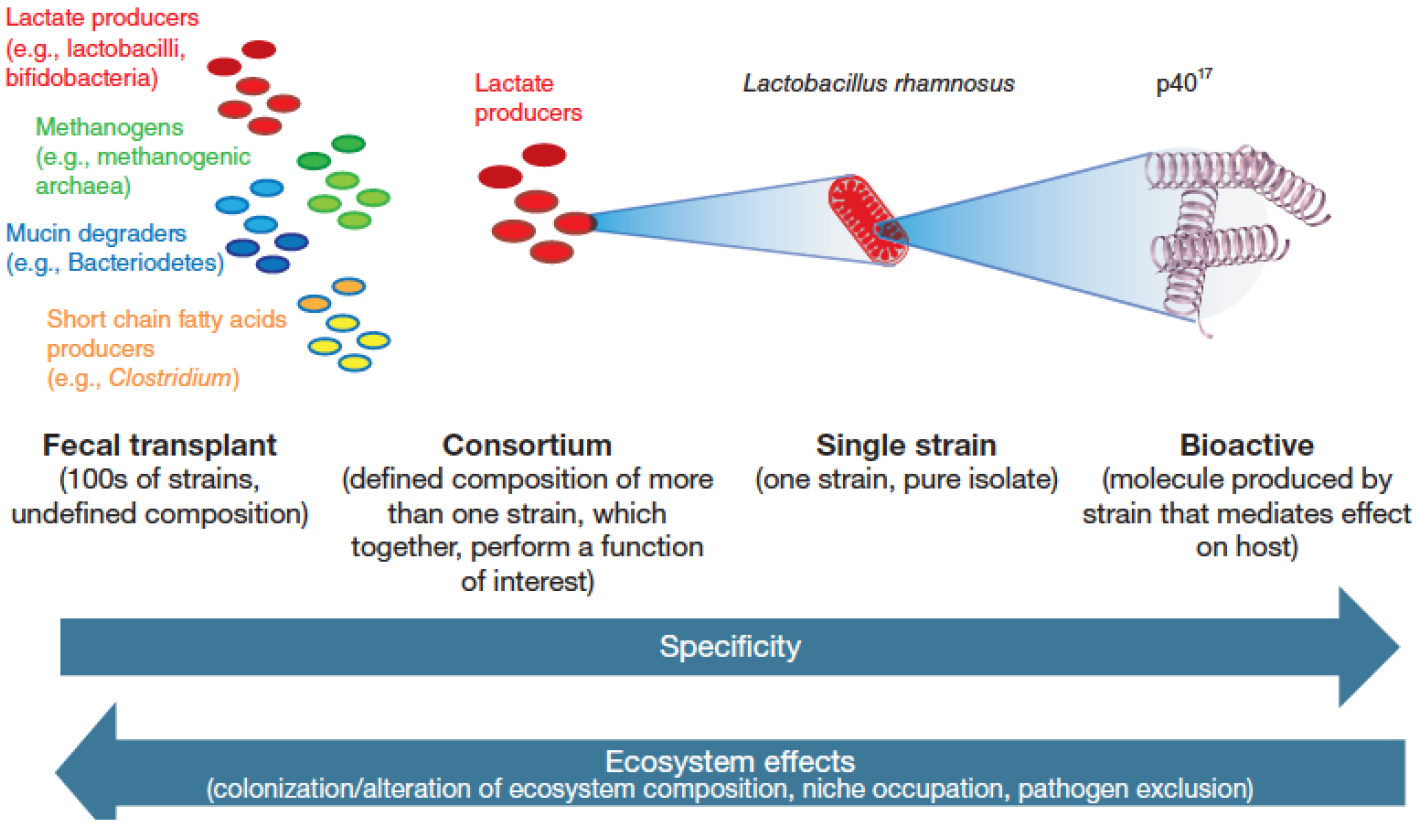
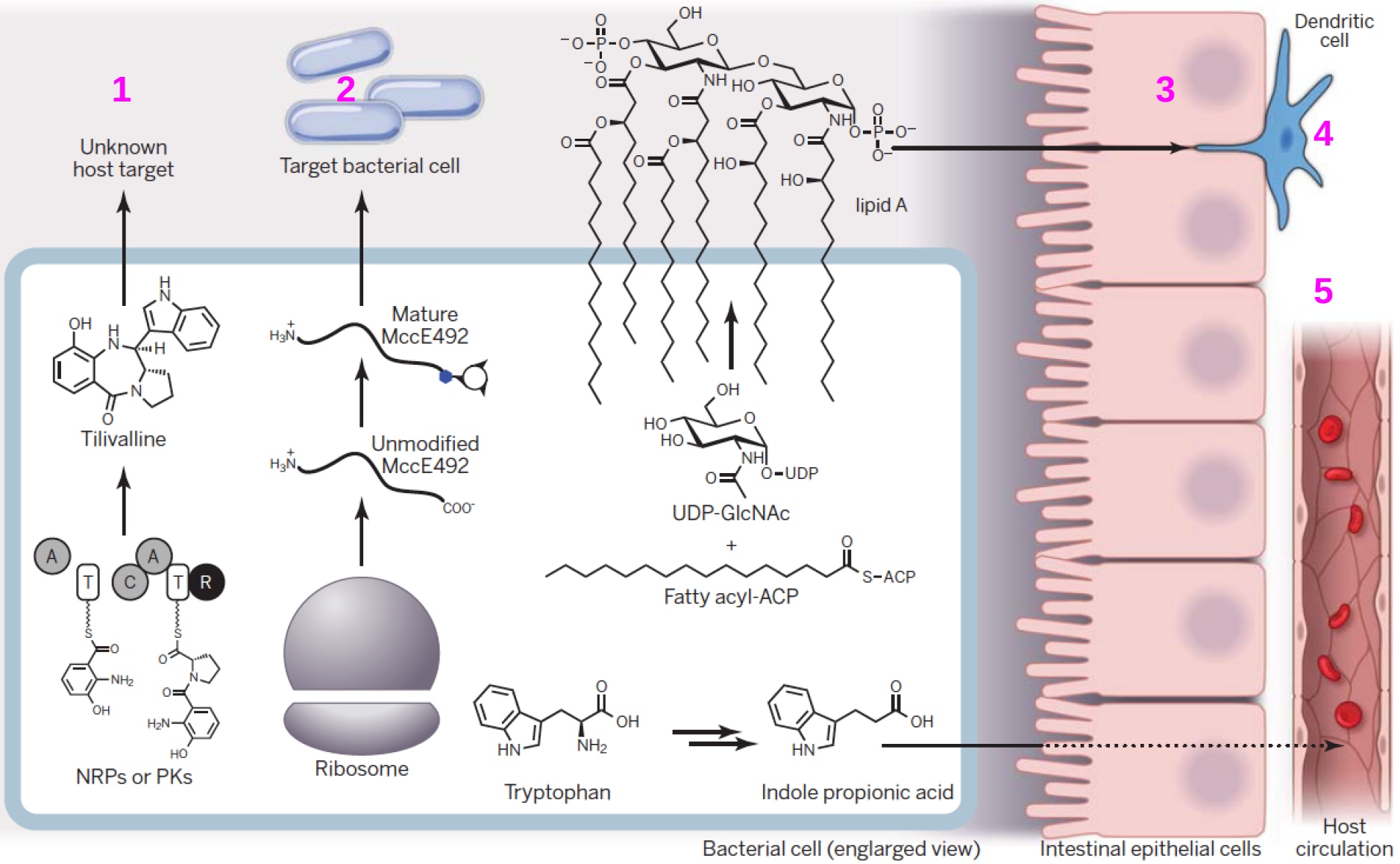


Figure 3 Spectrum of microbiome-derived modulators being pursued by biotech companies, ranging from ecosystem-level interventions to single-target approaches. 'Lactate producer' is used here as a functional attribute descriptive of a community. Species belonging to the 'lactate producers' community (e.g., *L. rhamnosus*) may also belong to other communities. A community may be described by a metabolic function (e.g., lactate production) or by any other functional attribute (e.g., regulatory T-cell induction or vitamin K production). p40 is a bioactive, soluble protein expressed by *L. rhamnosus*, which mediates intestinal epithelial homeostasis[17].

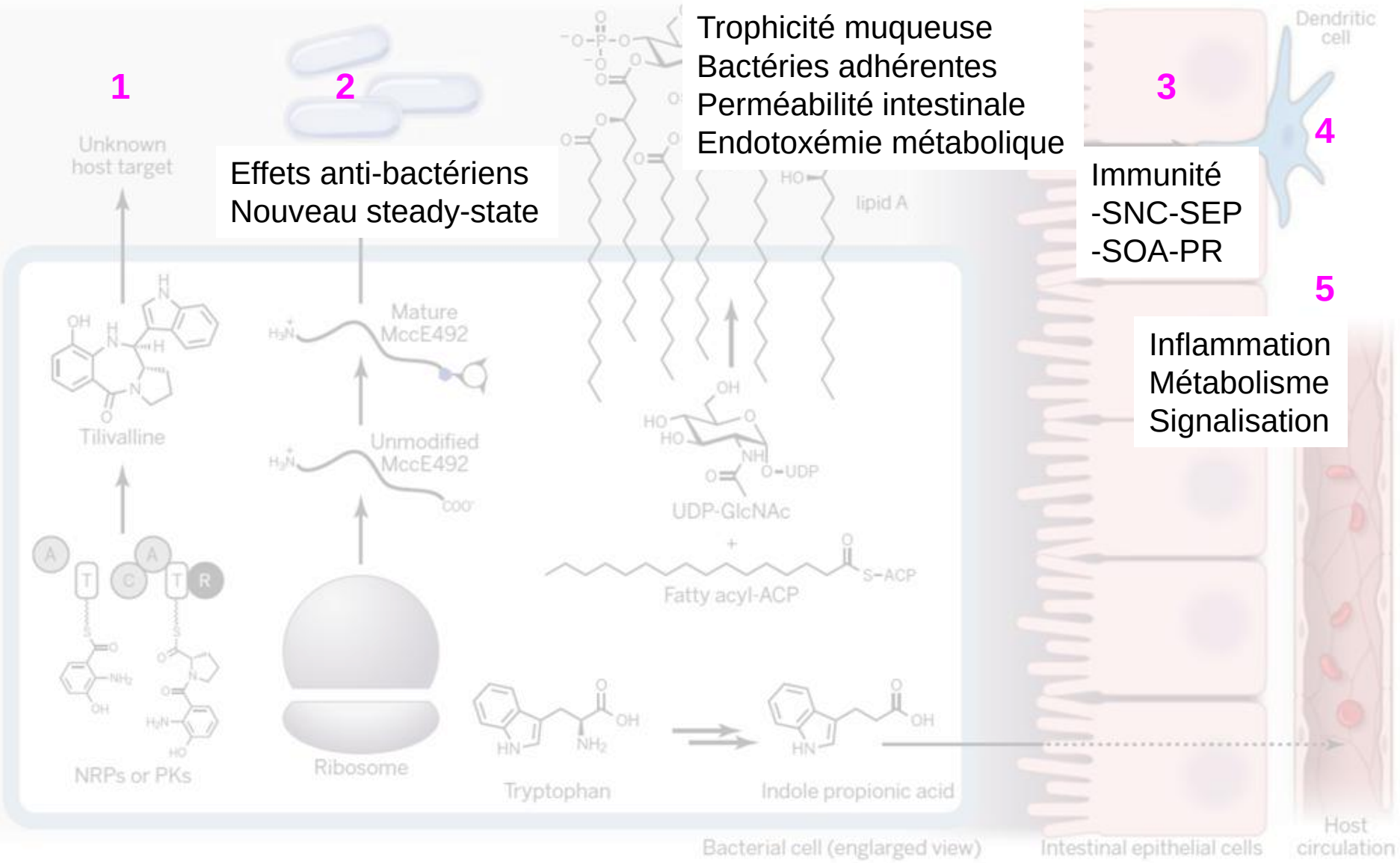
(Olle et al, Nat Biotech 31:309, 2013)

MOA of the microbiome?



(Donia et al, Science 349:395, 2015)

MOA of the microbiome?



Trophicité muqueuse
Bactéries adhérentes
Perméabilité intestinale
Endotoxémie métabolique

Effets anti-bactériens
Nouveau steady-state

Immunité
-SNC-SEP
-SOA-PR

Inflammation
Métabolisme
Signalisation

(Donia et al, Science 349:395, 2015)

Systemic effects of the microbiome

Binge OH drinking, IBD
NASH, HCV hepatitis….

Chronic HD (Bossola Clin J Am Soc Nephrol 2009)
CAPD (Kwan Nephrol Dial Transplant 2013)

Dysbiosis
Microbiota changes
Gut permeability

Microbial translocation
16S rDNA
Endotoxin (LPS)

Low level systemic inflammation
CRP, IL10, IL6
No leucocytosis

Metabolic changes
Insulin R
Increased CV hazard

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

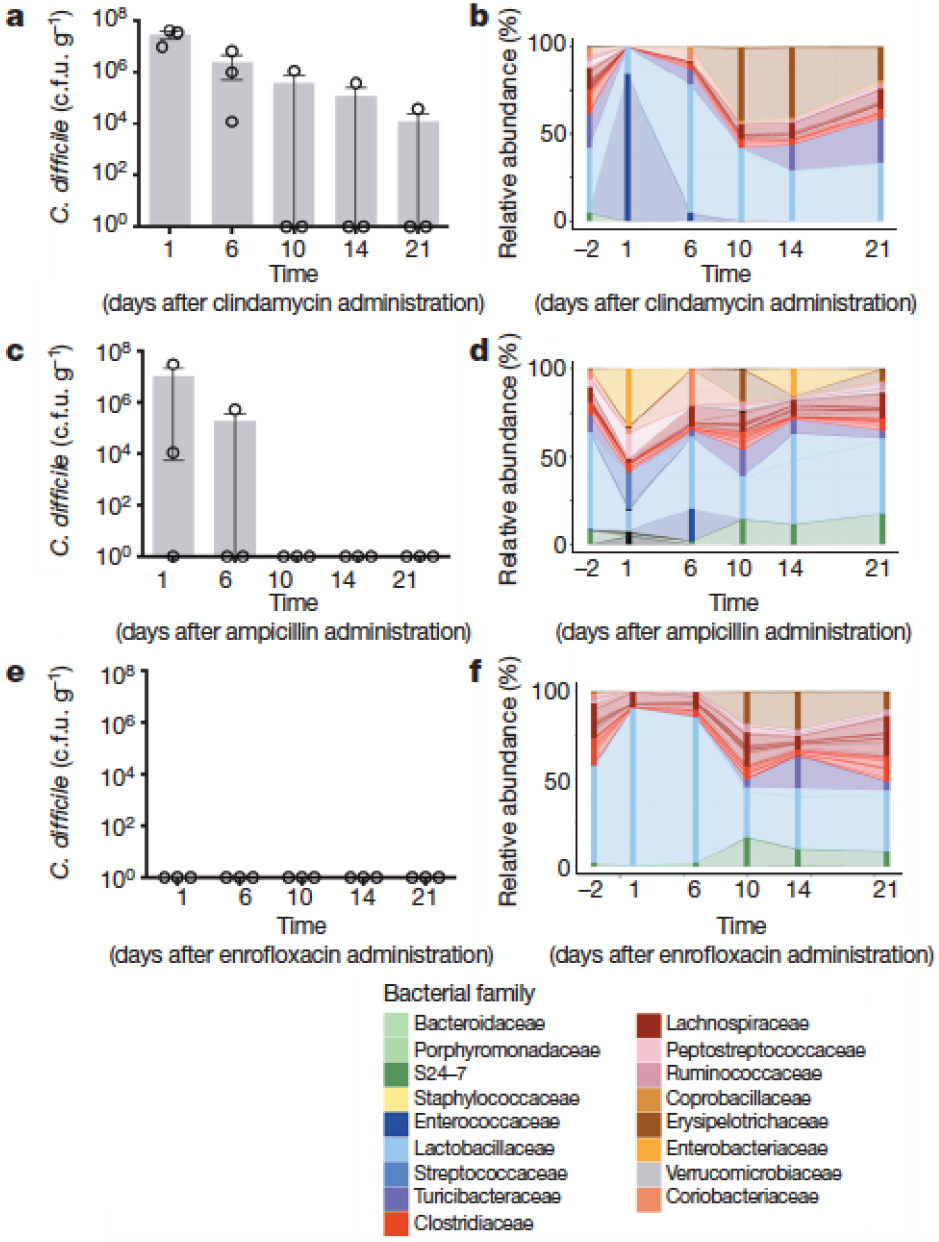
LETTER

October 2014

doi:10.1038/nature13828

Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*

Charlie G. Buffie[1,2], Vanni Bucci[3,4], Richard R. Stein[3], Peter T. McKenney[1,2], Lilan Ling[2], Asia Gobourne[2], Daniel No[2], Hui Liu[5], Melissa Kinnebrew[1,2], Agnes Viale[6], Eric Littmann[2], Marcel R. M. van den Brink[7,8], Robert R. Jenq[7], Ying Taur[1,2], Chris Sander[3], Justin Cross[5], Nora C. Toussaint[2,3], Joao B. Xavier[2,3] & Eric G. Pamer[1,2,8]



Different antibiotics induce distinct changes to *C. difficile*

Buffie C et al Nature Oct 2014

LETTER

October 2014

doi:10.1038/nature13828

Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*

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Here we correlate loss of specific bacterial taxa with development of infection, by treating mice with different antibiotics that result in distinct microbiota changes and lead to varied susceptibility to *C. difficile*. Mathematical modelling augmented by analyses of the microbiota of hospitalized patients identifies resistance-associated bacteria common to mice and humans. Using these platforms, we determine that *Clostridium scindens*, a bile acid 7α-dehydroxylating intestinal bacterium, is associated with resistance to *C. difficile* infection and, upon administration, enhances resistance to infection in a secondary bile acid dependent fashion.

LETTER

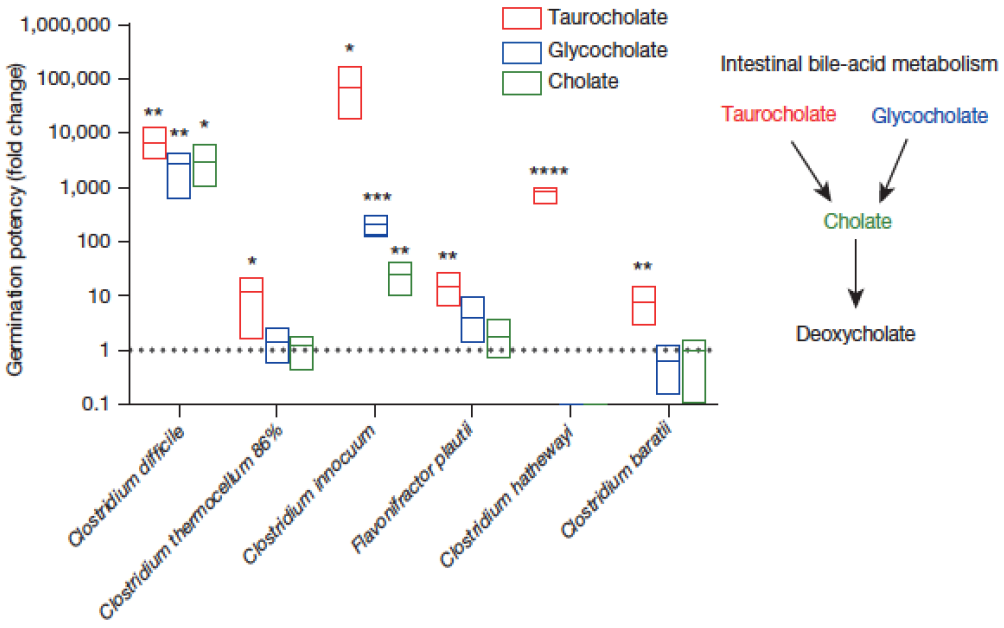
May 2016

OPEN

doi:10.1038/nature17645

Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation

Hilary P. Browne[1]*, Samuel C. Forster[1,2,3]*, Blessing O. Anonye[1], Nitin Kumar[1], B. Anne Neville[1], Mark D. Stares[1], David Goulding[4] & Trevor D. Lawley[1]



Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut

Elaine O Petrof[1*†], Gregory B Gloor[2†], Stephen J Vanner[1], Scott J Weese[3], David Carter[4], Michelle C Daigneault[5], Eric M Brown[5], Kathleen Schroeter[5] and Emma Allen-Vercoe[5]

Petrof *et al. Microbiome* 2013, 1:3

Background: Fecal bacteriotherapy ('stool transplant') can be effective in treating recurrent *Clostridium difficile* infection, but concerns of donor infection transmission and patient acceptance limit its use. Here we describe the use of a stool substitute preparation, made from purified intestinal bacterial cultures derived from a single healthy donor, to treat recurrent *C. difficile* infection that had failed repeated standard antibiotics. Thirty-three isolates were recovered from a healthy donor stool sample. Two patients who had failed at least three courses of metronidazole or vancomycin underwent colonoscopy and the mixture was infused throughout the right and mid colon. Pre-treatment and post-treatment stool samples were analyzed by 16 S rRNA gene sequencing using the Ion Torrent platform.

Results: Both patients were infected with the hyper virulent *C. difficile* strain, ribotype 078. Following stool substitute treatment, each patient reverted to their normal bowel pattern within 2 to 3 days and remained symptom-free at 6 months. The analysis demonstrated that rRNA sequences found in the stool substitute were rare in the pre-treatment stool samples but constituted over 25% of the sequences up to 6 months after treatment.

Conclusion: This proof-of-principle study demonstrates that a stool substitute mixture comprising a multi-species community of bacteria is capable of curing antibiotic-resistant *C. difficile* colitis. This benefit correlates with major changes in stool microbial profile and these changes reflect isolates from the synthetic mixture.

Trial registration: Clinical trial registration number: CinicalTrials.gov NCT01372943

MICROBIOME

SCIENCE

29 APRIL 2016 • VOL 352 ISSUE 6285

Durable coexistence of donor and recipient strains after fecal microbiota transplantation

Simone S. Li,[1,2] Ana Zhu,[1] Vladimir Benes,[3] Paul I. Costea,[1] Rajna Hercog,[3] Falk Hildebrand,[1] Jaime Huerta-Cepas,[1] Max Nieuwdorp,[4,5,6] Jarkko Salojärvi,[7,8] Anita Y. Voigt,[1,9,10] Georg Zeller,[1] Shinichi Sunagawa,[1]* Willem M. de Vos,[7,11,12]* Peer Bork[1,10,13,14]*

MICROBIOME

SCIENCE
29 APRIL 2016 • VOL 352 ISSUE 6285

Durable coexistence of donor and recipient strains after fecal microbiota transplantation

Fecal microbiota transplantation (FMT) has shown efficacy in treating recurrent *Clostridium difficile* infection and is increasingly being applied to other gastrointestinal disorders, yet the fate of native and introduced microbial strains remains largely unknown. To quantify the extent of donor microbiota colonization, we monitored strain populations in fecal samples from a recent FMT study on metabolic syndrome patients using single-nucleotide variants in metagenomes. We found extensive coexistence of donor and recipient strains, persisting 3 months after treatment. Colonization success was greater for conspecific strains than for new species, the latter falling within fluctuation levels observed in healthy individuals over a similar time frame. Furthermore, same-donor recipients displayed varying degrees of microbiota transfer, indicating individual patterns of microbiome resistance and donor-recipient compatibilities.

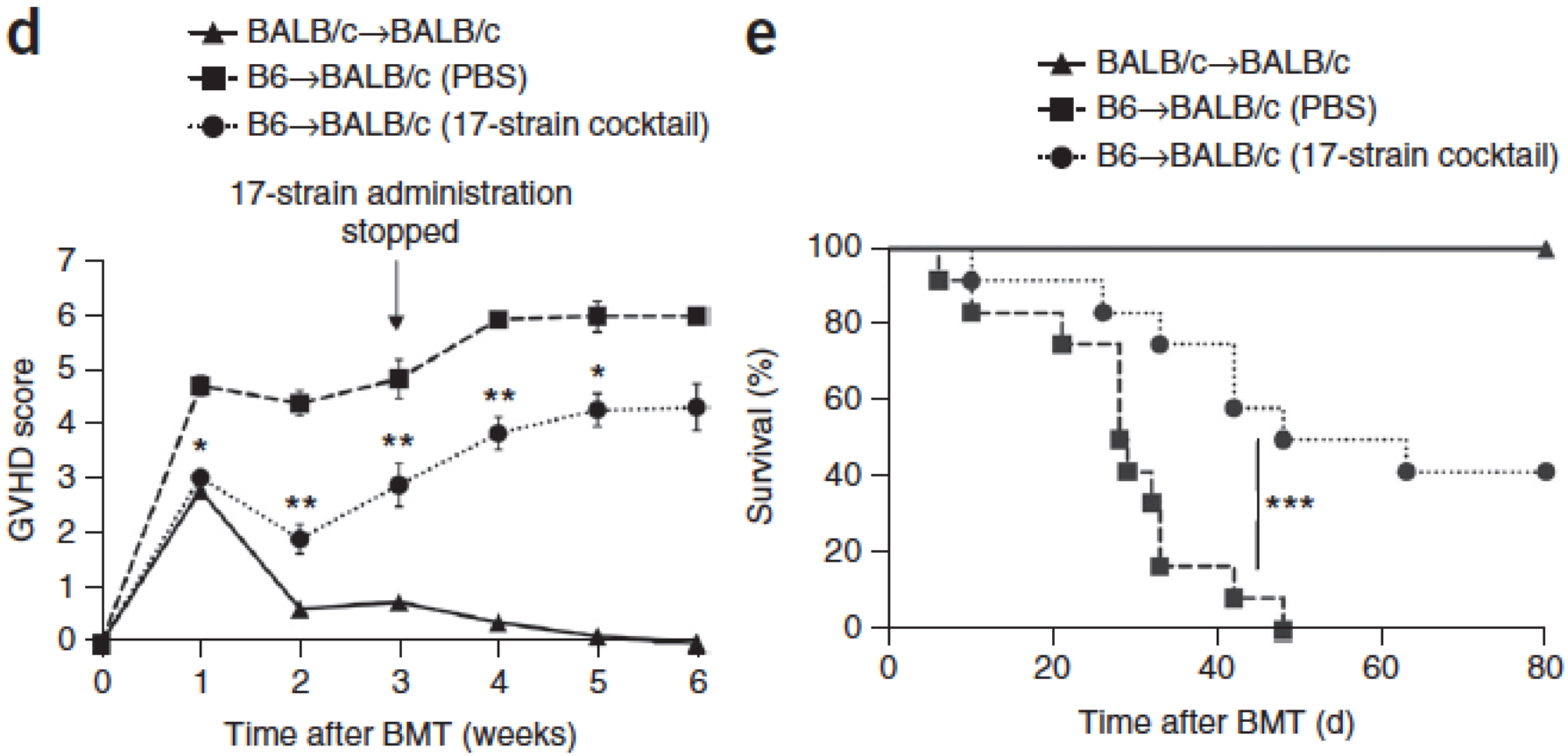
=> Détermination d'une autre forme de chimérisme

Gut microbiome–derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease

Nathan D Mathewson[1,2,7], Robert Jenq[3,7], Anna V Mathew[4,7], Mark Koenigsknecht[5,7], Alan Hanash[3,7], Tomomi Toubai[1], Katherine Oravecz-Wilson[1], Shin-Rong Wu[1,2], Yaping Sun[1], Corinne Rossi[1], Hideaki Fujiwara[1], Jaeman Byun[4], Yusuke Shono[3], Caroline Lindemans[3], Marco Calafiore[3], Thomas C Schmidt[5], Kenya Honda[6], Vincent B Young[5,7], Subramaniam Pennathur[4,7], Marcel van den Brink[3,7] & Pavan Reddy[1]

The effect of alterations in intestinal microbiota on microbial metabolites and on disease processes such as graft-versus-host disease (GVHD) is not known. Here we carried out an unbiased analysis to identify previously unidentified alterations in gastrointestinal microbiota–derived short-chain fatty acids (SCFAs) after allogeneic bone marrow transplant (allo-BMT). Alterations in the amount of only one SCFA, butyrate, were observed only in the intestinal tissue. The reduced butyrate in CD326$^+$ intestinal epithelial cells (IECs) after allo-BMT resulted in decreased histone acetylation, which was restored after local administration of exogenous butyrate. Butyrate restoration improved IEC junctional integrity, decreased apoptosis and mitigated GVHD. Furthermore, alteration of the indigenous microbiota with 17 rationally selected strains of high butyrate–producing Clostridia also decreased GVHD. These data demonstrate a heretofore unrecognized role of microbial metabolites and suggest that local and specific alteration of microbial metabolites has direct salutary effects on GVHD target tissues and can mitigate disease severity.

Mathewson Nat Immunol 2016

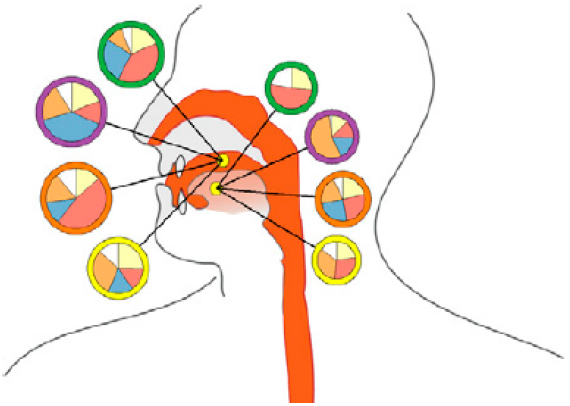


Mathewson Nat Immunol 2016

Opinion: Conservation and stewardship of the human microbiome

Kieran C. O'Doherty[a], Josh D. Neufeld[b], Fiona S. L. Brinkman[c], Humphrey Gardner[d], David S. Guttman[e], and Robert G. Beiko[f,1]

[a]Department of Psychology, University of Guelph, Guelph, ON, Canada N1G 2W1; [b]Department of Biology, University of Waterloo, Waterloo, ON, Canada N2L 3G1; [c]Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada V5A 1S6; [d]Department of Translational Medicine, Infection, AstraZeneca, Waltham, MA 02451; [e]Department of Cell and Systems Biology, Centre for the Analysis of Genome Evolution and Function, University of Toronto, Toronto, ON, Canada M5S 3B2; and [f]Faculty of Computer Science, Dalhousie University, Halifax, NS, Canada B3R 4R2



Odoherty KC et al PNAS 2014; 111:14312-3

Nouvel usage du web

http://americangut.org/

Anticipated developments

- Patient stratification
  (e.g. risk of NEC BB Warner Lancet Infect Dis 2016)

- Stool banks
- Auto-transplantation (e.g. MaaT Pharma)

- Engineered probiotic cocktails
  (e.g. convergence of food and pharma: Seres + Nestlé)

Take-home messages

- We are super-organisms
- New chapters on physiology and pathology
- Gut microbiome is highly individual and complex
- Precision medicine by fine tuning gut microbiota?
- Personalized medicine to be balanced with complexity

- Stay tune on the emergence of clinical metagenomics

And for the aficionados….

First
International
Conference on
Clinical
Metagenomics

GENEVA OCTOBER 13-14 2016

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www.genomic.ch

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- Stefano LEO
- Dr Etienne RUPPE

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