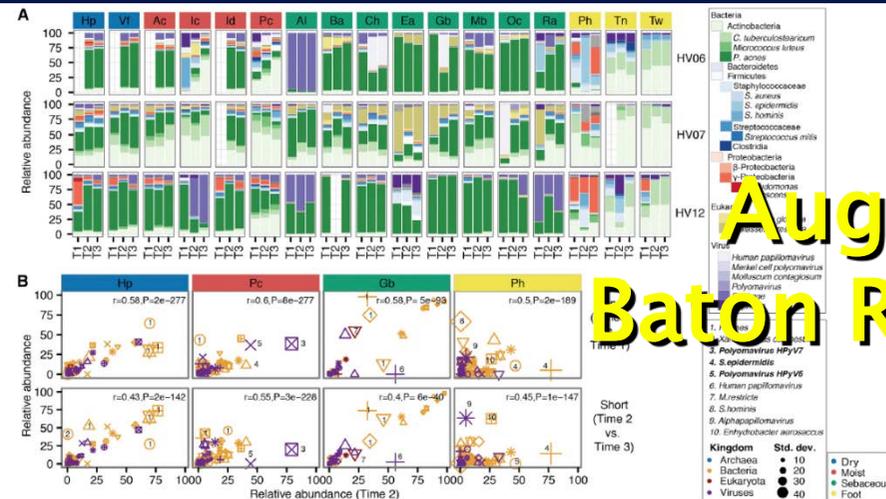
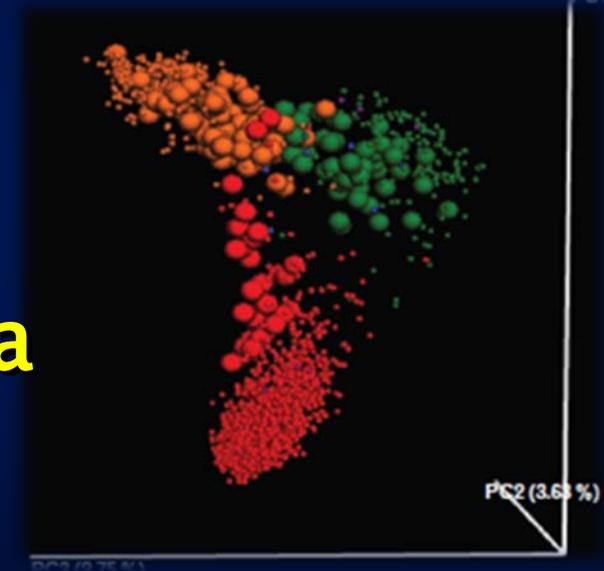


The Microbiome: Synergy Between Us & Our Flora

Louisiana Chapter of the
American Academy of Pediatrics



August 18, 2018
Baton Rouge, Louisiana



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University of California, San Diego

Antibiotic Update: Disclosure Statement: John S. Bradley, MD

Dr. Bradley has no personal financial relationship with any commercial interest that produces, markets, re-sells, or distributes antimicrobials.

Dr. Bradley's employer, the University of California, has received research funds for clinical trials during the past 12 months for study of daptomycin, ceftolozane/tazobactam, tedizolid (Cubist/Merck), dalbavancin (Durata/Allergan), oritavancin, lefamulin (Melinta), colistin (NIH), piperacillin/tazobactam (CHOP) and ceftaroline (AstraZeneca, Pfizer, RCHSD Foundation)

The Regents of the University of California hold consulting contracts with Cubist/Merck, AstraZeneca, Actavis/Allergan

This presentation will include discussion of unapproved or "off-label" uses of pharmaceuticals.

Microbiome and Metabolome

The genes of the bacteria that live on us and within us (microbiome), and the metabolic signature of their activity (metabolome)

Defined by gene sequencing/PCR and mass spectrophotometry

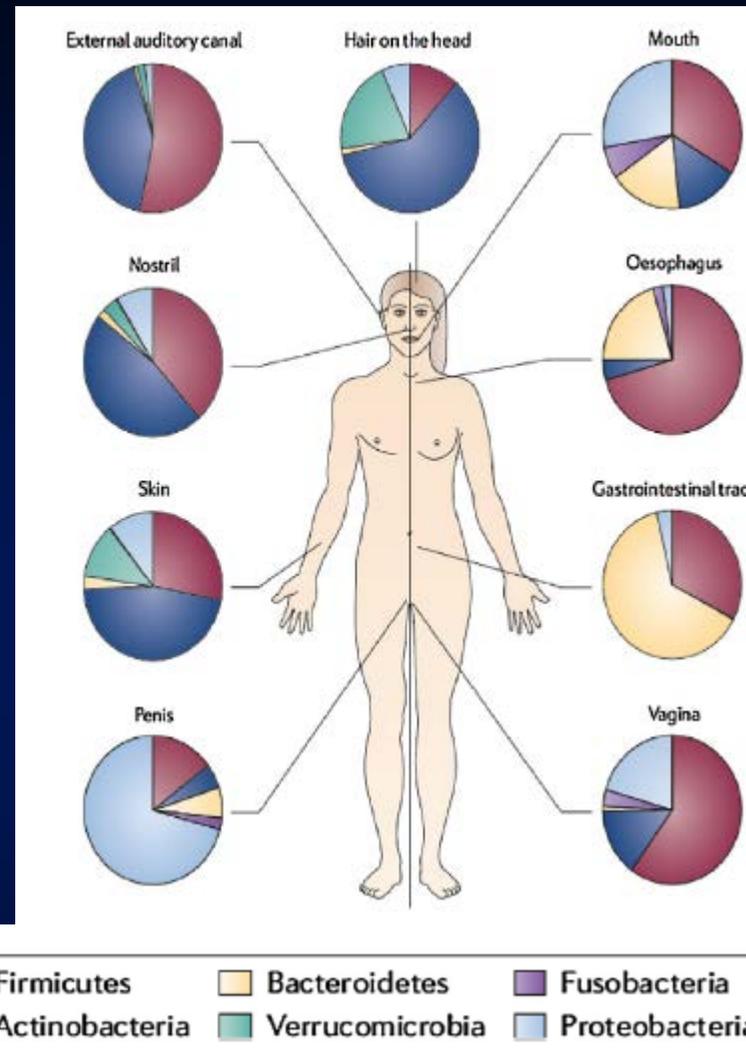
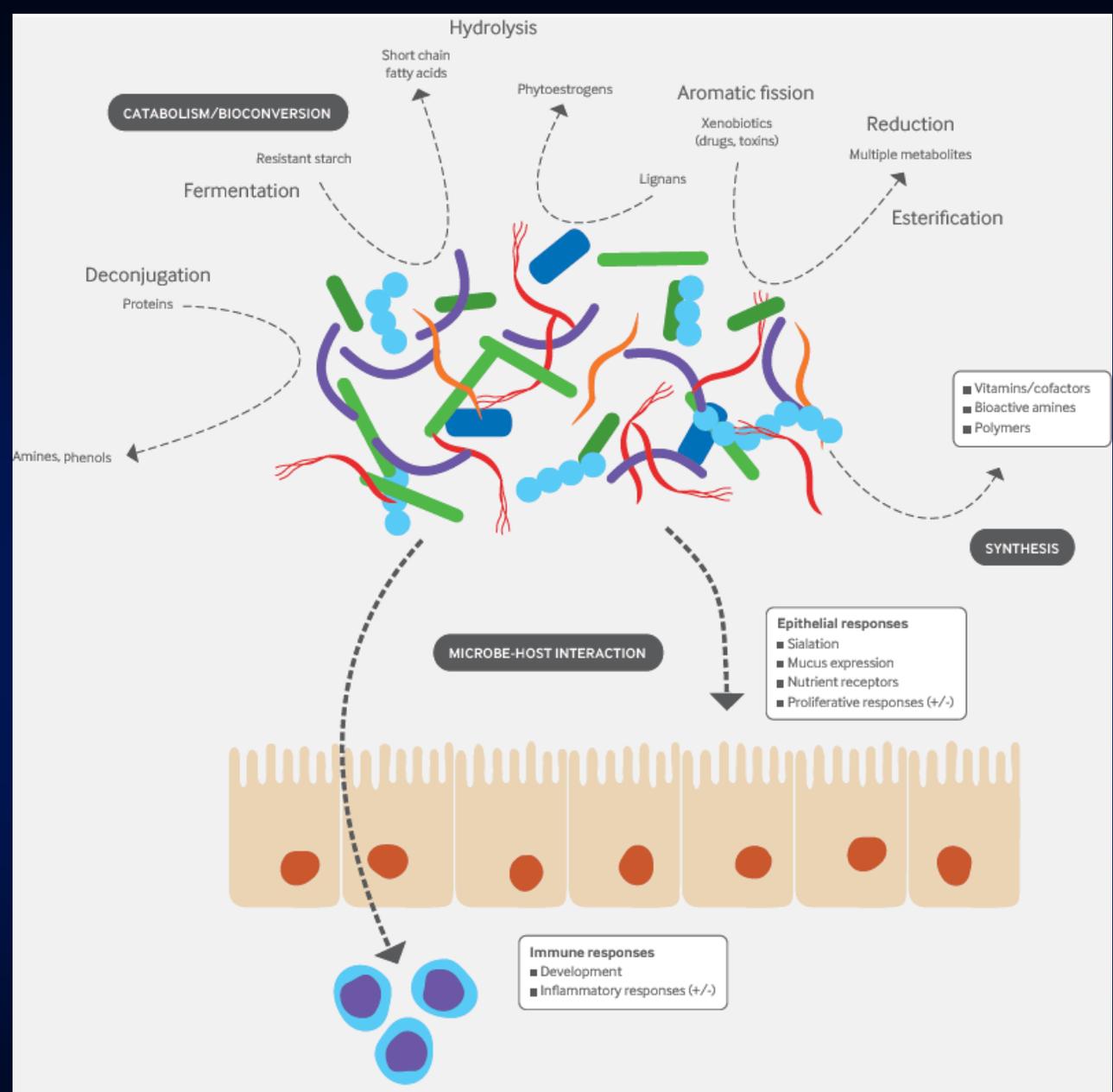


Fig. 1. (A) Different microbiomes in humans; (B) The intestinal microbiome in healthy individuals and patients [7].

Microbiome

- Each person has a unique 'signature'
- Homeostasis maintained between host and microbe for the good of BOTH
 - Inflammation
 - Infection
 - Cancer
 - Behavior
 - Obesity
 - Metabolism



Microbiome and Metabolome

- Think of your bacterial flora as you own personal microbial laboratory that produces metabolic products (like hormones and penicillin) that your body now needs and depends on
- Your body helps to nourish your flora 😊
- What you eat and the well-being of your flora (particularly treatment with antibiotics), may impact your health by impacting your microbiome

Microbiome and Metabolome

- Autism

- Assume for moment that autism is caused by abnormal flora: you can create a new flora by intervention (8 wks) (Fig 4a) or possibly by antibiotic therapy (not recommended yet!)
- Microbiome/metabolome

Fowlie G, Cohen N, Ming X. The Perturbance of Microbiome and Gut-Brain Axis in Autism Spectrum Disorders. *Int J Mol Sci.* 2018 Aug 1;19(8).

Grimaldi R, et al. A prebiotic intervention study in children with autism spectrum disorders (ASDs). *Microbiome.* 2018 Aug 2;6(1):133.

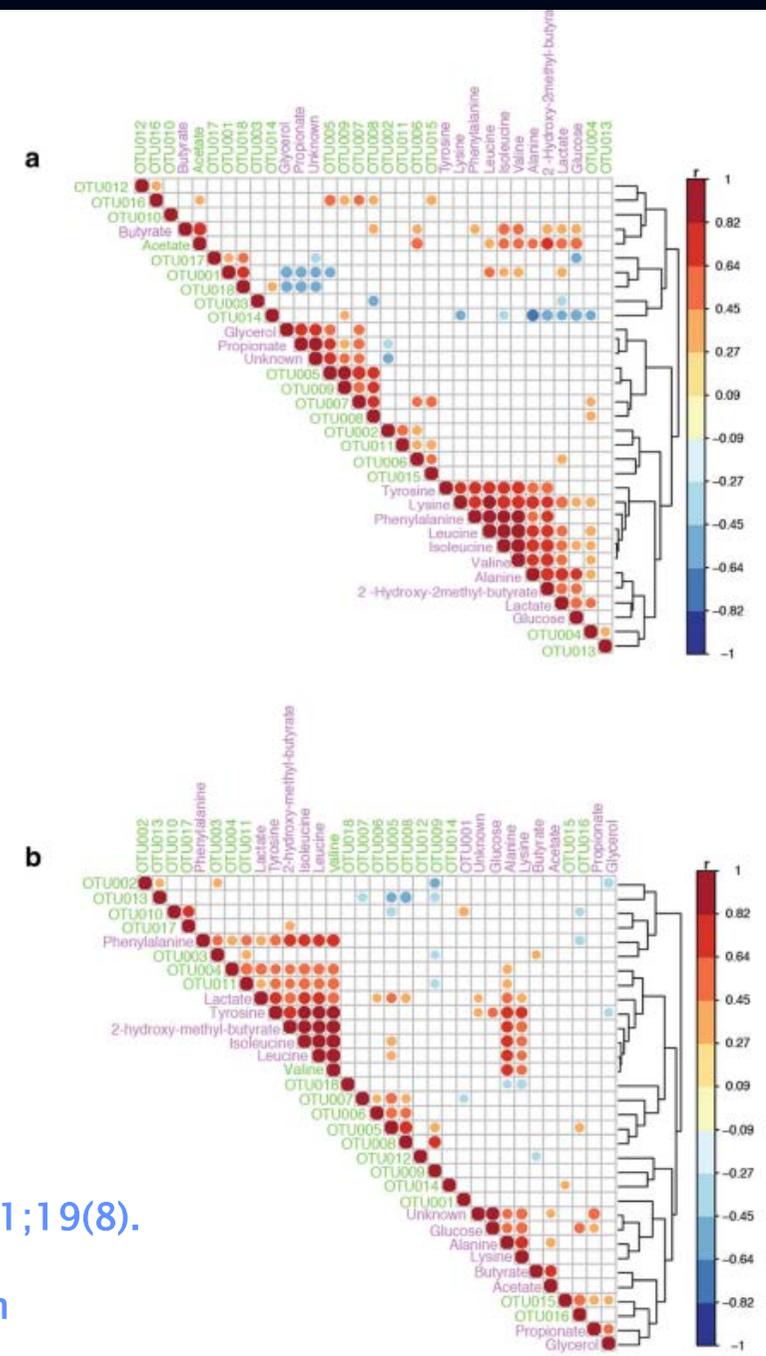
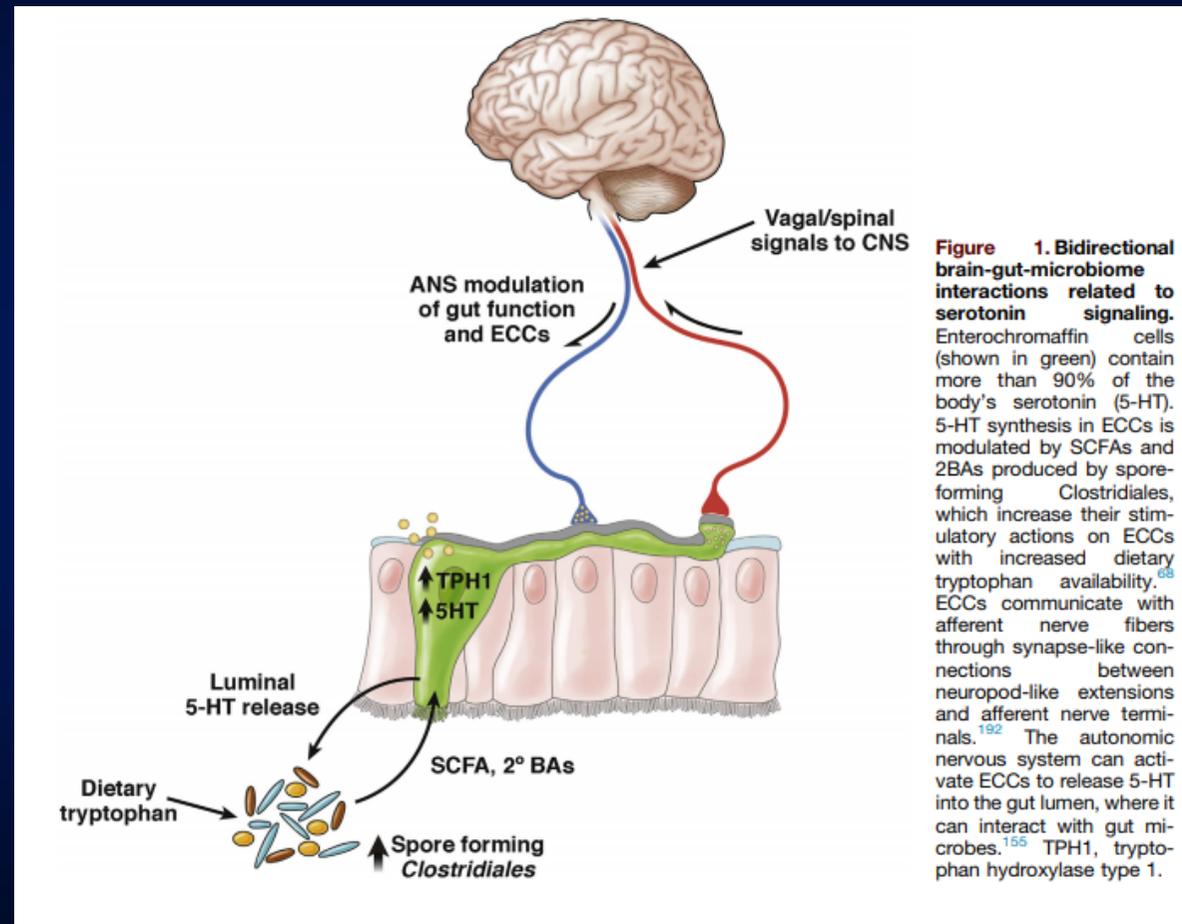


Fig. 4 (See legend on next page.)

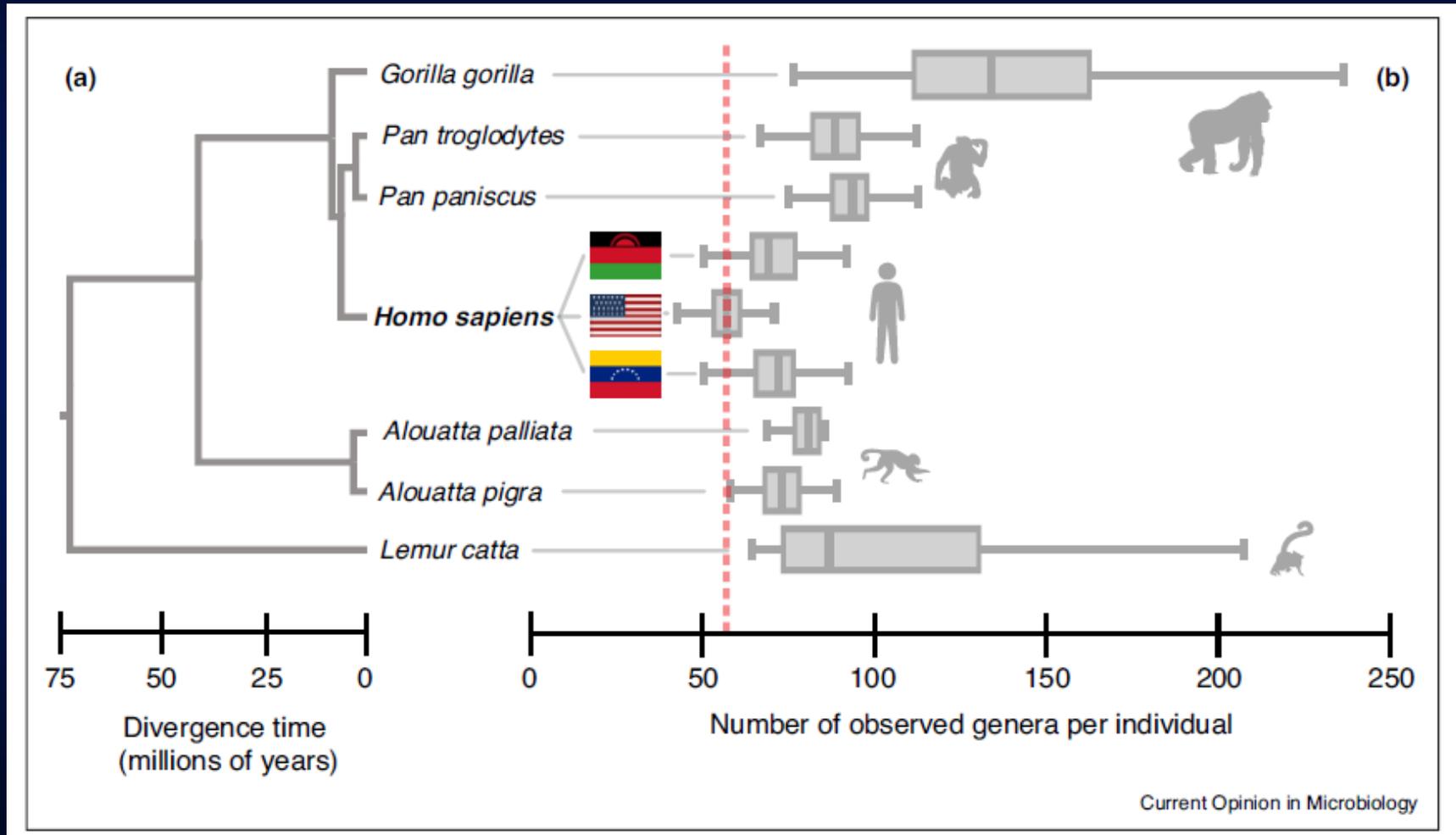
Microbiome

- Your microbiome actually creates who you are in more ways than we ever imagined...
- Homeostasis of serotonin: your body will regulate (and feed) the bacteria that facilitate production of serotonin if you don't get enough in your diet



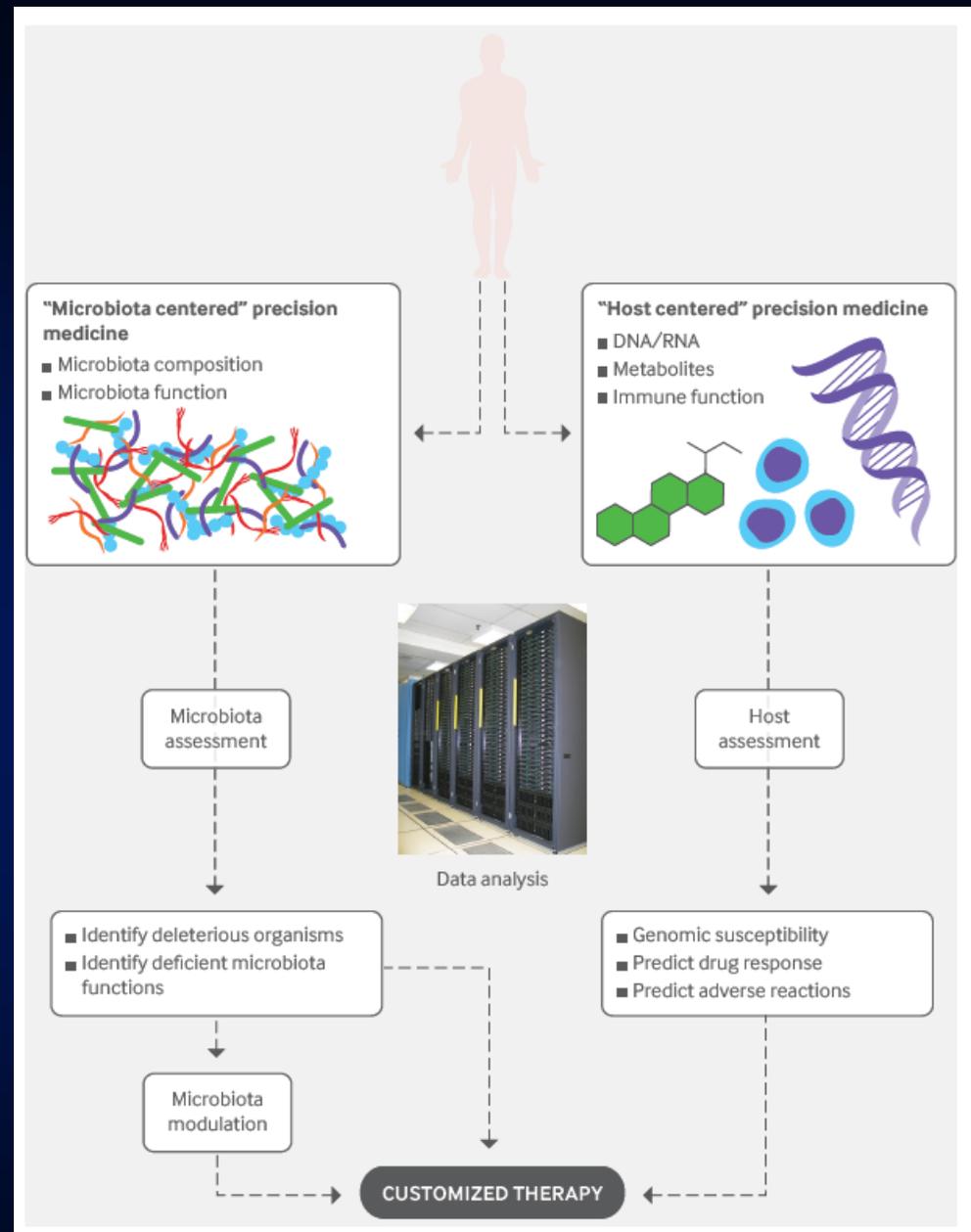
Microbiome Diversity in Humans

- Decreased diversity, compared with primates!



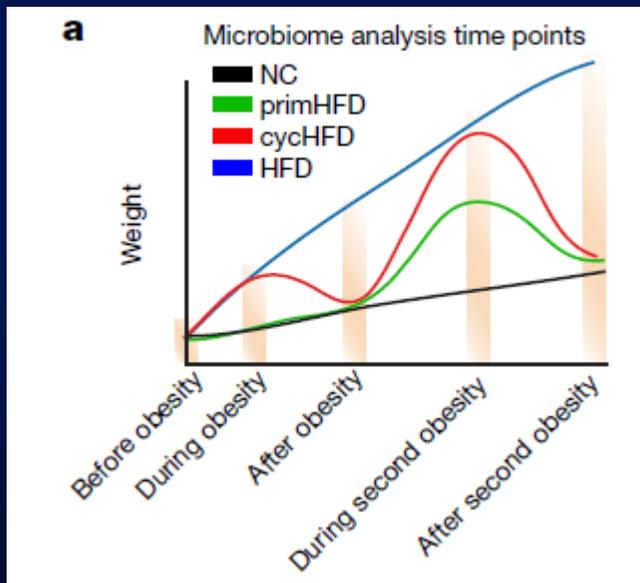
Microbiome

- Each person's unique microbiome should be maintained for optimal health the person
- Precision microbiome treatment is being developed to supplement (or restore) microbiome function
- In the coming years, my colleagues and I may be advising you on microbiome 'therapy' to treat illnesses

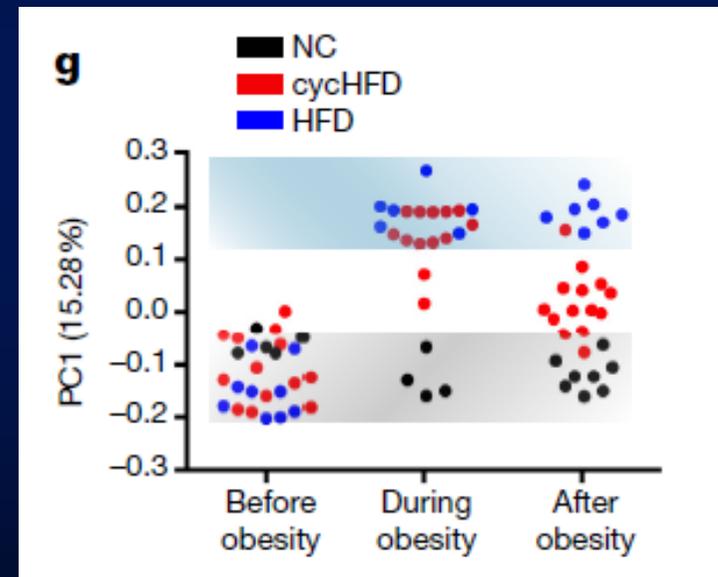


Microbiome

- A microbiome is associated with obesity in mice (as you have read). You may lose weight on a diet, but if your microbiome doesn't change, you gain it back
- Antibiotic or Microbiome treatment for obesity?



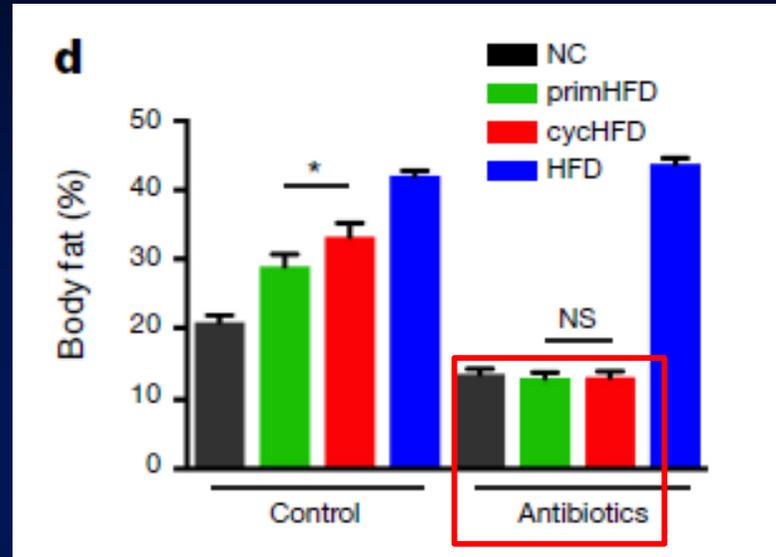
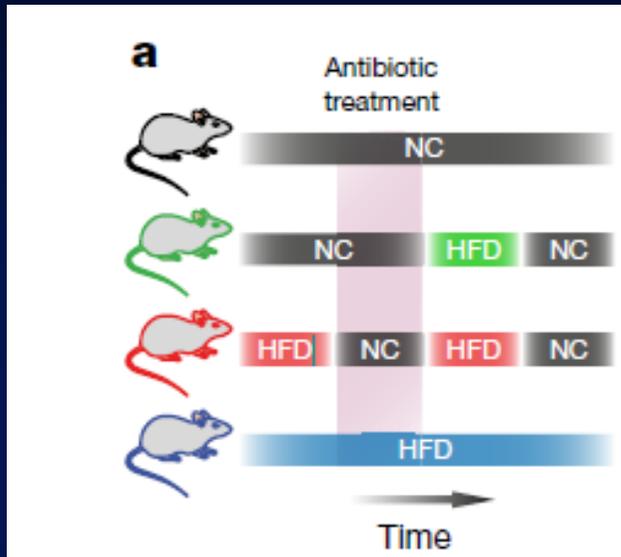
NC = normal chow
HFD = high fat diet



Thaiss CA, Itav S, Rothschild D, Meijer M, Levy M, Moresi C, Dohnalová L, Braverman S, Rozin S, Malitsky S, Dori-Bachash M, Kuperman Y, Biton I, Gertler A, Harmelin A, Shapiro H, Halpern Z, Aharoni A, Segal E, Elinav E. Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature*. 2016 Nov 24.

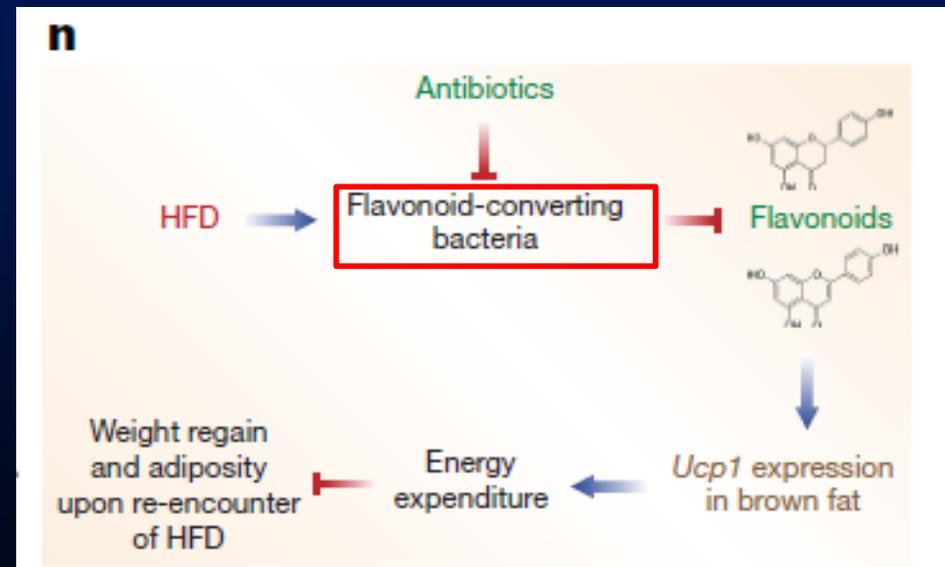
Microbiome

-Antibiotic treatment for obesity? (Of course not, yet!)



It's the flavonoids!

Thaiss CA, et al. Nature. 2016 Nov 24.

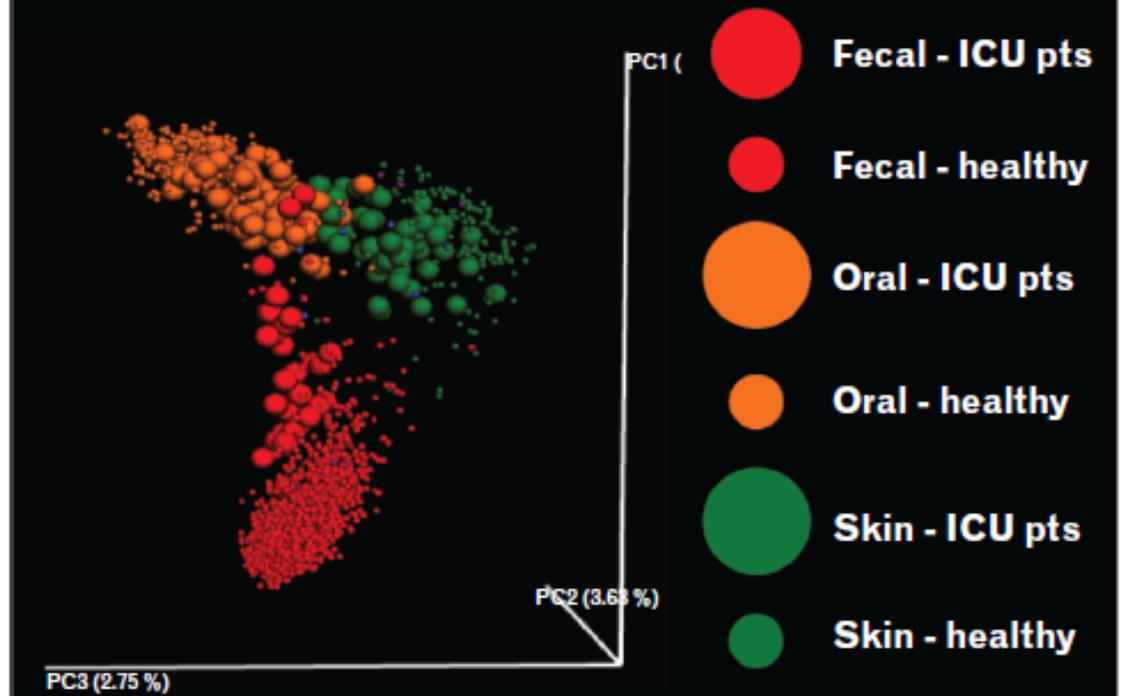


Microbiome Alteration with ICU Abx

- Decreased diversity following antibiotics
“Dysbiosis”

Microbiome of fecal, oral, skin begins to converge in critical illness showing potential loss of diversity and possible indication of less barrier function.

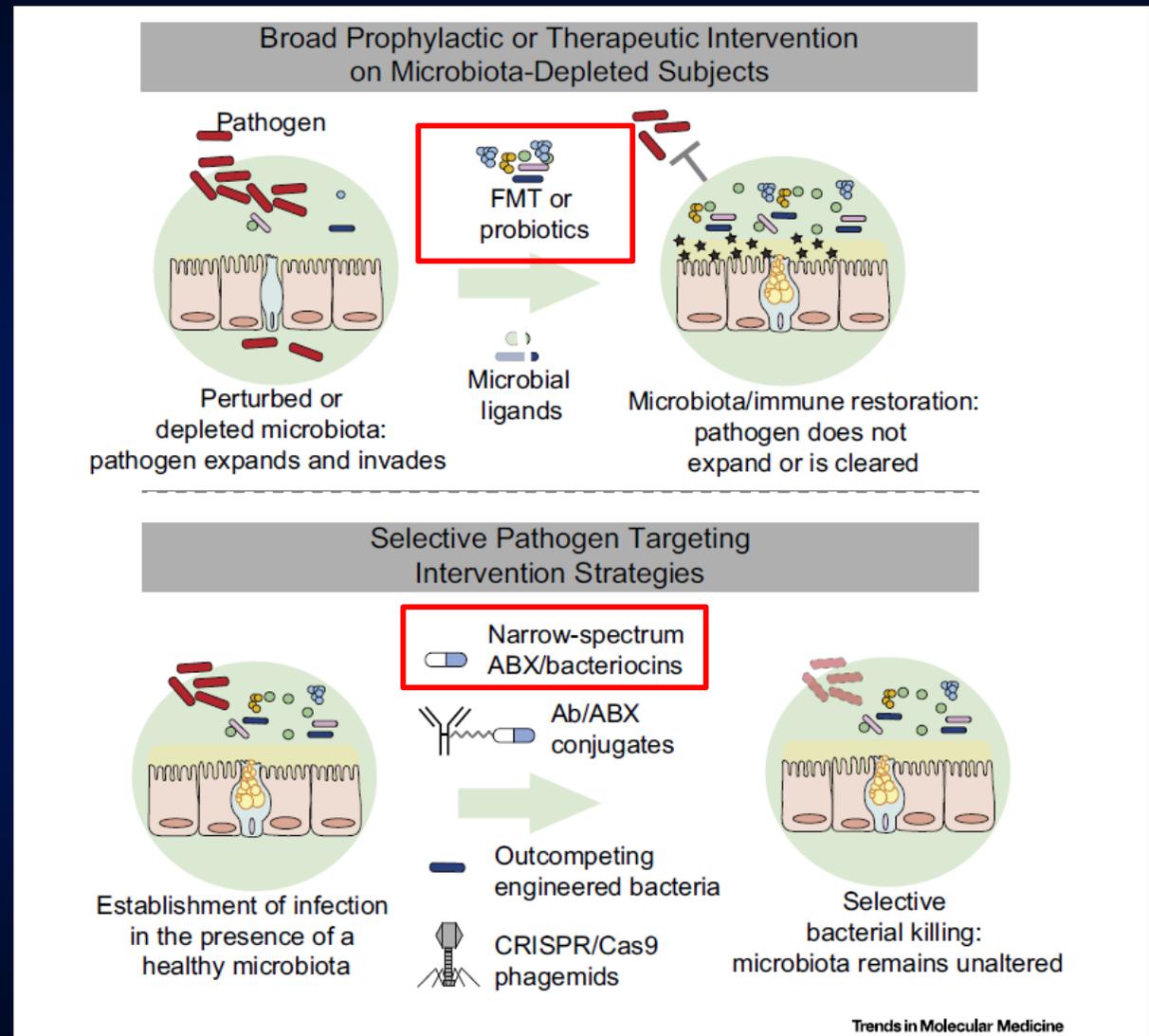
Microbiome in ICU patients is significantly altered from healthy subjects



Wischmeyer PE, McDonald D, Knight R. Role of the microbiome, probiotics, and 'dysbiosis therapy' in critical illness. *Curr Opin Crit Care*. 2016 Aug;22(4):347–53.

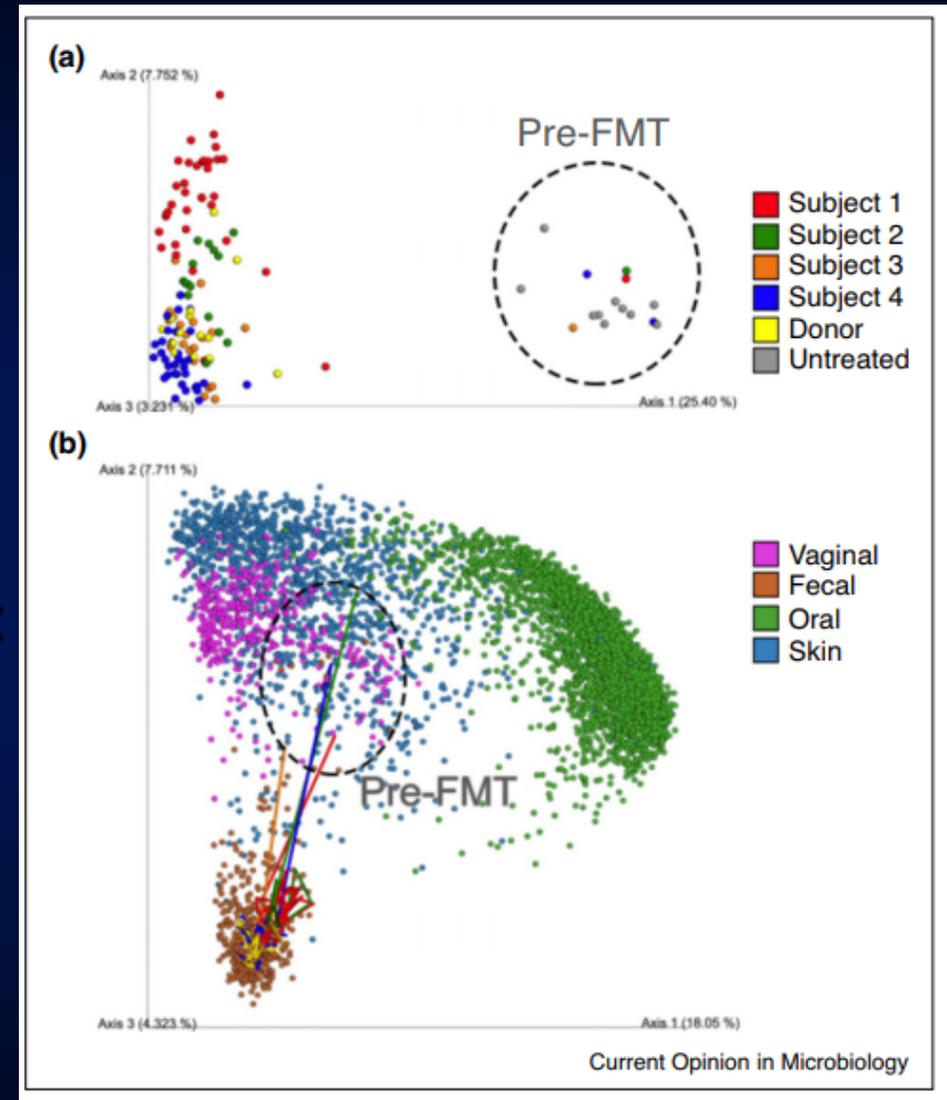
Microbiome Therapy after Antibiotics

- Probiotics and Fecal Transplant merge!

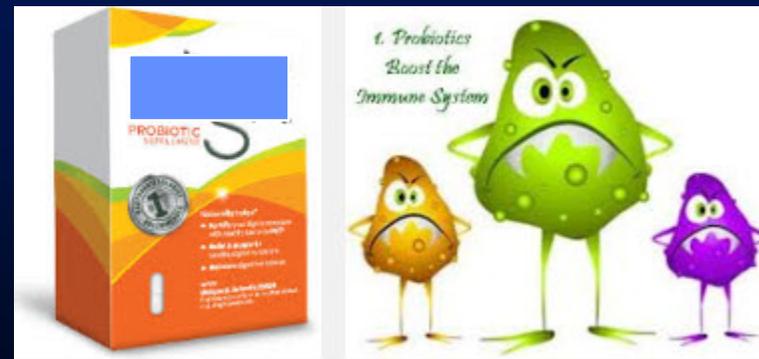
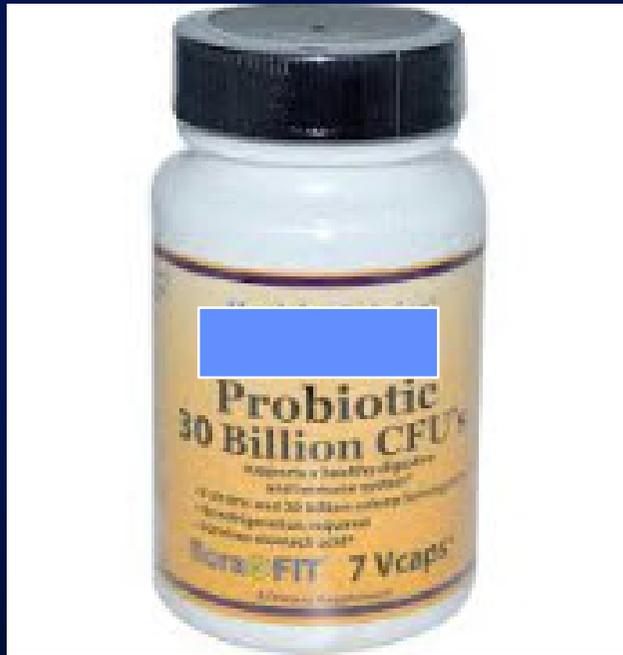


Microbiome and Fecal Transplant for C. diff

- Top left: patients pre-transplant
- Top right: donors and patients post transplant
- Bottom: Human Genome Project, plus treated patients (lines)
- Rob Knight TED talk on YouTube: <https://www.youtube.com/watch?v=i-icXZ2tMRM>



Probiotics to Restore the Microbiome



From Google Image search: Probiotics (accessed 2018)

Prebiotics and Probiotics

- No standardized protocol for treatment or for endpoint evaluation (no FDA Guidance)

EXPERT CONSENSUS DOCUMENT

The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic

- An international collaboration is attempting to bring definition to the field and scientific rigor to the investigations!

Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol.* 2017 Aug;14(8):491–502.

Probiotic Impact (Clinical/Microbiome)

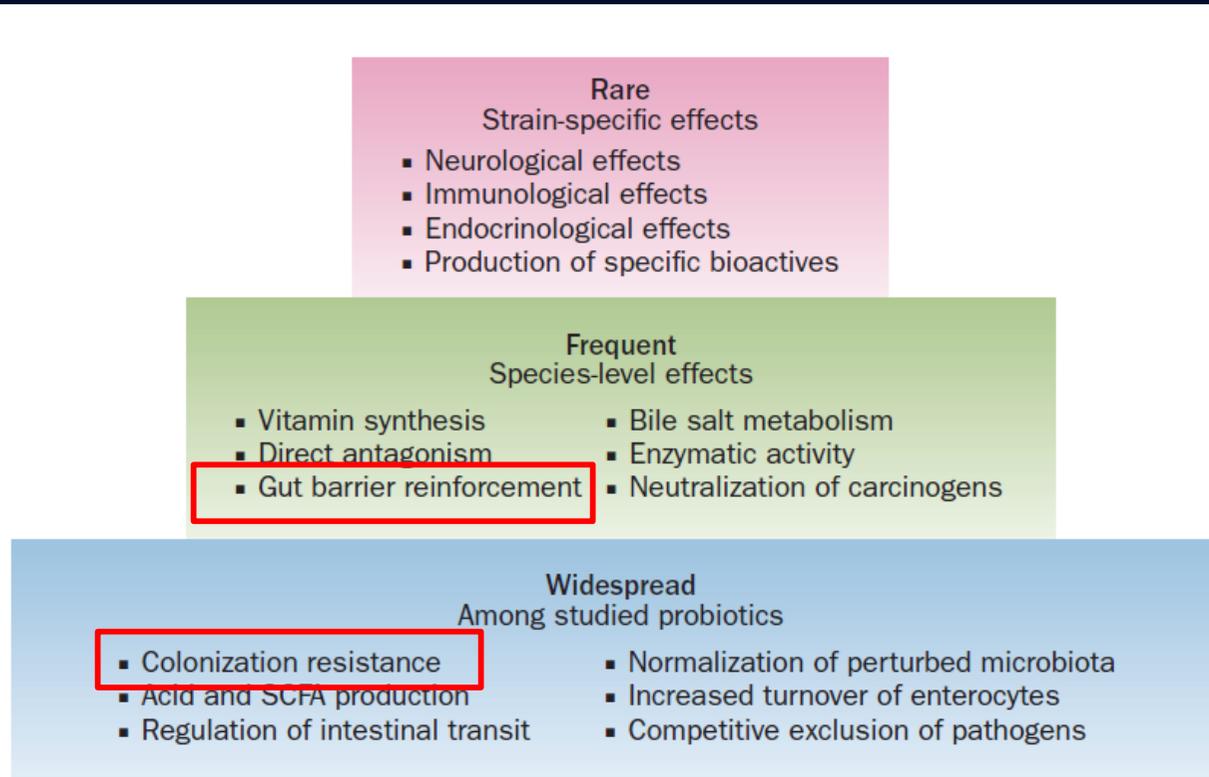


Figure 2 | Possible distribution of mechanisms among probiotics. Some mechanisms might be widespread among commonly studied probiotic genera; others might be frequently observed among most strains of a probiotic species; others may be rare and present in only a few strains of a given species.

Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014 Aug;11(8):506–14.

Probiotics and Marketing: Watch Out!

- “Probiotics” and “prebiotics” are not defined as a regulatory product category under the congressional law or the PHS Act, and products that may be considered to be “probiotics” or “prebiotics” may be foods or drugs under the Act, depending on the intended use of the product.
- Will be regulated by FDA if intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man



U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Probiotics and C. diff: A New Cochrane Review

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children (Review)
Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Probiotics compared to control for preventing *C. difficile* associated diarrhea

Patient or population: preventing *C. difficile* associated diarrhea

Setting: inpatient and outpatient

Intervention: probiotics

Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with probiotics				
Incidence CDAD: complete case	Study population		RR 0.40 (0.30 to 0.52)	8672 (31 RCTs)	⊕⊕⊕○ MODERATE ¹	Note: Risk with control calculated by pooled event rate across control groups
	40 per 1,000	→ 16 per 1,000 (12 to 21)				
CDAD (baseline risk 0-2%)	Study population		RR 0.77 (0.45 to 1.32)	5845 (15 RCTs)	⊕⊕⊕○ MODERATE ²	
	11 per 1,000	→ 8 per 1,000 (5 to 14)				
CDAD (baseline risk 3-5%)	Study population		RR 0.53 (0.16 to 1.77)	373 (3 RCTs)	⊕⊕○○ LOW ^{3,4}	
	38 per 1,000	→ 20 per 1,000 (6 to 67)				
CDAD (baseline risk >5%)	Study population		RR 0.30 (0.21 to 0.42)	2454 (13 RCTs)	⊕⊕⊕○ MODERATE ⁵	
	116 per 1,000	→ 35 per 1,000 (24 to 49)				

Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev. 2017 Dec 19;12:CD006095.

Probiotics and the Microbiome

- “Among the various probiotics evaluated [for adults and children], evidence suggests that *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day may be appropriate given the modest “Number Needed to Treat” and the likelihood that adverse events are very rare.”*

The Microbiome and Probiotics

- We need a study that looks at children treated with antibiotics (with microbiome sampled just before treatment), then given:
 - 1) a defined probiotic,
 - 2) fecal transplant (?their own stool sampled from them before antibiotic treatment)
 - 3) placebo
 - Endpoints: 1) the duration needed to restore the normal microbiome; 2) resolution of ?symptoms

The Microbiome and Probiotics

- Each year we are closer to identifying the pediatric populations that may benefit from analysis and modification of the microbiome resulting in *clinically significant benefits*
 - The FDA is now involved in regulation of fecal transplants to restore the microbiome
 - An FDA approved clinical trial is underway to look at a defined probiotic in a randomized, controlled trial in children with AOM

New Experimental Therapy to Save your Microbiome from Antibiotics

- You swallow a beta-lactamase, that cleaves antibiotics like ceftriaxone as they enter the gut!

The screenshot shows the BIOLOGICS website. The header includes the company logo and navigation links: about, product pipeline, news & media, investors, and contact. The main banner features a person in a white lab coat and gloves, with the text 'Microbiome-Focused Pipeline'. Below the banner is a navigation bar with 'Overview', 'Microbiome-Focused Pipeline' (selected), and 'Research Pipeline'. The main content area displays a table with the following structure:

Candidate & Indication	Development Stage				
	Preclinical	Phase 1	Phase 2	Phase 3	Market
SYN-004 (RIBAXAMASE) Prevention of CDI and AAD	Progressing	Progressing	Progressing		

Probiotics and the Microbiome/Metabolome

- Stayed tuned...

these fields are advancing quickly...

QUESTIONS????

