THE WORLD WITHIN US: A INTRODUCTION TO THE HUMAN GUT MICROBIOME

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Disclosures

- I have no relevant financial relationships to disclose

Microbiota: the group of microorganisms occupying a specific niche

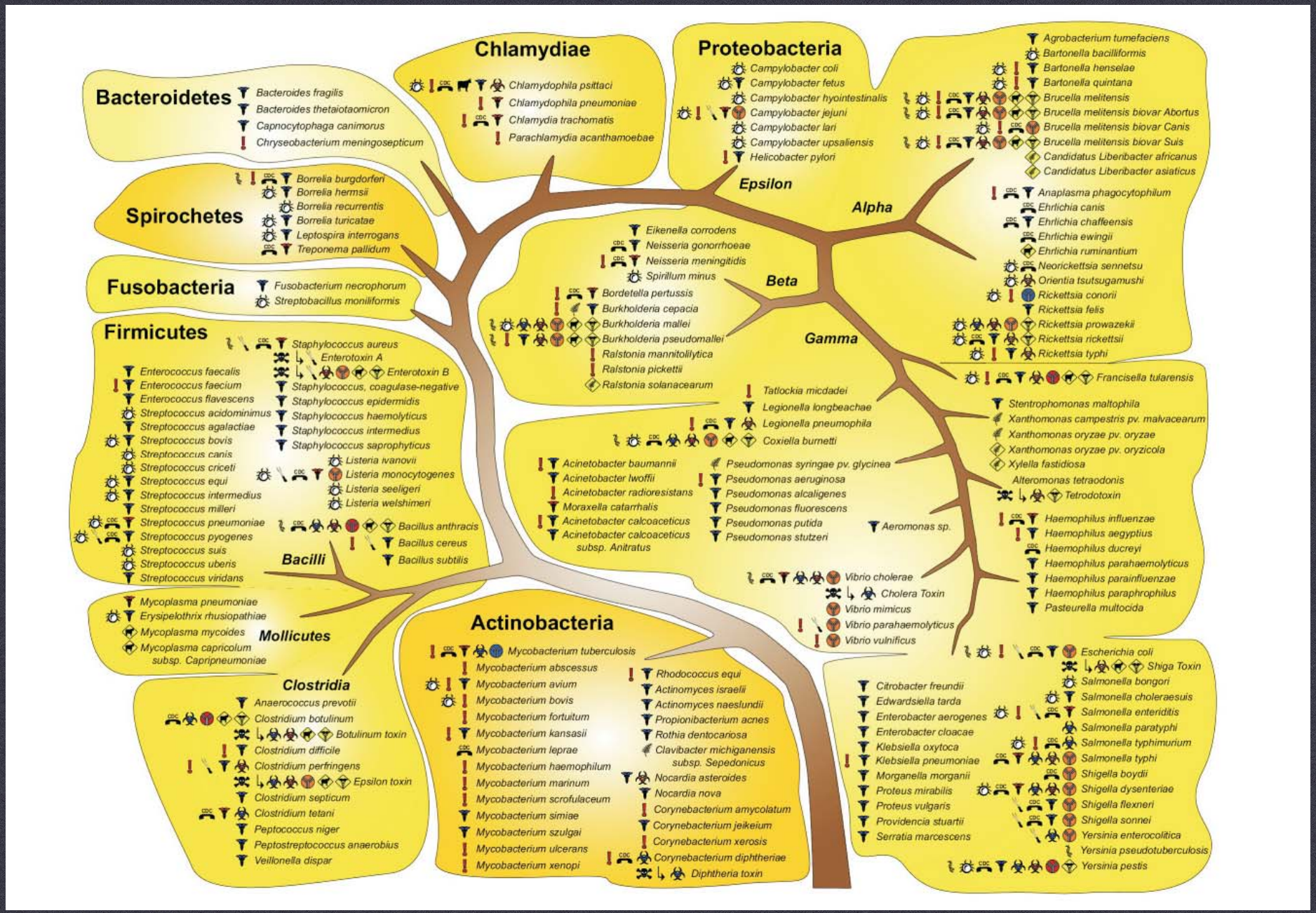
Microbiome: the sum of the microbiota and their habitat

- You have 10e13 cells BUT you support 10e14 microorganisms
  - YOU ARE 10 X MORE SOMETHING ELSE THAN YOURSELF!


~100 000 000 000 000
microbes are spread over the size of your kitchen and living room, separated from you by a one cell-thick wall. . .

Commensal relationship

- You provide:
  - Nutrients
  - A warm, moist environment
- They provide an almost unfathomable amount of things back
  - Metabolize complex nutrients to SCFA
  - Metabolize mucins and fibre to simple sugars
  - Produce useful substances like folate and Vit K
  - Enhance proliferation of epithelial cells
  - Protect against invasion of many pathogens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Chlamydiae
Chlamydophila psittaci
Chlamydophila pneumoniae
Chlamydia trachomatis
Parachlamydia acanthamoebae
Proteobacteria
Epsilon
Campylobacter coli
Campylobacter fetus
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Campylobacter jejuni
Campylobacter lari
Campylobacter upsaliensis
Helicobacter pylori
Alpha
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Bartonella henselae
Bartonella quintana
Brucella melitensis
Brucella melitensis biovar Abortus
Brucella melitensis biovar Canis
Brucella melitensis biovar Suis
Candidatus Liberibacter africanus
Candidatus Liberibacter asiaticus
Anaplasma phagocytophilum
Ehrlichia canis
Ehrlichia chaffeensis
Ehrlichia ewingii
Ehrlichia ruminantium
Neorickettsia sennetsu
Orientia tsutsugamushi
Rickettsia conorii
Rickettsia felis
Rickettsia prowazekii
Rickettsia rickettsii
Rickettsia typhi
Beta
Eikenella corrodens
Neisseria gonorrhoeae
Neisseria meningitidis
Spirillum minus
Bordetella pertussis
Burkholderia cepacia
Burkholderia mallei
Burkholderia pseudomallei
Ralstonia mannitolilytica
Ralstonia pickettii
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Gamma
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Stentrophomonas maltophila
Xanthomonas campestris pv. malvacearum
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Xylella fastidiosa
Alteromonas tetraodonis
Tetrodotoxin
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Pseudomonas syringae pv. glycinea
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Pseudomonas alcaligenes
Pseudomonas fluorescens
Pseudomonas putida
Pseudomonas stutzeri
Aeromonas sp.
Haemophilus influenzae
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Vibrio cholerae
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Vibrio mimicus
Vibrio parahaemolyticus
Vibrio vulnificus
Spirochetes
Borrelia burgdorferi
Borrelia hermsii
Borrelia recurrentis
Borrelia turicatae
Leptospira interrogans
Treponema pallidum
Fusobacteria
Fusobacterium necrophorum
Streptobacillus moniliformis
Firmicutes
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Actinobacteria
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Mycobacterium avium
Mycobacterium bovis
Mycobacterium fortuitum
Mycobacterium kansasii
Mycobacterium leprae
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Mycobacterium marinum
Mycobacterium scrofulaceum
Mycobacterium simiae
Mycobacterium szulgai
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Rothia dentocariosa
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Nocardia asteroides
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Corynebacterium xerosis
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Diphtheria toxin
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Shiga Toxin
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Salmonella enteriditis
Salmonella paratyphi
Salmonella typhimurium
Salmonella typhi
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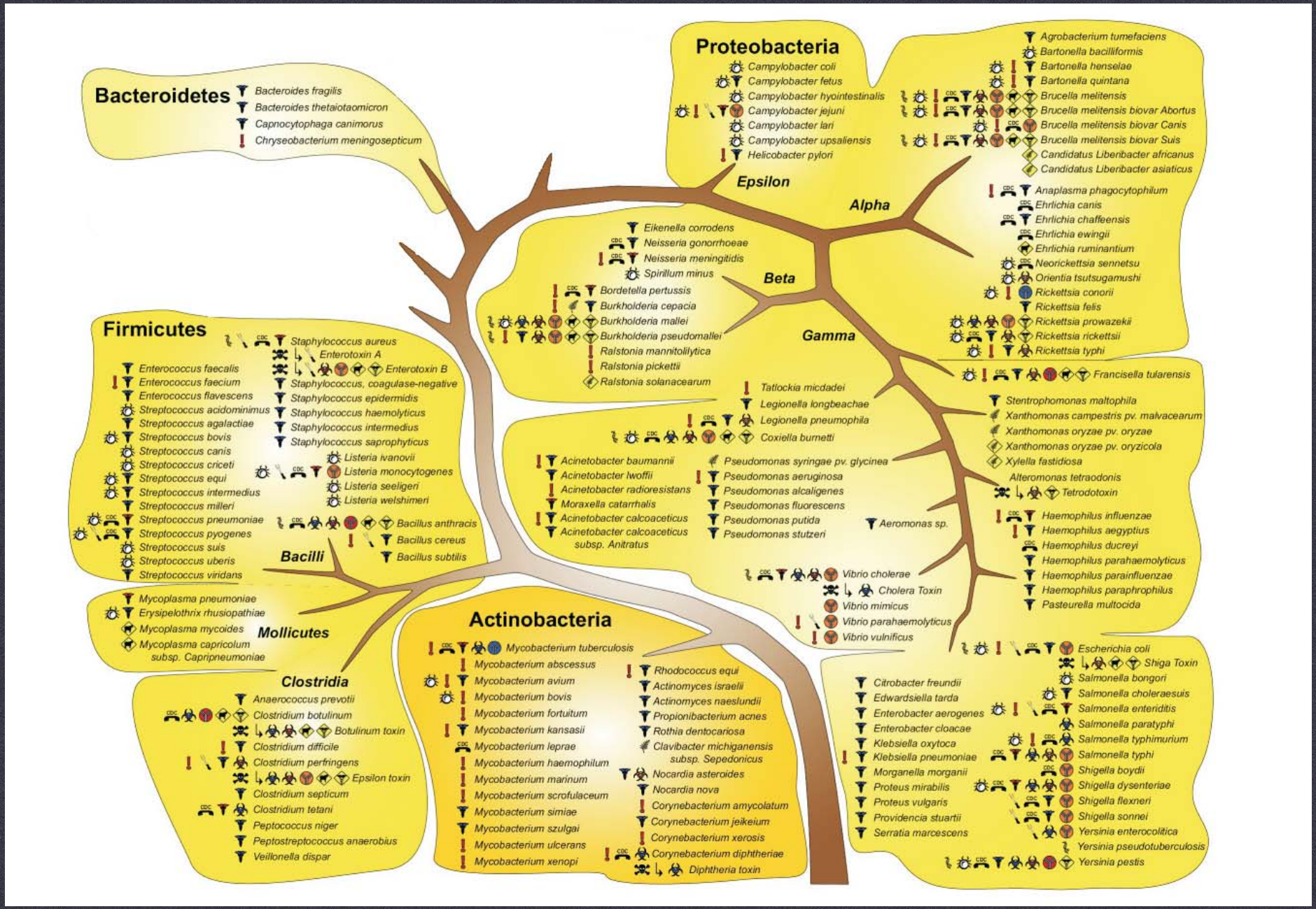
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia stuartii
Serratia marcescens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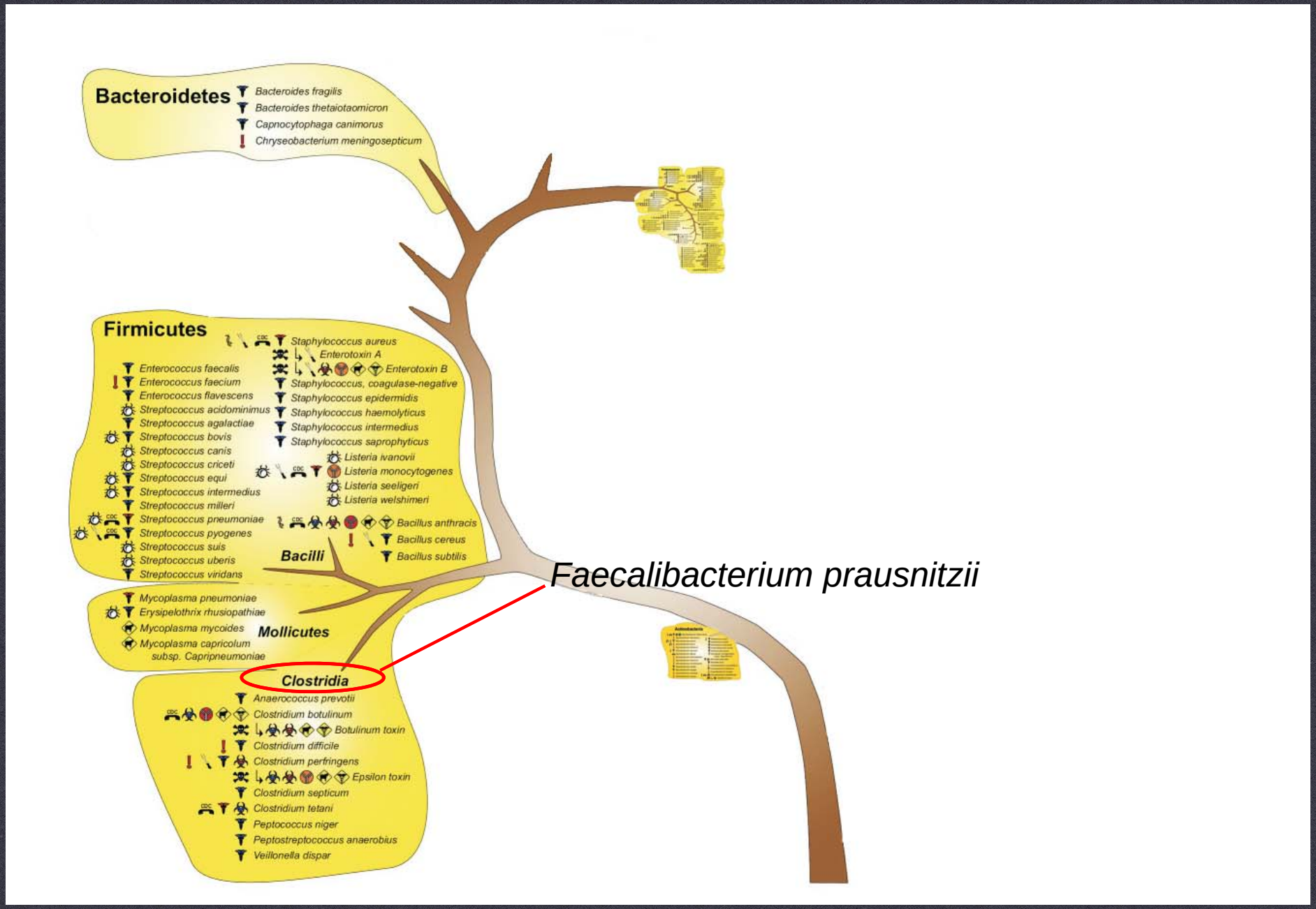
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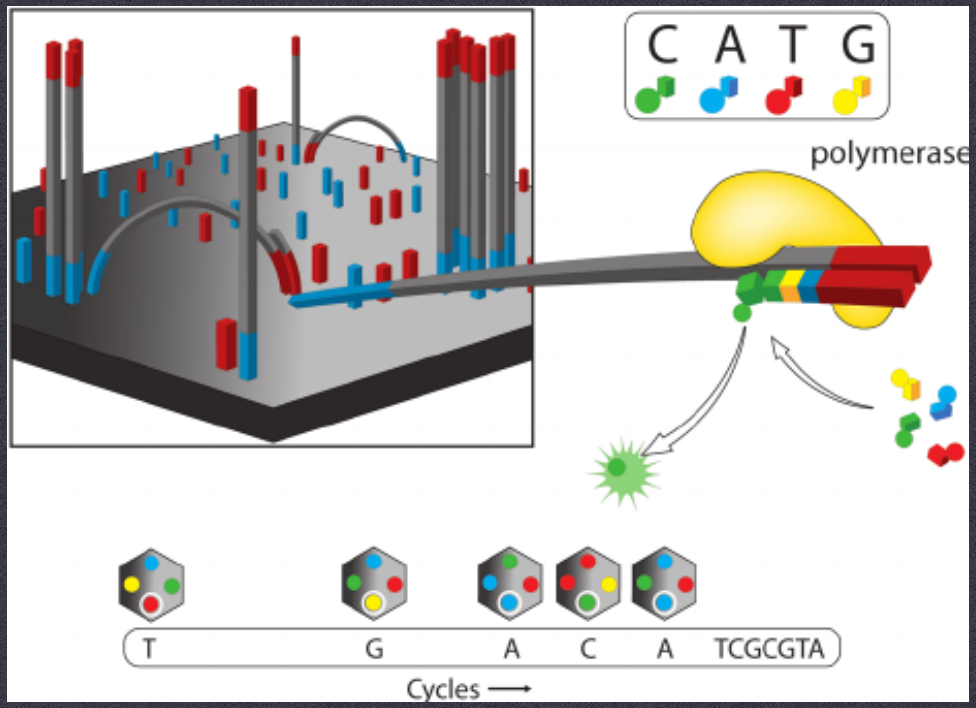
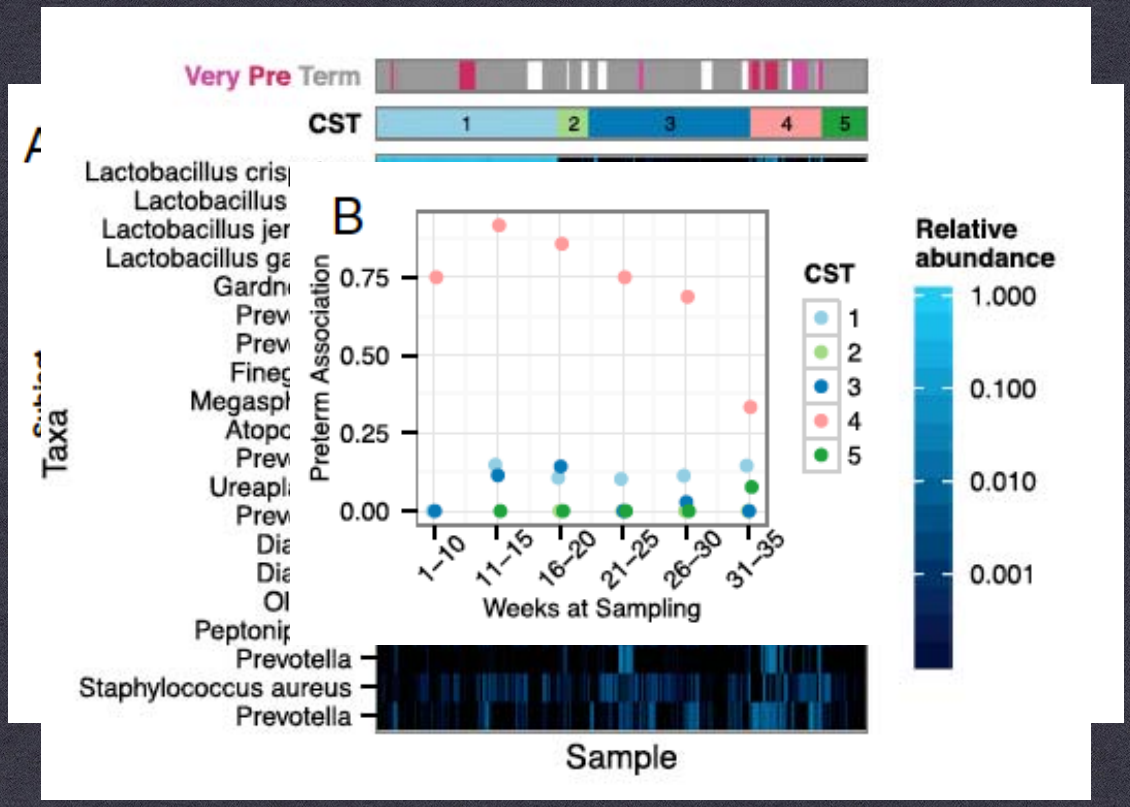
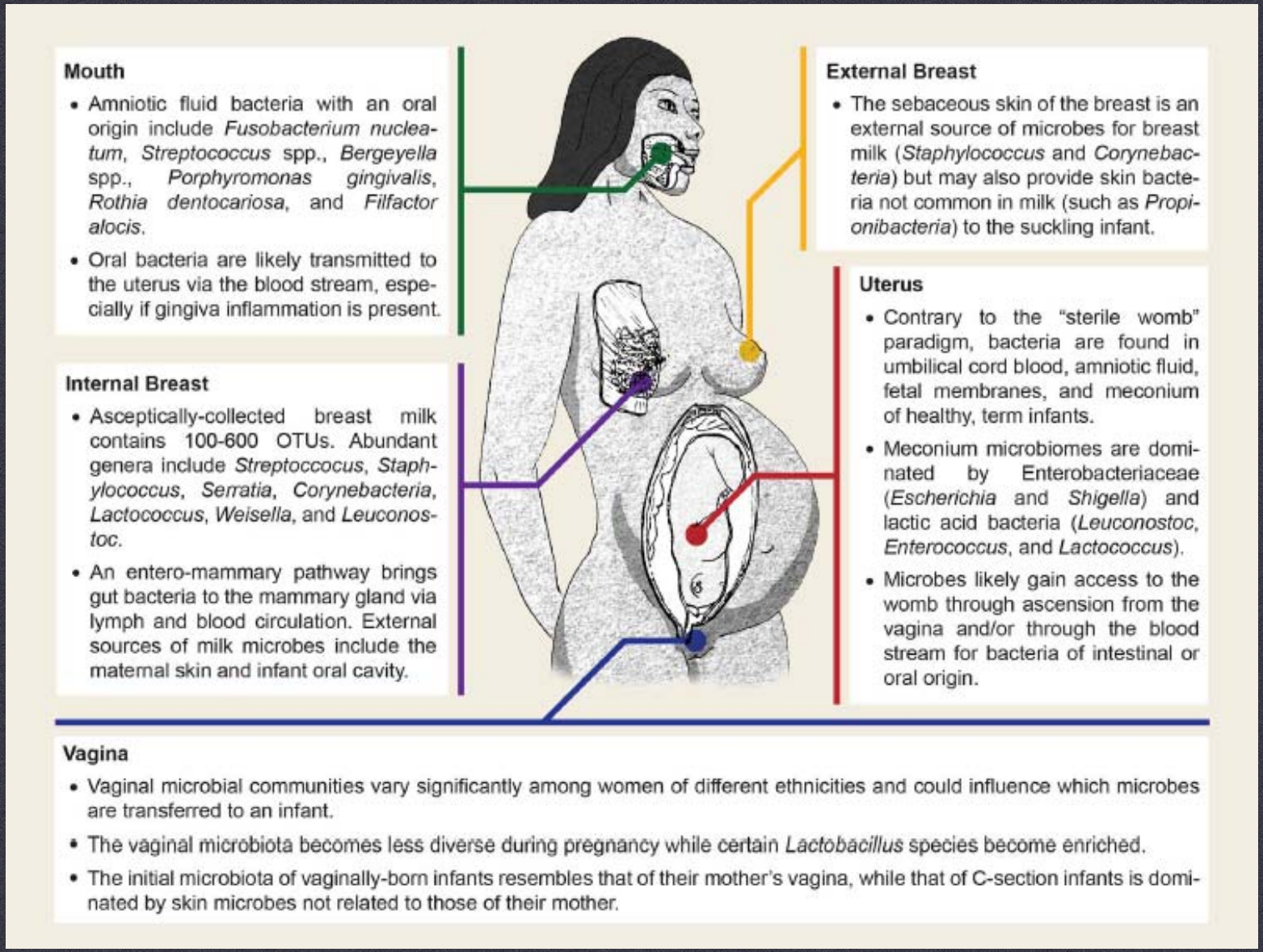
Faecalibacterium prausnitzii


C A T G
polymerase
T
G
A
C
A
TCGCGTA
Cycles

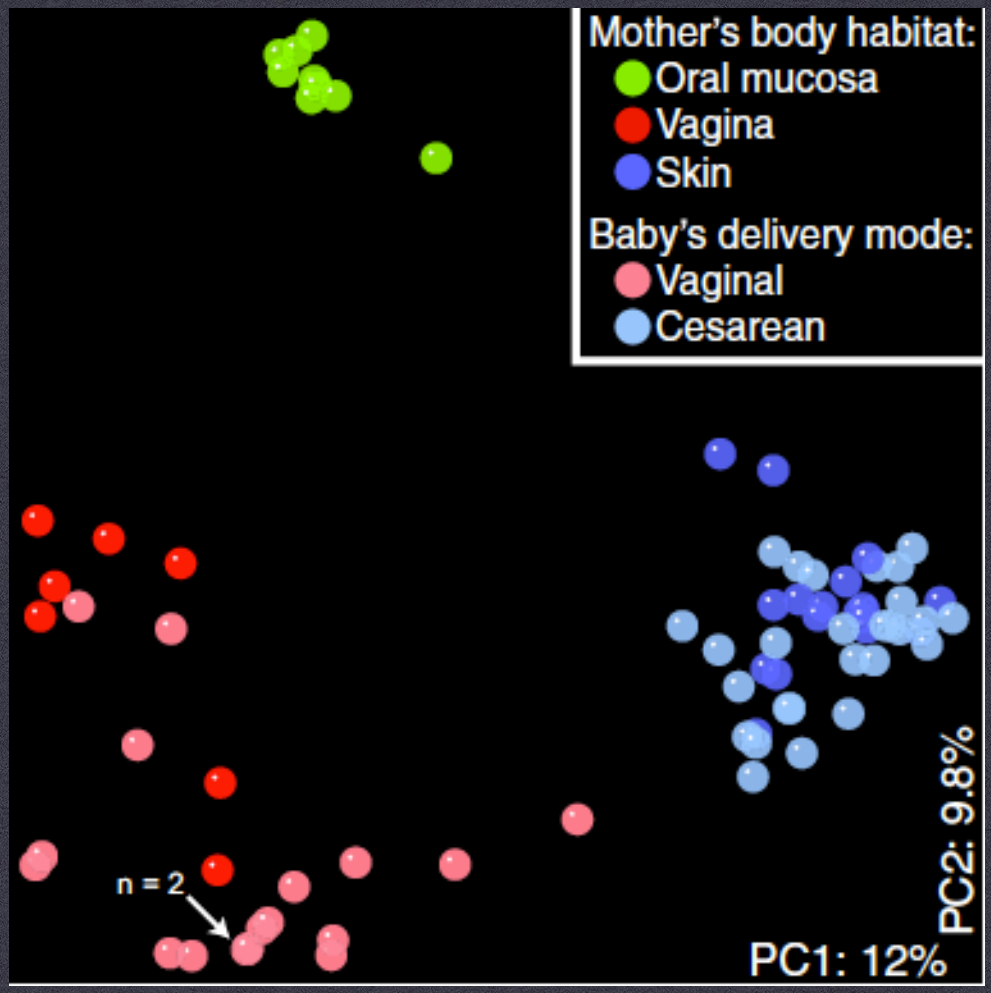
community state type



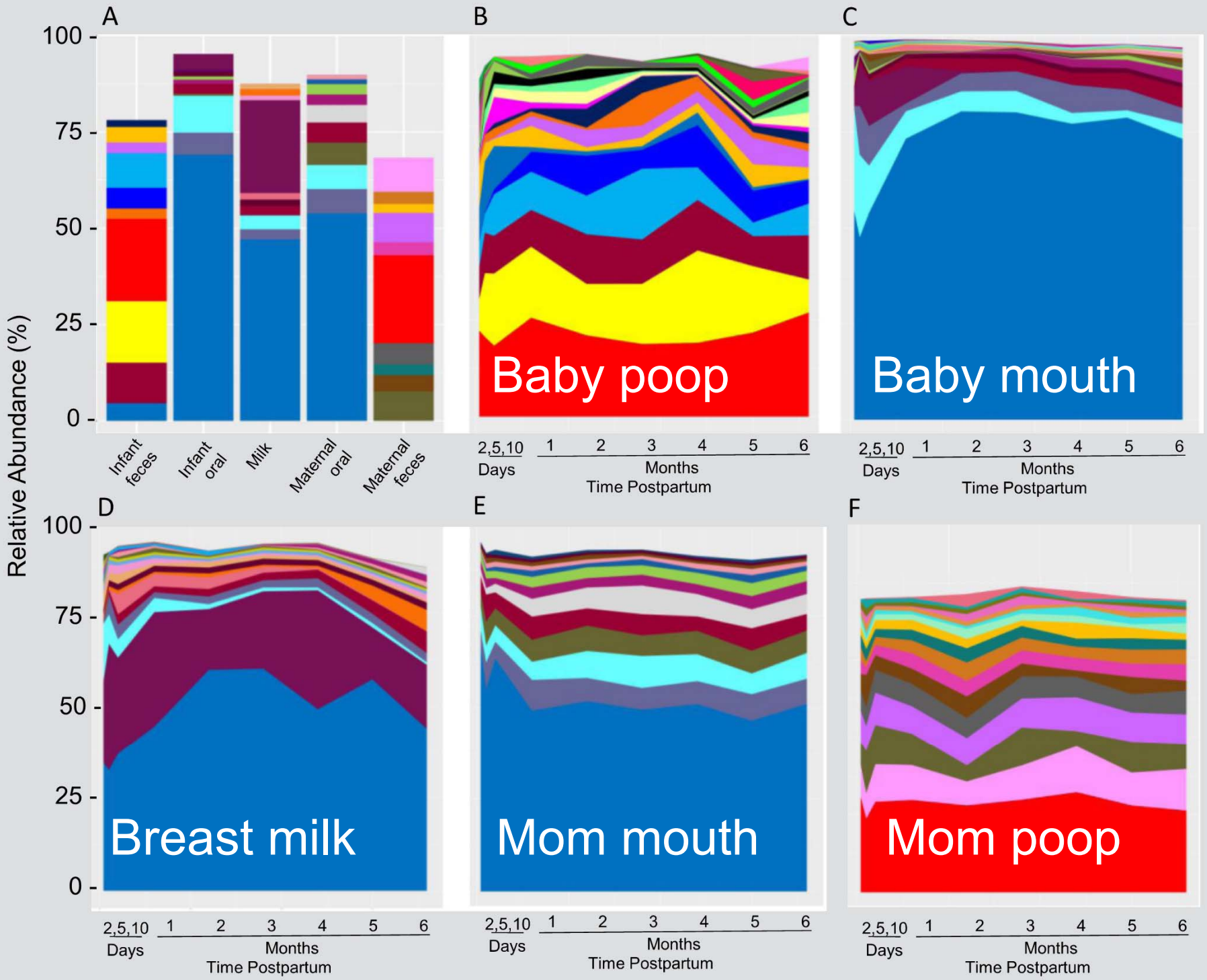
DEVELOPMENT OF THE NEONATAL MICRO BIOME



MODE OF DELIVERY



PNAS | June 29, 2010 | vol. 107 | no. 26 | 11971–11975


A
B
C
D
E
F
Relative Abundance (%)
100
75
50
25
0
Infant feces
Infant oral
Milk
Maternal oral
Maternal feces
Baby poop
Baby mouth
Breast milk
Mom mouth
Mom poop
2,5,10
Days
1
2
3
4
5
6
Months
Time Postpartum

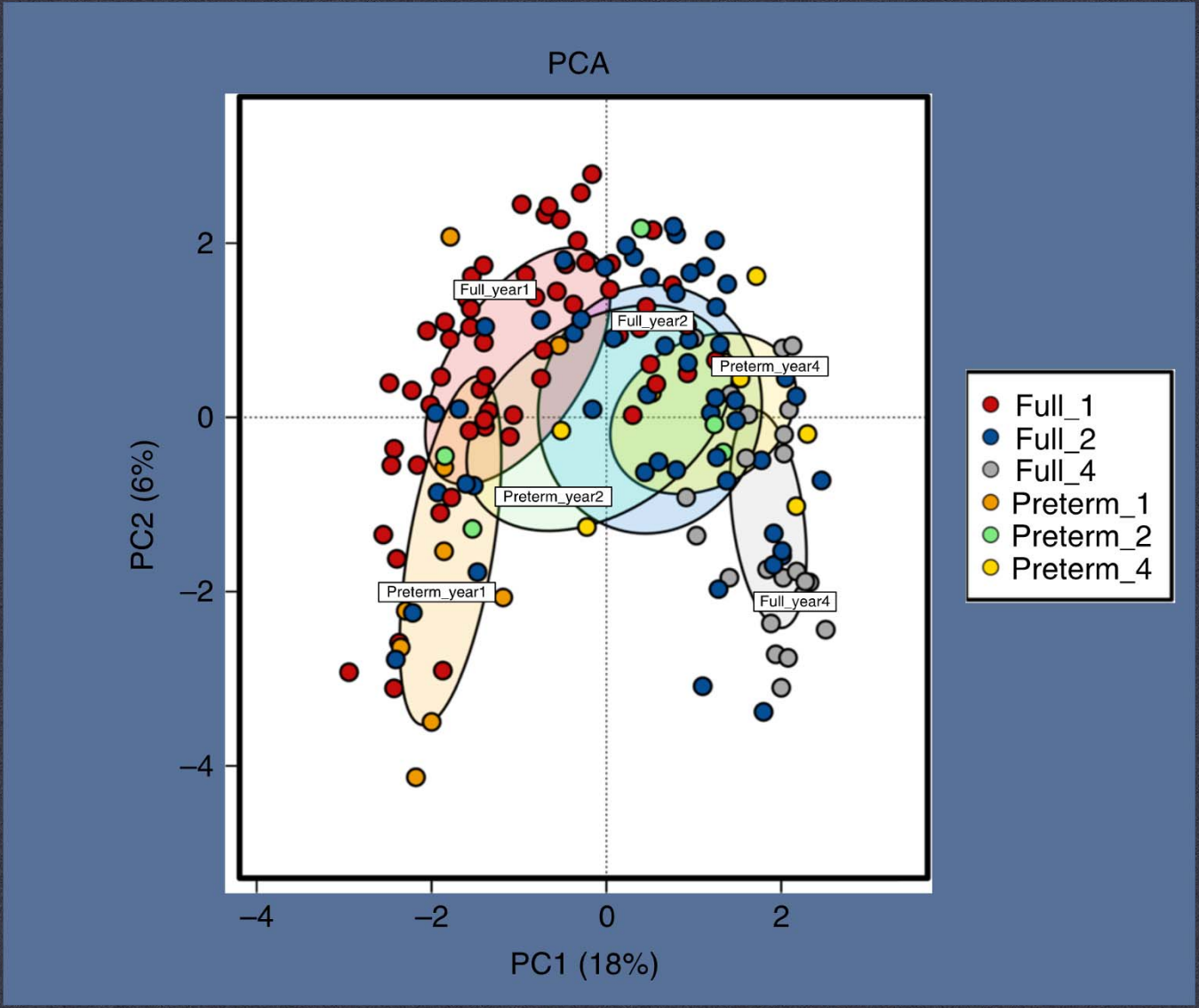
ARTICLE

https://doi.org/10.1038/s41467-019-09252-4 OPEN

Perinatal factors affect the gut microbiota up to four years after birth

Fiona Fouhy[1,2], Claire Watkins[1,2], Cian J. Hill[1], Carol-Anne O'Shea[3], Brid Nagle[2], Eugene M. Dempsey[3,4], Paul W. O'Toole[1,5], R. Paul Ross[1,5], C. Anthony Ryan[1,3] & Catherine Stanton[1,2]

Nature Commun 2019; 10: 1517



Clin Exp Allergy 2005; 35:1466–1472

Caesarean section delivery and the risk of allergic disorders in childhood

doi:10.1111/j.1365-2222.2005.02356.x

H. Renz-Polster*[1], M. R. David†[2], A. S. Buist*, W. M. Vollmer†, E. A. O'Connor†, E. A. Frazier† and M. A. Wall*
*Oregon Health & Science University, Portland OR, USA and †Kaiser Permanente Center for Health Research, Portland OR, USA

Caesarean section is associated with an increased risk of childhood-onset type 1 **diabetes mellitus**: a meta-analysis of observational studies.
Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, Parslow RC, Pozzilli P, Brigis G, Stoyanov D, Urbonaite B, Sipetić S, Schober E, Ionescu-Tirgoviste C, Devoti G, de Beaufort CE, Buschard K, Patterson CC.
Diabetologia. 2008 May;51(5):726-35. doi: 10.1007/s00125-008-0941-z. Epub 2008 Feb 22.

Cesarean Delivery Is Associated With Celiac Disease but Not Inflammatory Bowel Disease in Children

AUTHORS: Evalotte Decker,[a] Guido Engelmann, MD,[b] Annette Findeisen, MD,[c] Patrick Gerner, MD,[d] Martin Laaβ, MD,[e] Dietrich Ney, MD,[f] Carsten Posovszky, MD,[g] Ludwig Hoy, PhD,[h] and Mathias W. Hornef, MD[a]

WHAT'S KNOWN ON THIS SUBJECT: Alterati…
microflora have been linked t…
delivery (vagin…

69. Bager P, Simonsen J, Nielsen NM, Frisch M (2012) Cesarean section and offspring's risk of inflammatory bowel disease: a national cohort study. Inflamm Bowel Dis 18: 857–862.

These Two Guys Studied Their Feces for a Year

For science

LINA ZELDOVICH | SEP 3 2014, 6:59 AM ET

David et al. Genome Biology 2014, 15:R89
http://genomebiology.com/2014/15/7/R89

Genome Biology

RESEARCH

Open Access

Host lifestyle affects human microbiota on daily timescales

Lawrence A David[1,2,11], Arne C Materna[3], Jonathan Friedman[4], Maria I Campos-Baptista[5], Matthew C Blackburn[6], Allison Perrotta[7], Susan E Erdman[8] and Eric J Alm[4,9,10*]

Abstract

Background: Disturbance to human microbiota may underlie several pathologies. Yet, we lack a comprehensive understanding of how lifestyle affects the dynamics of human-associated microbial communities.

Results: Here, we link over 10,000 longitudinal measurements of human wellness and action to the daily gut and saliva microbiota dynamics of two individuals over the course of one year. These time series show overall microbial communities to be stable for months. However, rare events in each subjects' life rapidly and broadly impacted microbiota dynamics. Travel from the developed to the developing world in one subject led to a nearly two-fold increase in the Bacteroidetes to Firmicutes ratio, which reversed upon return. Enteric infection in the other subject resulted in the permanent decline of most gut bacterial taxa, which were replaced by genetically similar species. Still, even during periods of overall community stability, the dynamics of select microbial taxa could be associated with specific host behaviors. Most prominently, changes in host fiber intake positively correlated with next-day abundance changes among 15% of gut microbiota members.

Conclusions: Our findings suggest that although human-associated microbial communities are generally stable, they can be quickly and profoundly altered by common human actions and experiences.

Background

The temporal dynamics of host-associated microbial communities (the microbiota) are of growing interest due to these communities' relevance for health [1-5]. Normally, human microbiota remain stable for months, and possibly even years [6-8]. However, studies across mice and humans suggest that common aspects of the modern Western lifestyle, including antibiotics [1,9-11] and high-fat diets [2], can persistently alter commensal microbial communities. In turn, those microbial disturbances may increase pathogen susceptibility [3], obesity [4,12], and auto-inflammatory disease [5], maladies which are becoming more frequent in the developed world.

In spite of their potential health impact, a full list of lifestyle factors capable of altering human microbiota remains incomplete. Interventional studies are regularly performed to identify host behaviors that affect microbial dynamics, and they have notably demonstrated human gut microbial sensitivity to antibiotics [9-11], bowel surgery [13], and short-term diet shifts [14,15]. However, interventions by design only test a small number of hypotheses; thus, a large, and potentially unfeasible, number of interventional studies are needed to fully explore the rich diversity of human actions and behaviors.

An alternative approach for efficiently linking numerous host factors to microbial responses is to longitudinally observe both the host and microbiota, and to infer relationships between them. Such observational studies have recently been used to show that menstrual cycles are the primary driver of vaginal microbial dynamics in women [16], and to show that infant gut microbiota begin transitioning towards adult communities after weaning [17]. In these time series, the quantity of host lifestyle variables that can be related to microbial dynamics is only bound by the number of host factors that can be tracked. Still, host tracking is non-trivial for ethical and logistical reasons, such as the need to repeatedly survey participants and the enforcement of subject

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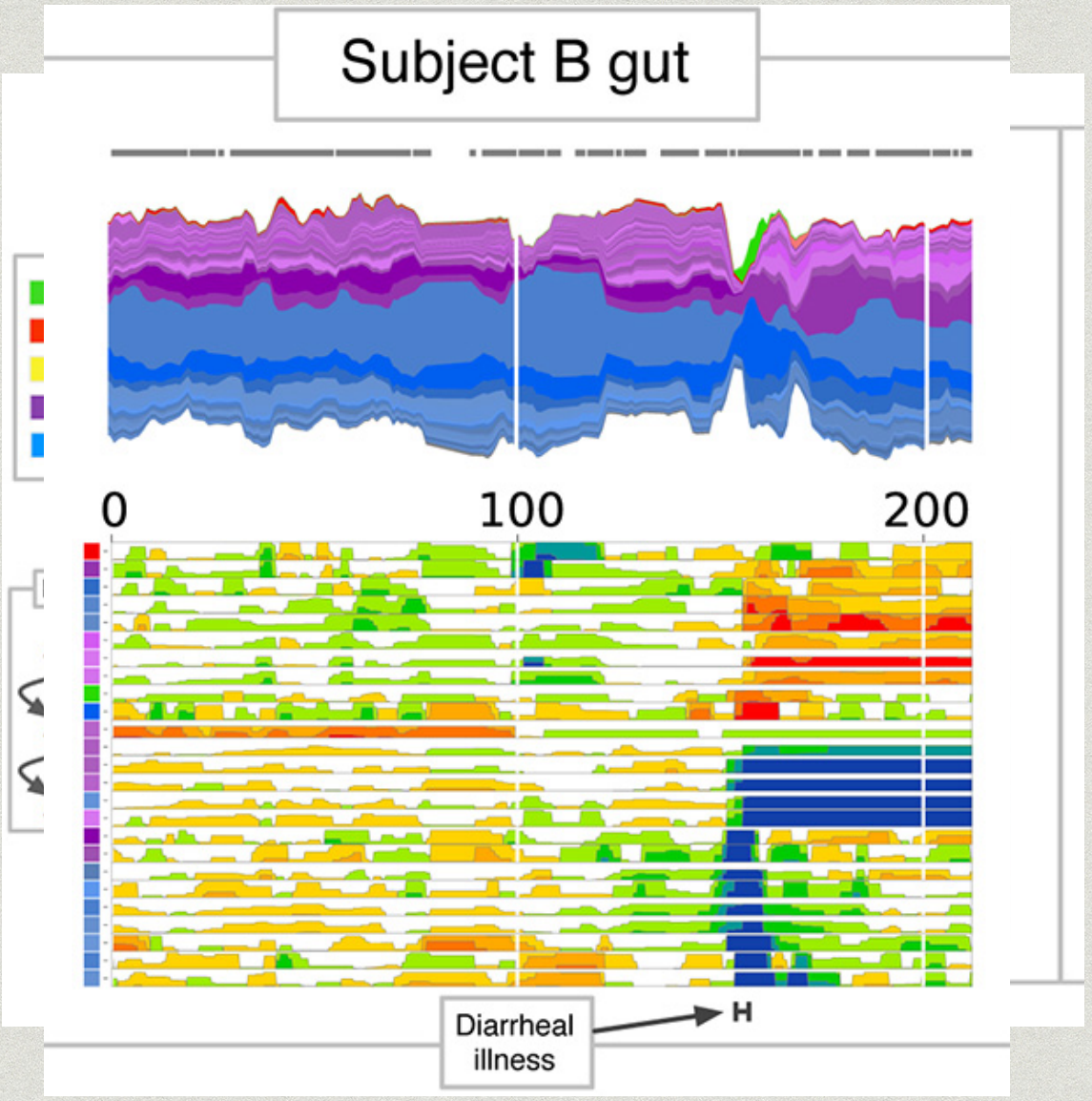
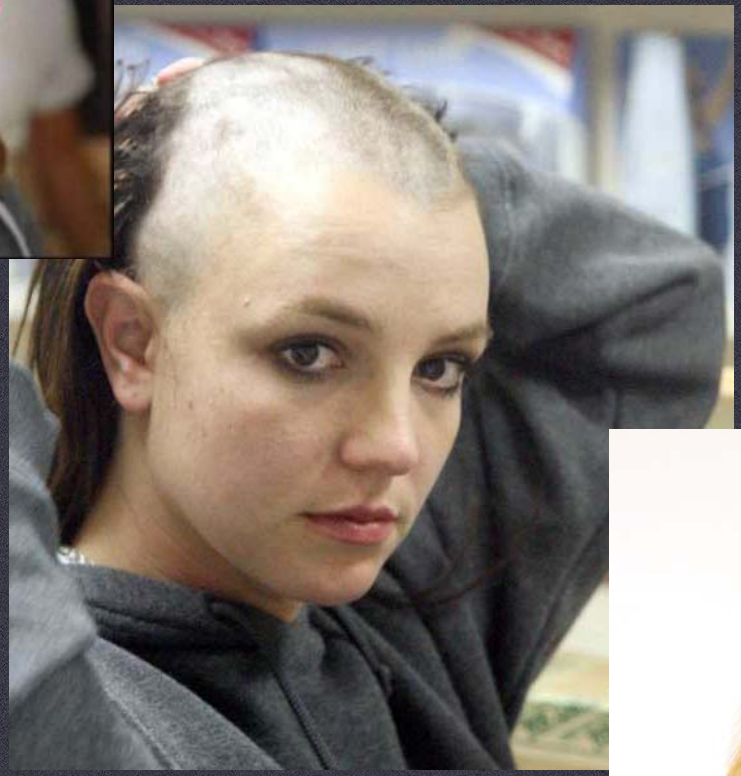
Full list of author information is available at the end of the article



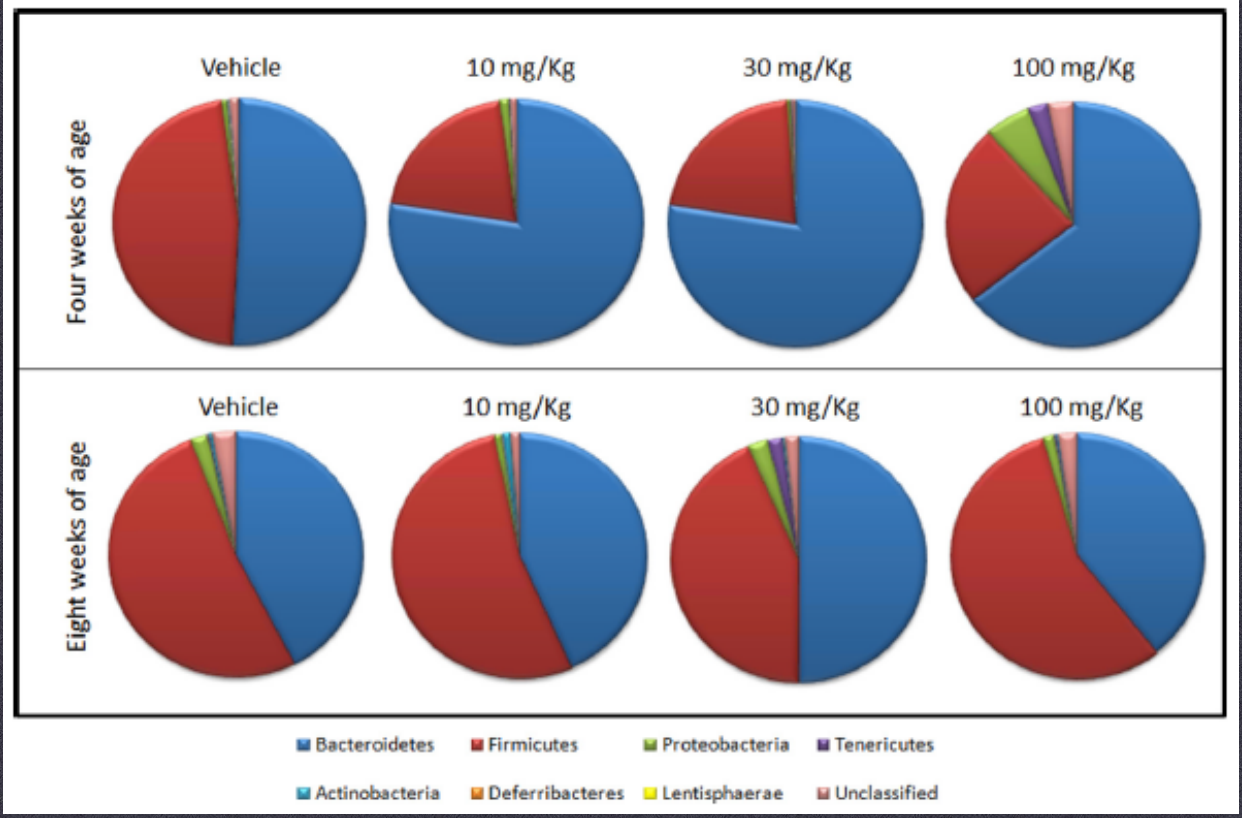
The brain-gut-microbiome axis

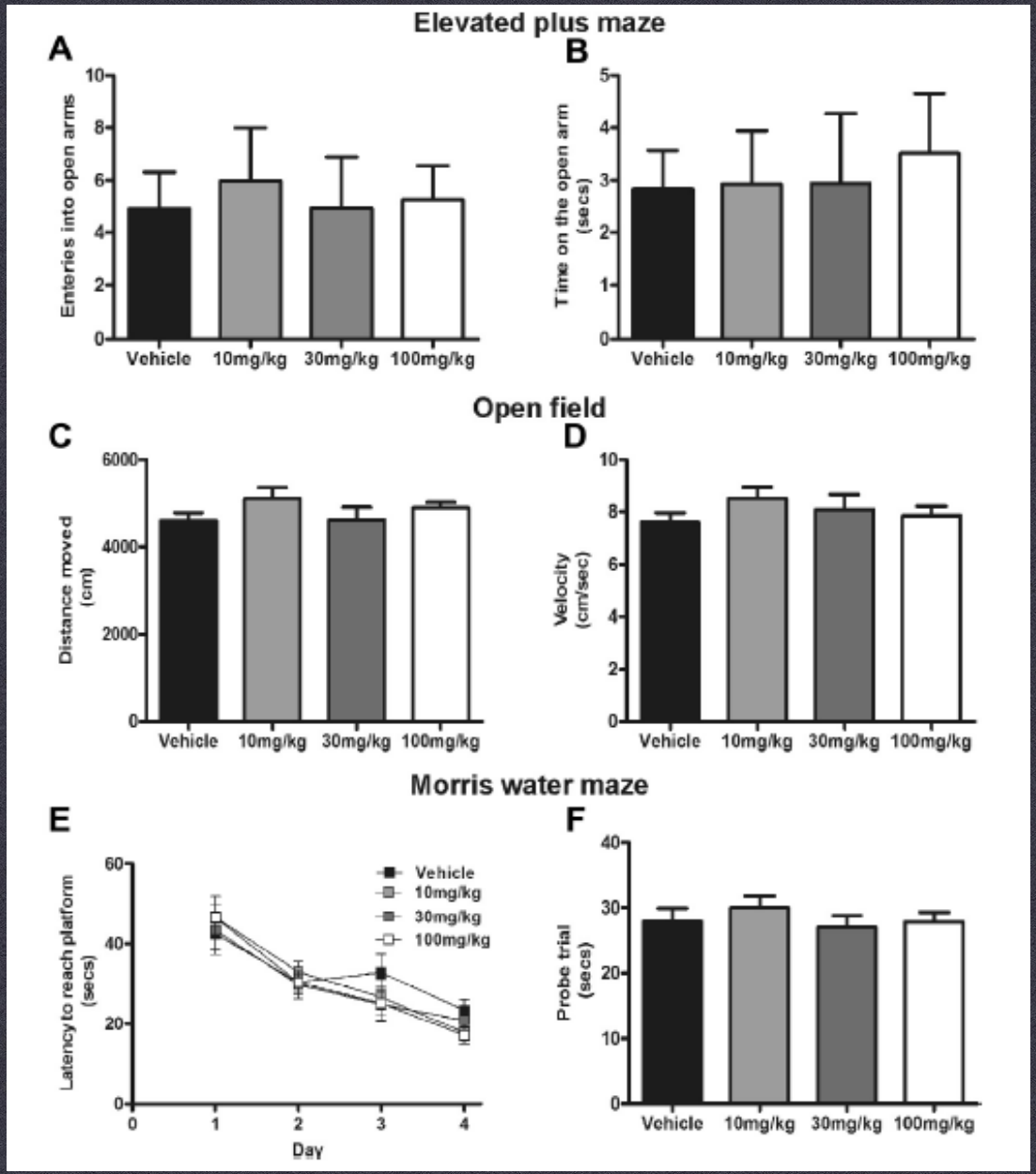
- “Gut feelings”
- “Trust your gut”
- “Butterflies in my stomach”

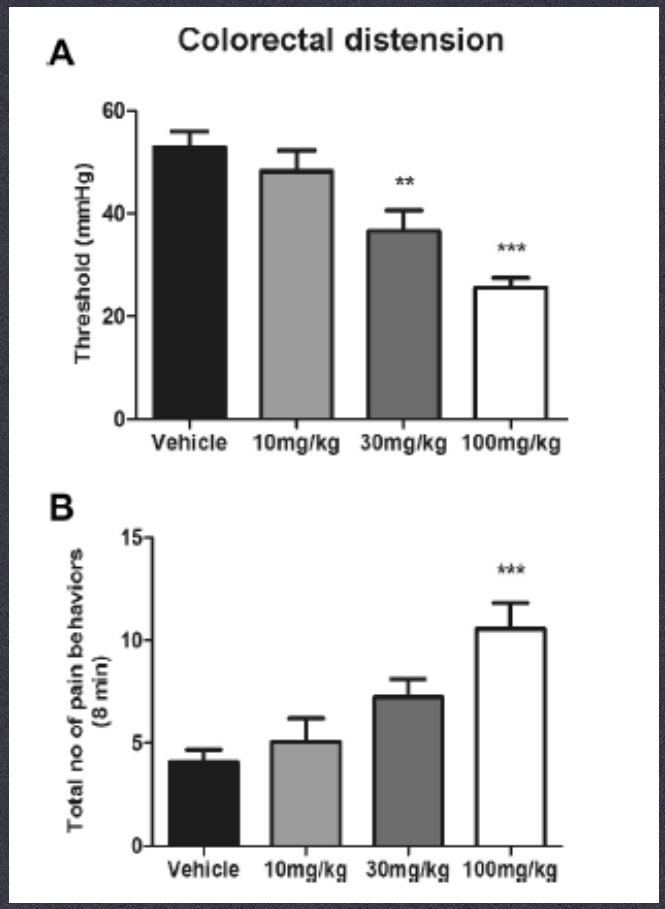


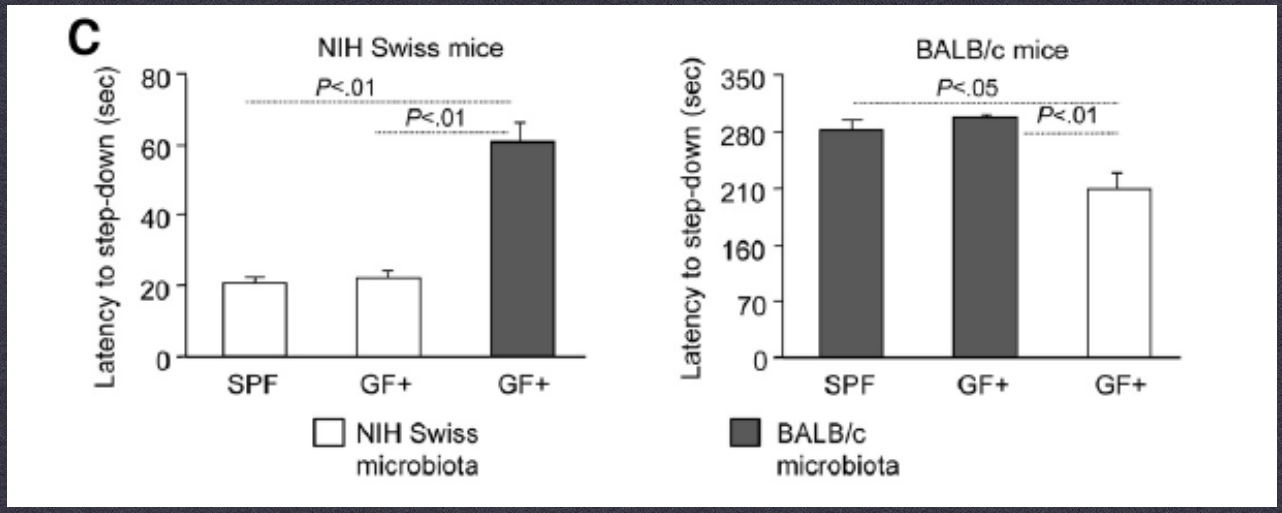
KEY EVENTS IN LIFE CAN CAUSE DRASTIC CHANGE. . .

Single course of vancomycin in newborn rats - 10 days of treatment starting at day 4 of life

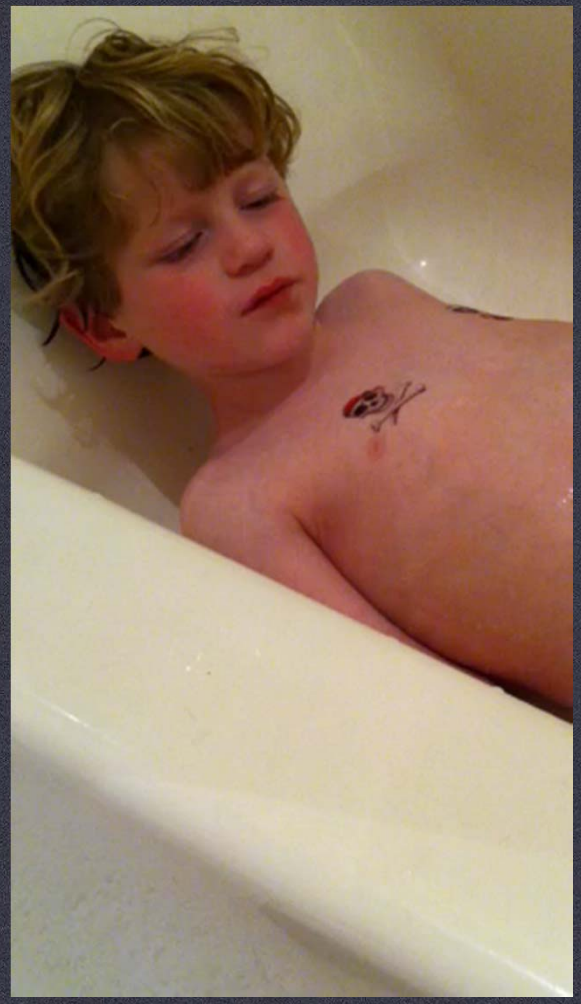


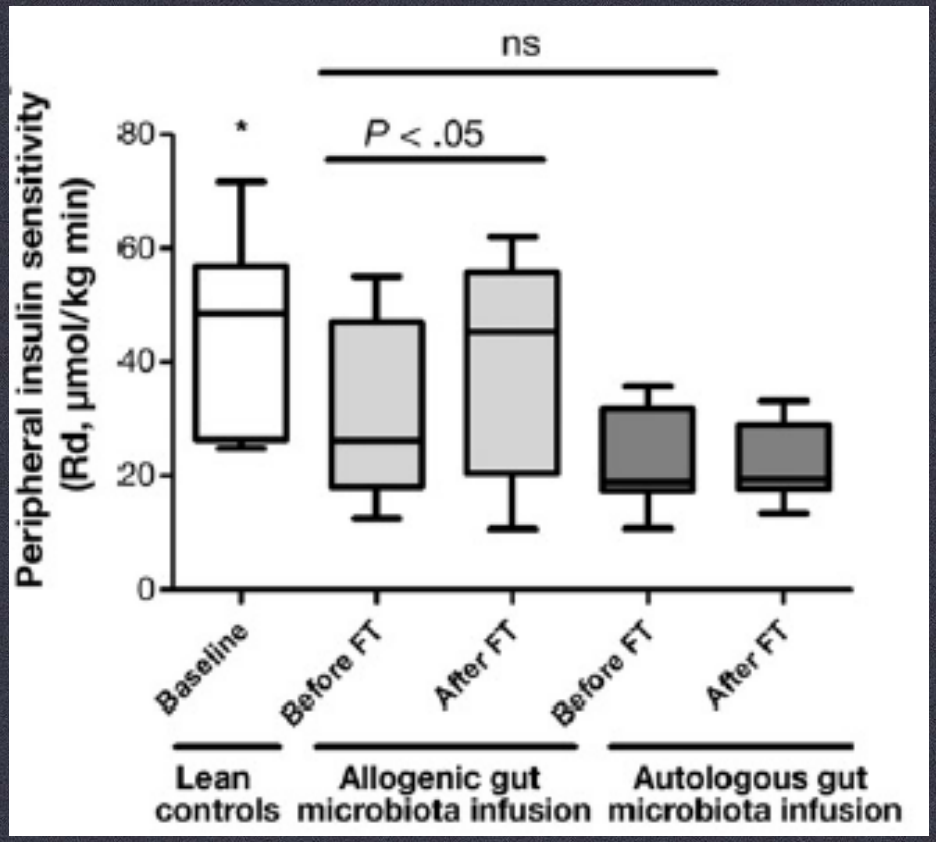

Elevated plus maze
A
Enteries into open arms
10
8
6
4
2
0
Vehicle
10mg/kg
30mg/kg
100mg/kg
B
Time on the open arm (secs)
5
4
3
2
1
0
Vehicle
10mg/kg
30mg/kg
100mg/kg
Open field
C
Distance moved (cm)
6000
4000
2000
0
Vehicle
10mg/kg
30mg/kg
100mg/kg
D
Velocity (cm/sec)
10
8
6
4
2
0
Vehicle
10mg/kg
30mg/kg
100mg/kg
Morris water maze
E
Latency to reach platform (secs)
60
40
20
0
0
1
2
3
4
Day
Vehicle
10mg/kg
30mg/kg
100mg/kg
F
Probe trial (secs)
40
30
20
10
0
Vehicle
10mg/kg
30mg/kg
100mg/kg


A
Colorectal distension
Threshold (mmHg)
60
40
20
0
**
***
Vehicle
10mg/kg
30mg/kg
100mg/kg
B
Total no of pain behaviors (8 min)
15
10
5
0
***
Vehicle
10mg/kg
30mg/kg
100mg/kg

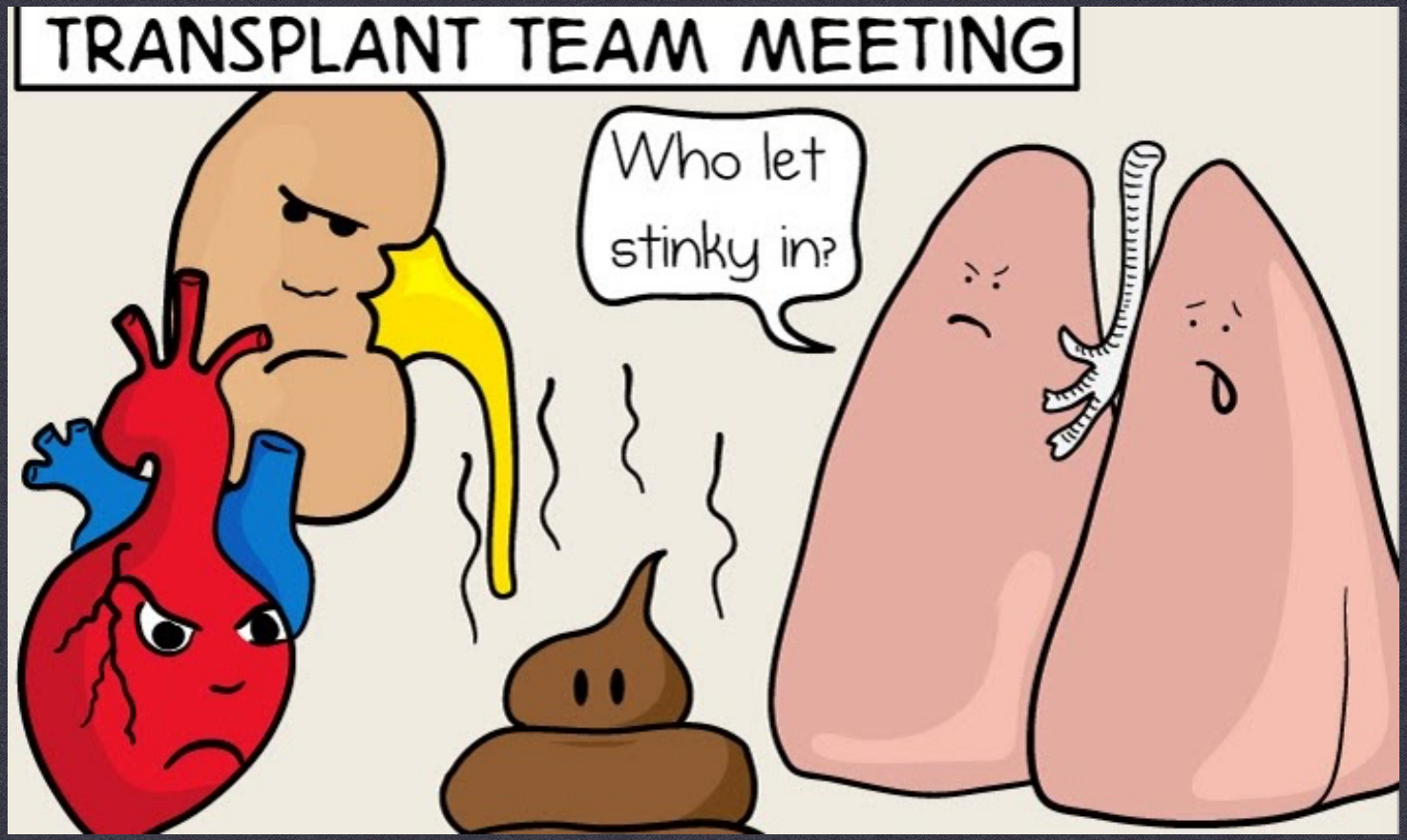

C
NIH Swiss mice
Latency to step-down (sec)
80
60
40
20
0
P<.01
P<.01
SPF
GF+
GF+
NIH Swiss microbiota
BALB/c mice
Latency to step-down (sec)
350
280
210
160
70
0
P<.05
P<.01
SPF
GF+
GF+
BALB/c microbiota

IS IT POSSIBLE YOU ARE NOT IN CONTROL OF YOUR OWN ACTIONS?




ns
*
P < .05
Peripheral insulin sensitivity (Rd, µmol/kg min)
80
60
40
20
0
Baseline
Before FT
After FT
Before FT
After FT
Lean controls
Allogenic gut microbiota infusion
Autologous gut microbiota infusion


Florastor®
Saccharomyces boulardii lyo
#1 PROBIOTIC
Now 100% Vegetarian
Culturelle
Digestive Health
Daily Probiotic Formula
30
Supplement Facts
Serving Size: One (1) Capsule
Amount Per Serving
% Daily Value ages 1-3
% Daily Value 4+ years of age**
Vitamin C 3 mg 8% 5%
Lactobacillus GG 10 billion CFUs***
Inulin (Chicory root extract) 200 mg
** Percent Daily Values are based on a 2,000 calorie diet.
Other ingredients: Gelatin, sucrose, maltode
ascorbate, magnesium stearate, silica, and tita
GOOD HOUSEKEEPING
Jarrow FORMULAS
Bifidus Balance +FOS
4 BIFIDOBACTERIA
100 CAPSULES PROBIOTIC SUPPLEMENT
5 BILLION
5 Billion Viable Cells
B. longum BB536
B. lactis Bi-04
Nutrition Facts
Strawberry
Blueberry
Peach
ACTIVIA
Stirred Yoghurt
Peach & Apricot
Mango
Plain
Strawberry
Low fat
Protein
8%
4g
8%
*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.
Calories: 2,000 2,500
Total Fat Less than 65g 80g
Sat Fat Less than 20g 25g
Cholesterol Less than 300mg 300mg
Sodium Less than 2,400mg 2,400mg
Potassium 3,500mg 3,500mg
Total Carbohydrate 300g 375g
Dietary Fiber 25g 30g
Protein 50g 65g
Vitamin A 0% Vitamin A 0% Vitamin A 0%
Vitamin C 0% Vitamin C 0% Vitamin C 0%
Calcium 15% Calcium 15% Calcium 15%
Iron 0% Iron 0% Iron 0%
Vitamin D 10% Vitamin D 10% Vitamin D 15%
Not a significant source of Trans Fat.
CONTAINS THE ACTIVE CULTURES L.BULGA
AND BIFIDOBACTERIUM LACTIS DN 173-010 (Bifidus Regularis®)
KEEP REFRIGERATED.


TRANSPLANT TEAM MEETING
Who let stinky in?


OPENBIOME
FMT Upper Delivery
Microbiota Preparation
OPENBIOME
FMT Lower Delivery
Microbiota Preparation
250 mL/8.45 oz
OPENBIOME
Capsule G3
Microbiota Preparation
with MEM Technology

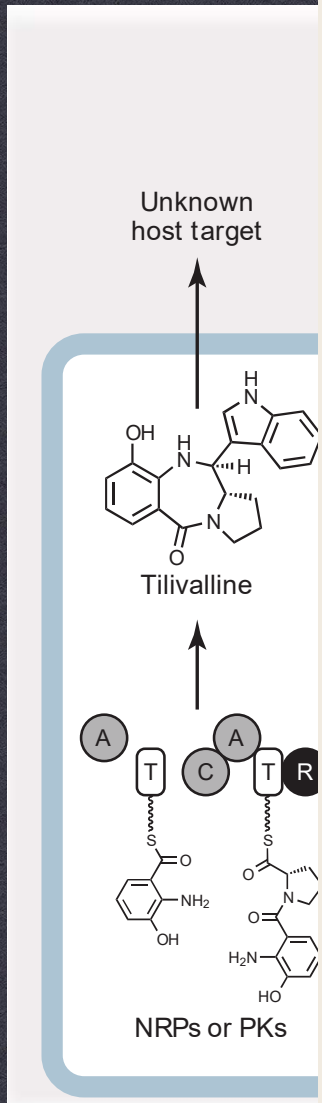
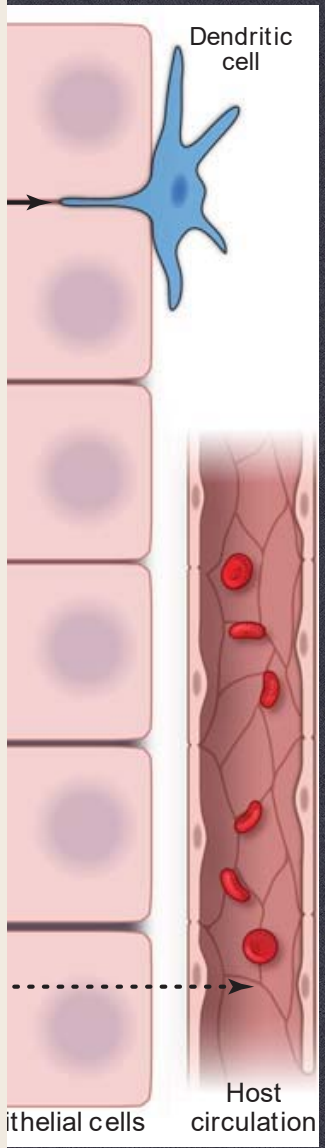


Table 1. Selected small molecules from the human microbiota. A representative set of compounds are shown that cover the chemical classes discussed in the review. Asterisks indicate bacterial pathogens that are not normally present in human-associated communities.

Class	Compound	Producer (example)	Phylum	Host site	Known/ predicted activity
RiPP (thiopeptide)	lactocillin	L. gasseri	Firmicutes	vagina	antibiotic
RiPP (lantibiotic)	epidermin	S. epidermidis	Firmicutes	skin	antibiotic
RiPP (lantibiotic)	salivaricin A2 and B	S. salivarius	Firmicutes	mouth	antibiotic
RiPP (lantibiotic)	cytolysin	E. faecalis*	Firmicutes	gut	antibiotic, cytotoxic
RiPP (lantibiotic)	ruminococcin A	R. gnavus	Firmicutes	gut	antibiotic
RiPP (lantibiotic)	staphylococcin Au-26 (Bsa)	S. aureus	Firmicutes	skin	antibiotic
RiPP (lantibiotic)	SA-FF22	S. pyogenes	Firmicutes	oral/ skin	antibiotic
RiPP (bacteriocin)	ruminococcin C	R. gnavus	Firmicutes	gut	antibiotic
RiPP (microcin)	microcin C7/ C51	E. coli	Proteobacteria	gut	antibiotic
RiPP (microcin)	microcin B17	E. coli	Proteobacteria	gut	antibiotic
RiPP (microcin)	microcin J25	E. coli	Proteobacteria	gut	antibiotic
RiPP (microcin)	microcin H47	E. coli	Proteobacteria	gut	antibiotic
RiPP (TOMM)	streptolysin S	S. pyogenes	Firmicutes	oral/ skin	cytotoxic
RiPP (TOMM)	clostridiolysin S	C. sporogenes	Firmicutes	gut	unknown
RiPP (TOMM)	listeriolysin S	L. monocytogenes	Firmicutes	gut	unknown
RiPP	heat-stable enterotoxin	E. coli	Proteobacteria	gut	GI motility (guanylate cyclase 2C)
Amino acid metabolite	indolepropionic acid	C. sporogenes	Firmicutes	gut	immunomodulatory
Amino acid metabolite	indole	unknown	unknown	gut	converted to indoxyl sulfate
Amino acid metabolite	skatole	Clostridium spp.	Firmicutes	gut	unknown
Amino acid metabolite	tryptamine	R. gnavus	Firmicutes	gut	neurotransmitter
Amino acid metabolite	phenyllactic acid	Bifidobacterium spp.	Actinobacteria	gut	unknown
Amino acid metabolite	phenethylamine	Lactobacillus spp.	Firmicutes	gut	neurotransmitter
Amino acid metabolite	d-aminovaleric acid	Clostridium spp.	Firmicutes	gut	unknown
Amino acid metabolite	GABA	unknown	unknown	gut	unknown
Amino acid metabolite	a-aminobutyric acid	unknown	unknown	gut	unknown
Amino acid metabolite	3-aminoisobutyric acid	Clostridium spp.	Firmicutes	gut	unknown
Amino acid metabolite	p-cresol	Clostridium spp.	Firmicutes	gut	unknown
Acid (short-chain)	propionic acid	Bacteroides spp.	Bacteroidetes	gut	immunomodulatory (GPR43)
Oligosaccharide	polysaccharide A	B. fragilis	Bacteroidetes	gut	immunomodulatory (TLR2)
Oligosaccharide	capsular polysaccharide	Streptococcus pneumoniae	Firmicutes	airways	immunomodulatory
Glycolipid	a-galactosylceramide	B. fragilis	Bacteroidetes	gut	immunomodulatory (CD1d)
Glycolipid	corynomycolic acid	Corynebacterium spp.	Actinobacteria	skin	unknown
Glycolipid	mycolic acid	Mycobacterium spp.	Actinobacteria	airways	immunomodulatory (CD1b)
Glycopeptide	muramyl di- and tripeptides	Fusobacterium nucleatum	Fusobacteria	oral	immunomodulatory (NOD1, NOD2)
Terpenoid	staphyloxanthin	S. aureus	Firmicutes	skin	unknown (antioxidant?)
Terpenoid	bile acids (e.g., deoxycholic acid)	Clostridium spp.	Firmicutes	gut	metabomodulatory [TGR5, farnesoid X receptor (FXR), VDR]
NRP	phevalin	S. aureus	Firmicutes	skin	unknown (virulence inducer?)
NRP	cereulide	B. cereus*	Firmicutes	gut	cytotoxic, immunomodulatory
NRP	yersiniabactin	Yersinia pestis*	Proteobacteria	bloodstream	siderophore
NRP	corynebactin	Corynebacterium spp.	Actinobacteria	skin	siderophore
NRP	tilivalline	K. oxytoca*	Proteobacteria	gut	cytotoxic
NRP-PK	zwittermicin	B. cereus*	Firmicutes	gut	antimicrobial
NRP-PK	mutanobactin	S. mutans	Firmicutes	mouth	unknown
NRP-PK	colibactin	E. coli	Proteobacteria	gut	cytotoxic
PK	mycolactone	M. ulcerans*	Actinobacteria	skin	immunomodulatory
Porphyrin	coproporphyrin III	Propionibacterium acnes	Actinobacteria	skin	unknown
Citrate amide	staphyloferrin B	S. aureus	Firmicutes	skin	siderophore



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Article

Cell

A Forward Chemical Genetic Screen Reveals Gut Microbiota Metabolites That Modulate Host Physiology

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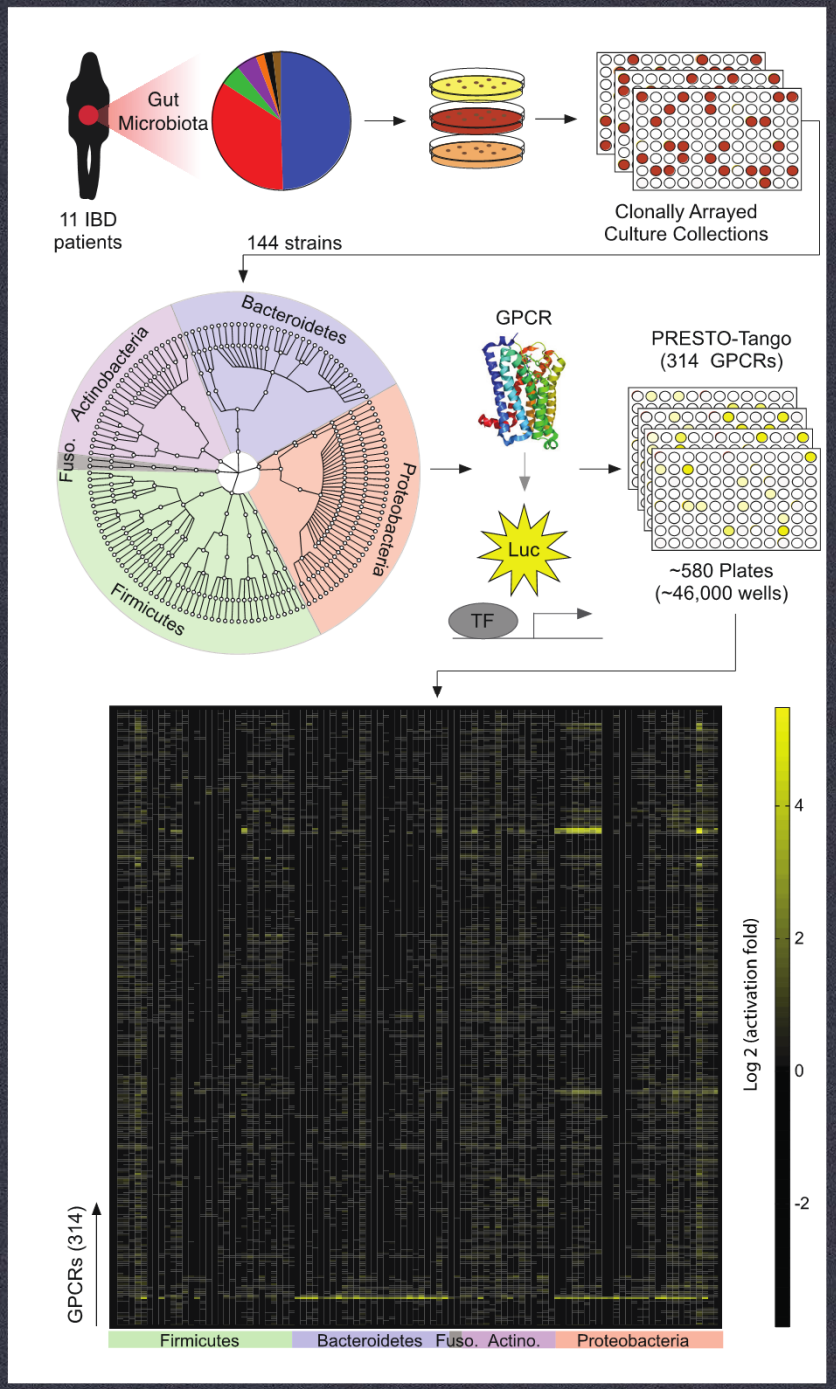
"Dauntingly complex"




The microbiome is a great frontier in medicine
We know almost nothing about it
It will change everything